National Clinical Guideline Centre

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Hepatitis B (chronic)

Diagnosis and management of chronic hepatitis B in children, young people and adults

Clinical guideline

Methods, evidence and recommendations

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FINAL

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1 Contents

Appendices A–O are in a separate file.

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2 Introduction

Chronic hepatitis B describes a spectrum of disease usually characterised by the presence of detectable hepatitis B surface antigen (HBsAg) in the blood or serum for longer than 6 months. In some people, chronic hepatitis B is inactive and does not present significant health problems, but others may progress to liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC). The progression of liver disease is associated with hepatitis B virus (HBV) DNA levels in the blood. Without antiviral treatment, the 5-year cumulative incidence of cirrhosis ranges from 8 to 20%. People with cirrhosis face a significant risk of decompensated liver disease if they remain untreated. Five-year survival rates among people with untreated decompensated cirrhosis can be as low as 15%. Chronic hepatitis B can be divided into e antigen- (HBeAg) positive or HBeAg-negative disease based on the presence or absence of e antigen. The presence of HBeAg is typically associated with higher rates of viral replication and therefore increased infectivity.

The goal of treatment for chronic hepatitis B is to prevent cirrhosis, HCC and liver failure. In clinical practice surrogate markers are used to monitor progression of disease and treatment response, and include normalisation of serum alanine aminotransferase (ALT) levels, decrease in inflammation scores with no worsening or improvement in fibrosis on liver biopsies, suppression of serum HBV DNA to undetectable levels, loss of HBeAg and seroconversion to HBe antibody (anti-HBe), and loss of HBsAg and seroconversion to HBs antibody (anti-HBs).

Antiviral therapy suppresses HBV replication and decreases hepatic inflammation and fibrosis, thereby reducing the likelihood of serious clinical disease. Since the introduction of effective treatment in the form of interferon alfa, several nucleoside and nucleotide analogues are now approved for use in adults with chronic hepatitis B, together with a pegylated form of interferon alfa. With multiple treatment options that are efficacious and safe, the key questions are which patients need immediate treatment and what sequence and combination of drug regimens should be used, and which patients can be monitored and delay treatment.

In this guideline we cover the following:

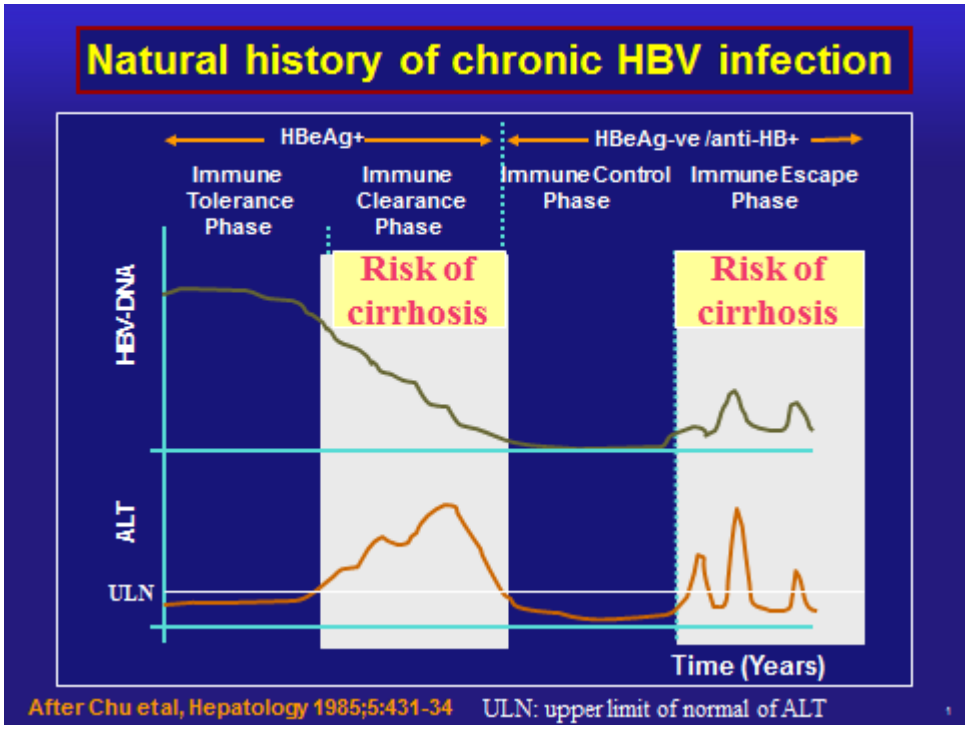
- information needs of people with chronic hepatitis B and their carers
- where children, young people and adults with chronic hepatitis B should be assessed
- assessment of liver disease, including the use of non-invasive tests and genotype testing
- criteria for offering antiviral treatment
- the efficacy, safety and cost effectiveness of currently available treatments
- selection of first-line therapy
- management of treatment failure or drug resistance
- whether there is a role for combination therapy
- when it is possible to stop treatment
- managing the care of pregnant and breastfeeding women and prevention of vertical transmission
- prophylactic treatment during immunosuppressive therapy
- monitoring for treatment response, severity of fibrosis and development of HCC.

The spontaneous mutation rate of HBV DNA is high. Exposure of HBV to nucleoside or nucleotide analogues selects for mutations in the polymerase gene that confer resistance or decreased susceptibility to the drugs. The relative risk of drug resistance must be taken into account when considering treatment with nucleoside or nucleotide analogues, including the level of cross resistance between different agents.

Figure 1 depicts the natural history of chronic HBV infection. The immune-tolerance phase is seen in HBeAg-positive disease and is characterised by high levels of HBV replication with normal ALT levels and limited liver necroinflammation. Because there is minimal immune response to the virus it is unusual for spontaneous HBeAg loss to occur. This phase is commonly seen in children. It is followed by an immune-clearance or immune-reactive phase in which the immune system recognises and starts to clear the virus. ALT levels are typically elevated or fluctuating, and there is a higher risk of liver fibrosis. This tends to be the initial phase in people infected with HBV as adults. It lasts from weeks to years and ends with HBeAg seroconversion.

With the loss of HBeAg the person may enter an immune-control phase with very low or undetectable HBV DNA levels, normal ALT and minimal fibrosis progression. However, some people may experience rising HBV DNA levels despite HBeAg negativity. This is caused by virions that do not express HBeAg because of genetic mutations. This immune-escape phase can lead to active necroinflammation and progression of fibrosis.

Figure 1: Chu, C. M. et al Natural History of chronic HBV infection in Taiwan: studies of hepatitis B virus DNA in serum. Hepatology 5(3), 431-434. 1985.



Substantial progress has been made in the treatment of chronic hepatitis B in the past decade but the appropriate time for starting treatment remains a topic of debate. Although currently available treatment is effective in suppressing HBV replication, it fails to eradicate the virus necessitating long treatment duration and perhaps lifelong treatment.

The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or those with authority to give consent on their behalf) should provide informed consent, which

should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are marked with a footnote in the recommendations.

3 Development of the guideline

3.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC)
- The NCGC establishes a guideline development group
- A draft guideline is produced after the group assesses the available evidence and makes recommendations
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline lists the recommendations
- information for the public ('information for patients') is written using suitable language for people without specialist medical knowledge.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk

3.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is:

To produce a clinical guideline on the assessment and management for hepatitis B, which will include consideration of:

- Which patients with hepatitis B should be referred for specialist assessment?
- How should such patients be assessed?
- Which patients should receive antiviral treatment?
- Which treatments are most cost effective for which groups of patients?

3.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Care Excellence funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Professor Howard Thomas in accordance with guidance from the National Institute for Health and Care excellence (NICE).

The group met every 5-6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (Appendix B).

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta analysis and cost effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

3.4 What this guideline covers

Groups that will be covered

Children, young people and adults with chronic hepatitis B virus infection including:

- People co-infected with hepatitis C or hepatitis delta (D) virus
- Immunocompromised people (such as those undergoing cancer treatments) who are carriers or have been previously infected, for whom prophylactic treatment might be beneficial
- Pregnant and lactating women
- People with cirrhosis, including those with liver decompensation

Key issues that will be covered

Identification and assessment of chronic hepatitis B

- Healthcare setting for pre-therapeutic tests

- Criteria for referral to specialist services
- Laboratory tests to determine severity of necro-inflammatory activity
- Diagnosis of concomitant infections, hepatitis C and hepatitis delta (D) virus

Pharmacological treatment

- Sequential and combination drug therapy

Monitoring stages of the condition

- Surveillance timing and frequency
- Patient Information

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

For further details please refer to the scope in Appendix A and review questions in section 3.1.

3.5 What this guideline does not cover

Groups that will not be covered

- People who have had a liver transplant
- People with acute hepatitis B
- People co-infected with HIV

Key issues that will not be covered

- Primary prevention of hepatitis B, including vaccination
- Case finding
- Signs and symptoms of advance hepatitis B with cirrhosis
- Non-pharmacological management of chronic hepatitis B
- Co-infection of chronic hepatitis B with HIV or hepatitis viruses A or E
- Guidance on working practices for infected healthcare workers
- Liver transplantation
- Acute hepatitis B

3.6 Relationships between the guideline and other NICE guidance

Health Technology Appraisals to be updated by this guidance:

- 1.2 - 1.4 of Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. NICE technology appraisal guidance 96 (2006). Available from www.nice.org.uk/guidance/TA96

Health Technology Appraisals to be incorporated in this guidance:

- Tenofovir disoproxil for the treatment of chronic hepatitis B. NICE technology appraisal guidance 173 (2009). Available from www.nice.org.uk/guidance/TA173
- Telbivudine for the treatment of chronic hepatitis B. NICE technology appraisal guidance 154 (2008). Available from www.nice.org.uk/guidance/TA154
- Entecavir for the treatment of chronic hepatitis B. NICE technology appraisal guidance 153 (2008). Available from www.nice.org.uk/guidance/TA153
- 1.1 of Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. NICE technology appraisal guidance 96 (2006). Available from www.nice.org.uk/guidance/TA96

Related NICE Clinical Guidelines:

- Alcohol-use disorders. NICE clinical guideline 115 (2011). Available from www.nice.org.uk/guidance/CG115
- Medicines adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76
- Obesity NICE clinical guideline 43 (2006). Available from www.nice.org.uk/guidance/CG43
- Patient experience in adult NHS services. 138 (2012) Available from www.nice.org.uk/guidance/CG138
- Antenatal care. NICE clinical guideline 62 (2008).

Related NICE Public Health Guidance:

- Increasing the uptake of HIV testing among men who have sex with men. NICE public health guidance 34 (2011). Available from: www.nice.org.uk/guidance/PH34
- Increasing the uptake of HIV testing among black Africans in England. NICE public health guidance 33 (2011). Available from: www.nice.org.uk/guidance/PH33
- Hepatitis B and C: ways to promote and offer testing. NICE public health guidance 43 (2012) Available from: www.nice.org.uk/guidance/PH43
- Reducing differences in the uptake of immunisations. NICE public health guidance 21 (2009). Available from: www.nice.org.uk/guidance/PH21
- Looked after children and young people. NICE public health guidance 28 (2010). Available from: www.nice.org.uk/guidance/PH28

NICE Related Guidance currently in development:

- Hepatitis C. NICE clinical guideline. Publication date to be confirmed.

4 Methods

This chapter sets out in detail the methods used to review the evidence and to generate the recommendations that are presented in subsequent chapters. This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009.

4.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews in a framework of population, index tests, reference standard and target condition for reviews testing for diagnostic test accuracy; and using population, presence or absence of factors under investigation (for example prognostic factors) and outcomes for prognostic reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the Guideline Development Group (GDG). The review questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical issues identified in the scope (Appendix A).

A total of 12 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Chapter	Type of review	Review question	Outcomes
6	Observational	What is the most appropriate healthcare setting to initiate pre-therapeutic tests (HBeAg, quantitative HBsAg, quantitative HBV DNA, anti HCV, anti HDV, anti HIV) in people who are HBsAg positive?	
9	Prognostic	What are the thresholds (e.g. HBV DNA and ALT levels) for referral to specialist services after initial diagnosis and pre-therapeutic tests of CHB?	Indications for management of CHB infection (treatment and further investigations) including the number of people with significant fibrosis or inflammation
7	Diagnostic	What is the diagnostic test accuracy of non-invasive methods (e.g. transient elastography, serum fibrosis markers, aspartate aminotransferase / platelet ration index, magnetic resonance spectroscopy) to assess the severity of necro-inflammatory activity and liver fibrosis?	Critical outcomes: • Sensitivity (%) and specificity (%) at pre-specified thresholds • Area under the ROC curve (AUC) – measure of test accuracy Other outcomes: • Positive/negative predictive value • Positive/negative likelihood ratios

Chapter	Type of review	Review question	Outcomes
			• Post-test probability
8	Prognostic	Does genotype testing enable better decisions on which antiviral treatment to offer and is it cost effective?	• Serum HBV DNA reduction (log copies) • Detectable HBV DNA HBeAg loss/ seroconversion • HBsAg loss/ seroconversion • ALT normalisation • Resistance • Any composite outcome including the above outcomes
10	Intervention	In people with CHB, what is the clinical and cost effectiveness of pharmacological monotherapies and combinations in achieving remission of the activity of CHB?	• Log reduction of HBV DNA • Number of people with continuing undetectable serum hepatitis B virus DNA • Number of people with ALT normalisation • Number of people with HBeAg loss and/or seroconversion • Number of people with HBsAg loss and/or seroconversion • Resistance • Quality of life measures (EQ-5D, SF-36, liver disease specific)
10	Intervention	In people with CHB, what is the clinical and cost-effectiveness of sequential drug therapy (add-on or switching monotherapies) in achieving remission of the activity of CHB?	• Log reduction of HBV DNA • Number of people with continuing undetectable serum hepatitis B virus DNA • Number of people with ALT normalisation • Number of people with HBeAg loss and/or seroconversion • Number of people with HBsAg loss and/or

Chapter	Type of review	Review question	Outcomes
			seroconversion • Resistance • Quality of life measures (EQ-5D, SF-36, liver disease specific)
10	Intervention	In chronic hepatitis B infected people with advanced cirrhosis, including those with liver decompensation, what is the clinical and cost effectiveness of antiviral treatment to prevent recurrent reactivation and liver transplantation?	• Log reduction of HBV DNA • Number of people with continuing undetectable serum hepatitis B virus DNA • Resistance • Quality of life measures • Hepatic decompensation and/or liver transplantation • Hepatocellular carcinoma • All cause mortality
11	Prognostic	How frequently should monitoring tests be done to ascertain virological, serological and biochemical response and resolution of fibrosis (HBeAg and antibody, HBsAg and antibody and transient elastography) and resistance (HBV DNA) in people with chronic hepatitis B?	• Virological response (undetectable HBV DNA, viral breakthrough) • serological response (HBeAg loss/seroconversion, HBsAg loss/seroconversion) • biochemical response (ALT normalization, ALT flare) • resolution of fibrosis (histological improvement) • incidence of side effects • incidence of resistance • composite outcomes coming from two or more of the above types of responses.
10	Intervention	In people who are immunocompromised, what is the clinical and cost effectiveness of prophylactic treatment in reducing risk of hepatitis B virus reactivation and severity of flares?	Critical outcomes: • Viral reactivation (defined as increase of HBV DNA) • Clinical reactivation (defined by increase

Chapter	Type of review	Review question	Outcomes
			in ALT) • All cause mortality Secondary outcomes: • Hepatic failure • Incidence of cirrhosis or hepatocellular carcinoma (HCC)
11	Prognostic	When and how frequently should surveillance testing be offered to detect early hepatocellular carcinoma in people with chronic hepatitis B?	• Hepatocellular carcinoma (HCC) (confirmed by CT scan, MRI scan, biopsy) • Liver cancer stage • Morbidity (end stage liver failure) • All cause mortality
10	Intervention	In pregnant/lactating women with chronic hepatitis B what is the clinical and cost-effectiveness of pharmacological or anti-viral therapy in order to reduce risk of vertical transmission from mother to infant?	Critical outcomes: • newborn (0-9 months) and infant (9-15 months) HBV DNA positivity • newborn (0-9 months) and infant (9-15 first months) HBeAg seropositivity • newborn (0-9 months) and infant (9-15 first months) HBsAg seropositivity Secondary outcomes: • Maternal HBV DNA reduction • congenital abnormalities • Adverse events • Resistance
5	Qualitative/ observational	What are the information needs of patients with CHB and their carers?	• Patients' understanding or satisfaction • Quality of life

In addition, the GDG requested that the technical team perform an additional in vivo/ in vitro review on the comparable efficacy of tenofovir, one of the antiviral treatments, for two different populations with CHB infection -nucleos(t)ide naïve (wild type or no mutation) and lamivudine resistant - to inform the assumptions for the network meta-analysis (further details on NMA protocol (Appendix J) .

4.2 Searching for evidence

4.2.1 Clinical literature search

The aim of the literature search was to systematically identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE Guidelines Manual [2009]. Databases were searched using medical subject headings and free-text terms. Foreign language studies were not reviewed and, where possible, searches were restricted to articles published in the English language. All searches were conducted in MEDLINE, Embase, and the Cochrane Library, and were updated for the final time on **10th October 2012**. No papers after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix D.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

4.2.2 Health economic literature search

Systematic searches were also undertaken to identify relevant health economic evidence within the published literature. The NHS Economic Evaluation Database (NHS EED), the Health Economic Evaluations Database (HEED) and Health Technology Assessment (HTA) database were searched using broad population terms and no date restrictions. A search was also run in MEDLINE and Embase using a specific economic filter with population terms. Where possible, searches were restricted to articles published in the English language. Economics search strategies are included in Appendix D. All searches were updated for the final time on **10th October 2012**. No papers published after this date were considered.

4.3 Evidence of effectiveness

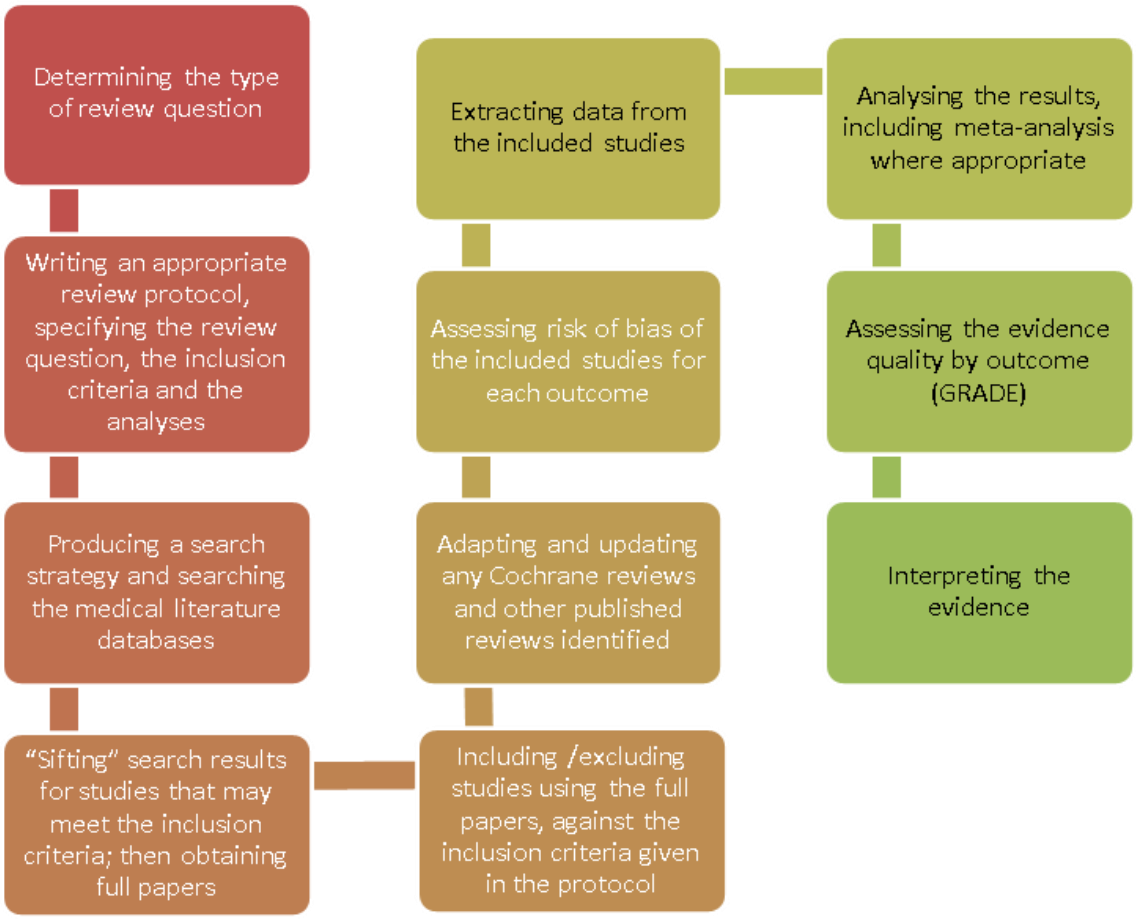
The evidence was reviewed following the steps shown schematically in Figure 2:

- potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- full papers were reviewed against pre-specified inclusion / exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C).
- relevant studies were critically appraised using the appropriate checklists as specified in The Guidelines Manual. For diagnostic questions, we followed the checklist developed by QUADAS II.
- key information was extracted on the study's methods and PICO factors and results were presented in evidence tables (Appendix E).
- summaries of the evidence were generated by outcome (included in the relevant chapter write-ups) and were presented in GDG meetings:
    - Randomised studies: meta-analysed, where appropriate and reported in GRADE profiles (for intervention reviews)
    - Prognostic studies: data were presented as a range of values, usually in terms of the relative effect as reported by the authors.

- Diagnostic studies were presented as measures of diagnostic test accuracy (sensitivity, specificity, positive and negative predictive value). Coupled values of sensitivity and specificity were summarized in Receiver Operating Curves (ROC) to allow visual comparison between different index tests (plotting data at different thresholds) and to investigate heterogeneity more effectively (given data were reported at the same thresholds). A meta-analysis could not be conducted because the studies reported data at various thresholds.

Twenty percent (20%) of each of the above stages of the reviewing process was quality assured by the second reviewer to eliminate any potential of reviewer bias or error.

Figure 2: Step-by-step process of review of evidence in the guideline



4.3.1 Inclusion/exclusion criteria

The inclusion/exclusion of studies was based on the review protocols (Appendix C). The GDG were consulted about any uncertainty regarding inclusion/exclusion.

The guideline population was defined to be people with chronic hepatitis B who were positive for HBsAg persistently for more than 6 months. For some review questions, the review population was confined to special groups such as people who are immunocompromised, co-infected with hepatitis C or Delta virus or have decompensated liver disease or pregnant women.

Randomised trials, non-randomised trials, and observational studies (including diagnostic or prognostic studies) were included in the evidence reviews as appropriate. Laboratory studies (in vivo or in vitro) were excluded with the exception of the additional review requested by the GDG

(examining whether the efficacy of tenofovir was comparable in nucleoside naïve and lamivudine resistant populations with CHB infection) to support an assumption in the network meta-analysis. The reason of including laboratory (in vivo/ in vitro) studies for that review is due to a lack of evidence on the efficacy of tenofovir in these two populations shown by human studies (randomised trial and observational studies), although it is widely accepted in clinical practice. In addition, the GDG considered laboratory studies as a reliable source of evidence for this particular review.

Conference abstracts were not automatically excluded from the review but were initially assessed against the inclusion criteria and then further processed only if no other full publication was available for that review question, in which case the authors of the selected abstracts were contacted for further information. The reviews that had included abstracts were:

- Health care setting to initiate pre-therapeutic tests
- Optimal timing/frequency of hepatocellular carcinoma surveillance
- Patient/carer information

Literature reviews, letters and editorials, foreign language publications and unpublished studies were excluded.

The review protocols are presented in Appendix C. Excluded studies by review question (with their exclusion reasons) are listed in Appendix L.

4.3.2 Methods of combining clinical studies

Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate pooled risk ratios (relative risk) for binary outcomes.

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation (SD)) were required for meta-analysis. Data for continuous outcomes were analysed using an inverse variance method for pooling mean differences, and where the studies had different scales, standardised mean differences were used. A generic inverse variance option in Review Manager was used if any studies reported solely the summary statistics and 95% confidence interval (or standard error) – this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics - p-values or 95% confidence intervals (95% CI); meta-analysis was then undertaken for the mean difference and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for evidence of this type.

Stratified analyses were predefined for some review questions at the protocol stage when the GDG identified that these strata are different in terms of biological and clinical characteristics and the interventions were expected to have a different effect on these groups of people with CHB. For example, analyses were performed stratifying by HBeAg status or whether people were treatment naïve or had developed specific drug resistance when the data allowed.

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at $p<0.1$ and the I-squared inconsistency statistic (with an I-squared value of more than50% indicating considerable heterogeneity). Where considerable heterogeneity

was present, we carried out sensitivity analyses, eliminating studies at overall high risk of bias (randomization, allocation concealment and blinding, missing outcome data). If the heterogeneity still remained, a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the individual studies in the meta-analysis. Absolute risk differences were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the GDG.

Follow up studies of RCTs were also included in order to examine the efficacy of antiviral treatments during a longer period of follow up usually longer than the 48-52 weeks finite period of treatment. If randomization was preserved in these follow up studies, then meta-analysis was performed. Otherwise, the results were summarised in a narrative form and presented in the evidence review.

Network meta-analyses (NMA) were conducted for the review questions in adults on the clinical effectiveness of antiviral treatments (monotherapies, combinations and sequential treatments) to achieve remission of CHB. This type of analysis simultaneously compared multiple treatments in a single meta-analysis, preserving the randomization of RCTs included in the reviews of direct comparisons. The aim of the NMA was to include all relevant evidence in order both to answer questions on the clinical effectiveness of interventions when no direct comparison was available and to give a ranking of treatments in terms of efficacy. The output was expressed as the probability of each antiviral treatment being the best for an outcome and as effect estimates for how much each treatment is better than the other treatments included in the network).

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS version 1.4. We used statistical models for fixed and random effects that allowed inclusion of multi arm trials and accounts for the correlation between arms in the trials with any number of trial armsThe model was based on original work from the University of Bristol (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). Before use in the analysis for one of our selected outcomes in the NMA (proportion of people achieved undetectable HBV DNA), the data were transformed to allow the use of different thresholds for the outcome HBV DNA. NICE DSU evidence synthesis of treatment efficacy in decision making: a reviewer's checklist was completed separately for HBeAg positive, HBeAg negative and lamivudine resistant populations (see NMA chapter in Appendix J for more details).

As it is the case for ordinary pairwise meta-analysis, NMA may be conducted using either fixed or random-effects models, and for pairwise meta-analysis, a fixed effects model was used in the first instance. For all the networks set up in our NMA, both models (fixed and random effect) were performed and then these models were compared based on residual deviance and deviance information criteria (DIC). The model with the smallest DIC is estimated to be the model that would best predict a replicate dataset which has the same structure as that currently observed. A small difference in DIC between the fixed and random effects models (3-5 points) implies that the better fit obtained by adding random effects does not justify the additional complexity. However, if the difference in DIC between a fixed and random effect model was less than 5 points, and the models make very similar inferences, then we would report the results from a fixed effects model results as it doesn't make as many assumptions as the random effect model, contains fewer parameters and it is easier for clinical interpretation than the random effects model.

Heterogeneity was assessed in the results of the random effects model by using the method described by Dias et al which compares the size of the treatment effect to the extent of between trials variation. This method tries to answer the question of what is the reasonable confidence

interval of the log ORs of an outcome for the prediction of the confidence interval of the log ORs of the same outcome of a future trial of infinite size.

Inconsistency in the networks was tested by comparing any available direct and indirect treatment comparison and testing the null hypothesis that the indirect evidence was not different than the direct evidence on the odd ratio scale using the normal distribution; inconsistency was identified if the mean estimates (mean odds ratios) of the direct comparisons were outside the confidence intervals of the odds ratios as generated from the NMA output.

There were three main outputs from the NMA: 1) the estimation of log odds ratios (ORs) (with their 95% credible intervals) were calculated for comparisons of the direct and indirect evidence, 2) the probability that each treatment was best based on the proportion of Markov chain iterations in which treatment had the highest probability of achieving the outcomes selected in the networks and 3) the ranking of treatments compared to baseline groups (presented as median rank and its 95% credible intervals).

Two types of sensitivity analyses were decided in the protocol stage to be conducted to test the robustness of our results: by including only studies that used the selected threshold of lowest detection of HBV DNA and by including only trials with purely homogeneous nucleos(t)ide naïve populations.

In the protocol, six networks were developed (separate for nucleos(t)ide naïve and lamivudine resistant adults) for the following binary outcomes:

For HBeAg positive and nucleos(t)ide naïve adults with CHB

1. The proportion of adults with CHB achieving undetectable HBV DNA (<300 copies/ml) at the end of 1 year of antiviral treatment
2. The proportion of adults with CHB achieving HBeAg seroconversion at the end of 1 year of antiviral treatment

For HBeAg positive and lamivudine resistant adults with CHB

3. The proportion of adults with CHB achieving undetectable HBV DNA (<300 copies/ml) at the end of 1 year of antiviral treatment
4. The proportion of adults with CHB achieving HBeAg seroconversion at the end of 1 year of antiviral treatment

For HBeAg negative and nucleos(t)ide naïve adults with CHB

5. The proportion of adults with CHB achieving undetectable HBV DNA (<300 copies/ml) at the end of 1 year of antiviral treatment

For HBeAg negative and lamivudine resistant adults with CHB

6. The proportion of adults with CHB achieving undetectable HBV DNA (<300 copies/ml) at the end of 1 year of antiviral treatment

Limited number of trials was identified for the network of lamivudine resistant HBeAg negative adults with CHB and for children and young people (both HBeAg positive and negative) to allow the formulation of networks for further NMA.

Data synthesis for prognostic reviews (frequency of monitoring tests, frequency of surveillance testing, selection of thresholds for referral)

Odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs), with their 95% confidence intervals (95% CI) for the effect of the pre-specified prognostic factors were extracted from the papers. Studies of lower risk of bias were preferred, taking into account the analysis and the study design; in particular, prospective cohort studies that reported multivariable analyses, which included key confounders as identified by the GDG at the protocol stage for that outcome. A narrative summary of results from univariate analyses was also given, highlighting the very high risk of bias as there was a high chance of unknown real effect due to lack of controlling for potential confounders. Data were not combined in meta-analyses for prognostic studies. For the review on referral thresholds, proportions of people with histological indication for treatment (measured by significant fibrosis or inflammation), below or above a single threshold of a parameter (e.g. serum HBV DNA levels) were extracted from the studies and presented in the review and the GDG used this information to decide what are the clinically acceptable thresholds, at which majority of people with significant fibrosis would be picked up for referral for further examinations or initiation of antiviral treatment

Data synthesis for diagnostic reviews (non-invasive methods to assess the severity of liver disease)

Data and outcomes

For the reviews of diagnostic test accuracy, a positive result on the index test was found if the patient had values of the measured quantity above a threshold value, and different thresholds could be used. Diagnostic test accuracy measures used in the analysis were: area under the Receiver Operating Characteristics (ROC) curve, and sensitivity and specificity, positive and negative predictive value and positive/negative likelihood ratio, for different thresholds. The threshold of a diagnostic test is defined as the value at which the test can best differentiate between those with and without the target condition (significant fibrosis or cirrhosis) and, in practice, it varies amongst studies. For this guideline, sensitivity and specificity were considered equally important. A high sensitivity (true positives) of a test can pick up the majority of the correct cases with fibrosis or cirrhosis in order to refer for antiviral treatment; conversely, a high specificity (true negatives) can correctly exclude people without significant fibrosis or cirrhosis, and these people would not require antiviral treatment and can be monitored at set time intervals. The GDG defined the clinically relevant threshold based on two sources: from manufacturer's guide and similar thresholds defined by hepatitis C studies when appropriate. All the clinically relevant thresholds can be found in the evidence review. In studies where results for more than one threshold were reported, the ones that are closer to the clinically relevant thresholds that had been agreed by the GDG were chosen.

Data synthesis

Coupled forest plots of sensitivity and specificity with their 95% confidence intervals across studies (at various thresholds) were produced for each test and fibrosis stage, using Cochrane Review Manager (RevMan5) software (for RevMan see Appendix X). In order to do that, 2 by 2 tables (the number of true positives, false positives, true negatives and false negatives) were either directly taken from the study if given or derived from raw data, or were calculated from the set of test accuracy statistics (calculated 2x2 tables can be found in Appendix O).

To allow comparison between tests, summary ROC curves (by stage of fibrosis) were generated for each diagnostic test from the pairs of sensitivity and specificity calculated from the 2 x 2 tables, selecting one threshold per study A ROC plot shows true positive rate (i.e. sensitivity) as a function of false positive rate (i.e. 1 – specificity). Data were entered into Review Manager 5 software and ROC curves were fitted using the Moses Littenburg approach. In order to compare diagnostic tests, two or more tests were plotted on the same graph. The performance of the different diagnostic tests

was then assessed by examining the summary ROC curves visually, i.e. the test that has a curve lying closer to the upper left corner (100% sensitivity and 100% specificity) was interpreted as the better test.

A second analysis was conducted by restricting the set of studies to those with clinically relevant thresholds agreed by the GDG (i.e. the same threshold to ensure the data were comparable. They were presented as forest plots and ROC curves and heterogeneity was investigated.

Area under the ROC curve (AUC) data for each study were also plotted on a graph, for each diagnostic test and fibrosis stage: the AUC describes the overall diagnostic accuracy across the full range of thresholds.. The GDG agreed on the following criteria for AUC: <=0.50 worse than chance; 0.50-0.60 = very poor; 0.61-0.70 = poor; 0.71-0.80 = moderate; 0.81-0.92 = good; 0.91-1.00 = excellent or perfect test.

Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots, if appropriate (only when there were similar thresholds). A diagnostic meta-analysis was not conducted mainly because of the different thresholds across studies and the complexity of the analysis and time and resource constraints of this guideline development.

4.3.3 Type of studies

For most intervention reviews in this guideline, parallel randomised trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. Cross over RCTs were not appropriate for estimating the intervention effects for antiviral therapies due to the issue of multiple drug resistance in people with CHB. If the GDG believed RCT data would not be appropriate or there was limited evidence from RCTs, well conducted non-randomised studies were to be included (Please refer to Appendix D for full details on the study design of studies selected per review question). For example, for the review of prophylactic treatment for immunocompromised patients, the GDG believed that it may be unethical to withhold a treatment for this group of patients, if a study was conducted after the value of prophylactic treatment has been established. Therefore, non-randomized trial using historical controls was the only available option of study design for this review question.

For diagnostic reviews, cross-sectional and retrospective studies were included and for prognostic reviews, prospective and retrospective cohort studies were included. Case control studies were not included. For most of the prognostic reviews, the GDG decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted.

4.3.4 Type of analysis

Estimates of effect from individual studies were based on available case analysis (ACA): that is, analysing only data that were available for participants at the end of follow-up, without making any imputations for missing data. The GDG recorded several potential reasons for people with CHB infection dropping out before trial completion;

- Adverse effects (including deaths)
- Lack of concordance (adherence)
- Withdrawal of consent
- Investigator's discretion (this is usually not defined in the studies but is likely to include clinical or laboratory-determined adverse events – or laboratory abnormalities meaning the drug may be contraindicated , or development of mutations)

- Loss to follow-up (e.g. moving house, second opinions from clinicians not in the study).

The ACA method was used rather than an intention-to-treat with imputation analysis (ITT), in order to avoid making assumptions about the participants for whom outcome data was not available, and furthermore assuming that those with missing outcome data have the same event rate as those who continue. In addition, ITT analysis tends to bias the results towards no difference, and therefore the effect may be smaller than in reality. Using ACA, we avoided incorrectly weighting studies in meta-analysis by using a denominator that does not reflect the true sample size with outcome data available. If there was a differential missing data rate between the two arms in a study that was greater than 10%, a sensitivity analysis was performed to determine whether the size and direction of effect would be changed by using an ITT or ACA analysis and whether there was an impact on the meta-analysis. If this were the case, a footnote in the GRADE tables was to be added to describe the dependence on the assumptions (see section 1.3.5), and results from both ACA and ITT analyses were to be presented in the forest plots section (Appendix G). However, the majority of trials included in the review of evidence for this guideline (98%) had less than 5% differential missing outcome data.

When the studies reported only ITT results (through imputation), and the number of events was larger than the number of completers in the trial (ACA), then we used the proportion of events from the ITT numbers to derive the number of events for the final sample size of completers. In the cases where it was not possible to extract data from the studies on ACA and authors reported only an ITT analysis, then the results of this analysis was included and a footnote was added to the GRADE tables.

4.3.5 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCTs and observational studies (when appropriate) was evaluated and presented using the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the evidence quality for each outcome, taking into account individual study quality factors and the meta-analysis results. Results were presented in GRADE profiles ('GRADE tables'), which consist of two adjacent sections: the "Clinical/Economic Study Characteristics" table includes details of the quality assessment while the "Clinical /Economic Summary of Findings" table includes pooled outcome data and an absolute measure of the intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the Clinical Study Characteristics table if it was apparent (funnel plots more than 4 studies).

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 1 and each graded using the quality levels listed in Table 2. The main criteria considered in the rating of these elements are discussed below (see Grading of Evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

Table 1: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias	Limitations in the study design and implementation may bias the estimates of the

Quality element	Description
('Study Limitations')	treatment effect. High risk of bias for the majority of the evidence decreases the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 2: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

Table 3: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

4.3.6 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

7. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW.
8. The rating was then downgraded for the specified criteria: Risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence from observational studies (that had not previously been downgraded) was upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have "serious" or "very serious" risk of bias was rated at 1 or2 points respectively.
9. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
10. The reasons used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality elements are discussed further in the following sections.

4.3.7 Risk of bias

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error (for example if a study were carried out several times there would be a consistently wrong answer, and the results would be inaccurate).

The risk of bias for a given study and outcome is associated with the risk of over-or underestimation of true effect.

The risks of bias are listed in Table 4.

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

Table 4: Risk of bias in randomised trials

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in "pseudo" or "quasi" randomised trials with allocation by day of week, birth date, chart number, etc)
Lack of blinding	Patients, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the trialists to adhere to the intention to treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other risks of bias	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of invalidated patient-reported outcomes • Recruitment bias in cluster randomised trials

Risk of bias (randomization method, blinding and allocation concealment, loss to follow up) and overall quality of included studies in the NMA was summarized and taken into account in the interpretation of results.

For diagnostic accuracy studies, the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklists were used. Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains (seeFigure 3):

- Patient selection
- Index test
- Reference standard
- Flow and timing

Figure 3: Summary of QUADAS-2 with list of signalling, risk of bias and applicability questions

DOMAIN	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Description	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting):	Describe the index test and how it was conducted and interpreted:	Describe the reference standard and how it was conducted and interpreted:	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:
Signalling questions (yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability: High/low/unclear	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

Source: University of Bristol –QUADAS-2 website (http://www.bris.ac.uk/quadas/quadas-2)

An optional domain, multiple test accuracy is applicable when a single study examined more than one diagnostic test (head-to-head comparison between two or more index tests reported within the same study). This optional domain contains three items of risk of bias: 1) did all patients undergo all index tests or were the index tests appropriately randomised amongst the patients; 2) were index tests conducted within a short time interval; 3) are index test results unaffected when undertaken together on the same patient.

The GDG raised a number of issues that needed to be taken into consideration when assessing study quality and they are listed as follows:

Patient selection:

Index test: the majority of the included studies selected thresholds according to the study data and did not pre-specify the thresholds; however, they would not be considered at high risk of bias for this reason, so long as there was an adequate description of how the threshold was derived and it was not subjectively selected. In addition, the GDG thought that the interpretation of the index tests was unlikely to be influenced by the knowledge of the results of the reference standard, as they are not subjective tests. Therefore, this would not be relevant in this domain for this particular review.

Reference standard: the length of a valid biopsy sample should be at least 1cm long with more than 5 portal tracts, as agreed by the GDG.

Target conditions: significant fibrosis is defined as METAVIR ≥F2 or Ishak staging 3-6; cirrhosis is defined as METAVIR F4 or Ishak staging 5-6)

Flow and timing: interval between reference standard and index test should be no more than 6 months, downgrade otherwise. The GDG thought that the stage of liver disease in chronic hepatitis B

infected patients were unlikely to change significantly (for example, changing from METAVIR F3 to F4) within the period of 6 months.

Reviewers assessed the risk of bias associated with each item and then came up with an overall risk of bias (low, moderate and high) and applicability. In addition, GRADE was adapted and an overall risk of bias for each outcome was produced.

For prognostic studies, quality was assessed using the checklist for Prognostic studies (NICE Guidelines Manual, 2009, [74]. The quality rating (low, high, unclear) was derived by assessing the risk of bias across 6 domains; selection bias, attrition bias, prognostic factor bias, outcome measurement bias, control for confounders and appropriate statistical analysis, with the last 4 domains being assessed per outcome. A summary table on the quality of prognostic studies is presented at the beginning of each review to summarize the risk of bias across the 5 domains. More details about the quality assessment for prognostic studies are shown below:

1. The study sample represents the population of interest with regard to key characteristics – hepatitis B population, source of sample and inclusion/ exclusion criteria adequately described,
2. Loss to follow up is unrelated to key characteristics, sufficient to limit potential bias – reasons for loss to follow up adequately described.
3. The prognostic factor of interest is adequately measured in study participants.
4. The outcome of interest is adequately measured in study participants.
5. Important potential confounders are appropriately accounted for.
6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of valid results.

4.3.8 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in the underlying treatment effect.

Heterogeneity in a meta-analysis was examined and sensitivity and subgroup analyses performed as pre-specified in the protocols (Appendix C). However, due to the natural history of chronic hepatitis B, the GDG has prespecified several strata (for example HBeAg positive and negative people with CHB, treatment naïve or people with specific drug resistance) in the protocol stage to address the distinction of different stages of this conditions that would potentially lead to separate recommendations.

When heterogeneity existed (Chi square $p<0.1$ or I- squared inconsistency statistic of >50% or evidence from examining forest plots), but no plausible explanation could be found (for example, duration of intervention, different follow-up periods), the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty in the evidence contributed by the inconsistency in the results. In addition to the I- square and Chi square values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes.

4.3.9 Indirectness

Directness relates to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size. The GDG

decided that, for specific questions (e.g the review of interventions to assess clinical and cost effectiveness of antiviral treatments to achieve remission of CHB), the review of evidence could include mixed populations, in which at least 2/3 of the sample had the defined HBeAg positivity (positive or negative), and/or had the defined category of prior use of antiviral treatment (prior use or none).

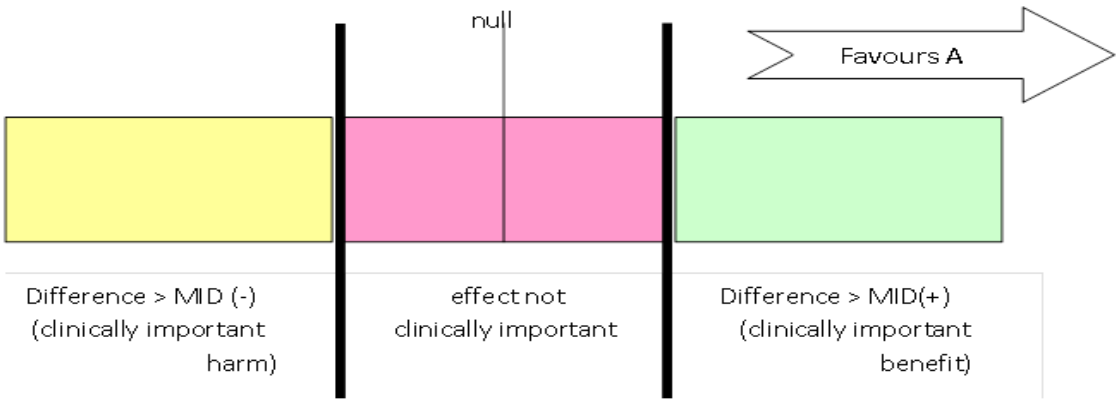
4.3.10 Imprecision

Imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that we don't know whether there is a clinically important difference between interventions. Therefore, imprecision differs from the other aspects of evidence quality, in that it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity) instead we are concerned with the uncertainty about what the point estimate is. This uncertainty is reflected in the width of the confidence interval.

The 95% confidence interval is defined as the range of values that contain the population value with 95% probability. The larger the trial, the smaller the confidence interval and the more certain we are in the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the confidence interval of the effect estimate is relevant to decision making, considering each outcome in isolation. Figure 4 considers a positive outcome for the comparison of treatment A versus B. Three decision making zones can be identified, bounded by the thresholds for clinical importance (MID) for benefit and for harm (the MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B and this difference is clinically important to patients (favours B).

Figure 4: Imprecision illustration



When the confidence interval of the effect estimate is wholly contained in one of the three zones (e.g. clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit or the effect is not clinically important or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of two zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone); the confidence interval is consistent with two decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by one ("serious imprecision").

If the confidence interval of the effect estimate crosses into three zones, this is considered to be very imprecise evidence because the confidence interval is consistent with three clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by two in the GRADE analysis ("very serious imprecision").

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the GDG to estimate an MID or to say whether they would make different decisions for the two confidence limits.

The literature was searched for established MIDs for the selected outcomes in the evidence reviews, but no results were found. In addition, the GDG was asked whether they were aware of any acceptable MIDs in the clinical community of hepatitis B but they confirmed the absence of research in the area. Finally, the GDG considered it clinically acceptable to use the GRADE default MID to assess imprecision: a 25% relative risk reduction or relative risk increase was used, which corresponds to a RR clinically important threshold of 0.75 or 1.25 respectively. This default MID was used for all the outcomes in the interventions evidence reviews.

4.3.11 Assessing clinical importance

The GDG assessed the evidence by outcome in order to determine if there was, or was potentially, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% confidence interval from the pooled risk ratio.

The assessment of benefit/harm/no benefit or harm was based on the point estimate of absolute effect for intervention studies which was standardized across the reviews. The GDG considered for

most of the outcomes in the intervention reviews that if at least 100 participants per 1000 (10% cut off) achieved the outcome of interest (if positive) in the intervention group compared to the comparison group then this intervention would be considered beneficial. The same point estimate but in the opposite direction would apply if the outcome was negative. For populations that are at a more advanced stage of the disease, such as people who are immunocompromised, cirrhotic patients who undergo hepatocellular surveillance and patients with decompensated cirrhosis, the GDG considered the intervention to be beneficial if there is at least 50 participants per 1000 (5% cut off) achieved the outcome of interest (given it is a positive outcome) in the intervention group, compared to the comparison group.

This assessment was carried out by the GDG for each critical outcome, and an evidence summary table was produced to compile the GDGs assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

4.3.12 Evidence statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarizing the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty/uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

The number of studies and the number of participants for a particular outcome

A brief description of the participants

An indication of the direction of effect (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the two tested treatments).

A description of the overall quality of evidence (GRADE overall quality)

4.4 Evidence of cost-effectiveness

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the economic literature
- Undertook new cost-effectiveness analysis in priority areas

4.4.1 Literature review

The Health Economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify relevant studies (see below for details).

- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual[74]
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix F).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter write-ups) – see below for details.

4.4.1.1 Inclusion/exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially applicable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to had an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country).

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual)[74].

When no relevant economic analysis was found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implication of the recommendation to make.

4.4.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The Guidelines Manual [74] guidelines manual]. It also shows incremental costs, incremental outcomes (for example, QALYs) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis..

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.

Table 5: Content of NICE economic profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Limitations	An assessment of methodological quality of the study*: • Minor limitations – the study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness.

Item	Description
	• Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusion about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making*: • Directly applicable – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost effectiveness. • Partially applicable – one or more of the applicability criteria are not met, and this might possibly change the conclusions about cost effectiveness. • Not applicable – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost effectiveness.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
ICER	Incremental cost-effectiveness ratio: the incremental cost divided by the respective QALYs gained.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

*Limitations and applicability were assessed using the economic evaluation checklist from The Guidelines Manual [74]

Where economic studies compare multiple strategies, results are presented in the economic evidence profiles for the pair-wise comparison specified in the review question, irrespective of whether or not that comparison was 'appropriate' within the analysis being reviewed. A comparison is 'appropriate' where an intervention is compared with the next most expensive non-dominated option – a clinical strategy is said to 'dominate' the alternatives when it is both more effective and less costly. Footnotes indicate if a comparison was 'inappropriate' in the analysis.

For particular studies comparing multiple strategies, results are not reported in the standard economic profile but are instead presented at the end of the relevant chapter in an alternative table summarising the study as a whole.

4.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the Health Economist in priority areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

Additional data for the analysis was identified as required through additional literature searches undertaken by the Health Economist, and discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

See Appendices H and I for details of the health economic analysis/analyses undertaken for the guideline.

4.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money [74].

In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a. The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
b. The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'from evidence to recommendations' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance' [73].

If a study reported the cost per life year gained but not QALYs, the cost per QALY gained was estimated by multiplying by an appropriate utility estimate to aid interpretation. The estimated cost per QALY gained is reported in the economic evidence profile with a footnote detailing the life-years gained and the utility value used. When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

4.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices E and F.
- Summary of clinical (GRADE tables) and economic evidence and quality (as presented in chapters 5-11).
- Forest plots and ROC curves (Appendix G).
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix H and I).

Recommendations were drafted on the basis of the GDG's interpretation of the available evidence, taking into account the trade-off between benefits, harms and costs of different courses of action. This was either done formally in an economic model, or informally. Firstly, the net benefit over harm was considered (clinical effectiveness), using the critical outcomes. When this was done informally, the GDG took into account the clinical benefits/harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, it was assessed whether the net benefit justified the costs. Results of the NMA

was also taken into account in the drafting of recommendations and were incorporated in the health economic modelling for considering the most clinical and cost effective antiviral treatment.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus based recommendations included the balance between potential harms and benefits, economic or other implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were done through discussions in the GDG. The GDG could also consider whether the uncertainty is sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (See Appendix K). The wording of recommendations was agreed by the GDG and focused on the following factors:

• on the actions health professionals need to take

• include what readers need to know

• reflect the strength of the recommendation (for example the word “offer” was used for strong recommendations and “consider” for weak recommendations)

• emphasise the involvement of the patient (and/or their carers if needed) in decisions on treatment and care

• follow NICE’s standard advice on recommendations about drugs, waiting times and ineffective interventions.

The main considerations specific to each recommendation are outlined in the ‘Recommendations and link to evidence’ sections within each chapter.

4.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility

4.5.2 Validation process

The guidance is subject to a six week public consultation and feedback as part of the quality assurance and peer review the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

4.5.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will ask a National Collaborating Centre or the National Clinical Guideline Centre to advise NICE’s Guidance executive whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

4.5.4 Disclaimer

Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

4.5.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

5 Guideline summary

5.1 Key priorities for implementation

From the full set of recommendations, the GDG selected 5 key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The Guidelines Manual [74]. The reasons that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

1. Assesment and referral

- Arrange the following tests in primary care for adults who are hepatitis B surface antigen (HBsAg) positive:
  - hepatitis B e antigen (HBeAg)/antibody (anti-HBe) status
  - HBV DNA level
  - lgM antibody to hepatitis B core antigen (anti-HBc lgM)
  - hepatitis C virus antibody (anti-HCV)
  - hepatitis delta virus antibody (anti-HDV)
  - HIV antibody (anti-HIV)
  - lgG antibody to hepatitis A virus (anti-HAV)
  - additional laboratory tests including alanine aminotransferase (ALT) or aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), serum albumin, total bilirubin, total globulins, full blood count and prothrombin time
  - tests for hepatocellular carcinoma (HCC), including hepatic ultrasound and alpha-fetoprotein testing.

- Include the results of the initial tests with the referral (see recommendation 6).

2. Treatment sequence in adults with HBeAg-positive chronic hepatitis B and compensated liver disease

- Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-positive chronic hepatitis B and compensated liver disease[a].
- Offer tenofovir disoproxil as second-line treatment to people who do not undergo HBeAg seroconversion or who relapse (revert to being HBeAg positive following seroconversion) after first-line treatment with peginterferon alfa-2a.
- Offer entecavir as an alternative second-line treatment to people who cannot tolerate tenofovir disoproxil or if it is contraindicated.

a Avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

3. Treatment sequence in adults with HBeAg-negative chronic hepatitis B and compensated liver disease

- Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-negative chronic hepatitis B and compensated liver disease[b].
- Offer entecavir or tenofovir disoproxil as second-line treatment to people with detectable HBV DNA after first-line treatment with peginterferon alfa-2a.

4. Women who are pregnant or breastfeeding

- Offer tenofovir disoproxil to women with HBV DNA greater than 10^7 IU/ml in the third trimester to reduce the risk of transmission of HBV to the baby[c].

5. Prophylactic treatment during immunosuppressive therapy

- In people who are HBsAg positive and have HBV DNA greater than 2000 IU/ml, offer prophylaxis with entecavir or tenofovir disoproxil[d].
  - Start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after HBeAg seroconversion and HBV DNA is undetectable.
- In people who are HBsAg positive and have HBV DNA less than 2000 IU/ml, offer prophylaxis:
  - consider lamivudine[e] if immunosuppressive therapy is expected to last less than 6 months
    - monitor HBV DNA monthly in people treated with lamivudine and change to tenofovir disoproxil if HBV DNA remains detectable after 3 months
  - consider entecavir or tenofovir disoproxil[f] if immunosuppressive therapy is expected to last longer than 6 months
  - start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after stopping immunosuppressive therapy.

b Avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

[c] At the time of publication (June 2013), tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[d] At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[e] At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[f] At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

5.2 Full list of recommendations

5.2.1 Patient Information

1. Provide information on the following topics to people with chronic hepatitis B and to family members or carers (if appropriate) before assessment for antiviral treatment:

- the natural history of chronic hepatitis B, including stages of disease and long-term prognosis
- lifestyle issues such as alcohol, diet and weight
- family planning
- monitoring
- routes of hepatitis B virus (HBV) transmission
- the benefits of antiviral treatment, including reduced risk of serious liver disease and death and reduced risk of transmission of HBV to others
- treatment options and contraindications based on the patient's circumstances, including peginterferon alfa-2a and nucleoside or nucleotide analogues
- short- and long-term treatment goals
- causes of treatment failure, including non-adherence to prescribed medicines, and options for re-treatment
- risks of treatment, including adverse effects and drug resistance.

2. Offer a copy of the personalised care plan to people with chronic hepatitis B and to family members or carers (if appropriate) outlining proposed treatment and long-term management, for example, a copy of the hospital consultation summary.
3. Provide information on self-injection techniques to people beginning peginterferon alfa-2a or to family members or carers.
4. NICE has produced public health guidance on ways to promote and offer testing to people at increased risk of infection with hepatitis B. All healthcare professionals should follow the recommendations in Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (NICE public health guideline 43).
5. NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services (NICE clinical guideline 138).

5.2.2 Assessment and referral in primary care

5.2.2.1 Adults who are HBsAg positive

6. Arrange the following tests in primary care for adults who are hepatitis B surface antigen (HBsAg) positive:

- hepatitis B e antigen (HBeAg)/antibody (anti-HBe) status

- HBV DNA level
- IgM antibody to hepatitis B core antigen (anti-HBc lgM)
- hepatitis C virus antibody (anti-HCV)
- hepatitis delta virus antibody (anti-HDV)
- HIV antibody (anti-HIV)
- lgG antibody to hepatitis A virus (anti-HAV)
- additional laboratory tests including alanine aminotransferase (ALT) or aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), serum albumin, total bilirubin, total globulins, full blood count and prothrombin time
- tests for hepatocellular carcinoma (HCC), including hepatic ultrasound and alpha-fetoprotein testing.

7. Refer all adults who are HBsAg positive to a hepatologist or to a gastroenterologist or infectious disease specialist with an interest in hepatology.

8. Include the results of the initial tests with the referral (see recommendation 6).

5.2.2.2 Pregnant women who test HBsAg positive at antenatal screening

9. Refer pregnant women who are HBsAg positive to a hepatologist, or to a gastroenterologist or infectious disease specialist with an interest in hepatology, for assessment within 6 weeks of receiving the screening test result and to allow treatment in the third trimester (see recommendation 63).

5.2.2.3 Adults with decompensated liver disease

10. Refer adults who develop decompensated liver disease immediately to a hepatologist or to a gastroenterologist with an interest in hepatology. Symptoms of decompensated liver disease include (but are not limited to) ascites, encephalopathy and gastrointestinal haemorrhage.

5.2.2.4 Children and young people who are HBsAg positive

11. Arrange the following tests for children and young people who are HBsAg positive:

- HBeAg/anti-HBe status
- HBV DNA level
- anti-HBc lgM
- anti-HCV
- anti-HDV
- anti-HIV
- anti-HAV

- o additional laboratory tests, including ALT or AST, GGT, serum albumin, total bilirubin, total globulins, full blood count and prothrombin time
- o tests for HCC, including hepatic ultrasound and alpha-fetoprotein testing.

12. Refer all children and young people who are HBsAg positive to a paediatric hepatologist or to a gastroenterologist or infectious disease specialist with an interest in hepatology.
13. Include the results of the initial tests with the referral (see recommendation 11).

5.2.3 Assessment of liver disease in secondary specialist care

5.2.3.1 Adults with chronic hepatitis B

14. Ensure all healthcare professionals who refer adults for non-invasive tests for liver disease are trained to interpret the results and aware of co-factors that influence liver elasticity (for example, fatty liver caused by obesity or alcohol misuse).
15. Discuss the accuracy, limitations and risks of the different tests for liver disease with the patient.
16. Offer transient elastography as the initial test for liver disease in adults newly referred for assessment.
17. Offer antiviral treatment without a liver biopsy to adults with a transient elastography score greater than or equal to 11 kPa[g], in line with recommendation 29.
18. Consider liver biopsy to confirm the level of fibrosis in adults with a transient elastography score between 6 and 10 kPa[h]. Offer antiviral treatment in line with recommendations 22, 23 and 27 to 29.
19. Offer liver biopsy to adults with a transient elastography score less than 6 kPa if they are younger than 30 years and have HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 IU/ml for males and greater than or equal to 19 IU/ml for females) on 2 consecutive tests conducted 3 months apart[i]. Offer antiviral treatment in line with recommendations 22, 23 and 27 to 29.
20. Do not offer liver biopsy to adults with a transient elastography score less than 6 kPa who have normal ALT (less than 30 IU/ml in males and less than 19 IU/ml in females) and HBV

[g] Adults with a transient elastography score greater than or equal to 11 kPa are very likely to have cirrhosis and confirmation by liver biopsy is not needed.
[h] The degree of fibrosis cannot be accurately predicted in adults with a transient elastography score between 6 to 10 kPa. Some people may choose to have a liver biopsy in these circumstances to confirm the extent of liver disease.
[i] Adults with a transient elastography score less than 6 kPa are unlikely to have significant fibrosis.

DNA less than 2000 IU/ml as they are unlikely to have advanced liver disease or need antiviral treatment (see recommendations 22, 23 and 27 to 29.)[j]

21. Offer an annual reassessment of liver disease using transient elastography to adults who are not taking antiviral treatment.

22. Offer antiviral treatment to adults younger than 30 years who have HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 in males and greater than or equal to 19 in females) on 2 consecutive tests conducted 3 months apart if there is evidence of necroinflammation or fibrosis on liver biopsy or a transient elastography score greater than 6kPa.

23. Consider antiviral treatment in adults with HBV DNA greater than 2000 IU/mL and evidence of necroinflammation or fibrosis on liver biopsy.

5.2.3.2 Children and young people with chronic hepatitis B

24. Discuss the accuracy, limitations and risks of liver biopsy in determining the need for antiviral treatment with the child or young person and with parents or carers (if appropriate).

25. Consider liver biopsy to assess liver disease and the need for antiviral treatment in children and young people with HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 IU/ml for males and greater than or equal to 19 IU/ml for females) on 2 consecutive tests conducted 3 months apart. Offer biopsy under a general anaesthetic to children who are too young to tolerate the procedure under a local anaesthetic.

5.2.4 Genotype testing

26. Do not offer genotype testing to determine initial treatment in people with chronic hepatitis B.

5.2.5 Thresholds for treatment

5.2.5.1 Adults with chronic hepatitis B

27. Offer antiviral treatment to adults aged 30 years and older who have HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 in males and greater than or equal to 19 in females) on 2 consecutive tests conducted 3 months apart.

28. Offer antiviral treatment to adults who have HBV DNA greater than 20,000 IU/ml and abnormal ALT (greater than or equal to 30 in males and greater than or equal to 19 in females) on 2 consecutive tests conducted 3 months apart regardless of age or the extent of liver disease.

j Adults with a transient elastography score less than 6 kPa are unlikely to have significant fibrosis.

29. Offer antiviral treatment to adults with cirrhosis and detectable HBV DNA, regardless of HBeAg status, HBV DNA and ALT levels.

5.2.5.2 Children and young people with chronic hepatitis B

30. Offer antiviral treatment if there is evidence of significant fibrosis (METAVIR stage greater than F2 or Ishak stage greater than or equal to 3) or abnormal ALT (greater than or equal to 30 IU/ml for males and greater than or equal to 19 IU/ml for females) on 2 consecutive tests conducted 3 months apart.

5.2.6 Antiviral therapies

5.2.6.1 Adults with chronic hepatitis B

31. Discuss treatment options, adverse effects and long-term prognosis with the patient before starting treatment.

32. Re-assess the person's risk of exposure to HIV before starting treatment and offer repeat testing if needed.

33. Peginterferon alfa-2a is recommended as an option for the initial treatment of adults with chronic hepatitis B (HBeAg-positive or HBeAg-negative), within its licensed indications. [This recommendation is from Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (NICE technology appraisal guidance 96).]

34. Entecavir, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated. [This recommendation is from Entecavir for the treatment of chronic hepatitis B (NICE technology appraisal guidance 153).]

35. Tenofovir disoproxil, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated. [This recommendation is from Tenofovir disoproxil fumarate for the treatment of hepatitis B (NICE technology appraisal guidance 173).]

36. Telbivudine is not recommended for the treatment of chronic hepatitis B. [This recommendation is from Telbivudine for the treatment of chronic hepatitis B (NICE technology appraisal guidance 154).]

37. People currently receiving telbivudine should have the option to continue therapy until they and their clinicians consider it appropriate to stop. [This recommendation is from Telbivudine for the treatment of chronic hepatitis B (NICE technology appraisal guidance 154).]

38. Do not offer adefovir dipivoxil for the treatment of chronic hepatitis B.

39. People currently receiving adefovir dipivoxil should be offered the option to switch to a different treatment. Offer tenofovir disoproxil or entecavir depending on previous antiviral exposure:

- offer tenofovir disoproxil to people with a history of lamivudine resistance.

40. Antiviral treatment should be initiated only by an appropriately qualified healthcare professional with expertise in the management of viral hepatitis. Continuation of therapy under shared-care arrangements with a GP is appropriate.

5.2.6.2 Treatment sequence in adults with HBeAg-positive chronic hepatitis B and compensated liver disease

41. Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-positive chronic hepatitis B and compensated liver disease[k].

42. Consider stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and/or if HBsAg is greater than 20,000 IU/ml, and offer second-line treatment in line with recommendations 43 and 44.

43. Offer tenofovir disoproxil as second-line treatment to people who do not undergo HBeAg seroconversion or who relapse (revert to being HBeAg positive following seroconversion) after first-line treatment with peginterferon alfa-2a.

44. Offer entecavir as an alternative second-line treatment to people who cannot tolerate tenofovir disoproxil or if it is contraindicated.

45. Review adherence in people taking tenofovir disoproxil who have detectable HBV DNA at 48 weeks of treatment and, if appropriate, provide support in line with Medicines adherence (NICE clinical guidance 76).

- If HBV DNA remains detectable at 96 weeks, and there is no history of lamivudine resistance, consider adding lamivudine to tenofovir disoproxil.
- In people with a history of lamivudine resistance, consider adding entecavir to tenofovir disoproxil.

46. Do not stop nucleoside or nucleotide analogue treatment 12 months after HBeAg seroconversion in people with cirrhosis.

5.2.6.3 Treatment sequence in adults with HBeAg-negative chronic hepatitis B and compensated liver disease

[k] Avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

47. Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-negative chronic hepatitis B and compensated liver disease[l].

48. Offer entecavir or tenofovir disoproxil as second-line treatment to people with detectable HBV DNA after first-line treatment with peginterferon alfa-2a.

49. Consider switching from tenofovir disoproxil to entecavir, or from entecavir to tenofovir disoproxil, as third-line treatment in people who have detectable HBV DNA at 48 weeks of treatment.

50. Do not stop nucleoside or nucleotide analogue treatment after achieving undetectable HBV DNA and HBsAg seroconversion in patients with cirrhosis.

5.2.6.4 Children and young people with chronic hepatitis B and compensated liver disease

51. Discuss treatment options, adverse effects and long-term prognosis with the child or young person and with parents or carers (if appropriate) before starting treatment.

52. Re-assess the child or young person's risk of exposure to HIV before starting treatment and offer repeat testing if necessary.

53. Consider a 48-week course of peginterferon alfa-2a as first-line treatment in children and young people with chronic hepatitis B and compensated liver disease[mn].

54. Consider a nucleoside or nucleotide analogue as second-line treatment in children and young people with detectable HBV DNA after first-line treatment with peginterferon alfa-2a[o].

5.2.6.5 Adults who are co-infected with hepatitis C

55. Offer peginterferon alfa and ribavirin in adults co-infected with chronic hepatitis B and C[p].

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l Avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

[m] At the time of publication (June 2013), peginterferon alfa-2a did not have a UK marketing authorisation for use in children for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[n] Avoid use of peginterferon alfa-2a in pregnancy uless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

[o] At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[p] Avoid use of peginterferon alfa-2a in pregnancy uless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

5.2.6.6 Adults who are co-infected with hepatitis D

56. Offer a 48-week course of peginterferon alfa-2a in people co-infected with chronic hepatitis B and hepatitis delta infection who have evidence of significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3)[q].

57. Consider stopping peginterferon alfa-2a if there is no decrease in HDV RNA after 6 months to 1 year of treatment. Otherwise continue treatment and re-evaluate treatment response annually.

58. Stop treatment after HBsAg seroconversion.

5.2.6.7 Adults with liver decompensation

59. Manage decompensated liver disease in adults in conjunction with a liver transplant centre.

60. Do not offer peginterferon alfa-2a to people with chronic hepatitis B and decompensated liver disease.

61. Offer entecavir as first-line treatment in people with decompensated liver disease if there is no history of lamivudine resistance

- Offer tenofovir disoproxil to people with a history of lamivudine resistance.
- Reduce the dose of tenofovir disoproxil in people with renal impairment, in line with guidance in the summary of product characteristics.

5.2.6.8 Women who are pregnant or breast feeding

62. Discuss with pregnant women the benefits and risks of antiviral treatment for them and their baby.

63. Offer tenofovir disoproxil to women with HBV DNA greater than 10^7 IU/ml in the third trimester to reduce the risk of transmission of HBV to the baby[r].

64. Monitor quantitative HBV DNA 2 months after starting tenofovir disoproxil and ALT monthly after the birth to detect postnatal HBV flares in the woman.

[q] Avoid use of peginterferon alfa-2a in pregnancy uless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

[r] At the time of publication (June 2013), tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

65. Stop tenofovir disoproxil 4 to 12 weeks after the birth unless the mother meets criteria for long-term treatment (see recommendations 22, 23 and 27 to 29).

66. Offer active and passive hepatitis B immunisation in infants and follow up in line with the guidance below:

- Hepatitis B antenatal screening and newborn immunisation programme: best practice guidance
- Immunisation against infectious disease (the Green book)
- Hepatitis B and C: ways to promote and offer testing. NICE public health guidance 43 (2012).
- Reducing differences in the uptake of immunisations. NICE public health guidance 21 (2009).

67. Advise women that there is no risk of transmitting HBV to their babies through breastfeeding if guidance on hepatitis B immunisation has been followed, and that they may continue antiviral treatment while they are breastfeeding.

5.2.6.9 Prophylactic treatment during immunosuppressive therapy

68. Perform the following tests in people who are HBsAg and/or anti-HBc positive before starting immunosuppressive therapy for autoimmune or atopic diseases, chemotherapy, bone marrow or solid organ transplantation:

- antibody to hepatitis B surface antigen (anti-HBs)
- plasma or serum HBV DNA level
- ALT.

69. In people who are HBsAg positive and have HBV DNA greater than 2000 IU/ml, offer prophylaxis with entecavir or tenofovir disoproxil[s].

- Start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after HBeAg seroconversion and HBV DNA is undetectable.

70. In people who are HBsAg positive and have HBV DNA less than 2000 IU/ml, offer prophylaxis:

- Consider lamivudine[t] if immunosuppressive therapy is expected to last less than 6 months.
  - Monitor HBV DNA monthly in people treated with lamivudine and change to tenofovir disoproxil if HBV DNA remains detectable after 3 months.
- Consider entecavir or tenofovir disoproxil[u] if immunosuppressive therapy is expected to last longer than 6 months.

[s] At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

t At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

u At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility

- Start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after stopping immunosuppressive therapy.

71. In people who are HBsAg negative and anti-HBc positive (regardless of anti-HBs status) and are starting rituximab or other B cell-depleting therapies:

- offer prophylaxis with lamivudine[v]
- start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after stopping immunosuppressive therapy.

72. In people who are HBsAg negative, anti-HBc positive and anti-HBs negative and are not taking rituximab or other B cell-depleting therapies:

- monitor HBV DNA monthly and offer prophylaxis to people whose HBV DNA becomes detectable
  - consider lamivudine[w] in people with HBV DNA less than 2000 IU/ml and for whom immunosuppressive therapy is expected to last less than 6 months; change to tenofovir disoproxil if HBV DNA remains detectable after 6 months
  - consider entecavir or tenofovir disoproxil[x] in people with HBV DNA greater than 2000 IU/ml and for whom immunosuppressive therapy is expected to last longer than 6 months
  - continue antiviral therapy for a minimum of 6 months after stopping immunosuppressive therapy.

73. Do not offer prophylaxis to people who are HBsAg negative and anti-HBc and anti-HBs positive who are not taking rituximab or other B cell-depleting therapies.

5.2.7 Monitoring

5.2.7.1 Monitoring in people who do not meet criteria for antiviral treatment

Adults with HBeAg-positive disease in the immune-tolerant and immune clearance phase

74. Monitor ALT levels every 24 weeks in adults with HBeAg-positive disease who are in the immune-tolerant phase (defined by active viral replication and normal ALT levels [less than 30 IU/ml in males and less than 19 IU/ml in females]).

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for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

v At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

w At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

x At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

75. Monitor ALT every 12 weeks on at least 3 consecutive occasions if there is an increase in ALT levels.

Adults with inactive chronic hepatitis B (immune-control phase)

76. Monitor ALT and HBV DNA levels every 48 weeks in adults with inactive chronic hepatitis B infection (defined as HBeAg negative on 2 consecutive tests with normal ALT [less than 30 IU/ml in males and less than 19 IU/ml in females] and HBV DNA less than 2000 IU/mL).

- Consider monitoring more frequently (for example, every 12-24 weeks) in people with cirrhosis who have undetectable HBV DNA.

Children and young people

77. Monitor ALT levels every 24 weeks in children and young people with HBeAg-positive disease who have normal ALT levels (less than 30 IU/ml for males and less than 19 IU/ml for females) and no evidence of significant fibrosis (METAVIR stage less than F2 or Ishak stage less than 3).

78. Review annually children and young people with HBeAg-negative disease who have normal ALT (less than 30 IU/ml for males and less than 19 IU/ml for females), no evidence of significant fibrosis (METAVIR stage less than F2 or Ishak stage less than 3) and HBV DNA less than 2000 IU/ml.

79. Review every 12 weeks children and young people with HBeAg-negative disease who have abnormal ALT (greater than or equal to 30 IU/ml for males and greater than or equal to 19 IU/ml for females) and HBV DNA greater than 2000 IU/ml.

5.2.7.2 Monitoring in people taking antiviral treatment

Children, young people and adults taking peginterferon alfa-2a

80. Review injection technique and adverse effects weekly during the first month of treatment with peginterferon alfa-2a[y].

81. Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels) and thyroid function (and in children, weight and height) before starting peginterferon alfa-2a and 2, 4, 12, 24, 36 and 48 weeks after starting treatment to detect adverse effects[z].

y At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

z At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in

82. Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting peginterferon alfa-2a at 12, 24 and 48 weeks after starting treatment to determine treatment response[aa].

Stopping peginterferon alfa-2a treatment

Children and young people

83. Consider stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and/or if HBsAg is greater than 20,000 IU/ml.

Adults with HBeAg positive chronic hepatitis B and compensated liver disease - see recommendation 42

Adults with HBeAg negative chronic hepatitis B and compensated liver disease

84. Consider stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and HBsAg has not decreased, and consider second-line treatment in line with recommendation 48.

Children, young people and adults with compensated liver disease taking entecavir or lamivudine

85. Monitor full blood count, liver function (including bilirubin, albumin and ALT) and renal function (including urea and electrolyte levels) in people with compensated liver disease before starting entecavir or lamivudine, 4 weeks after starting treatment and then every 3 months to detect adverse effects[bb].

86. Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting entecavir or lamivudine, 12, 24 and 48 weeks after starting treatment and then every 6 months to determine treatment response and medicines adherence[cc].

87. Monitor HBV DNA levels every 12 weeks in people with HBeAg-negative disease who have been taking lamivudine for 5 years or longer[dd].

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children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

aa At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

bb At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

cc At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Children, young people and adults with compensated liver disease taking tenofovir disoproxil

88. Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels and urine protein/creatinine ratio), and phosphate levels in people with compensated liver disease before starting tenofovir disoproxil, 4 weeks after starting treatment and then every 3 months to detect adverse effects[ee].

89. Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting tenofovir disoproxil, 12, 24 and 48 weeks after starting treatment and then every 6 months to determine treatment response and medicines adherence[ff].

Stopping nucleos(t)ide analogue treatments in HBeAg positive adults with compensated liver disease.

90. Consider stopping nucleoside or nucleotide analogue treatment 12 months after HBeAg seroconversion in people without cirrhosis.

Stopping nucleos(t)ide analogue treatments in HBeAg negative adults with compensated liver disease.

91. Consider stopping nucleoside or nucleotide analogue treatment 12 months after achieving undetectable HBV DNA and HBsAg seroconversion in people without cirrhosis.

Children, young people and adults with HBeAg or HBsAg seroconversion after antiviral treatment

92. In people with HBeAg seroconversion after antiviral treatment, monitor HBeAg, anti-HBe, HBV DNA level and liver function at 4, 12 and 24 weeks after HBeAg seroconversion and then every 6 months.

93. Monitor HBsAg and anti-HBs annually in people with HBsAg seroconversion after antiviral treatment and discharge people who are anti-HBs positive on 2 consecutive tests.

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dd At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

ee At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

ff At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Children, young people and adults with decompensated liver disease who are taking entecavir or lamivudine

94. Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels and urine protein/creatinine ratio), blood clotting, HBV DNA level and HBeAg status in people with decompensated liver disease before starting entecavir or lamivudine and weekly after starting treatment to assess treatment response and adverse effects. When the person is no longer decompensated, follow the recommendations in 'Children, young people and adults with compensated liver disease taking entecavir or lamivudine'[gg].

Children, young people and adults with decompensated liver disease who are taking tenofovir disoproxil

95. Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels and urine protein/creatinine ratio) and phosphate, blood clotting, HBV DNA level and HBeAg status in people with decompensated liver disease before starting tenofovir disoproxil and weekly after starting treatment to assess treatment response and adverse effects. When the person is no longer decompensated, follow the recommendations in 'Children, young people and adults with compensated liver disease taking tenofovir disoproxil'[hh].

5.2.8 Surveillance testing for hepatocellular carcinoma in adults with chronic hepatitis B

96. Perform 6-monthly surveillance for HCC by hepatic ultrasound and alpha-fetoprotein testing in people with significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3) or cirrhosis.

97. In people without significant fibrosis or cirrhosis (METAVIR stage less than F2 or Ishak stage less than 3), consider 6-monthly surveillance for HCC if the person is older than 40 years and has a family history of HCC and HBV DNA greater than or equal to 20,000 IU/ml.

98. Do not offer surveillance for HCC in people without significant fibrosis or cirrhosis (METAVIR stage less than F2 or Ishak stage less than 3) who have HBV DNA less than 20,000 IU/ml and are younger than 40 years.

gg At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

hh At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

5.3 Key research recommendations

Stopping antiviral treatment in HBeAg negative disease

Further research should be undertaken to determine the clinical and cost effectiveness of HBsAg quantitative assays in determining treatment duration in HBeAg-negative disease.

ALT values for children and young people

Further research should be undertaken to examine whether the upper limit of normal ALT values for adults (below 30 IU/ml for males and below 19 IU/ml for females) are appropriate for use in children and young people with chronic hepatitis B when making decisions on when to initiate treatment.

Long-term safety of tenofovir disoproxil in chronic hepatitis B

Further research should be undertaken to determine the long-term safety of tenofovir disoproxil, including the risk of clinically significant hypophosphataemia and related bone toxicity, in people with chronic hepatitis B. The cost effectiveness of routine monitoring for phosphate loss and bone disease in people with chronic hepatitis B who are receiving tenofovir disoproxil treatment needs further evaluation.

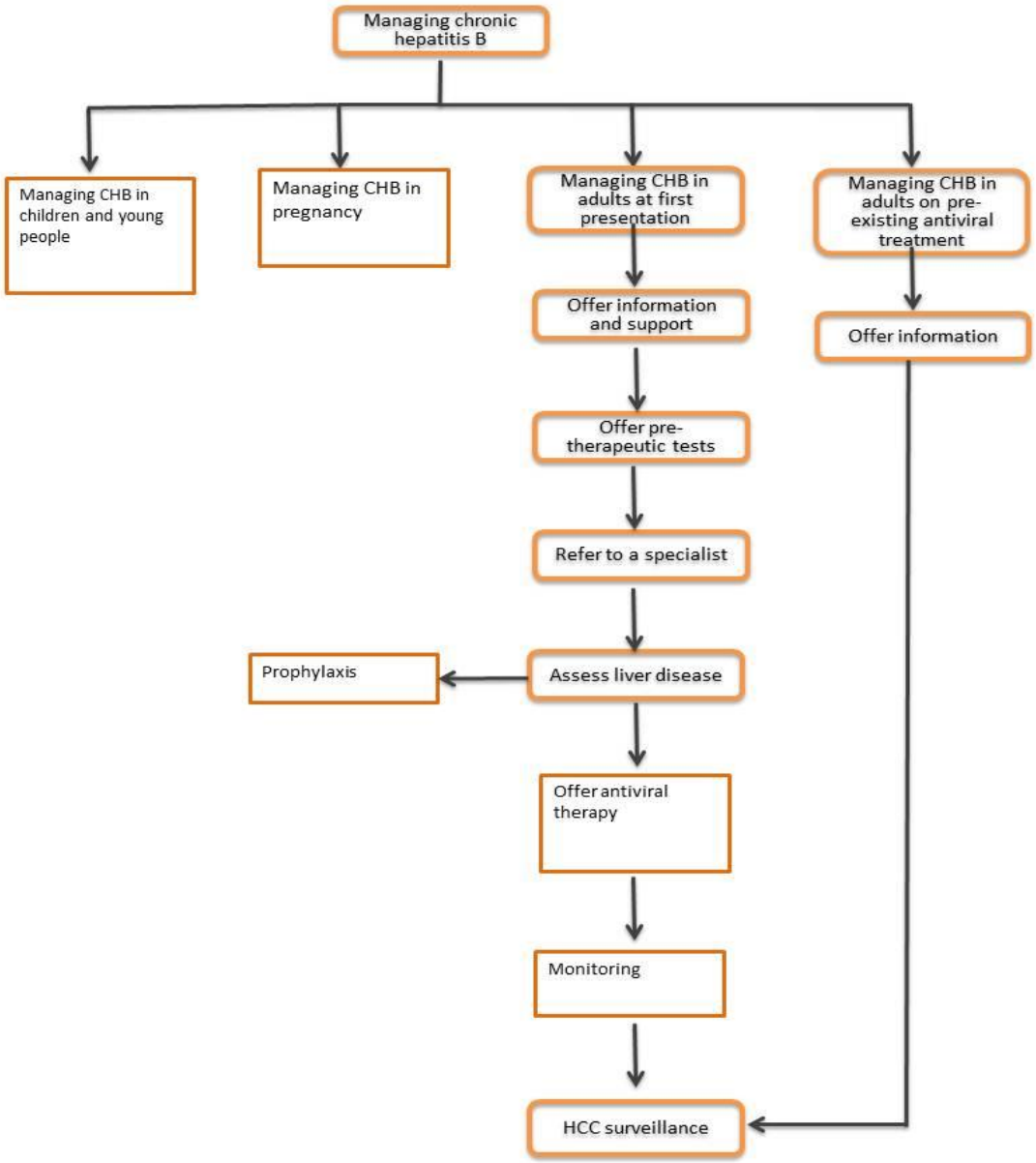
Prophylactic treatment in people receiving immunosuppressive therapy

Further research should be undertaken to determine whether long-term use of mild immunosuppressive agents for autoimmune and allergic problems presents a risk for reactivation of HBV infection in people with previous or current chronic hepatitis B, including occult HBV infection. The cost effectiveness of routine tests for HBV in this population, including HBV DNA for occult HBV infection, and the need for prophylactic treatment with nucleoside or nucleotide analogues needs further evaluation.

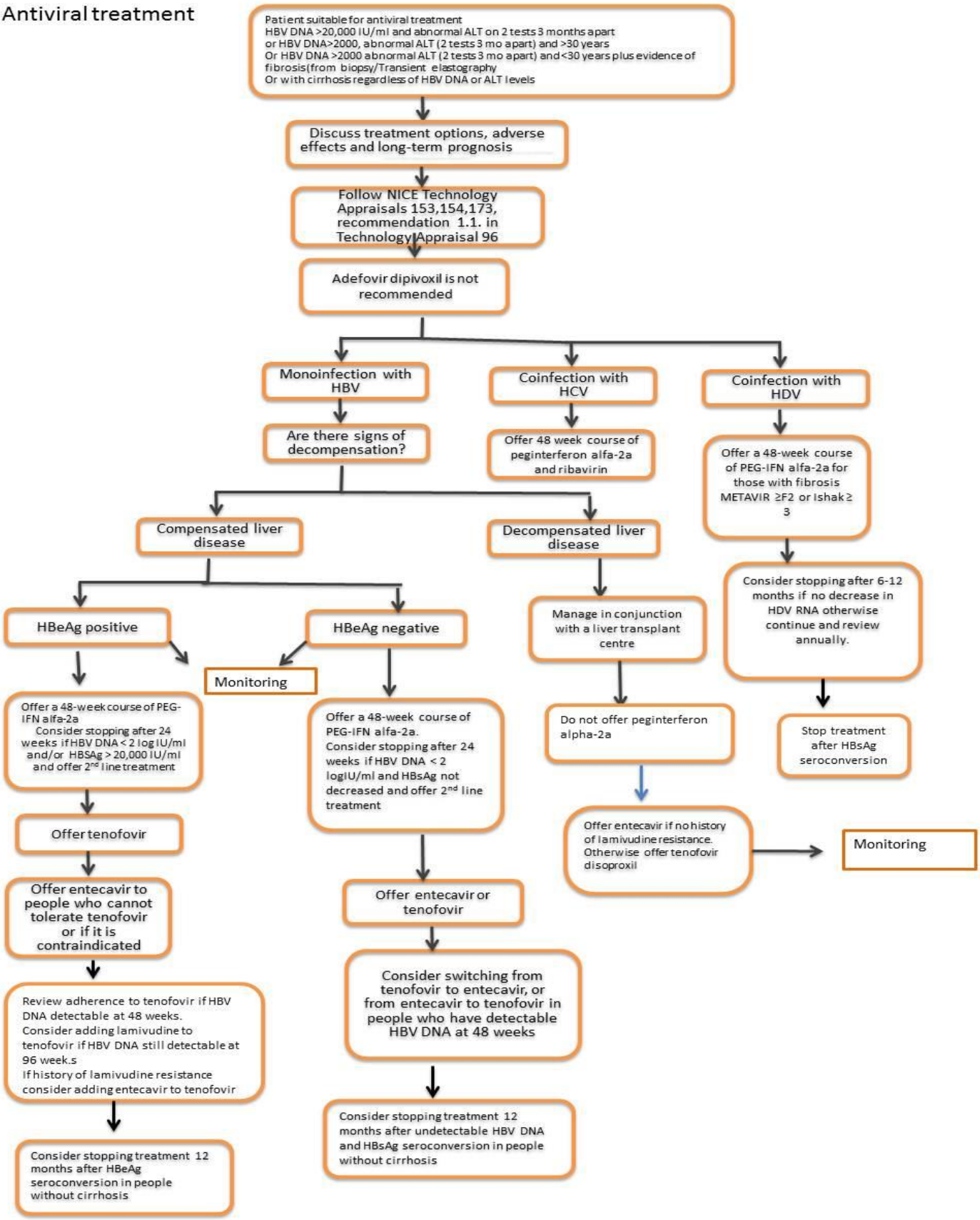
Full details of research recommendations can be found in appendix K.

5.4 Algorithms

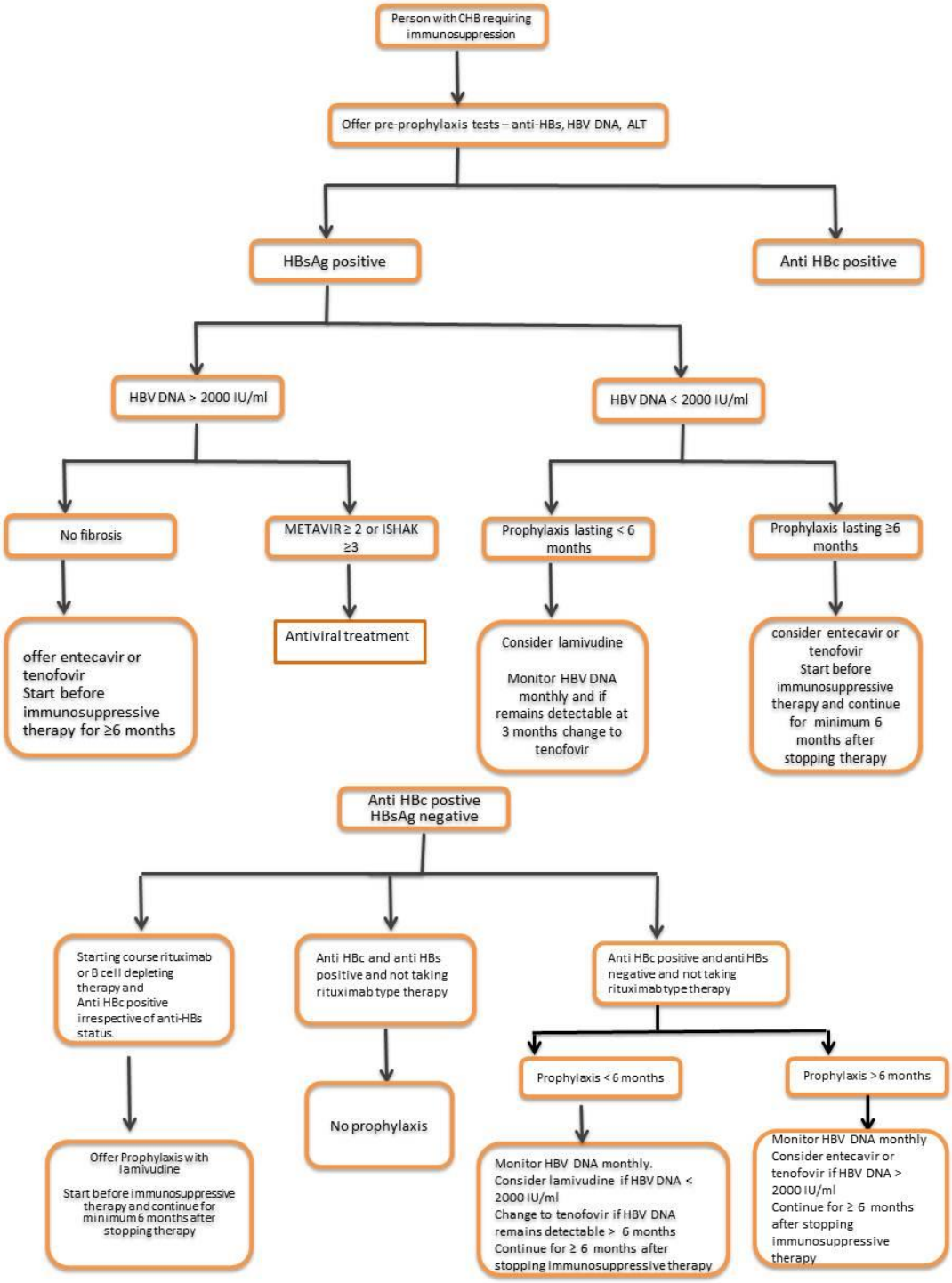
Chronic hepatitis B management pathway



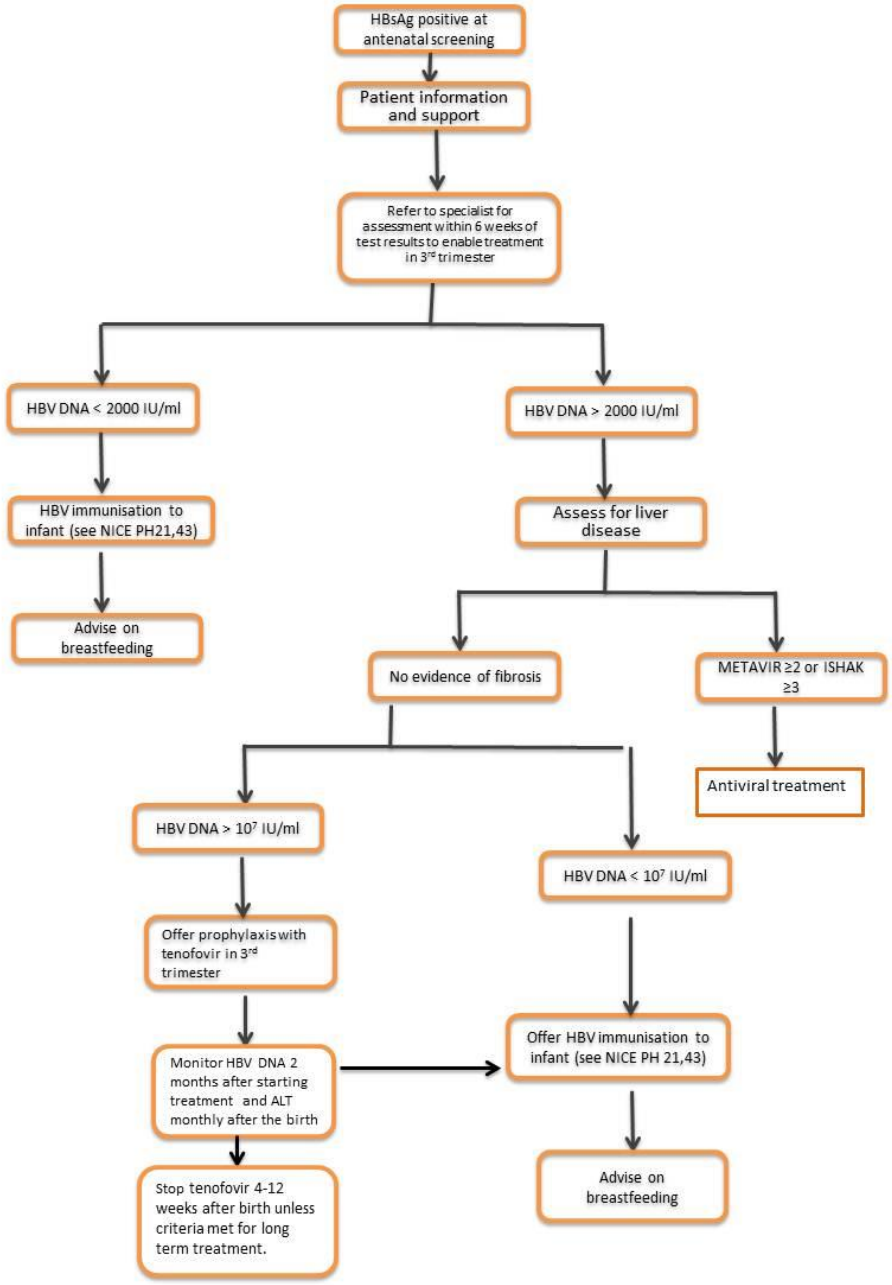
Antiviral treatment



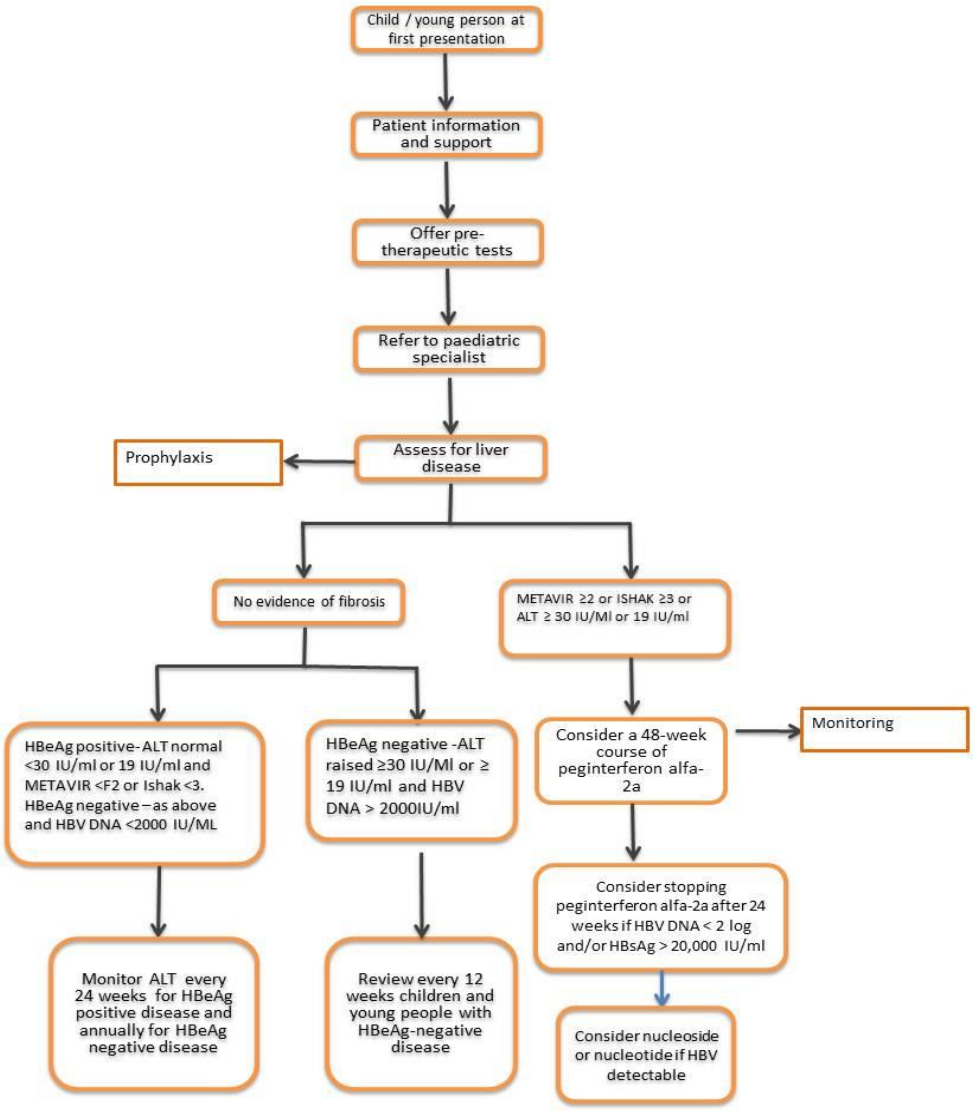
Prophylactic treatment



Managing chronic hepatitis B in pregnancy



Managing chronic hepatitis B in children and young people



6 Patient information

6.1 Introduction

Informing patients of the implications of infection with chronic hepatitis B (CHB) requires a comprehensive understanding of the virus and the ability to impart this information in a clear manner. This is important because adequately meeting patient information needs is a pre-requisite for patient compliance as an active partner, a key factor for optimising treatment benefits.

Doctors and other primary health care professionals have a role in ensuring that people with CHB understand the natural history of the virus, the rationale for clinical monitoring and the available treatments and screening. The often asymptomatic nature of the condition, with absence of symptoms being no assurance that all is well, should be emphasised as should the fluidity between disease phases, requiring that within a short space of time a patient may change from a status requiring watchful monitoring to one requiring treatment. At present a cure is a relatively rare event in CHB, and patients and carers need information and support in accepting this disease as a life-long condition. For example, where long term viral suppressive treatment is indicated, the benefits of therapy in reducing mortality from liver failure and cancer, and also rates of transmission. Essentially patients and carers will often require on-going education in what can be done in self-care, in relation to pregnancy and protection of the new-born and significant others. Health professionals play a role in ensuring the patient is informed about the importance of treatment compliance, and is encouraged to take an active role in monitoring viral and liver biomarkers and in screening for fibrotic, cirrhotic and cancerous changes in the liver.

It is known that there are cultural misconceptions of CHB in some minority ethnic groups in UK, particularly those with links to countries in which the disease is endemic. To reduce the adverse impact of such perceptions and to encourage patient motivation, it is important to provide information on treatment options in the context of advances in efficacy and the benefits of early treatment in ameliorating or even reversing disease progression. Provision of support and information to patients and carers in the form of written care management plans, ensuring that opportunities are made available for the patient/carer to ask questions and express any concerns and expectations, and signposting to other patient education and support groups that can give advice on the disease and on required lifestyle changes (especially protective sexual practices and alcohol reduction/abstinence) are valued by patients and promote informed decision making .

6.2 Review question: What information do patients with CHB and their carers need about the benefits and risks of treatment options?

For full details see review protocol in Appendix C.

Table 6: PICO characteristics of review question

Protocol	
Population	Children, young people and adults with CHB infection and their carers
Factors under investigation	• Prognosis and risk associated with no treatment • Benefits of treatment (reduced mortality from liver disease/liver cancer, reduced infectivity within the family)

Protocol	
	• Side effects of treatments • Risk of transmission during different phases, for both untreated and treated people
Outcomes	• Patients' understanding and satisfaction • Quality of life

6.3 Clinical evidence

We searched for studies (including qualitative, questionnaire/interview/focus group based studies and surveys) examining the information needs for patients with CHB and their carers about the benefits and risks of treatment options. A total of two studies (of which one is an abstract) are identified and included in this review.

6.3.1 Summary characteristics of included studies

6.3.1.1 People with CHB infection

Table 7: Included studies

Included studies Study design	N	Population	Group 1	Group 2	Length of F/U	Outcomes
Noghabi et al 2010 Quasi-experimental study (using pre-test post-test method)	60	Mixed population of hepatitis B and C <40% hepatitis B patients Country: Iran	Cases Education sessions and pamphlets (n=30) Education session duration: one month (classes held once a week, a total of 4 sessions)	Controls Pamphlets were distributed after the study (n=30)	12 weeks	Quality of life Between groups Within groups
Ho et al 2011 Cross-sectional survey (abstract)	60	Asian pregnant women 100% hepatitis B patients Country: USA	A translated questionnaire was given at various obstetrics/ gynaecology clinics.		N/A	Number of patients that would take medication during pregnancy Number of patients who planned on breast feeding

6.3.2 Information needs for people with CHB infection and their carers about benefits and risks of treatment options

Noghabi et al 2010

A total of 60 participants (with less than 40% chronic hepatitis B patients) were randomly allocated into two groups in a quasi-experimental (pre-test, post-test) study. Group 1 received education sessions and pamphlets (n=30) and group 2 was the control group (n=30). There were a total of four education sessions:

Session 1: the nature of disease, transmission routes, the diagnosis and treatment of their disease.

Session 2: the effect of interferon on their disease, the frequent side effects after injection, methods of protecting themselves and controlling these side effects.

Session 3: the method of the self-injection of IFN.

Session 4: the injection by IFN was by the patient was observed and their problems were corrected, if any.

Educational pamphlets were also distributed in the first two sessions. Duration of education sessions was one month and all participants were followed for a further 12 weeks. Self-reported data on quality of life (QoL) was collected at baseline and 12 weeks after therapy initiation. The QoL questionnaire (patients for chronic liver disease) consists of a number of items, including abdominal symptoms, activity, fatigue, systemic symptoms, emotional and worry. The total score can range from 29 to 203. After the study, the controls received the pamphlets for ethical reasons and the correct method of IFN injection was also shown to them.

The mean total quality of life in the control group did not differ significant after 12 weeks (before: 154.5; after: 136.9) (p=0.143). Whereas, it was significant different before and after the intervention in the cases (before: 158.6; after: 170) (p=<0.001). Before the intervention, there was no significant difference between cases and controls (p=0.351). However, the cases had a significantly higher total QoL score than the controls after the intervention (p=<0.001).

Table 8 shows quality of life before and after 12 weeks within groups. Among the cases, there were statistically significant differences in abdominal symptoms (p=0.00), activity (p=<0.001), emotional (p=<0.001) and worry (p=<0.001) between before and after the intervention. No significant difference was observed in systemic symptoms and fatigue in the group.

Table 9 shows quality of life before and after 12 weeks between groups. Before the intervention, there was significant difference in the emotional domain (p=0.006) between the cases and the controls. After the intervention, there was significant difference in systemic symptoms (p=0.04) between the cases and the controls.

Study quality

The main limitation of this study was the use of a mixed population of hepatitis B and C. The treatment regimen in hepatitis C is IFN plus ribavirin and in hepatitis B is IFN only and this difference was not been accounted for in the study. Another limitation was the inclusion of a small number of participants and it was unclear about patient withdrawal/dropout rates.

Table 8: Quality of life before and after 12 weeks within groups

	Cases			Controls		
	Before	After	P (Wilcoxon test)	Before	After	P (Wilcoxon test)
Score (min-max)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Abdominal symptoms (3-21)	17.7 (3.1)	19.5 (3.2)	**0.00**	15.9 (5.3)	15.9 (5.6)	0.48
Activity (3-21)	20 (1.9)	18 (3.6)	**<0.001**	19.8 (1.9)	18.7 (2.7)	**0.01**
Fatigue (5-35)	26.3 (6.3)	26 (6.9)	0.08	23.4 (8)	23 (7.2)	0.68
Systemic symptoms (5-35)	29.9 (4.1)	29.1 (5.1)	0.29	28.5 (5.2)	26.4 (6.6)	**0.03**
Emotional (8-56)	40.1 (9.2)	46.5 (10.6)	**<0.001**	33.3 (9.9)	33 (9.2)	**0.03**
Worry (5-35)	24.1 (5.3)	30.2 (6.3)	**<0.001**	22.3 (6.8)	21.9 (7.4)	0.21
Total (29-203)	158.6 (21.4)	170 (23.6)		154.5 (28.5)	136.9 (30.6)	

Table 9: Quality of life before and after 12 weeks between groups

	Before intervention			After intervention		
	Cases	Controls	P (Mann-Whitney test)	Cases	Controls	P (Mann-Whitney test)
Score (min-max)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Abdominal symptoms (3-21)	17.7 (3.1)	15.9 (5.3)	0.43	19.5 (3.2)	15.9 (5.6)	0.94
Activity (3-21)	20 (1.9)	19.8 (1.9)	0.8	18 (3.6)	18.7 (2.7)	0.08
Fatigue (5-35)	26.3 (6.3)	23.4 (8)	0.26	26 (6.9)	23 (7.2)	0.84
Systemic symptoms (5-35)	29.9 (4.1)	28.5 (5.2)	0.35	29.1 (5.1)	26.4 (6.6)	**0.04**
Emotional (8-56)	40.1 (9.2)	33.3 (9.9)	**0.006**	46.5 (10.6)	33 (9.2)	0.8
Worry (5-35)	24.1 (5.3)	22.3 (6.8)	0.06	30.2 (6.3)	21.9 (7.4)	0.64
Total (29-203)	158.6 (21.4	154.5 (28.5)		170 (23.6)	136.9 (30.6)	

Ho et al. 2011 (abstract)

This is a cross-sectional survey of 60 pregnant women with majority (91%) of Asian origin in the USA. A translated questionnaire was given in waiting rooms at various obstetrics/ gynaecology clinics. The data suggested that 67% women (95% CI 55-79%) would take hepatitis B medication while pregnant. All respondents planned on breastfeeding, but 58% (95% CI 46-70%) stated that they would not breastfeed if they knew they had hepatitis B. And over 97% women thought the main reason was they would be afraid to transmit hepatitis B to their baby. The authors concluded that patients still perceive a high risk of HBV transmission via breastfeeding despite current recommendations, further supporting the need for patient education.

Study quality

Response rate was 80%. It was unclear whether it was a self-administered questionnaire or one with interview by trained persons and this study had a small sample size.

6.4 Economic evidence

Published literature

No published cost-effectiveness analyses were identified.

6.5 Evidence statements

6.5.1 Clinical evidence statements

6.5.1.1 Adults with CHB infection

One cross sectional survey (Ho 2011) of 60 pregnant women showed that they would not breastfeed if they knew they had hepatitis B [very low quality].

One quasi-experimental study (Noghabi 2010) of a mixed hepatitis B and C population found that provision of education sessions improved total quality of life scores (abdominal symptoms, activity, emotional and worry) among the intervention group after the intervention and the intervention group demonstrated an improved total quality of life score (systemic symptoms) compared to the control after intervention [very low quality].

6.5.2 Economic evidence statement

No published cost-effectiveness analyses were identified.

6.6 Recommendations and Links to evidence

Recommendations	**1. Provide information on the following topics to people with chronic hepatitis B and to family members or carers (if appropriate) before assessment for antiviral treatment:** o the natural history of chronic hepatitis B, including stages of disease and long-term prognosis o lifestyle issues such as alcohol, diet and weight o family planning o monitoring o routes of hepatitis B virus (HBV) transmission o the benefits of antiviral treatment, including reduced risk of serious liver disease and death and reduced risk of transmission of HBV to others o treatment options and contraindications based on the patient's circumstances, including peginterferon alfa-2a and nucleoside or nucleotide analogues o short- and long-term treatment goals o causes of treatment failure, including non-adherence to prescribed medicines, and options for re-treatment o risks of treatment, including adverse effects and drug resistance. **2. Offer a copy of the personalised care plan to people with chronic hepatitis B and to family members or carers (if appropriate) outlining proposed treatment and long-term management, for example, a copy of the hospital consultation summary.** **3. Provide information on self-injection techniques to people**

	beginning peginterferon alfa-2a or to family members or carers. **4. NICE has produced public health guidance on ways to promote and offer testing to people at increased risk of infection with hepatitis B. All healthcare professionals should follow the recommendations in Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection (NICE public health guideline 43).** **5. NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services (NICE clinical guideline 138).**
Relative values of different outcomes	Patients' understanding and satisfaction Quality of life The changes in phases of the disease require careful monitoring and compliance with treatments, and the patient needs to have the necessary information in which to take an active role in the decision making and management of their condition. The GDG agreed that patients and carers increased understanding can have a positive impact on patient satisfaction and quality of life as they are enabled to make informed decisions when discussing their treatment and care with health professionals.
Trade-off between clinical benefits and harms	The GDG expects that by offering relevant, comprehensive information, patients will gain an increased understanding of their disease and be better able to make informed decisions about the treatment they receive. There were four main areas which the GDG considered to be important in terms of information provision: prognosis and risk associated with no treatment; benefits of treatment; side effects of treatment; and risk of transmission during different phases (for both treated and untreated people). The patient representatives on the group highlighted the asymptomatic nature of the viral infection and the fluidity between the phases, which can rapidly change from a status managed by watchful monitoring to that requiring treatment. Therefore it was very important that patients are treated as an equal partner, assisted in fully understanding the treatment plan, thereby promoting compliance, and encouraged to take an active role in ensuring that the required monitoring and/or screening tests are carried out in a timely manner
Economic considerations	The GDG discussed the provision of patient information in the context of routine healthcare practice. It was expected that any impact on time and resource use would be minimal and would likely be offset by an improvement in quality of life.
Quality of evidence	One study has randomised the patients using adequate randomisation procedure and allocation concealment. Both studies contain a relatively small sample size (60 patients in each). In addition, one study has a mixed population with less than 40% hepatitis B patients. And the other study is an abstract with a general inadequate reporting of study methods. Therefore, results should be interpreted with caution. A quasi-experimental (pretest, posttest) (Noghabi et al, 2010) study of <40% hepatitis B patents has shown that by giving education sessions, that include general information along with pamphlets about the disease (natural history, transmission routes, diagnosis), the effect of interferon on the disease, the side effects and ways of controlling these side effects and the demonstration of self-injection of interferon, for a duration of one month improved the total quality of life score (particularly abdominal symptoms, activity, emotional and worry) among the cases, compared to before the intervention. There was no difference in any of the quality of life domains between cases and controls before the intervention. However, after the

	intervention, the cases scored statistically significantly higher total quality of life, compared to the controls (mainly systemic symptoms). The study generally supported the use of education sessions and pamphlets as effective formats of giving patients the information about the disease condition. A cross-sectional survey (Ho et al 2011), has suggested that 58% of pregnant women infected with chronic hepatitis B (mostly of Asian family origin) said they would not breastfeed if they knew they had the disease and the main reason was they would be afraid to transmit the disease to the baby. The GDG were not aware of any evidence suggesting harms (risk of vertical transmission is low) associated with breastfeeding in the mothers, given that the new born or infants are immunised by following the vaccination schedules (Green book) and the status of the mother and the baby are monitored accordingly. Further education is needed in this area. No evidence has been identified for children.
Other considerations	The recommendations are based on patient views and the experience and opinion of the GDG. The evidence has focused on interferon treatment and no studies have been identified for nucleos(t)ide analogues. The GDG considered that there are no major side effects associated with nucleos(t)ide analogues, except for the potential of developing drug resistance, especially in the case of lamivudine. The patient representatives emphasised the importance for the health professional to stress the efficacy and benefits of treatment, and that patients should be provided with a personalised care management plan, explaining what his/her expectations and role in it should be. This should include lifestyle advice, e.g. alcohol, sexual practices, where appropriate and where to find additional local information and support. The GDG agreed that useful information is provided by national organisations such as the British Liver Trust. It was agreed that it was important for the health professional to ensure that there were regular opportunities for the patient or carer to discuss their treatment and ask any questions or concerns they may have. Patient education was also highlighted as very important in order for people to make informed decisions and self-manage their condition.

7 Assessment and referral

7.1 Introduction

People with chronic hepatitis B are often asymptomatic and usually present with no physical signs. In order to undertake a meaningful assessment of the patient a number of biochemical, virological and haematological parameters are needed. Frequently these tests are undertaken at the first visit to the specialist, but there are differing views on whether it may be more efficient and a better use of resources if these tests were undertaken in primary care prior to referral.

At present the amount of information that will flow from primary to secondary/tertiary care is extremely variable and very much depends on the referrer's knowledge of hepatitis B infection. There are currently occasions where tests may have been completed within primary care but the results are not always readily available to the specialist, which leads to time being wasted finding out the results.

It is also important that waiting for tests should not delay certain referrals where time is important such as with pregnant women or a patient with suspected hepatic decompensation.

7.2 Review question: What is the most appropriate healthcare setting to initiate relevant diagnostic tests (for example, Liver Function Tests, HBeAg, quantitative HBsAg, quantitative HBV DNA, anti HCV, anti HDV, anti HIV) in people who are HBsAg positive?

For full details see review protocol in Appendix C.

Table 10: PICO characteristics of review question

Protocol	
Population	HBsAg positive children, young people and adults with chronic hepatitis B virus infection (CHB)
Study group	Initiation of diagnostic tests in primary setting (GP practice)
Comparison group	Initiation of diagnostic tests in secondary setting (such as hospital)
Outcomes	any outcome

7.3 Clinical evidence

We searched for studies comparing different healthcare settings to initiate diagnostic tests in HBsAg positive adults and children with CHB. Two studies in abstract form are identified and included in this review.

7.3.1 Summary characteristics of included studies in adults with CHB

Table 11: Included studies

Included studies Study design	N Setting Patient characteristics	Study group	Comparison group	Outcomes
Smith 2010 Retrospective (abstract)	N=1094 UK Patients found to be HBsAg positive	Primary care	Hospital	Proportion of patients who attended at least one hepatology clinic (referred to specialist)
Taylor 2010 Cross-sectional survey (abstract)	N=45 UK	N/A	N/A	GP knowledge 1.Proportion of those who would appropriately refer patients to a specialist

7.3.2 Summary result findings in adults with CHB infection

7.3.2.1 Smith et al, 2010

This is a UK retrospective study. HBsAg positive patients were identified via screening HBsAg data obtained by the virology department at a hospital over a 3 year period. Source of data came from primary care, hospital out-patient, in-patient, accident and emergency or antenatal clinic. The aim of the study was to examine the proportion of patients who were found to be HBsAg referred to a hepatology clinic (specialist service) in two settings, primary care vs. hospital.

Table 12: Proportion of patients did not attend a hepatology clinic (did not get referred)

Request site	n/N (%) did not reach hepatology clinic (specialist care)
Hospital	81/912 (9%)
Primary care	151/182 (83%)

Main study findings:

- Referral rates were considerably better for patients tested within a hospital setting.
- Patients tested in primary care were less likely to be referred to specialist care

Because the study is published as an abstract, there is little information provided on the methods and no baseline characteristics have been given. Therefore, it is graded as being of very low quality. In addition, the results are based on a single-centre, and thus unlikely to be representative of the general population. There was no information on patients' characteristics, such as HBV DNA levels, ALT levels, HBeAg status; and it was unclear whether the patients who were referred needed further assessment for antiviral treatment (e.g. proportion of correct referrals). The authors stated they cannot exclude the possibility that some patients may have been attending a hepatology clinic outside the study hospital and this information was not documented in the notes. Therefore, results of this study need to be interpreted with caution.

7.3.2.2 Taylor et al. 2010

This is a UK cross-sectional study. The aim of the study was to assess GPs' knowledge on viral hepatitis. A survey containing 32 questions was sent to GPs within the catchment area. A total of 161 questionnaires were sent, of which 45 were completed and returned. Mean duration of working within the General Practice was 14 years (range of 1-35).

36% (16/45) of GPs thought all patients with CHB should be managed in secondary care.

Table 13: Proportion (%) of GPs who knew how to correctly screen for HBV

Outcome	n/N (%)
Proportion of GPs who knew how to correctly screen for HBV	8/45 (17%)

Two scenarios for hepatitis B virus were presented:

1) A pregnant woman found to be HBsAg positive on screening;
2) A Nigerian man known to be HBsAg positive, who had an ALT 4 x Upper Limit of Normal (ULN).

Table 14: Proportion (%) of GPs who would refer patients to a specialist

Scenarios	Proportion of those who would refer patients to a specialist, n/N (%)
A pregnant woman found to be HBsAg positive on screening	24/45 (53%)
A Nigerian man known to be HBsAg positive, who had an ALT 4 x ULN	16/45 (36%)

90% (41/45) of GPs said they would attend an education session on viral hepatitis.

The study is published as an abstract and little information on methods used is provided. It contains a small sample size with poor response rate (28%); therefore it is graded as being of very low quality.

7.4 Economic evidence

Published literature

No published cost-effectiveness analyses were identified.

Economic considerations

It is important to consider the costs and consequences associated with each alternative course of action. Patients who present to specialist care without relevant test results must be referred for diagnostic testing before returning to discuss treatment options. Therefore, the cost of two consultations is incurred when only one would have been necessary if the tests had been carried out in a primary setting.

The national average cost of a first consultation with a hepatologist is £194 (cost of a hepatology consultant led first attendance non-admitted face to face, service code 306, from the NHS Reference Cost 2010-11, NHS Trusts and PCTs combined).[24] Although patients may also present to a gastroenterologist with an interest in hepatology or a prescribing pharmacist, the unit cost for a hepatologist was assumed to represent an average estimate of the clinician the patient would likely visit.

7.5 Evidence statements

7.5.1 Clinical evidence statements

7.5.1.1 Adults with CHB infection

One retrospective study (Smith et al, 2010) of 1093 patients who are HBsAg positive, found that patients were less likely to be referred to a hepatology clinic from primary care, compared to those from hospital. [Very low quality; applicable]

One cross-sectional survey (Taylor et al, 2010) (N=45) showed that many GPs did not know when to appropriately refer HBsAg positive patients to specialist care. [Very low quality; applicable]

7.5.2 Economic evidence statement

No published cost-effectiveness analyses were identified.

7.6 Recommendations and Link to evidence

Recommendations	**Adults who are HBsAg positive** **6. Arrange the following tests in primary care for adults who are hepatitis B surface antigen (HBsAg) positive:** o hepatitis B e antigen (HBeAg)/antibody (anti-HBe) status o HBV DNA level o IgM antibody to hepatitis B core antigen (anti-HBc IgM) o hepatitis C virus antibody (anti-HCV) o hepatitis delta virus antibody (anti-HDV) o HIV antibody (anti-HIV) o IgG antibody to hepatitis A virus (anti-HAV) o additional laboratory tests including alanine aminotransferase (ALT) or aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), serum albumin, total bilirubin, total globulins, full blood count and prothrombin time o tests for hepatocellular carcinoma (HCC), including hepatic ultrasound and alpha-fetoprotein testing. **7. Refer all adults who are HBsAg positive to a hepatologist or to a gastroenterologist or infectious disease specialist with an interest in hepatology.** **8. Include the results of the initial tests with the referral (see recommendation 6).** **Pregnant women who test HBsAg positive at antenatal screening** **9. Refer pregnant women who are HBsAg positive to a hepatologist, or to a gastroenterologist or infectious disease specialist with an interest in hepatology, for assessment within**

	6 weeks of receiving the screening test result and to allow treatment in the third trimester (see recommendation 63). **Adults with decompensated liver disease** **10. Refer adults who develop decompensated liver disease immediately to a hepatologist or to a gastroenterologist with an interest in hepatology. Symptoms of decompensated liver disease include (but are not limited to) ascites, encephalopathy and gastrointestinal haemorrhage.** **Children and young people who are HBsAg positive** **11. Arrange the following tests for children and young people who are HBsAg positive:** o HBeAg/anti-HBe status o HBV DNA level o anti-HBc lgM o anti-HCV o anti-HDV o anti-HIV o anti-HAV o additional laboratory tests, including ALT or AST, GGT, serum albumin, total bilirubin, total globulins, full blood count and prothrombin time o tests for HCC, including hepatic ultrasound and alpha-fetoprotein testing . **12. Refer all children and young people who are HBsAg positive to a paediatric hepatologist or to a gastroenterologist or infectious disease specialist with an interest in hepatology.** **13. Include the results of the initial tests with the referral (see recommendation 11).**
Relative values of different outcomes	The two most important outcomes of having a complete set of diagnostic and prognostic tests prior to a patient's presentation to a specialist are: firstly, to provide the full set of information of the profile of the acute or chronic hepatitis B infection to aid the decision making for the specialist and secondly, to facilitate the patient's/carer's understanding of their situation and to guide informed joint decision-making. **Pregnant women** If a pregnant woman has an HBV infection then there is a 70–90% likelihood that the infection will be transferred to the baby in the 10% of women who are highly infectious (HBeAg positive). If she is infected but not highly infectious then this likelihood reduces to 10%. 90% of infected babies will go on to develop chronic HBV infection, leading to serious liver disease in later life. Timely immunisation and completion of the schedule of the same can prevent the development of chronic HBV infection in over 90% of these cases. A timely referral to a specialist will increase the likelihood that effective preventive treatment is given.
Trade off between clinical benefits and harms	Based on evidence of the level of knowledge about hepatitis B in primary care and clinical experience concerning the risk of harm associated with incorrect

	treatment of people with hepatitis B, the GDG thought that GPs should refer all patients who are HBsAg positive for specialist assessment. Currently, many patients are referred for specialist treatment without the necessary pre-therapeutic tests. These tests must then be completed before the patient is seen on a repeat visit to the specialist. This is costly in terms of resource use, inconvenient for the patient and delays the initiation of appropriate treatment for the patient as well as others who otherwise could have been seen. To ensure that all patients are treated as quickly and efficiently as possible, the GDG thought that all the pre-therapeutic test results should be available at the time of the first specialist consultation. These are standard tests that would be carried out prior to offering treatment and the GDG considered that these could be arranged within primary care. The GDG agreed that ultrasound should be performed in all patients to exclude hepatocellular carcinoma and cirrhosis. The GDG noted the low number of pregnant women referred in the Taylor study and agreed that it was important that pregnant women are referred to a specialist without delay. A complete course of hepatitis B immunisations is necessary for full protection of the baby to be achieved. The GDG considered that early referral of all pregnant women will ensure that appropriate treatment is initiated during pregnancy if necessary and prophylaxis is given to the child upon birth with appropriate follow-up in primary or secondary care instituted.
Economic considerations	The GDG considered the cost of each test as well as the cost of a consultation with a hepatitis specialist. They considered the increased cost to GP budgets that would be incurred by performing the recommended tests. The GDG thought however that, from the perspective of the entire healthcare system, reducing the total number of consultations within secondary care and ensuring that all patients are treated as quickly as possible would represent the most efficient use of NHS resources. They agreed that any perceived risk of over-testing and over-referral was justified by the increase in quality of life and reduction in mortality associated with appropriate treatment and monitoring of patients with hepatitis B.
Quality of evidence	The evidence in this area was limited and of poor quality. However, the study by Smith et al (2010) revealed that 83% of patients with CHB that have been tested in primary care did not reach a hepatology clinic in secondary care. This study was graded as being of very low quality as it was a retrospective, single centred trial and with no information on methods or characteristics of patients included. No studies were found that examined the referral of HBsAg positive pregnant women, children or young people to specialist services.
Other considerations	These recommendations are based on the experience and opinion of the GDG. The GDG considered that currently local circumstances determine where preparatory diagnostic and prognostic tests take place and thought that this disparity in practice represents an inefficient use of resources. The GDG acknowledged there may be a need for information and education to be provided to General Practitioners in order to update their knowledge of chronic hepatitis B infection.

8 Assessment of liver disease in secondary specialist care

8.1 Introduction

Liver fibrosis is caused by the deposition of excessive extracellular matrix in the liver in response to the chronic inflammation resulting from the interplay between hepatitis B virus and the immune system. Liver fibrosis and its end-point cirrhosis are the main causes of morbidity and mortality in chronic hepatitis B infection (CHB), and as such its presence is important for prognosis and management.

The assessment of the degree of liver fibrosis and necroinflammation is essential for the initial work-up of a patient with CHB and for longitudinal monitoring. It is also important in ruling out other causes of liver disease when a patient first presents with abnormal liver function tests. Liver histology can improve upon treatment, but can also worsen rapidly when patients have recurrent exacerbations and reactivations of the virus.

Liver biopsy is still considered the gold standard for the assessment of fibrosis. Histological assessment is based upon semi-quantitative scoring systems (METAVIR and Ishak score) [4,40]. These staging criteria are based upon a combined assessment of the level of fibrosis present and the degree of disorganisation of the liver architecture.

However, liver biopsy is an invasive procedure that involves the introduction of a needle into the parenchyma of the liver. Although the risk of complications such as haemoperitoneum, biliary peritonitis and pneumothorax is low (0.3–0.5%), pain, anxiety and discomfort are common [8,11] Each biopsy only samples a small part of the liver and therefore is not as useful where the disease is heterogeneous or important localised abnormalities, such as hepatocellular carcinoma, are present [40]. Its sensitivity depends upon the operator getting a large enough biopsy specimen – a 25mm fragment is considered the optimum [18]. The skill of the person assessing the histology will lead to variation between observers, although this is somewhat controlled for by the use of the scoring systems.

A number of options currently exist for the non-invasive assessment of liver fibrosis. These can mainly be categorised as either physical approaches that measure liver stiffness via transient elastography (TE) or biochemical approaches based on serum markers of fibrosis[12]. TE measures the elasticity of the liver as pressure in kPa. The FibroTest score is calculated from six serum markers: total bilirubin, gamma-glutamyl transpeptidase (GGT), alpha2-macroglobulin, apolipoprotein A1 and haptoglobins, all corrected for age and gender. The ActiTest is has the same serum markers but also includes ALT in the score. The APRI score (aspartate aminotransferase to platelet ratio index) uses routinely collected laboratory data to give a score based on the AST and platelet count.

8.2 Review question: What is the diagnostic accuracy of non-invasive methods (e.g. transient elastography, serum fibrosis markers, aspartate aminotransferase/ platelet ratio index, magnetic resonance spectroscopy) to assess severity of necro-inflammatory activity and liver fibrosis?

For full details see review protocol in Appendix C.

Table 15: PICO characteristics of review question

Protocol	
Population	Children, young people and adults with chronic hepatitis B virus infection (CHB)
Index tests	Non-invasive methods: • Serum fibrosis markers (e.g. fibrotest, actitest) • Transient elastography (e.g. fibroscan) • Aspartate aminotransferase/platelet ratio index (APRI) • Enhanced liver fibrosis test (ELF) • Magnetic resonance spectroscopy
Target condition or reference standard	Liver biopsy • METAVIR • Knodell score • Ishak fibrosis score
Outcomes	Main outcomes: • Sensitivity (%) and specificity (%) for particular thresholds • Area under the ROC curve (AUC) – measure of predictive accuracy Other outcomes: • Positive/negative predictive value • Positive/negative diagnostic likelihood ratios • Post-test probability (at a set pre-test probability)

Studies that used scoring systems other than METAVIR, Ishak and Knodell scores for fibrosis staging are excluded from this review.

METAVIR

F0=no fibrosis, F1=portal fibrosis without septa, F2=portal fibrosis with few septa, F3=numerous septa without cirrhosis, F4=cirrhosis

Ishak

F2=fibrous expansion of most portal areas, with or without short fibrous septa

F3=fibrous expansion of most portal areas with occasional porta-to-portal bridging

F4=fibrous expansion of most portal areas with marked bridging

F5=incomplete cirrhosis characterised by marked bridging and occasional nodules

F6=probable or definite cirrhosis

Knodell

0=no inflammation

1-4=minimal inflammation

5-8=mild inflammation

9-12=moderate inflammation

13-18=marked inflammation

Some widely used clinically relevant thresholds for identifying fibrosis/cirrhosis for each index test are listed in the table below:

Table 16: Thresholds for each index test

Index test	Thresholds
Fibrotest	Fibrosis: >0.48 Severe fibrosis: >0.58 Cirrhosis: >0.74
Transient Elastography	Fibrosis: >7.2kPa Cirrhosis: >13kPa
APRI	Fibrosis: >1.5 and >0.5 Cirrhosis: >2.0 and >1.0

Table 17: Definitions of summary measures for diagnostic accuracy studies

Measure	Definition
True positives (TP)	Correct positive test result – number of people diagnosed with fibrosis/cirrhosis with a positive index test result
True negatives (TN)	Correct negative test result – number of people diagnosed as not having fibrosis/cirrhosis with a negative index test result
False positives (FP)	Incorrect positive test result – number of people diagnosed as not having fibrosis/cirrhosis with a positive index test result
False negatives (FN)	Incorrect negative test result – number of people diagnosed with fibrosis/cirrhosis with a negative index test result
Sensitivity (%)	*Proportion* of those *with* the disease (based on a reference standard) who are *positive* on the index test.
Specificity (%)	*Proportion* of those *without* the disease (based on a reference standard) who are *negative* on the index test.
Positive predictive values (PPV)	*Probability* of having the disease in a patient with a positive index test result
Negative predictive values (NPV)	*Probability* of not having the disease in a patient with a negative index test result
Positive likelihood ratio (LR+)	How many times more likely a *positive* test result occurs in patients with compared to those without fibrosis.
Negative likelihood ratio (LR-)	How many times more likely a *negative* test result occurs in patients with compared to those without fibrosis.
Area under the curve	Overall summary of performance or diagnostic accuracy of an

Measure	Definition
	index test (compared against a reference standard)

8.3 Clinical evidence

We searched for diagnostic accuracy studies comparing different non-invasive methods of assessing liver fibrosis versus liver biopsy for adults, for children and young people with CHB. A total of 31 studies (cross-sectional and retrospective) are included in this review. The following tests are reported here:

- Seven studies examined Fibrotest versus liver biopsy (Castera 2011, Kim 2012B, Myers 2003, Poynard 2009, Raftopoulos 2012, Sebastiani 2007, Sebastiani 2011)
- Fifteen studies examined Transient Elastography versus liver biopsy (Cardoso 2012, Castera 2011, Chan 2009, Chen 2012, Gaia 2011A, Kim 2009, Kim 2010B, Kim 2012B, Lesmana 2011, Marcellin 2009A, Myers 2010B, Verveer 2012, Vigano 2011, Wong 2010, Zhu 2011)
- Sixteen studies examined APRI versus liver biopsy (Castera 2011, Chen 2012, Kim 2010A, Lesmana 2011, Liu 2011, Raftopoulos 2012, Sebastiani 2007, Sebastiani 2011, Seto 2011, Shin 2008, Wai 2006, Wong 2010, Wu 2010, Yilmaz 2011, Zhang 2008, Zhu 2011)
- Two studies compared ActiTest versus liver biopsy (Myers 2003, Poynard 2009)

Some studies included more than one index test:

- Two studies compared Fibrotest and Transient Elastography head to head against liver biopsy (Castera 2011, Kim 2012B)
- Six studies compared TE and APRI head to head against liver biopsy (Castera 2011, Chen 2012, Kim 2009, Lesmana 2011, Wong 2010, Zhu 2011)
- Three studies compared Fibrotest and APRI head to head against liver biopsy (Castera 2011, Raftopoulos 2012, Sebastiani 2007)
- One study compared TE, APRI and Fibrotest head to head against liver biopsy (Castera 2011)
- Two studies were conducted in children and investigated Actitest and Fibrotest (Sokuco2010) and APRI (McGoogan 2010)

8.3.1 Summary characteristics of included studies in adults with CHB

Table 18: Included studies comparing serum fibrosis markers (Fibrotest) with liver biopsy

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes*	Thresholds (pre-specified?)	Multiple test comparison?
Castera 2011 Cross-sectional	N=329 France HBeAg negative (and inactive carriers)	Liver biopsy (METAVIR) • Fibrosis (F2-4) • Cirrhosis (F4)	Within the same day of liver biopsy	AUC (95%CI) Sen Spec PPV NPV LR+/-	Fibrosis: 0.48 Cirrhosis: 0.74 (Pre-specified)	Y (TE, APRI)
Kim2012B	N=194 Korea	Liver biopsy • Significant	On the same day as liver	AUC (95%CI) Sen	Fibrosis: 0.32	Y (TE)

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes*	Thresholds (pre-specified?)	Multiple test comparison?
Cross sectional	HBeAg status not reported ALT mean 58.4 U/l	fibrosis (F2-4) • Severe fibrosis (F3-4) • Cirrhosis (F4)	biopsy	Spec PPV NPV	Severe fibrosis: 0.52 Cirrhosis: 0.68 (Not pre specified)	
Myers 2003 Cross-sectional + retrospective	N=209 France Mixed population (largely negative) (9% with HDV coinfection) Mean ALT 41 IU/l	Liver biopsy (METAVIR) • Fibrosis (F2-4)	Up to 6 months (95% within 3 months; 78% within 10 days)	AUC (SE) Sen Spec PPV NPV	0.20 0.40 0.60 0.80 0.90 (Not pre-specified)	Y (Actitest)
Poynard 2009 Retrospective (from RCT)	N=695 Greece Mixed HBeAg population	Liver biopsy (Knodell/Ishak scoring) • Fibrosis (F2-4) • Cirrhosis	<180days (6 months)	AUC (95%CI) Sen Spec PPV NPV	Fibrosis 0.48 (Not pre-specified)	Y (Actitest)
Raftopoulos 2012	N=179 Australia and France Largely HBeAg negative (35% positive)	Liver biopsy (METAVIR) • Fibrosis (≥F2) • Advanced fibrosis (F3-4) • Cirrhosis (F4)	At the time of liver biopsy	AUC (95%CI) Sen Spec PPV NPV LR	Fibrosis 0.48 and 0.37 (Youden) Cirrhosis 0.73 and 0.63 (Youden)	Y (APRI)
Sebastiani 2007 Retrospective	N=110 Italy Largely HBeAg negative	Liver biopsy (METAVIR) • Fibrosis (≥F2) • Cirrhosis (F4)	Within the same day of live biopsy	AUC (95%CI) Sen Spec PPV NPV LR+	Fibrosis: F2 Cirrhosis: F4 (Pre-specified, according to original studies)	Y (APRI)
Sebastiani 2011 Retrospective	N=253 Europe (9 centres) HBeAg 18% positive	Liver biopsy (METAVIR) • Fibrosis (≥F2) • Cirrhosis	Not stated	AUC (95%CI) Sen Spec PPV	Fibrosis: 0.48 Cirrhosis: 0.75	N

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes*	Thresholds (pre-specified?)	Multiple test comparison?
		(F4)		NPV LR+ LR-	(pre-specified)	

**AUC, area under the ROC curve; sen, sensitivity; spec, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.*

Table 19: Included studies comparing serum fibrosis marker (ActiTest) with liver biopsy

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes *	Thresholds (Pre-specified?)	Multiple test comparison?
Myers 2003 Retrospective and cross-sectional	N=209 France Largely HBeAg negative (9% with HDV coinfection)	Liver biopsy • Necro-inflammatory activity (A2-3)	Up to 6 months (95% within 3 months; 78% within 10 days)	AUC (SE)	--	Y (FibroTest)
Poynard 2009 Retrospective (from RCT)	N=695 Greece Mixed HBeAg population	Liver biopsy (Knodell/ Ishak scoring) • Advanced necro-inflammatory activity (A2-3)	<180days (6 months)	AUC (95%CI) Sen Spec PPV NPV	A2-3: 0.52 (Not pre-specified)	Y (Actitest)

**AUC, area under the ROC curve; sen, sensitivity; spec, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.*

Table 20: Included studies comparing transient elastography (Fibroscan) with liver biopsy

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes *	Thresholds (pre-specified?)	Multiple test comparison ?
Cardoso 2012	N=202 France HBeAg 24% positive	Liver biopsy • Fibrosis (F2-4) • Bridging fibrosis: ≥F3 • Cirrhosis F4 •	Measured before liver biopsy on same day as procedure	AUC (SE) Sen Spec PPV NPV LR+ LR- Also split by ALT levels	Fibrosis 7.2kPa Advanced fibrosis 8.1kPa Cirrhosis 11kPa	N
Castera	N=329	Liver biopsy	At the time	AUC	Fibrosis:	Y (Fibrotest,

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes *	Thresholds (pre-specified?)	Multiple test comparison ?
2011 Cross-sectional	France HBeAg (-) (201 inactive carriers) ALT (<50/329) mean 46 IU/l	(METAVIR) • Fibrosis (F2-4) • Cirrhosis (F4)	of LB	Sen Spec PPV NPV LR+/-	7.1kPa Cirrhosis: 9.6kPa 11kPa Pre-specified	APRI)
Chan 2009 Cross-sectional	N=161 Hong Kong Largely HBeAg (-) 57% ALT not stated	Liver biopsy • Bridging fibrosis: ≥F3 • Cirrhosis: F4	Within 4 weeks from LB.	AUC Sen Spec PPV NPV LR+/-	Any fibrosis/cirrhosis: • Sen: 5kPa • Sen+Spec: 6.8kPa • Spec: 9kPa Bridging fibrosis: • Sen:6kPa • Sen+Spec: 8.4kPa • Spec: 11.3kPa Cirrhosis: • Sen: 8.4kPa • Sen+Spec: 9kPa • Spec: 13.4kPa (Not pre-specified)	N
Chen 2012 Cross-sectional	N=389 China Treatment naïve, largely HBeAg (+) ALT mean 83 U/l Pop. consists of training and validation group	Liver biopsy (METAVIR) • Cirrhosis F4	Within one week of LB	AUC (95%CI) Sen Spec PPV NPV LR +/-	Excluding cirrhosis: 10.4 Confirming cirrhosis: 22.3	Y (APRI)
Gaia 2011A	N=70 Italy	Liver biopsy • Mild	Within 6 months of LB	AUC (95%CI) Sen	Moderate fibrosis: 7.2kPa	N

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes *	Thresholds (pre-specified?)	Multiple test comparison ?
Cross-sectional	Treatment naïve, HBeAg status unknown (subgroup analysis) ALT mean 70 IU/l	fibrosis F1 • Moderate fibrosis F2 • Severe fibrosis F3 • Cirrhosis F4		Spec PPV NPV	Severe fibrosis: 8.9kPa Cirrhosis: 10.6kPa (Not pre-specified)	
Kim 2009 Cross-sectional	N=130 Korea Treatment naïve, mixed HBeAg status (59% positive) ALT mean 45.1	Liver biopsy • Cirrhosis (F4)	Measured on the same day as liver biopsy	AUC Sensitivity Specificity PPV NPV LR+/-	10.1kPa (Not pre-specified)	Y (APRI)
Kim 2010B Cross-sectional	N=330 Korea HBeAg status unknown ALT mean 77 IU/l	Liver biopsy (METAVIR) • Cirrhosis (F4)	Within 2 days of liver biopsy	AUC	--	N
Kim 2012B Cross sectional	N=194 Korea HBeAg status not reported ALT mean 58.4 U/l	Liver biopsy • Significant fibrosis (F2-4) • Severe fibrosis (F3-4) • Cirrhosis (F4)	On the same day as liver biopsy	AUC (95%CI) Sen Spec PPV NPV	Fibrosis: 8.8kPa Severe fibrosis: 10.2kPa Cirrhosis: 14.1kPa (Not pre specified)	Y (Fibrotest)
Lesmana 2011 Cross-sectional	N=117 Indonesia Mixed HBeAg status ALT > 5 x ULN excluded (mean 31.9 F0-1 and 57.1	Liver biopsy • Fibrosis (F2-4) • Severe fibrosis (F3-4)	On the same day with LB	AUC Sen Spec PPV NPV LR (+/-)	Fibrosis: 5.85kPa Severe fibrosis: 7kPa (Not pre-specified)	Y (APRI; also combination of TE and APRI)

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes *	Thresholds (pre-specified?)	Multiple test comparison ?
	F2-4)					
Marcellin 2009A Cross-sectional	N=202 France (multicentre) HBeAg status unknown	Liver biopsy • Significant fibrosis (F2-4) • Severe fibrosis (F3-4) • Cirrhosis (F4)	Within 3 months of LB	AUC Sen Spec PPV NPV LR (+/-)	Fibrosis (F2-4): 7.2kPa Severe fibrosis (F3-4): 8.1kPa Cirrhosis: 11kPa (Not pre-specified)	N
Myers 2010B Cross-sectional	N=68 Canada, multicentre HBeAg status 17% positive (subgroup analysis) ALT median 61 U/l	Liver biopsy (METAVIR) • Fibrosis (F≥2) • Bridging fibrosis (F≥3) • Cirrhosis (F4)	Up to 6 months (median interval: 18 days)	AUC Sen Spec PPV NPV	Fibrosis: ≥7.7kPa Bridging fibrosis: ≥10.3kPa Cirrhosis: ≥11.1kPa (not pre-specified)	N
Verveer 2012 Retrospective	N=125 The Netherlands HBeAg 41% positive	• Fibrosis (F2-4) • Advanced fibrosis (F3-4)	Measured on same day	AUC	NA	N
Vigano 2011 Cross-sectional	N=254 Italy Treatment naïve, largely HBeAg (-) 78% ALT mean 68 IU/l Pop. consists of training group and validation group.	Liver biopsy • Fibrosis (F2-4) • Cirrhosis (F4)	Unclear	AUC Sen Spec PPV NPV	Fibrosis: 8.7kPA *Dual cut off:* Fibrosis Sen: <6.2 Spec: >9.4 Cirrhosis Sen: ≤9.4 Spec: >13.1 (Not pre-specified)	N
Wong 2010 Cross-sectional	N=156 Hong Kong Treatment naïve, HBeAg	Liver biopsy (METAVIR) • Advanced fibrosis (F3-4)	Unclear	AUC Sen Spec PPV NPV	Advanced fibrosis: ≤6kPA for normal ALT	Y (APRI)

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes *	Thresholds (pre-specified?)	Multiple test comparison ?
	status unknown Exclusion ALT > 1-5 times ULN; ALT normal 37% training cohort; 6% validation cohort			LR+/-	≤7.5kPa for elevated ALT	
Zhu 2011 Cross-sectional	N=175 China Both HBeA g (+) and (-); ALT > 2 x ULN exclusion (mean 40.1 U/l) 85% HBeAg positive	Liver biopsy • Significant fibrosis (F2-3) • Cirrhosis (F4)	Within 24 hours of LB	AUC Sen Spec PPV NOV	Fibrosis: 7.9kPa Cirrhosis: 13.8kPa (Not pre-specified)	Y (APRI)

**AUC, area under the ROC curve; sen, sensitivity; spec, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.*

Table 21: Included studies comparing aspartate aminotransferase platelet ratio index (APRI) score with liver biopsy

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes *	Thresholds (pre-specified?)	Multiple test comparison ?
Castera 2011 Cross-sectional	N=329 France HBeAg (-) (201 inactive carriers)	Liver biopsy (METAVIR) • Fibrosis (F2-4) • Cirrhosis (F4)	At the time of LB	AUC Sen Spec PPV NPV LR+/-	Fibrosis: <0.5 ≥1.5 Cirrhosis: <1.0 ≥2.0 Pre-specified	Y (Fibrotest, transient elastography)
Chen 2012 Cross-sectional	N=389 China Treatment naïve, largely HBeAg (+) 61% Pop. consists	Liver biopsy (METAVIR) • Cirrhosis F4	Within 3 days of transient elastography	AUC (95%CI) Sen Spec Predictive value (+/-) LR +/-	Excluding cirrhosis: 10.4 Confirming cirrhosis: 22.3	Y (Transient elastography)

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes *	Thresholds (pre-specified?)	Multiple test comparison ?
	of training and validation group					
Kim 2010A Cross-sectional	N=521 Korea HBeAg status unknown	Liver biopsy (METAVIR) Cirrhosis: F4	Within one day of liver biopsy	AUC	--	N
Lesmana 2011 Cross-sectional	N=117 Indonesia Mixed HBeAg status	Liver biopsy (METAVIR) • Significant fibrosis (F2-4) • Severe fibrosis (F3-4)	Unclear	AUC Sen Spec PPV NPV LR (+/-)	Sig. fibrosis: 0.235 Severe fibrosis: 0.27 (Not pre-specified)	Y (Transient elastography; also combination of TE and APRI)
Liu 2011 Retrospective	N=623 China Mixed HBeAg status (65% F0-1, 45% F2-4	Liver biopsy (METAVIR) • Fibrosis (F2-4)	Within a week of LB.	AUC Sen Spec PPV NPV LR+/-	Fibrosis: 0.3 Unclear whether threshold was pre-specified	N
Raftopoulos 2012 Prospective database, retrospective review	N=179 Australia and France 24/68 (59%) HBeAg +ve ALT mean 88.6 U/l)	Liver biopsy (METAVIR) • Fibrosis (F2-4) • Bridging fibrosis: ≥F3 • Cirrhosis F4	Serum markers measured at the time of liver biopsy	AUC (95%CI) Sen Spec PPV NPV LR+ LR-	Fibrosis: 0.5 1.5 0.55 Cirrhosis: 1.0 0.81 (pre-specified and determined)	Y (Fibrotest)
Sebastiani 2007 Retrospective	N=110 Italy Largely HBeAg negative (7.3% with HDV coinfection)	Liver biopsy (METAVIR) • Fibrosis: ≥F2 • Cirrhosis: F4	Obtained on the day of LB.	AUC Sen Spec PPV NPVLR+/-	Fibrosis: 0.5 Cirrhosis: 2 Pre-specified, according to original	Y (FibroTest)

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes *	Thresholds (pre-specified?)	Multiple test comparison ?
					studies	
Seto 2011 Retrospective (from a trial)	N=129 (validation group only) Hong Kong Treatment naïve, mixed HBeAg status (58% positive)	Liver biopsy (Knodell HAI and Ishak score) Fibrosis: ≥3 (at least bridging fibrosis)	At the time of liver biopsy.	AUC Sen Spec PPV NPV LR+/-	Fibrosis (Ishak≥3): 0.5 1.5 (Not pre-specified)	N
Shin 2008 Retrospective	N=264 Korea HBeAg status unknown Pop. consists of training and validation groups	Liver biopsy • Significant fibrosis (F2-4)	Unclear	AUC (95%CI) Sen Spec PPV NPV	>0.5 >1.0 >1.4 >1.5 >2.0 (Not pre-specified)	N
Wai 2006 Retrospective	N=377 Singapore Treatment naïve, HBeAg status 76% and 86% positive Pop. consists of training and validation groups	Liver biopsy (Ishak scoring) • Significant fibrosis ≥3 • Cirrhosis 5-6	Lab results performed within 4 months before the LB were used.	AUC (95% CI)	--	N
Wong 2010 Cross-sectional	N=156 Hong Kong Treatment naïve, HBeAg status unknown	Liver biopsy (METAVIR) • Advanced fibrosis (F3-4)	Unclear	AUC Sen Spec PPV NPV LR+/-	Exclusion strategy ≤6kPa for normal ALT ≤7.5kPa for elevated ALT Confirmatory strategy >9kPa for normal ALT >12kPa for elevated ALT	Y (transient elastography)
Wu 2010	N=78	Liver biopsy	Both index	AUC	Fibrosis:	N

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes *	Thresholds (pre-specified?)	Multiple test comparison ?
Retrospective	China Largely HBeAg(+) 71%	(METAVIR) • Fibrosis (F≥2) Severe fibrosis (F≥3)	test and ref std obtained at admission	Sen Spec PPV NPV LR+/-	<0.50 >1.50 Pre-specified (according to original studies)	
Yilmaz 2011 Retrospective	N=207 Turkey HBeAg status unknown (subgroup analysis)	Liver biopsy • Fibrosis (F1-4) vs. no fibrosis (F0)	Unclear	AUC (95%CI) Sen Spec	0.36 (Not pre-specified)	N
Zhang 2008 Retrospective	N=137 China HBeAg status unknown	Liver biopsy (METAVIR) • Fibrosis (F2-4)	With 2 weeks after LB.	Sen Spec PPV NPV LR+/-	Fibrosis: ≥1.5 Pre-specified	N
Zhu 2011 Cross-sectional	N=175 China	Liver biopsy • Significant fibrosis (F2-3) • Cirrhosis (F4)	Within 7 days of LB	Sen Spec PPV NPV	Sig. fibrosis: 0.5 Cirrhosis: 1.0 (Not pre-specified)	Y (Transient elastography)

**AUC, area under the ROC curve; sen, sensitivity; spec, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.*

8.3.2 Summary characteristics of included studies in children with CHB

Table 22: Included studies comparing serum fibrosis markers (FibroTest) with liver biopsy

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes*	Thresholds (pre-specified?)	Multiple test comparison ?
Sokucu 2010 Cross-sectional	N=25 Turkey children up to 18 years, unknown HBeAg status	Liver biopsy (Ishak score) • Fibrosis (F3-6) • Insignificant fibrosis (F0-2)	Unclear	Sen Spec PPV NPV	Fibrosis: 0.31 (Pre-specified)	Y (ActiTest)

**AUC, area under the ROC curve; sen, sensitivity; spec, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.*

Table 23: Included studies comparing serum fibrosis markers (ActiTest) with liver biopsy

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes*	Thresholds (pre-specified?)	Multiple test comparison ?
Sokucu 2010 Cross-sectional	N=25 Turkey Children (up to 18 years) (unknown HBeAg status)	Liver biopsy (Ishak scoring) • Significant necro-inflammatory activity (A2-4) • Insignificant necro-inflammatory activity (A0-1)	Unclear	Sen Spec PPV NPV	Sig. activity: 0.37	Y (FibroTest)

Table 24: Included studies comparing APRI with liver biopsy

Included studies Study design	N Setting Patient characteristics	Reference standard/ target condition	Interval between ref std and index test	Outcomes*	Thresholds (pre-specified?)	Multiple test comparison ?
McGoogan 2010	11 children (0-20 years) USA Subgroup analysis	Liver biopsy • Fibrosis: F2/3 • Cirrhosis: F4	Within 4 months of liver biopsy	AUC Mixed Hep B and C patients: Sen Spec PPV NPV LR+/-	Fibrosis: >0.5 >1.5 Cirrhosis: >0.5 >1.5 (pre-specified)	N

**AUC, area under the ROC curve; sen, sensitivity; spec, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.*

8.3.3 Summary results in adults with CHB infection

For each test, the following results are presented:

- Summary tables across all studies, reporting the median value (of AUC, sensitivity and specificity) with its 95%CI and the range of values across all studies. For sensitivity-specificity pairs, the median sensitivity is reported (with its 95%CI) and the specificity for the median study is given. Quality is indicated using similar principles to GRADE
- Area under the Receiver Operating Characteristics (ROC) curve (AUC) with its 95%CI is represented for each study on a forest plot for each fibrosis stage (Appendix G 1.1)
- Sensitivity and specificity pairs for the optimum threshold in each study are represented in ROC space (sensitivity versus 1-specificity) for each fibrosis stage (Appendix G 1.1), using data from 2x2 tables (shown in Appendix O)
- Forest plots of coupled sensitivity and specificity pairs for those studies reporting values at the "standard" thresholds (Appendix G 1.1).

At the end of the sections on individual tests, results across tests are compared. This includes visual inspection of the ROC curves for each test and fibrosis stage (Appendix G 1.1).

Across all studies, quality assessment using QUADAS II showed:

- 5 studies were assessed to be at very high risk of bias (Liu 2011, Myers 2003, Wai 2006, Wu 2010A, Yilmaz 2011)
- 12 at high risk of bias (Castera 2011, Chan 2009, Chen 2012, Gaia 2011, Myers 2010B, Poynard 209, Raftopoulos 2012, Seto 2011, Shin 2008, Verveer 2012, Vigano 2011A, Wong 2010)
- 9 at unclear risk of bias (Cardoso 2012, Kim 2010B, Kim 2009, Kim 2012B, Lesmana 2011, Marcellin 2009A, Sebastiani 2007, Sebastiani 2011, Zhu 2011)
- 2 at low risk of bias (Kim 2010A, Zhang 2008).

Risk of bias issues were mainly concerned with whether "difficult to diagnose" patients were excluded (e.g. for having unsuccessful TE measurements, or inadequate sample for biopsy), retrospective studies giving selection bias, choice of threshold (only relevant for sensitivity and specificity) and inappropriate durations between tests. The Yilmaz 2011 study was excluded from the analysis because it defined fibrosis as F1 to F4.

Generally the studies were likely to be applicable to the review population, except that nearly all of them only included people who had a liver biopsy or were scheduled for a biopsy. Reasons for this were not usually explained and did not depend on the stage of hepatitis. Exceptions to this were Castera 2011 (which was conducted in patients who were largely – 61% - inactive carriers), possibly Lesmana 2011 (in which people with signs of cirrhosis were excluded), possibly Liu 2011 (patients from the histology lab database), and possibly Raftopoulos 2012 (patients referred to a tertiary referral centre).

8.3.3.1 Diagnostic accuracy of Fibrotest

The FibroTest score is calculated from serum markers, including total bilirubin, GGT, α2-macroglobulin, apolipoprotein A1 and haptoglobin, corrected for age and gender.

Seven studies examined the diagnostic accuracy of FibroTest for liver fibrosis/cirrhosis in adult patients with CHB (Castera 2011, Kim 2012B, Myers 2003, Poynard 2009, Raftopoulos 2012, Sebastiani 2007, Sebastiani 2011).

Two studies also reported results by HBeAg status (Myers 2003; Poynard 2009). The AUCs of Fibrotest are 0.89 (SE 0.06) (Myers 2003) and 0.78 (Poynard 2009) in HBeAg positive patients and 0.76 (SE 0.05) (Myers 2003) and 0.74 (Poynard 2009) in HBeAg negative patients.

Generally the studies were considered to be at high or unclear risk of bias and generally directly applicable, although all selected patients who had an adequate liver biopsy and non-invasive measurements. One study (Castera 2011) was conducted in a cohort of 61% inactive carriers. Three studies had high risk of bias (Castera 2011, Raftopoulos 2012; Poynard 2009); one study was considered to be at very high risk of bias (Myers 2003) and it was unclear if there was a risk of bias for the two Sebastiani studies and Kim 2012B. More details on quality assessment can be found in Appendix N.

All the reported AUCs are summarised in section G.1.1 of Appendix G. Forest plots of sensitivity and specificity for fibrosis and cirrhosis can also be found in Appendix G. These are reported for standard thresholds only.

A sensitivity analysis (not shown) excluding the Myers 2003 study, which was considered at very high risk of bias, gave similar results.

Table 25: Summary of evidence for Fibrotest for different fibrosis levels

Outcome measured	Results: median value with its 95%CI and range across all studies	Quality issues
Significant Fibrosis (≥ F2)		
AUC (7 studies)	76% (95%CI 73 to 80) Range: 69 to 90%	Serious inconsistency; generally high risk of bias and no serious indirectness LOW QUALITY
Sensitivity at 0.48 threshold (5 studies)	61% (95%CI 45 to 76) Range 54 to 81%	No serious inconsistency, generally high risk of bias and no serious indirectness LOW QUALITY
Corresponding specificity at 0.48 threshold (5 studies)	81% (54 to 96%) Range 69 to 91%	Serious inconsistency, generally high risk of bias and no serious indirectness LOW* QUALITY
Cirrhosis (F4)		
AUC (6 studies)	76% (95%CI 67 to 85%) range:68 to 92%	Serious inconsistency; generally high risk of bias and no serious indirectness LOW QUALITY
Sensitivity at 0.74 threshold (4 studies)	47% (21 to 73%) Range 42 to 78%	Serious inconsistency; generally high risk of bias and no serious indirectness LOW QUALITY
Corresponding specificity at 0.74 threshold (4 studies)	91% (79 to 98%) Range 89 to 97%	No serious inconsistency; generally high risk of bias and no serious indirectness LOW* QUALITY

***led by sensitivity**

8.3.3.2 Diagnostic accuracy of transient elastography (Fibroscan)

Transient elastography measures liver stiffness by using elastic waves. The results are expressed in kilopascals (kPa).

Fifteen cross-sectional studies are included in this review, examining the diagnostic accuracy of transient elastography in prediction of liver fibrosis/cirrhosis in adult patients with CHB (Cardoso 2012, Castera 2011, Chan 2009, Chen 2012, Gaia 2011A, Kim 2009, Kim 2010B, Kim 2012B, Lesmana 2011, Marcellin 2009A, Myers 2010B, Verveer 2012, Vigano 2011, Wong 2010, Zhu 2011)

Seven studies are of unclear risk of bias (Cardoso 2011, Kim 2009, Kim 2010B, Kim 2012B, Lesmana 2011, Marcellin 2009A, Zhu 2011), and the rest are of high risk of bias; no studies were at very high risk of bias. More details on quality assessment can be found in Appendix N. The Wong 2010 study

used an algorithm containing different thresholds for different ALT levels – this should be viewed as at high risk of bias and potentially indirect evidence.

All the reported AUCs are summarised in section G.1.1 of Appendix G. Coupled forest plots of sensitivity and specificity for fibrosis and cirrhosis at the standard thresholds can be found in section G.1.1 of Appendix G.

Sensitivity analysis without the Wong 2010 study only affected advanced fibrosis and there was little effect.

Table 26: Area under the ROC curve (95% CI) of transient elastography (FibroScan) for the absence of liver fibrosis (F0)

Included study	N	AUC (95% CI)
Gaia 2011A	70	0.59 (0.47-0.71)

Table 27: Summary of evidence for transient elastography (Fibroscan) for different fibrosis stages

Outcome measured	Results: median value with its 95%CI and range across all studies	Quality issues
Significant Fibrosis (≥ F2)		
AUC (8 studies)	81% (95%CI 73 to 86) Range: 61 to 95%	Serious inconsistency; half the studies were considered at high risk of bias; no serious indirectness LOW QUALITY
Sensitivity at 7.2kPa threshold (4 studies)	68% (95%CI 52 to 81) Range 62 to 74%	No serious inconsistency; half the studies were considered at high risk of bias and there was no serious indirectness MODERATE QUALITY
Corresponding specificity at 7.2kPa threshold (4 studies)	63% (35 to 85%) Range 63 to 88%	Serious inconsistency; half the studies were considered at high risk of bias and there was no serious indirectness MODERATE* QUALITY
Severe fibrosis (≥F3)		
AUC (8 studies)	87% (95%CI 82 to 93%) range:66 to 99%	No serious inconsistency; generally high risk of bias and no serious indirectness MODERATE QUALITY
Cirrhosis F4		
AUC (11 studies)	92% (95%CI 89 to 95%) Range:76 to 98%	No serious inconsistency; majority (6) of studies were considered at high risk of bias, no serious indirectness MODERATE QUALITY
Sensitivity at 11.0kPa threshold (4 studies)	75% (48 to 93%) Range 73 to 100%	Serious inconsistency, half the studies were considered to be at high risk of bias, no serious indirectness

		LOW QUALITY
Corresponding specificity at 11.0kPa threshold (4 studies)	90% (85 to 94%) Range 87 to 92%	No serious inconsistency; half the studies were considered to be at high risk of bias, no serious indirectness

Effect of ALT levels on diagnostic accuracy of transient elastography (TE)

One limitation of transient elastography is that the liver stiffness measurement increases with higher ALT levels regardless of the fibrosis staging (Wong 2010), i.e. in people with higher ALT levels, a positive result on transient elastography is more likely to give false positives than in people with lower ALT levels and can lead to over diagnosing in people with cirrhosis. This has led to the proposal to have different thresholds for different ALT levels, e.g. >9.0kPa and >12.0kPa for the diagnosis of cirrhosis for normal and elevated ALT (1-5 times ULN) (Wong 2010). Chan 2009 has also proposed different thresholds for different ALT levels: for fibrosis 6.0kPa (≤1 x ULN) and 7.5kPa (1-5 x ULN); for advanced fibrosis: 9.0kPa (≤1 x ULN) and 12.0kPa (1-5 x ULN); and for cirrhosis: 12.0 (≤1 x ULN) and 13.4kPa (1-5 x ULN).

Cardoso 2011 investigated the effect on sensitivity and specificity of different ALT levels and different thresholds for the 186/202 patients with clear ALT values, and found the following:

Degree of liver fibrosis	**ALT ≤1 x ULN**	**ALT 1-5 x ULN**
Significant fibrosis **Same threshold (7.2)**	Sensitivity 61% Specificity 92%	Sensitivity 74% Specificity 86%
Significant fibrosis **Different thresholds**	**Threshold 6.0kPa** Sensitivity 78% Specificity 69%	**Threshold 7.5kPa** Sensitivity 70% Specificity 88%
Advanced fibrosis **Same threshold 8.1**	Sensitivity 86% Specificity 93%	Sensitivity 90% Specificity 76%
Advanced fibrosis **Different thresholds**	**Threshold 9.0kPa** Sensitivity 71% Specificity 95%	**Threshold 12.0kPa** Sensitivity 53% Specificity 96%
Cirrhosis **Same threshold 11.0**	Sensitivity 67% Specificity 97%	Sensitivity 73% Specificity 88%
Cirrhosis Different thresholds	**Threshold 12.0kPa** Sensitivity 67% Specificity 98%	**Threshold 13.4kPa** Sensitivity 55% Specificity 96%

There were no significant differences between using different thresholds and the same thresholds for different ALT levels.

Table 28: Diagnostic accuracy of TE for fibrosis (≥F2) according to ALT levels

Study	**ALT**	**Threshold (kPa)**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Vigano 2011	≤1x ULN	--	100	100	--	--
	>1x ULN	--	94	93	--	--

Study	ALT	Threshold (kPa)	Sensitivity	Specificity	PPV	NPV
Myers 2010	<100 U/L	7	70	64	63	71
	≥100 U/L	8.6	67	92	97	44
Cardoso 2011	≤1x ULN	7.2	61	92	73	87
	1-5 x ULN	7.2	74	86	83	78
	≤1x ULN	6.0	78	69	48	89
	1-5 x ULN	7.5	70	88	84	76

Table 29: Diagnostic accuracy of TE for cirrhosis (F4) according to ALT levels

Study	ALT	Threshold (kPa)	Sensitivity	Specificity	PPV	NPV
Chan 2009	Normal ALT	12	71	100	100	79
	1-5x ULN	13.4	75	93	78	92
Vigano 2011	≤1x ULN	--	100	97	--	--
	>1x ULN	--	97	94	--	--
Chen 2012	<5x ULN	10.4	93	71	46	97
	≥5x ULN	13.7	95	76	59	97
Myers 2010	<100 U/L	11.1	94	84	37	99
	≥100 U/L	11.5	100	73	45	100
Cardoso 2011	≤1x ULN	11.0	67	97	50	98
	1-5 x ULN	11.0	73	88	40	97
	≤1x ULN	12.0	67	98	67	98
	1-5 x ULN	13.4	55	96	60	95

8.3.3.3 Diagnostic accuracy of APRI score

APRI is a simple index using serum biomarkers collected from routine laboratory tests.

Formula = Aspartate aminotransferase to platelet ratio index (APRI)

= [(AST/ULN)/platelet count (10^9/l)] x 100

Sixteen studies examined the diagnostic accuracy of APRI score in prediction of liver fibrosis/cirrhosis in adult patients with CHB are included (Castera 2011, Chen 2012, Kim 2010A, Lesmana 2011, Liu 2011, Raftopoulos 2012, Sebastiani 2007, Sebastiani 20011, Seto 2011, Shin 2008, Wai 2006, Wong 2010, Wu 2010, Yilmaz 2011, Zhang 2008, Zhu 2011).

Four studies were considered to be at very high risk of bias (Liu 2011, Wai 2006, Wu 2010, Yilmaz 2011), and Yilmaz 2011 was excluded from the analysis because it had an incorrect definition of fibrosis. Six studies are of high risk of bias (Castera 2011, Chen 2012, Raftopoulos 2012, Seto 2011, Shin 2008, Wong 2010), three were of unclear risk of bias (Lesmana 2011, Sebastiani 2007, Sebastiani 2011, Zhu 2011) and two studies are considered to be of low risk of bias (Kim 2010A, Zhang 2008). More details on quality assessment can be found in Appendix G. It is noted that Castera 2011 contained a high proportion of inactive carriers (61%).

All reported AUCs are summarised section G.1.1 of Appendix G. Forest plots of sensitivity vs. specificity for fibrosis and cirrhosis for standard thresholds can be found in section G.1.1 of Appendix G.

One study (Yilmaz 2011; N=207) reported an AUC of 0.54 (95%CI 0.46 to 0.62) for fibrosis stage F1-4.

The studies considered to be at very high risk of bias are indicated using red and underlined names. Their exclusion does not make much difference.

Table 30: Summary of evidence for APRI score for different stages of fibrosis

Outcome measured	Results: median value with its 95%CI and range across all studies	Quality issues
Significant Fibrosis (≥ F2)		
AUC (11 studies)	71% (95%CI 63 to 80) Range: 63 to 86%	Serious inconsistency; most studies at high or very high risk of bias; no serious indirectness LOW QUALITY
Sensitivity at 1.5 threshold (8 studies)	30% (95%CI 17 to 45) Range 14 to 75%	Serious inconsistency and one outlier; most studies at high risk of bias; no serious indirectness LOW QUALITY
Corresponding specificity at 1.5 threshold (8 studies)	88% (79 to 94%) Range 80 to 100%	No serious inconsistency; most studies at high risk of bias; no serious indirectness MODERATE QUALITY
Sensitivity at 0.5 threshold (7 studies)	82% (69-91) Range 61 to 97%	Serious inconsistency; most studies at high risk of bias; no serious indirectness LOW QUALITY
Corresponding specificity at 0.5 threshold (7 studies)	83% (75 to 89) Range 34 to 86%	Very serious inconsistency; most studies at high risk of bias; no serious indirectness VERY LOW QUALITY
Severe fibrosis (≥F3)		
AUC (3 studies)	78% (95%CI 68 to 87%) range:76 to 80%	No serious inconsistency; one study at very high risk of bias, one at high risk and one at unclear risk; no serious indirectness MODERATE QUALITY
Cirrhosis F4		
AUC (7 studies)	78% (95%CI 70 to 86%) Range:61 to 84%	Very serious inconsistency; most studies at unclear risk of bias, no serious indirectness LOW QUALITY
Sensitivity at 2.0 threshold (2 studies)	41% (21 to 64%) and 20% (10 to 35%)	Serious inconsistency, unclear risk of bias, no serious indirectness MODERATE QUALITY
Corresponding specificity at 2.0 threshold (2 studies)	85% (76 to 92%) and 84% (78 to 88%)	No serious inconsistency; unclear risk of bias, no serious indirectness MODERATE QUALITY

Outcome measured	Results: median value with its 95%CI and range across all studies	Quality issues
Sensitivity at 1.0 threshold (3 studies)	67% (95%CI 35 to 90) Range: 47 to 76%	Serious inconsistency; 2/3 studies at high risk; possible indirectness in 1/2 studies; LOW QUALITY
Corresponding specificity at 1.0 threshold (3 studies)	81% (95%CI 73 to 87) Range: 69 to 81%	Serious inconsistency; 2/3 studies at high risk; possible indirectness in 1/2 studies; LOW QUALITY

8.3.3.4 Diagnostic accuracy of ActiTest

ActiTest includes the 6 serum markers from FibroTest, as well as ALT (also corrected for age and gender).

Two studies are included in this review, examining the diagnostic accuracy of ActiTest in prediction of liver fibrosis/cirrhosis in adult patients with CHB. Both studies are of very high risk of bias (2 or more of the following: not a consecutive/random sample, thresholds not pre-specified, inappropriate interval between index test and reference standards, unclear blinding of reference standard results). More details on quality assessment can be found in Appendix N.

One study reported AUC data by HBeAg status (Poynard 2009). The AUCs are 0.71 and 0.84 in HBeAg positive and negative patients, respectively.

All the reported AUCs are summarised in section G.1.1 of Appendix G. Forest plots of sensitivity vs. specificity can be found in section G.1.1 of Appendix G.

Table 31: Area under the ROC curve (95% CI) – Actitest

Necro-inflammatory activity	Included study	N	AUC (95% CI)
A2-3 vs. A0-1	Myers 2003	209 35 174	– 0.82 (SE 0.04) HBeAg (+): 0.71 (SE 0.09) HBeAg (-): 0.84 (SE 0.05)
	Poynard 2009	462	0.81 (95%CI 0.78 to 0.83)

Table 32: Summary - AUC ranges for prediction of fibrosis and cirrhosis - Actitest

	AUC ranges reported by included studies
Necro- inflammatory activity	0.81-0.82 [2 studies]

Table 33: Sensitivity, specificity, predictive values and likelihood ratios – Actitest

Threshold	Included study	Sensitivity	Specificity	PPV	NPV	LR+	LR-
0.52	Poynard 2009	70	60	88	32	-	-

8.3.3.5 Enhanced liver fibrosis (ELF) test

No relevant studies on the ELF test in predicting liver fibrosis have been identified.

8.3.3.6 Magnetic resonance spectroscopy

No relevant studies on magnetic resonance spectroscopy in predicting liver fibrosis have been identified.

8.3.3.7 Combination of transient elastography (TE) and APRI

Two studies (Lesmana 2011; Kim 2009) are included in this review, examining the diagnostic accuracy of the combination of transient elastography and APRI in prediction of liver fibrosis/ cirrhosis in adult patients with CHB. One study is of high risk of bias (unclear blinding of reference standard results) and one study is of very high risk of bias (threshold not specified, unclear blinding of index test and reference standard results, unclear interval between index test and reference standard). More details on quality assessment can be found in appendix N.

All the reported AUCs are summarised in section G.1.1 of Appendix G. Forest plots of sensitivity vs. specificity for fibrosis, severe fibrosis and cirrhosis can be found in section G.1.1 of Appendix G.

Table 34: Area under the ROC curve (95% CI) of TE and APRI in predicting fibrosis (≥F2)

Included study	N	AUC (95% CI)
Lesmana 2011	117	0.70 (0.60-0.80)

Table 35: Area under the ROC curve (95% CI) of TE and APRI in predicting severe fibrosis (≥F3)

Included study	N	AUC (95% CI)
Lesmana 2011	117	0.79 (0.65-0.86)

Table 36: Area under the ROC curve (95% CI) of TE and APRI in predicting cirrhosis (≥F4)

Included study	N	AUC (95% CI)
Kim 2009	130	0.85 (0.78-0.91)

Table 37: Diagnostic value of TE and APRI for fibrosis (≥F2)

Threshold	Included study	Sensitivity	Specificity	PPV	NPV	LR+	LR-
0.31	Lesmana 2011	67.1	61.4	74.2	52.9	1.74	0.54

Table 38: Diagnostic value of TE and APRI for severe fibrosis (≥F3)

Threshold	Included study	Sensitivity	Specificity	PPV	NPV	LR+	LR-
0.31	Lesmana 2011	72.4	71.6	45.7	88.7	2.55	0.39

8.3.4 Summary result findings in children with CHB infection

8.3.4.1 FibroTest

One study (Sokucu 2010) (N=25) has been included in this review, examining the diagnostic accuracy of FibroTest in prediction of liver fibrosis/cirrhosis in children with CHB. This study has a small sample size; therefore results should be interpreted with caution. It is of high risk of bias (unclear blinding of reference standard results, unclear interval between reference standard and index test). More details on quality assessment can be found in Appendix N.

Table 39: 2 x 2 contingency table for FibroTest

	Ishak score		
Fibrotest Cut off	Presence of sig. fibrosis ≥F3-6	Absence of sig. fibrosis <F0-2	Total
>0.31	0 (TP)	9 (FP)	9
<0.31	2 (FN)	14 (TN)	16
Total	2	23	25

Table 40: Diagnostic value of FibroTest in predicting fibrosis (≥F3-6) *(calculated from 2x2 table provided by the study)*

Threshold	Included study	Sensitivity	Specificity	PPV	NPV	LR+	LR-
0.31	Sokucu 2010	0	14/23*100 =60.9	0	14/16*100 = 87.5	0	100-0/60.9 =1.64

8.3.4.2 ActiTest

One study (Sokucu 2010) (N=25) has been included in this review, examining the diagnostic accuracy of ActiTest in prediction of liver fibrosis/cirrhosis in children with CHB. This study contains a small sample size; therefore results should be interpreted with caution. It is of high risk of bias (unclear blinding of reference standard results, unclear interval between reference standard and index test, small sample size). More details on quality assessment can be found in Appendix N.

Table 41: 2 x 2 contingency table for ActiTest

	Ishak score		
ActiTest Cut off	Presence of sig. activity ≥A2-4	Absence of sig. activity <A0-1	Total
>0.36	4 (TP)	0 (FP)	4
<0.36	15 (FN)	6 (TN)	21
Total	19	6	25

Table 42: Diagnostic value of ActiTest in predicting fibrosis (≥F3-6) *(calculated from 2x2 table provided by the study)*

Threshold	Included study	Sensitivity	Specificity	PPV	NPV	LR+	LR-
0.36	Sokucu 2010	4/19*100	6/6*100	4/4*10	6/21*1	0	100-

Threshold	Included study	Sensitivity	Specificity	PPV	NPV	LR+	LR-
		=21.1	= 100	0 =100	00= 28.6		21.1/100 =0.79

8.3.4.3 APRI score

One study (McGoogan 2010) (N=11) has been included in this review, examining the diagnostic accuracy of APRI score in prediction of liver fibrosis/cirrhosis in children with CHB. The study also included HCV children (N=25). Statistics such as sensitivity and specificity were based on the overall mixed group (N=36) and were not restricted to the CHB patients. Therefore, results should be interpreted with caution. The evidence was of very high risk of bias (small sample size, retrospective design and only patients with complete data were included, inappropriate interval between reference standard and index test, unclear blinding of index test and reference standard results) and was also indirect evidence (mixed population of HBV and HCV, with 69% hepatitis C). More details on quality assessment can be found in Appendix N. No data were available to calculate 2x2 tables, so sensitivity and specificity are reported without confidence intervals.

Table 43: Area under the ROC curve (95% CI) of APRI score in predicting fibrosis (F2-3)*

Included study	N	AUC (95% CI)
McGoogan 2010	11	0.64 (0.28-1.00)

**based on children with CHB only (N=11)*

Table 44: Diagnostic test accuracy of APRI for fibrosis (≥F2)*

Threshold	Included study	Sensitivity	Specificity	PPV	NPV	LR+	LR-
>0.5	McGoogan 2010	47	90	80	65	4.5	N/A
>1.5		18	100	100	58	0.6	0.8

**based on the overall study (HBV + HCV (69%); N=36)*

Table 45: Diagnostic test accuracy of APRI for cirrhosis (F4)*

Threshold	Included study	Sensitivity	Specificity	PPV	NPV	LR+	LR-
>0.5	McGoogan 2010	33	73	10	92	1.2	0.9
>1.5		0	91	0	91	0	1.1

**based on the overall study (HBV + HCV (69%); N=36)*

8.3.5 Summary of the evidence for three index tests: Fibrotest, Transient Elastography and APRI in adults with CHB infection

Two studies compared Fibrotest and Transient Elastography head to head against liver biopsy (Castera 2011, Kim 2012B); Castera 2011 was considered to be at high risk of bias and was conducted in patients who were 61% inactive carriers. The results were as follows:

– AUC (95%CI)	Kim 2012B Castera 2011	90% (95%CI 84 to 97) 71% (95%CI 58 to 85)	87% (95%CI 80 to 94) 76% (95%CI 63 to 90)
– AUC (95%CI)	Kim 2012B Castera 2011	87% (95%CI 82 to 92) 74% (95%CI 58 to 90)	91% (95%CI 87 to 95) 89% (95%CI 80 to 98)

Table 46

		Fibrotest	**Transient Elastography**
Fibrosis			
Sensitivity at standard threshold	Castera 2011	61% (95%CI 45 to 76)	68% (95%CI 52 to 81)
Specificity at standard threshold	Castera 2011	81% (95%CI 54 to 96)	63% (95%CI 35 to 85)
Cirrhosis			
Sensitivity at standard threshold	Castera 2011	47% (95%CI 21 to 73)	73% (95%CI 45 to 92)
Specificity at standard threshold	Castera 2011	91% (95%CI 79 to 98)	87% (95%CI 73 to 95)

Table 47 compares three tests across all studies reporting evidence.

Table 47: Evidence summary for different tests at different stages of fibrosis

Median and range across studies	**Fibrotest**	**Transient Elastography**	**APRI**
Fibrosis			
AUC (median (95%CI) and range across studies)	76% (73-80) R: 69 to 90% (7 studies) LOW	81% (73-86) R: 61 to 95% (8 studies) LOW	71% (63-80) Range: 63 to 86% (11 studies) LOW
Sensitivity at standard threshold	<u>0.48</u> 61% (45-76) R: 54 to 81% (5 studies) LOW	<u>7.2kPa</u> 68% (52-81) R: 62 to 74% (4 studies) MODERATE	<u>0.5</u> 82% (69-91) (7 studies) R: 61 to 97% LOW <u>1.5</u> 30% (17-45) (8 studies) R: 14 to 75% LOW
Corresponding Specificity	81% (54-96) R: 69 to 91% (5 studies)	63% (35-85) R: 63 to 88% (4 studies)	83% (75-89) (7 studies; 0.5) R:34 to 86% 88% (79-94) (8 studies; 1.5) R: 80 to 100%
Cirrhosis			
AUC	76% (67-85) R:68 to 92% (6 studies) LOW	92% (89-95) R: 76 to 98% (11 studies) MODERATE	78% (70-86) Range:61 to 84% (7 studies) LOW
Sensitivity at standard threshold	<u>0.74</u> 47% (21-73) R: 42 to 78% (4 studies) LOW	<u>11.0kPa</u> 75% (48-93) R: 73 to 100% (4 studies) LOW	<u>1.0</u> 67% (35-90); range 47 to 76% (3 studies) LOW <u>2.0</u> 41% (21-64) and 20% (10-35) (2 studies) MODERATE
Corresponding Specificity	91% (79-98) R: 89 to 97% (4 studies)	90% (85-94) R: 87 to 92% (4 studies)	81% (73-87); range 69 to 81% (3 studies; threshold 1.0) 85% (76-92%) and 84% (78-88%) (2 studies; threshold 2.0)

This is also illustrated in the ROC curves comparing tests in section G.1.1 of Appendix G. There appears to be little difference between Fibrotest, Transient Elastography and APRI for fibrosis, but for cirrhosis, the ROC curves are different, with TE appearing to be the best test and APRI the worst.

8.4 Economic evidence

Published literature

No relevant economic evaluations comparing different methods to assess severity of necro-inflammatory activity and liver fibrosis were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 48: Costs of methods to assess severity of necro-inflammatory activity and liver fibrosis

Test	Unit cost	Source
Liver biopsy (day case)	£528	NHS Reference Costs[a]
Transient elastography (FibroScan)	£250 to £300	Expert opinion
Serum fibrosis markers (FibroTest)	£150	Expert opinion
Enhanced liver fibrosis test (ELF)	£75	Expert opinion
Aspartate aminotransferase/platelet ration index (APRI)	£10	Expert opinion [b]
Magnetic resonance spectroscopy	£163	Expert opinion

(a) NHS Reference Costs 2010-2011 NHS Trusts and PCTs combined Day Cases HRG Data; GB04Z Endoscopic/Radiology category 1.

(b) Approximation based on the combined costs of AST (£5.20) and full blood count analysis (£4.50) obtained by GDG members from their business services unit.

Economic considerations

The costs and consequences of non-invasive methods of liver function testing must be considered in comparison to those associated with liver biopsy, currently considered the gold standard for evaluating liver fibrosis in people with CHB.

Liver biopsy is an invasive procedure with an associated mortality of between 0.13% and 0.33%[34]. Pain is the most common complication of liver biopsy occurring in up to 30% of people, with moderate to severe pain in 3% and 1.5% respectively. The majority of liver biopsies performed in adults in the UK are carried out as day cases using local anaesthetic and requiring the patient to rest for several hours after the procedure. Under this resource category, the cost of a liver biopsy is approximately twice that of the most effective non-invasive alternative.

The adverse events associated with liver biopsy are also worth noting. A patient with a more severe form of fibrosis or cirrhosis is more likely to have a bleed and these are also the patients that are more likely to be picked up using a non-invasive method. Therefore using non-invasive methods could reduce the risk of complications and lower costs.

Non-invasive methods are associated with a lower cost, minimal patient discomfort and no risk of mortality or morbidity. However, they are also less accurate than liver biopsy. A misdiagnosis carries a lifetime of unnecessary antiviral treatment. This results in a large cost (approximately £500,000 for a young adult) decreased quality of life and risks associated with pregnancy, however a patient is likely to be monitored and the full cost of lifetime treatment is unlikely to be incurred.

Patients will still have to be biopsied on order either to confirm in unclear scans or in patients where the scan is negative but there is clinical suspicion. It is the hope however that the less costly non-invasive tests will help to remove the need for some biopsies and thereby reduce costs and improve patient experience and outcomes.

8.5 Evidence statements

8.5.1 Clinical evidence statements

8.5.1.1 Adults with CHB infection

For the target condition of fibrosis:

- Eighteen studies reported the area under the ROC curve across the index tests of FibroTest (7 studies), transient elastography (TE; 8 studies) and APRI (11 studies), some studies compared two or more tests. There was some inconsistency across studies in the AUC for each index test. There is little difference in the median area under the ROC curve between tests, with the median ranging from 71% for APRI to 81% for FibroTest (low quality evidence).
- Sensitivity-specificity pairs for optimal thresholds, one per study, were plotted on a ROC curve and assessed visually. There was little difference between index tests, although there was some heterogeneity within tests.
- Sensitivities and specificities for 'standard thresholds' showed the median sensitivities, with the corresponding specificity for that median study to be:
    - FibroTest at 0.48 (5 studies): sensitivity 61% (95%CI 45 to 76); specificity 81% (95CI 69 to 91%) (moderate quality evidence)
    - TE 7.2kPa (4 studies): sensitivity 68% (95%CI 52 to 81); specificity 63%(95%CI 35 to 85) (moderate quality evidence
    - APRI 0.5 (7 studies): sensitivity 82% (95%CI 69 to 91); specificity 83% (95%CI 75 to 89) (low quality evidence)
- Within studies comparisons of FibroTest and TE in two studies showed very similar AUCs and sensitivities for the two index tests, with the corresponding specificities being about 20% higher in one study for FibroTest,

For cirrhosis as the target condition:

- Sixteen studies reported the area under the ROC curve across the index tests of FibroTest (6 studies), transient elastography (11 studies) and APRI (7 studies), some studies compared two or more tests. There was some inconsistency between studies within each of TE and FibroTest, but serious inconsistency for APRI. The area under the curve was larger for TE than for the other index tests: median AUC 92% (95%CI 89 to 95) for TE; 76% (95%CI 67 to 85%) for FibroTest and 78% (95%CI 70 to 86) for APRI (all low quality evidence).
    - Sensitivity-specificity pairs for optimal thresholds, one per study, were plotted on a ROC curve and assessed visually. There was a noticeable difference between index tests, in the order TE> FibroTest > APRI, although there was some heterogeneity within tests
    - Sensitivities and specificities for 'standard thresholds' showed the median sensitivities, with the corresponding specificity for that median study to be:
        - FibroTest at 0.74 (4 studies): sensitivity 47% (95%CI 21 to 73); specificity 91% (95CI 79 to 98%) (low quality evidence)
        - TE 11.0kPa (4 studies): sensitivity 75% (95%CI 48 to 93); specificity 90%(95%CI 85 to 94) (low quality evidence)
        - APRI 1.0 (3 studies): sensitivity 67% (95%CI 35 to 90); specificity 81% (95%CI 73 to 87) (low quality evidence)
    - Within studies comparisons of FibroTest and TE in two studies showed very similar AUCs in one study and 15% higher value for TE in the other study. Sensitivities for the two index tests within one study showed a 26% difference in favour of TE, with the corresponding specificities being similar.

Three studies examined transient elastography in patients with different ALT levels; one large study showed no significant difference in sensitivity or specificity between ALT levels of 1 x ULN and below versus ALT 1 to 5 x ULN, either for fibrosis or for cirrhosis. There was limited evidence from two other studies that suggested use of a higher threshold in people with higher ALT levels might be appropriate.

8.5.1.2 Children with CHB infection

- Two small studies in children showed the following results for the target condition fibrosis:
  - FibroTest – at the threshold of 0.31, sensitivity is 0% and specificity is 61%, with a PPV of 0% and a NPV of 87.5% [1 study, N=25] (very low quality evidence)
  - APRI – at the threshold of 1.5, sensitivity is 18% and specificity is 100%, with a PPV of 100% and a NPV of 58% [1 study, N=36]. However, this study is based on a mixed HBV and HCV population with less than a third of the patients have hepatitis B (very low quality evidence);
- Two small studies in children showed the following results for the target condition cirrhosis; this was very low quality evidence:
  - APRI – at the threshold of 1.5, sensitivity is 0% and specificity is 91%, with a PPV of 0% and a NPV of 91% [1 study, N=36]. However, this study is based on a mixed HBV and HCV population (n HBV=11); therefore, it should be interpreted with caution (low applicability).
- Necro-inflammatory activity:
  - ActiTest – at the threshold of 0.36, sensitivity is 21% and specificity is 100%, with a PPV of 100% and a NPV of 28.6% [1 study; N=25].

8.5.2 Economic evidence statements

- No relevant economic evaluations were identified that compared different methods to assess severity of necro-inflammatory activity and liver fibrosis.

8.6 Recommendations and links to evidence

Recommendations	**14. Ensure all healthcare professionals who refer adults for non-invasive tests for liver disease are trained to interpret the results and aware of co-factors that influence liver elasticity (for example, fatty liver caused by obesity or alcohol misuse).** **15. Discuss the accuracy, limitations and risks of the different tests for liver disease with the patient.** **16. Offer transient elastography as the initial test for liver disease in adults newly referred for assessment.** **17. Offer antiviral treatment without a liver biopsy to adults with a transient elastography score greater than or equal to 11 kPa[ii], in line with recommendation 29.**

[ii] Adults with a transient elastography score greater than or equal to 11 kPa are very likely to have cirrhosis and confirmation by liver biopsy is not needed.

	18. Consider liver biopsy to confirm the level of fibrosis in adults with a transient elastography score between 6 and 10 kPa[jj]. Offer antiviral treatment in line with recommendations 22, 23 and 27 to 29. **19. Offer liver biopsy to adults with a transient elastography score less than 6 kPa if they are younger than 30 years and have HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 IU/ml for males and greater than or equal to 19 IU/ml for females) on 2 consecutive tests conducted 3 months apart[kk]. Offer antiviral treatment in line with recommendations 22, 23 and 27 to 29.** **20. Do not offer liver biopsy to adults with a transient elastography score less than 6 kPa who have normal ALT (less than 30 IU/ml in males and less than 19 IU/ml in females) and HBV DNA less than 2000 IU/ml as they are unlikely to have advanced liver disease or need antiviral treatment (see recommendations 22, 23 and 27 to 29.)[3]** **21. Offer an annual reassessment of liver disease using transient elastography to adults who are not taking antiviral treatment.** **22. Offer antiviral treatment to adults younger than 30 years who have HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 in males and greater than or equal to 19 in females) on 2 consecutive tests conducted 3 months apart if there is evidence of necroinflammation or fibrosis on liver biopsy or a transient elastography score greater than 6kPa.** **23. Consider antiviral treatment in adults with HBV DNA greater than 2000 IU/mL and evidence of necroinflammation or fibrosis on liver biopsy.** **Children and young people** **24. Discuss the accuracy, limitations and risks of liver biopsy in determining the need for antiviral treatment with the child or young person and with parents or carers (if appropriate).** **25. Consider liver biopsy to assess liver disease and the need for antiviral treatment in children and young people with HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 IU/ml for males and greater than or equal to 19 IU/ml for females) on 2 consecutive tests conducted 3 months apart. Offer biopsy under a general anaesthetic to children who are too young to tolerate the procedure under a local anaesthetic.**
Relative values of different outcomes	• Sensitivity and specificity for pre-defined thresholds • Area under the ROC curve

[jj] The degree of fibrosis cannot be accurately predicted in adults with a transient elastography score between 6 to 10 kPa. Some people may choose to have a liver biopsy in these circumstances to confirm the extent of liver disease.

[kk] Adults with a transient elastography score greater than or equal to 11 kPa are very likely to have cirrhosis and confirmation by liver biopsy is not needed.

	• Summary ROC curves across studies for optimum thresholds The GDG considered the relative importance of having a high false negative rate and a high false positive rate. In the former case, patients missed by the test would not receive appropriate treatment and would then be at risk of developing advanced liver disease and hepatocellular carcinoma, although monitoring might pick this up. In the latter case, patients with a false positive test result would either have a biopsy or would start antiviral treatment and be monitored for effectiveness. The GDG considered it essential to avoid false negative assignment, so the sensitivity was considered more important than specificity. Measurement of sensitivity and specificity requires a threshold to be defined, but this is not always clearly defined. Therefore three approaches were taken to investigate the relative usefulness of the non-invasive tests: The area under the receiver operating characteristics (ROC) curve (AUC or AUROC) was compared across studies for each test, with median values being reported Sensitivity-specificity forest plots were produced at pre-defined thresholds and median values reported (in the absence of sufficient studies for a diagnostic meta-analysis) Sensitivity-specificity pairs at optimal thresholds or author-chosen thresholds, one per study, were plotted in ROC space and the curves compared visually.
Trade off between clinical benefits and harms	The GDG considered liver biopsy to be an imperfect gold standard. Liver biopsy is an invasive procedure and is prone to sampling errors. Considering the risk of complications and patient reluctance to undergo liver biopsy, non-invasive tests may be preferred by some patients. Liver biopsy may be avoided in some patients especially those who are classified as having minimal fibrosis (METAVIR <F2) or those with definite cirrhosis (METAVIR F4) by the non-invasive tests. Identifying advanced fibrosis and cirrhosis can reduce the risk of further complications such as hepatocellular carcinoma and liver transplantation. The evidence from 18 studies demonstrates that, for fibrosis, there is little difference between the index tests of FibroTest, transient elastography and APRI for each of the outcomes reported: AUC, summary ROC curves , and sensitivity and specificity values at standard thresholds. The median sensitivity across tests at the standard thresholds was between 61 and 82%, which means a large proportion of patients with fibrosis could potentially be missed. Corresponding specificities ranged from 63 to 83%. The evidence for cirrhosis was different: the evidence from 16 studies showed that the median AUC was much higher for TE (92% (95%CI 89 to 95)) compared with FibroTest (76% (95%CI 67 to 85%)) and APRI (78% (95%CI 70 to 86)), with no overlap of the confidence intervals. Visual inspection of the ROC curves showed TE to be a better test than FibroTest or APRI. Median sensitivities and specificities for standard thresholds showed that TE had about 26% higher sensitivity than FibroTest, for a similar specificity. This median sensitivity for TE at a threshold of 11.0 kPa was 75% (95%CI 48 to 93%) and the corresponding specificity was 90% (95%CI 85 to 94).
Economic considerations	Non-invasive imaging tests are associated with a lower cost and less patient discomfort than liver biopsy. Although non-invasive tests may be slightly less accurate than liver biopsy (and therefore associated additional costs and decreased quality of life of inappropriate antiviral treatment in a tiny minority of patients), the GDG thought on average, the use of non-invasive imaging was likely to result in lower costs and higher quality of life and was therefore likely to represent the most cost-effective use of NHS resources. Biopsies would still have to take place however and non-invasive tests will simply diagnose the more severe patients thus removing the need for biopsies

	in these patients. This will reduce costs and complications and improve patient experience. Transient elastography was shown to be the most accurate test and given the high cost of false positives and the high cost of the comparator, biopsy, it was decided that this test was likely to be a cost effective use of resources.
Quality of evidence	Generally the quality of the evidence was low, with much variability amongst studies, but not unusually so for diagnostic test accuracy studies. The majority of studies were not at high risk of bias.
Other considerations	The GDG considered the role of the non-invasive tests to be initial tests in some circumstances, but replacement tests in other cases depending on the target condition (i.e. fibrosis or cirrhosis). The GDG decided that the sensitivity and specificity of the tests for fibrosis was too low to make recommendations for that condition, but for cirrhosis, they considered that the tests could be recommended as replacement tests for liver biopsy in people positive on the test. The GDG noted that the number of people who would have a false positive result was sufficiently small and the TE test could identify 75% of those who had cirrhosis, and those people should be offered treatment. The GDG recognised that the remaining patients who are negative on TE would include a small proportion of people with cirrhosis (false negatives), people with clinically important fibrosis and those with no clinically important fibrosis or cirrhosis (true negatives) . The GDG considered it inappropriate to subject this whole group to liver biopsy because this would mean that people who did not have clinically important fibrosis would have an invasive procedure unnecessarily. They therefore sought to identify people who they were confident were very unlikely to have clinically important fibrosis and used the lowest thresholds in the research studies to guide this choice (see Appendix O.2.2). A value of 6 kPa was used in two studies for the identification of advanced fibrosis. The GDG noted that even if some people were missed, follow up would identify development of more severe fibrosis, and this would still be reversible with adequate viral suppression; this could be identified by further fibroscanning. The GDG also prespecified that people below this threshold had to have normal ALT and HBV DNA below 2000 IU/ml to make sure that these people, who would not be offered treatment, were very unlikely to have underlying fibrosis. The remaining patients who had a TE value of between 6 and 11 kPa should be managed as follows: those with elevated ALT and HBV DNA above 2000 IU/ml and were older than 30 years were considered likely to require treatment without the need for liver biopsy; those with elevated ALT and HBV DNA above 2000 IU/ml but who were younger than 30 years should be investigated further by liver biopsy and offered treatment if they had histological evidence of necro-inflammation and/or fibrosis; finally, those people who had normal ALT levels and HBV DNA below 2000 IU/ml did not fulfil the requirements for treatment and so should be monitored appropriately. It was noted that transient elastography is often difficult to perform in people with higher BMI levels, perhaps as low as 26 kg/m^2 The GDG were aware of other non-invasive tests such as the ELF test. All studies of the ELF test are on HCV patients and no studies have been identified for the HBV population. All non-invasive tests are surrogate tests that do not directly measure fibrosis. Therefore they are influenced by other factors including the level of liver inflammation and fatty infiltration. Although the evidence on the effect of ALT on test accuracy was inconsistent, the GDG noted that raised ALT levels may

due to causes other than chronic hepatitis B. The GDG anticipated that this would be part of the awareness training offered in the recommendation.

The GDG noted that there may be a subgroup of patients with raised ALT due to non-alcohol-related fatty liver disease or alcohol-related liver disease and who are also hepatitis B virus carriers; there is a risk that these patients could be treated inappropriately for hepatitis B because of the lack of contradictory evidence from a biopsy.

The GDG therefore decided to differentiate between an active CHB and an inactive CHB infection, in which the ALT elevation is due to some other chronic liver disease, by adding an HBV DNA requirement to the transient elastography recommendation for cirrhosis. In the case of active CHB, the HBV DNA will be detectable and in the inactive group the HBV DNA will be undetectable; the GDG set the threshold at the detectable/undetectable level on any one occasion, rather than at 2000 IU/ml on two consecutive occasions, because they considered it likely that the majority with high TE would have cirrhosis due to CHB, and that it was important to start people with cirrhosis on antiviral treatment as soon as possible.

The GDG considered that people with fatty-liver disease and alcohol-related liver disease superimposed on cirrhosis might be at risk of complications following liver biopsy and so did not wish to recommend a biopsy for these people. Instead they recommended fairly frequent monitoring of people with high TE levels, for example every 12-24 weeks, at the discretion of the clinician. If HBV DNA levels became detectable on any one occasion, the patient would be offered antiviral treatment.

Patients with raised ALT levels due to other factors, who had a TE score between 6 and 10 kPa, would be offered a biopsy and other causes would be distinguished.

No data are available on the use of non invasive tests in children and the GDG noted that the definitive test for children was a liver biopsy. However, their view was that not every child/young person requires a biopsy before starting treatment, particularly not children/young people that have been followed from the immune tolerant phase through to immune clearance, and in these people treatment can be initiated on the basis of continuing viraemia in the presence of abnormal ALT.

In other young people, for example those arriving as migrants from endemic regions with high viral loads and active transaminitis, it will be unclear how long they have been in an immune-reactive phase of infection and they may have advanced fibrosis. In addition, the liver biopsy may reveal other pathologies and save the need for embarking on antiviral treatment. Therefore, a liver biopsy would be an appropriate precursor to treatment for these young people.

For these reasons the biopsy recommendation for children and young people is to *consider* liver biopsy for the purpose of assessing liver disease in those who have HBV DNA levels above 2000 IU/ml and elevated ALT. It is likely that the group offered biopsy will be patients who have these levels on first presentation, but the recommendation still allows liver biopsy to be carried out for other young people with these levels at the clinician's discretion. The corresponding treatment recommendation indicates that treatment may be initiated on the basis of either evidence of fibrosis following biopsy (usually for new patients) or more simply on the basis of raised ALT in the presence of viraemia on two occasions, as a measure of disease progression (usually in existing patients). The treatment recommendation thus covers more than one type of patient. Usual practice would be for very young children to have a liver biopsy performed under a general anaesthetic.

9 Genotype testing

9.1 Introduction

There are ten genotypes of hepatitis B virus (A–J), classified as an intergroup divergence of over 8% in the complete nucleotide sequence[9,49,70]. The prevalence of each genotype varies with geographical location but also each genotype is introduced by the migration of infected people. In a study of 293 patients in the UK the most common genotype was D (42.7%), followed by C (18%), B (17%), A (14%), E (8%) and G (0.3%). HBV genotypes differed according to ethnicity with white people predominantly carrying genotypes A (46%) and D (46%), Chinese genotypes B (44%) and C (46%), black Africans genotypes A (21%) and E (43%) and Pakistani genotype D (97%)[30].

A review in 2002 summarised the observations that genotypes B and C were most prevalent in those countries where endemicity was highest; fuelled by the perinatal or vertical transmission that occurs in Asian countries [46]. Therefore HBV genotypes are thought to play an important role in the progression of HBV-related liver disease as well as the response to interferon therapy [32]. In particular, different genotypes are associated with age of HBeAg seroconversion, sustainability of remission, activity of necroinflammation and rate of hepatocellular carcinoma (HCC) development.

Genotyping is still used as a research tool in the UK and isn't currently used to guide treatment with interferon based therapies However, with such a high proportion of the CHB population carrying genotype there is a question as to whether genotyping should now be incorporated. Genotypes can serve as an epidemiological marker for the investigation of maternal transmission, familial clustering and the geographic distribution of HBV strains as well as providing important information on the prognosis and treatment outcomes of the patient. It is possible that the use of routine genotyping could help identify those who are at higher risk of liver disease progression so that IFN-based therapies can be targeted earlier [19,47].

9.2 Review question: What is the clinical and cost-effectiveness of genotypic testing in determining whether to offer antiviral treatment in people with CHB?

This review can be considered from two angles, either by conducting subgroup analyses within the intervention reviews according to genotype and looking at interactions (e.g. in comparisons of particular antivirals with placebo/other comparator), or by investigating the prognostic ability of the different genotypes for people on particular antiviral treatments in order to predict treatment response.

The protocol for the intervention review is given in the antivirals chapter and the protocol for the prognostic review is given in this chapter, with full details of both in Appendix C.

Table 49: PICO characteristics of review question

Population	Children, young people and adults with chronic hepatitis B virus infection on antiviral treatment
Prognostic factor	• Presence versus absence of particular genotypes • Different genotypes compared with each other

Outcomes	• Serum HBV DNA reduction (log copies) • Detectable HBV DNA • HBeAg loss/ seroconversion • HBsAg loss/ seroconversion • ALT normalization • Incidence of resistance • Any composite outcome including the above outcomes
Study design	• RCTs comparing antiviral treatments versus placebo/lamivudine, stratified by genotype • Prospective and retrospective cohort studies

9.3 Clinical evidence for the response of patients with CHB to antiviral treatment by genotype

For the prognostic review, we searched for prospective and retrospective cohort studies in patients on antiviral treatments to compare the response based on patients' HBV genotype. Results are presented separately for patients who are HBeAg positive and negative, and patients on different antiviral treatments. Treatments were restricted to pegylated interferons (because these were recommended first line treatments) and to lamivudine and adefovir (which were considered representative of the nucleos(t)ides).

The evidence is presented below for the following subgroups:

- Pegylated interferon α (2a and 2b) treatment
  - HBeAg positive patients
  - HBeAg negative patients
- Lamivudine treatment
  - HBeAg positive patients
  - HBeAg negative patients
- Adefovir treatment
  - HBeAg positive patients
  - HBeAg negative patients

In the antivirals intervention review, there were insufficient studies to allow between-study subgroup analyses and only one trial, Lau 2005, reported a within-trial subgroup analysis by genotype.

In the prognostics review, 40 observational studies were included. Full details of all studies are given in the evidence tables and forest plots, but in this section, only evidence from multivariable analyses is summarised; this was reported in 15 studies. See the forest plots in Appendix G, study evidence tables in Appendix E and exclusion list in Appendix L.

Generally, the study quality was acceptable in the 15 studies. One study (Hsieh 2009) reported a linear regression analysis of the continuous variable, time to resistance, and this was not considered an appropriate analysis. The GDG had pre-specified that the key covariate to be included in the multivariable analysis (alongside genotype) was ALT level and all the multivariable analyses except one (Suzuki 2003) included this. The ratio of events to covariates was more than 10 in 5 studies (Kobayashi 2006, Suzuki 2003, Westland 2003, Yuen 2004, Zheng 2008), between 5 and 10 in 5 studies (Bonino 2007, Chien 2003, Fan 2012, Janssen 2005, Sonneveld 2012,) and below 5 in 4 studies (Buti 2007, Chen 2011, Tseng 2008, Zhao 2007).

Five studies (Buti 2007, Fan 2012, Kobayashi 2006, Suzuki 2003, Westland 2003) were in a mixed HBeAg positivity population and all but one of these (Westland 2003) included HBeAg status in the multivariable model; this mixed positivity was regarded as a measure of population indirectness. Four studies had mixed interventions which were not usually accounted for in the analysis (Bonino 2007, Janssen 2005, Sonneveld 2012, Zhao 2007).

9.3.1 Patients with CHB on pegylated interferon alfa

9.3.1.1 Summary of included studies with multivariable analyses

Table 50: Summary of studies included in the review of genotype testing for patients with CHB on pegylated interferon (α-2a and α-2b)

Study	Genotypes tested	Population	Outcomes	Details of multivariable analyses
HBeAg positive				
Chen 2011 (N=88)	B versus C; also investigating precore and core promoter mutations	• HBeAg + • Patients receiving PEG IFN for 6 months;24 weeks post treatment follow up • Pre-treatment HBV DNA 41% > 108 copies/ml	• HBeAg loss at end of 24 weeks follow up (34 events) • HBeAg seroconversion after 24 weeks follow up 32 events) • composite response: HBV DNA<10^5 copies/ml + HBeAg seroconversion + normal ALT (24 weeks follow up) (25 events)	9 predictors: genotype B versus C, age, gender, ALT ≤200, T-bilirubin, HBeAg pretreatment sample: cutoff ratio ≤200, HBV DNA≤ 8 log10, T1846 mutation, A1896 mutation. Events/covariate 3.8
Janssen 2005	A versus C, A versus D, B versus C	• HBeAg + • Patients receiving PEG IF ± lamivudine for 52 weeks	• HBeAg loss (end of 26 weeks follow up) (89 events)	For sustained response at week 26 post-treatment: about 17 predictors - age, gender, weight, ethnicity (White, Asian, Other/mixed), HBV transmission (vertical, sexual/parenteral, unknown), ALT, HBV DNA, HBV genotype (A, B, C, D, other), history of cirrhosis, history of previous interferon therapy, previous lamivudine. Ratio events/covariate = 5.2
Sonneveld 2012 (based on Janssen 2005)	A versus B, C, D, investigating PC/BCP mutants	• HBeAg + • Patients receiving PEG IF ± lamivudine for 52 weeks	• response defined as serum HBeAg loss and HBV DNA level <10,000 copies per ml at the end of 26 weeks follow up (n=41 events)	7 predictors: ALT, HBV DNA, HBV genotype (A, B, C, D), age, presence of wild type (wild type virus versus non-WT (detectable PC and/or BCP mutants). . Events/covariate = 5.9
Zhao 2007	B versus C	• HBeAg + • Patients receiving PEG IFN or IFN for 24	• composite response: HBV DNA<10^5 copies/ml+HBeAg loss+normal ALT (24 weeks follow up) (29	6 predictors - age, gender, genotype (C versus B), baseline ALT level, HBV DNA (baseline) and treatment (no effect). Events/covariate 4.8

Study	Genotypes tested	Population	Outcomes	Details of multivariable analyses
		weeks	events)	
HBeAg negative				
Bonino 2007	A versus B versus C versus D	• HBeAg – • Patients receiving PEG IF ± lamivudine for 48 weeks	• composite response: ALT normalization +HBV DNA<20,000 (24 weeks follow up; 131 events)	14 predictors - age, gender, genotype (4 categories), ethnicity, body weight, HAI score, serum ALT (screening and baseline), serum HBV DNA (baseline). Ratio events/covariates 9.4
Mixed HBeAg positive and negative				
Fan 2012	B versus C; investigating IFNAR2 expression	• Mixed group of HBeAg + and - (60.6% / 73.7% positive for genotype B / C • Peg IFN for 6 months	• Composite response: ALT normalisation26 and HBV DNA loss at 24 weeks follow up (30 events)	6 predictors – IFNAR2 expression in the liver, ALT level, age, gender, HBeAg status, Genotype, HBV DNA level. Events/covariate 5.0

9.3.1.2 Findings of subgroup analysis for treatment comparisons

One study (Lau 2005) reported data by genotype, allowing a within-trial subgroup analysis to be conducted for the comparisons pegylated interferon alfa 2a plus placebo versus lamivudine and for pegylated interferon plus lamivudine versus lamivudine. The trial was not stratified by genotype before randomisation, and this subgroup analysis did not appear to be prespecified. Results for the number of patients with HBeAg seroconversion at 24 weeks are shown in Appendix G. For both comparisons, the test for subgroup differences shows no difference between genotypes (I^2=0%), including for genotype A versus non-A, but there are few patients with genotype A.

9.3.1.3 Findings of included studies with multivariable analyses

Five cohort studies reporting multivariable analyses were identified to compare the response across genotypes to pegylated interferon alfa (2a and 2b) in HBeAg positive patients with CHB (Chen 2011, Fan 2012, Janssen 2005, Sonneveld 2012 Zhao 2007). Sonneveld 2012 was a separate analysis of the Janssen 2005 data; the population in Fan 2012 were 61-73% HBeAg positive, depending on genotype.

Two studies (Janssen 2005, Zhao 2007) investigated "conventional" baseline characteristics as covariates alongside genotype in their multivariable analyses, and three investigated the independent predictive ability of genotype in the presence of (1) expression of the type 1 IFN-α receptor β subunit in the liver (Fan 2012) and (2) the presence of mutations in the precore and basal core promoter regions (Chen 2011, Sonneveld 2012). All analyses included ALT levels (which was the GDG's key confounder).

Zhao 2007 included the treatment comparison (Peg IFN versus IFN) but reported that there was no treatment effect, and so combined data from all patients

Fan 2012 did not give any numerical results, but reported that Genotype B versus C was not significant for patients (who were a mixture of HBeAg positive and negative). The other results are shown Appendix G and reported in the GRADE tables below.

Table 51: Genotype B versus C

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Genotype B	Genotype C	Relative (95% CI)	Absolute	
HBeAg loss (end of 26 weeks follow up)											
1 Janssen 2005	Cohort study	Serious risk of bias [a]	no serious inconsistency	No serious indirectness[b]	Serious[c]	Multivariable analysis	10/23 (44%)	11/39 (28%)	OR 2.20 (0.70 to 7.0)	157 more per 1000 (from 52 fewer to 439 more)	LOW
HBeAg loss+undetectable HBV DNA+ALT normal (end of 26 weeks follow up)											
2 Chen 2011 Zhao 2007	Cohort studies	Serious risk of bias [d]	No serious inconsistency	No serious indirectness [f]	No serious imprecision	Multivariable analyses	25/48 and 16/60	9/40 and 13/170	OR 7.20 (2.10 to 24.69) and 5.29 (2.18 to 12.82)	451 more per 1000 (from 154 more to 653 more) and 228 more per 1000 (from 76 more to 438 more)	MODERATE
HBeAg clearance (loss or seroconversion) at end of 24 weeks follow up											
Chen 2011	Cohort study	Serious risk of bias [e]	No serious inconsistency	No serious indirectness	No serious imprecision	Multivariable analysis	20/48	5/40	OR 4.40 (1.20 to 16.13)	261 more per 1000 (from 21 more to 572 more)	MODERATE

(a) Events/covariates 5; but downgraded 1 in combination with indirectness
(b) 48.8% of the sample had received combination treatment of pegylated interferon α-2b plus lamivudine. However, the authors reported that there was no difference in the response between the two treatment groups.
(c) The confidence interval is wide and crosses null.
(d) Chen 2011 events/covariate 3.8; Zhao 2007 events/covariate 4.8
(e) Chen 2011 events/covariate 2.8
(f) 1 of 2 studies (Zhao 2007) had 50% patients receiving IFN, but authors said there was no difference between interventions

Table 52: Genotype A versus C

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Genotype A	Genotype C	Relative (95% CI)	Absolute	
HBeAg loss (end of 26 weeks follow up)											
1 Janssen 2005	Cohort study	Serious risk of bias [(a)]	no serious inconsistency	Serious[(b)]	No serious imprecision	Multivariable analysis	42/90 (46.7%)	11/39 (28.2%)	OR 3.60 (1.40 to 8.90)	304 more per 1000 (from 73 more to 496 more)	MODERATE
HBeAg loss + HBV DNA level <10,000 copies (end of 26 weeks follow up)											
1 Sonneveld 2012	Cohort study	Serious risk of bias [(c)]	No serious inconsistency	Serious[(b, d)]	No serious imprecision	Multivariable analyses	NA	NA	OR 9.09 (1.40 to 9.26)	Not calculable	LOW

(a) Events/covariates 5; but downgraded 1 in combination with indirectness
(b) ~50% of the sample had received combination treatment of pegylated interferon α-2b plus lamivudine. However, the authors reported that there was no difference in the response between the two treatment groups.
(c) Events/covariates 5.9; but downgraded 1 in combination with indirectness
(d) HBV DNA threshold at 10,000 copies

Table 53: Genotype A versus B

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Genotype A	Genotype B	Relative (95% CI)	Absolute	
HBeAg loss + HBV DNA level <10,000 copies (end of 26 weeks follow up)											
1 Sonneveld 2012	Cohort study	Serious risk of bias [(a)]	No serious inconsistency	Serious [(b, d)]	Serious imprecision [(d)]	Multivariable analyses	NA	NA	OR 1.79 (0.45 to 7.14)	Not calculable	VERY LOW

(a) Events/covariates 5.9; but downgraded 1 in combination with indirectness of prognostic factor
(b) ~50% of the sample had received combination treatment of pegylated interferon α-2b plus lamivudine. However, the authors reported that there was no difference in the response between the two treatment groups
(c) HBV DNA threshold at 10,000 copies
(d) Wide confidence interval crossing null

Table 54: Genotype A versus D

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Genotype A	Genotype D	Relative (95% CI)	Absolute	
HBeAg loss (end of 26 weeks follow up)											
1 Janssen 2005	Cohort study	Serious risk of bias [(a)]	no serious inconsistency	Serious[(b)]	No serious imprecision	Multivariable analysis	42/90 (46.7%)	26/103 (25%)	OR 2.40 (1.30 to 4.43)	195 more per 1000 (from 53 more to 347 more)	MODERATE
HBeAg loss + HBV DNA level <10,000 copies (end of 26 weeks follow up)											
1 Sonneveld 2012	Cohort study	Serious risk of bias [(c)]	No serious inconsistency	Serious indirectness [(b and d)]	Serious imprecision [(e)]	Multivariable analyses	NA	NA	OR 2.86 (0.90 to 9.09)	Not calculable	VERY LOW

(a) Events/covariates 5; but downgraded 1 in combination with indirectness
(b) ~50% of the sample had received combination treatment of pegylated interferon α-2b plus lamivudine. However, the authors reported that there was no difference in the response between the two treatment groups
(c) Events/covariates 5.9; but downgraded 1 in combination with indirectness of prognostic factor
(d) HBV DNA threshold at 10,000 copies
(e) Wide CI crossing null

9.3.2 HBeAg negative patients with CHB on pegylated interferon treatment (α-2a and α-2b)

9.3.2.1 Findings of subgroup analysis for treatment comparisons

One study (Bonino 2007) reported data from the Marcellin 2004 RCT, by genotype, for the comparisons of pegylated interferon alfa 2a plus placebo versus lamivudine and peginterferon plus lamivudine versus lamivudine. The Marcellin trial was not stratified by genotype before randomisation, and this subgroup analysis did not appear to be prespecified. Results are shown in Appendix G. The test for subgroup differences shows no

difference between genotypes (I^2=0%), even for genotype C versus non-C (I^2=23%).

However, for the comparison peginterferon plus lamivudine versus lamivudine, there was a significant difference between genotypes the test for subgroup differences across genotypes was I^2=78% and for genotype B versus non-B was I^2=93%.

The study also investigated interactions between treatment arm and genotype for the subset of patients receiving either pegylated interferon monotherapy or lamivudine monotherapy in a multivariable logistic regression analysis (see below). There was no significant interaction (p=0.637), indicating that the rates of combined response were higher with peginterferon versus lamivudine, regardless of genotype.

On the other hand, when the multivariable analysis was restricted to the subset of patients receiving PEG interferon monotherapy and PEG interferon + lamivudine, the interaction between treatment arm and genotype was significant (p=0.027). After adjusting for age, gender, body weight, screening ALT, baseline ALT and baseline HBV DNA, the comparison of PEG interferon plus Lamivudine versus PEG interferon monotherapy gave the following results on multivariable analysis:

- In genotype B: OR 3.5 (95%CI 1.3 to 9.1); control group risk 19/43 (44%)
- In genotype D: OR 0.4 (95%CI 0.1 to 1.2); control group risk 9/55 (16%)

9.3.2.2 Findings of included studies with multivariable analyses

One follow up study (Bonino 2007) from an RCT (Marcellin, 2004) was identified to compare the response to pegylated interferon α in HBeAg negative patients with CHB. Multivariable analysis was reported for the subset of patients given peginterferon with or without lamivudine (N=294 patients; n=139 events); only one comparison of genotypes was found to be significant, C versus D; see Appendix G.

Table 55: Clinical evidence profile: Genotype C versus D treated on pegylated interferon in patients who are HBeAg negative

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Genotype A	Genotype D	Relative (95% CI)	Absolute	
HBV DNA<20,000 copies/ml+ALT normal (end of 24 weeks follow up)											

Quality assessment							No of patients		Effect		Quality
1 Bonino 2007	Cohort study	No serious risk of bias [a]	no serious inconsistency	Serious[b]	No serious imprecision	Multivariable analysis	3/11 (27%)	9/55 (16%)	OR 3.30 (1.70 to 6.41)	229 more per 1000 (from 86 more to 393 more)	MODERATE

(a) Events/covariates >10
(b) ~50% of the sample had received combination treatment of pegylated interferon α-2b plus lamivudine; HBV DNA threshold at 20,000 copies

9.3.3 Patients with CHB on lamivudine and adefovir

9.3.3.1 Summary of included studies with multivariable analyses

Table 56: Summary of studies included in the review of genotype testing for patients with CHB on lamivudine

Study	Genotypes tested	Population	• Outcomes	Details of multivariable analyses
Yuen 2004	B versus C	HBeAg +	• Virological breakthrough with resistance (43 events)	Cox regression analysis on 3 predictors: genotype (B versus C), HBV DNA levels, ALT levels on presentation. Ratio of events / covariates = 14.3. Only p-values reported for genotype (p=0.95)
Tseng 2008 (retrospective analysis)	B versus C	HBeAg +, 3.6% cirrhosis	• HBeAg seroconversion (end of treatment, 6m follow up) (29 events)	Multivariable analysis on 8 predictors: age, gender, pre-therapy ALT levels, treatment duration, additional therapy after HBeAg seroconversion, viral load and genotypes B versus C; previous lamivudine usage. Ratio of events/covariate = 3.6. Only significance level given ("no significant difference")
Suzuki 2003	B versus C	HBeAg -**, 13.2% cirrhosis 47% were HBeAg positive	• ALT normalization, undetectable HBV DNA (end of 1, 2 yrs treatment) • Resistance	For emergence of resistance during treatment, (n=60 events), 3 predictors - HBV DNA level, HBeAg (positive versus negative) and stage of hepatitis. Genotype not significant on univariate analysis
Kobayashi 2006	B versus C	HBeAg-** 53% HBeAg positive	• Resistance (208 events) • Development of breakthrough hepatitis (about 176 events)	Cox multivariable analysis for development of breakthrough hepatitis and for resistance, Predictors unclear but, for resistance, at least genotype A versus B versus C and HBeAg status. For breakthrough hepatitis, at least ALT level, cirrhosis, HBeAg status, HBV DNA, genotype
Chien 2003	B versus C	HBeAg+	• ALT normalization+undetectable HBV DNA +HBeAg seroconversion (43 events)	For sustained response during treatment, (n=43 events), 5 predictors – age, ALT level, genotype B versus C, additional treatment time after seroconversion and total treatment time Ratio events / covariates = 8.6. Patients with missing values not included
Hsieh	B versus C	Majority	• Early emergence	Multivariable linear regression

Study	Genotypes tested	Population	• Outcomes	Details of multivariable analyses
2009[(b)]		HBeAg+	lamivudine resistance (within first 12 months of treatment) • Lamivudine resistance (end of treatment)	analysis on the continuous variable, time to resistance

Table 57: Summary of studies included in the review of genotype testing for patients with CHB on adefovir

Study	Genotypes tested	Population	Outcomes	Details on multivariable analysis
Zheng 2008	B versus C	HBeAg +	• early virological response (24 weeks on treatment), (57 events) • HBeAg loss (end of 48 weeks of treatment), • HBeAg seroconversion (end of 48 weeks of treatment), • ALT normalization (end of 48 weeks of treatment)	For outcome initial virological response, 3 predictors: age, ALT levels and HBV DNA. Genotype B versus C not statistically significant on univariate analysis
Westland 2003	A, B, C,D	HBeAg +, -	• reduction in HBV DNA after 48 weeks (269 events)	Multivariable analysis included 9 predictors: age, ALT levels , HBV DNA level and genotypes A to G Ratio events: covariates > 10. HBeAg status combined and not adjusted for
Buti 2007	A versus D	Mixed group of HBeAg + and -	• virological response after 12 months (38 events), HBeAg loss	For Virological response, 10 predictors – age, BMI, duration of Lamividune therapy, baseline serum ALT levels and HBV DNA levels, gender, HBV genotype, HBeAg status, cirrhosis, treatment group (ADV monotherapy or ADV+Lam combination). Ratio of events/covariates = 3.8

9.3.4 HBeAg positive patients with CHB treated with lamivudine treatment

Five studies (Chien 2003, Kobayashi 2006, Suzuki 2003, Tseng 2008, and Yuen 2004) reported multivariable analyses of different genotypes for people receiving lamivudine treatment. Multivariable analyses were conducted for efficacy outcomes and for resistance.

Four studies reported that the effect of genotype was not significant for the following outcomes:

- HBeAg seroconversion (Tseng 2008; "no significant differences between genotypes B and C)
- Virological breakthrough with YMDD mutations (Yuen 2004; p value = 0.95 for genotype B versus C)
- Breakthrough hepatitis during treatment (Kobayashi 2006; not significant for genotype B versus C)
- Emergence of resistance (Suzuki 2003; "not significant" for genotype B versus C, although 96% of patients had genotype C)

Two other studies are reported in forest plots in appendix G and in the GRADE tables below.

Table 58: Clinical evidence profile: Genotype B versus C

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Genotype B**	**Genotype C**	**Relative (95% CI)**	**Absolute**	
Complete response (Normal ALT level + loss of HBV DNA + seroconversion to anti-HBe) at 12 months											
1 Chien 2003	Cohort study	No serious risk of bias[(a)]	no serious inconsistency	No serious indirectness	No serious imprecision	Multivariable analysis	38/62 (61.3%)	5/20 (25%)	OR 5.92 (1.61 to 21.77)	414 more per 1000 (from 88 more to 629 more)	MODERATE
Resistance – emergence of resistance during treatment											
1 Kobayashi 2006	Cohort study	No serious risk of bias	no serious inconsistency	Serious indirectness [(b)]	Serious imprecision [(c)]	Multivariable analysis	11/38 (28.9%)	185/449 (41.2%)	HR 0.81 (0.41 to 1.61)	62 fewer per 1000 (from 216 fewer to 163 more)	LOW

(a) Ratio events/covariate = 8.6.
(b) Mixed HBeAg positivity
(c) Wide confidence interval crossing null.

Table 59: Clinical evidence profile: Genotype A versus B

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Genotype A**	**Genotype B**	**Relative (95% CI)**	**Absolute**	
Resistance – emergence of resistance during treatment											
1 Kobayashi 2006	Cohort study	Serious [(a)]	no serious inconsistency	Serious indirectness [(b)]	No serious imprecision	Multivariable analysis	12/15 (80%)	11/38 (28.9%)	HR 2.78 (1.08 to 7.12)	324 more per 1000 (from 19 more to 623 more)	LOW

(a) Proportion of patients with genotype A is low (3%)
(b) Mixed HBeAg positivity

9.3.5 Patients with CHB treated with adefovir treatment

Three studies (Buti 2007, Westland 2003, Zeng 2008) reported multivariable analyses of different genotypes for people receiving adefovir treatment. The studies all showed no significant independent effect of genotype, although no details were given.

The studies reported that the effect of genotype was not significant for the following outcomes:

- Initial virological response (Zeng 2008; not statistically significant on univariate analysis between genotypes B and C in people who were HBeAg positive)
- Virological response after 48 weeks (Westland 2003; no significant differences in response amongst genotypes A to D in people with mixed HBeAg positivity)
- Virological response after 12 months (Buti 2007; no significant difference between genotypes A and D in people with mixed HBeAg positivity and with lamivudine resistance)

9.4 Economic evidence

Published literature

No relevant economic evaluations comparing genotyping testing to no genotyping testing were identified.

New cost-effectiveness analysis

This area was prioritised for new cost-effectiveness analysis.

The methods and results summary presented below are based on the drug treatment model which was adjusted to include an analysis on genotyping. The full methods and results can be found in appendix I.

Model Summary

In the model, the cost of genotyping was applied to the total cost of the most cost effective treatment to see if this impacted which treatment would be considered cost effective overall. The combined effectiveness of the two peginterferon interventions (pegIFN and pegIFN + LAM) was also included based on genotype. The odds ratios and costs are included below.

The clinical review conducted for the question on genotypes of hepatitis B showed differences in the effectiveness of pegIFN in different genotypes. For people who are HBeAg positive, the genotypes A and B produced better loss of e antigen than C and D. The odds ratios for the effectiveness of peg IFN in the various genotypes for reduction in e antigen can be found in Table 60.

Table 60: Table of odds ratios for HBeAg loss with peg IFN compared between genotypes

Odds Ratios for HBeAg loss (end of 26 weeks follow up) comparing Genotypes on peg IFN (+ve)			
Comparison of genotype	**OR**	**LCI**	**UCI**
A versus C	3.6	1.4	8.9
A versus B	1.79	0.45	7.14
A versus D	2.4	1.3	4.43
Odds Ratios for undetectable DNA (end of 26 weeks follow up) comparing Genotypes on peg IFN (-ve)			
C versus A	0.29	0.1	0.82
B versus A	0.63	0.21	1.88
D versus A	0.86	0.29	2.56

The different genotypes will be analysed for cost effectiveness and then if one treatment comes out favourable compared to the others, the costs of genotyping will be added to the overall costs to determine whether it would be cost effective to undertake the assays prior to treatment. The cost of line probe assays was estimated to be around £88 based on expert opinion. .

Results

The results of the analysis can be found in Table 61. The results show that the sequence Peg IFN (plus or minus LAM) leading to tenofovir followed by tenofovir plus lamivudine is still cost effective in all the patients who have positive HBV. In patients with genotype C and D, adding LAM to Peg IFN is cost-effective; however the ICER is very close to the £20,000 per QALY threshold and given the

high uncertainty and the resistence due to LAM, the GDG were not convinced that adding LAM would be cost-effective in reality.

In patients who are HBV negative, in genotypes A and D the most cost-effective treatment was entecavir followed by tenofovir rather than Peg IFN, however the difference in costs and QALYs was borderline. .

Table 61: Cost effectiveness of treatment strategies depending on genotype

Treatment strategy	Cost	QALY	ICER (£ per QALY vs previous strategy)
Genotype A (+ve)			
No treatment	£31,623	14.869	-
Peg IFN > TDF > TDF + LAM	£43,794	16.403	£7,934
Peg + LAM > TDF > TDF + LAM	£44,296	16.405	£25,100
Genotype B (+ve)			
No treatment	£31,623	14.869	-
Peg IFN > TDF > TDF + LAM	£43,640	16.409	£7,802
Peg + LAM > TDF > TDF + LAM	£44,136	16.411	£24,800
Genotype C (+ve)			
No treatment	£26,2284	13.871	-
Peg IFN > TDF > TDF + LAM	£41,185	15.309	£10,401
Peg + LAM > TDF > TDF + LAM	£41,736	15.312	£18,367
Genotype D (+ve)			
No treatment	£26,228	13.871	-
Peg IFN > TDF > TDF + LAM	£41,189	15.309	£10,405
Peg + LAM > TDF > TDF + LAM	£41,740	15.312	£18,367
Genotype A (-ve)			
No treatment	£49,337	12.056	-
ETV > TDF	£57,515	13.350	£6,314
Peg IFN > ETV > TDF	£57,611	13.284	Dominated
Genotype B (-ve)			
No treatment	£49,337	12.055	-
Peg IFN > ETV > TDF	£57,737	13.441	£2,416
Peg IFN > TDF > TDF + LAM	£59,245	13.444	£502,667
Genotype C (-ve)			
No treatment	£49,337	12.055	-

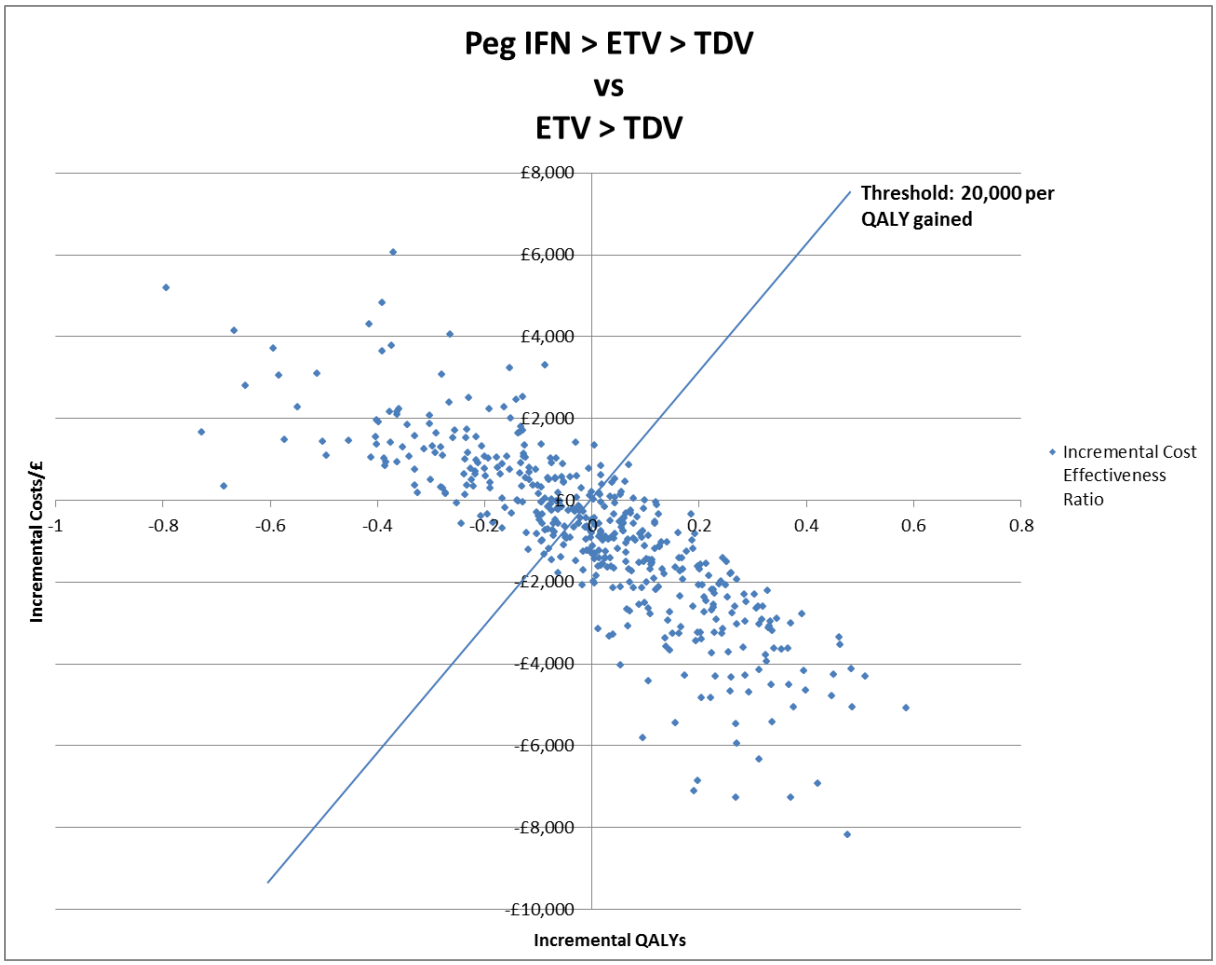
Treatment strategy	Cost	QALY	ICER (£ per QALY vs previous strategy)
Peg IFN > ETV > TDF	£57,913	13.633	£1,402
Peg IFN > TDF > TDF + LAM	£59,568	13.636	£551,667
Genotype D (-ve)			
No treatment	£49,337	12.054	
ETV > TDF	£57,515	13.349	£6,314
Peg IFN > ETV > TDF	£57,652	13.336	Dominated

In Table 62 the cost of genotyping is added to the cost effective strategy, this is to simulate the effects of genotyping to determine whether peg interferon treatment is cost effective.Results are similar to the analysis reported on Table 61. The scatter plot in Figure 5 shows that the difference in costs and effectiveness of ETV > TDF compared with Peg IFN > ETV > TDF in negative population with genotype A is marginal.. The dots in the picture represent the combination of incremental cost and incremental effectiveness in each probabilistic simulation. They are almost equally divided between the area above and the area below the £20,000 per QALY threshold.

Table 62: Adjusted costs to determine the cost effectiveness of genotyping in negative population

Treatment strategy	Adjusted total Cost	QALY	Adjusted ICER (£ per QALY vs previous strategy)
Genotype A (-ve)			
No treatment	£49,337	12.056	-
Peg IFN > ETV > TDF	£57,611	13.284	£6,738
ETV > TDF	£57,773	13.350	£2,454
Genotype B (-ve)			
No treatment	£49,337	12.055	-
Peg IFN > ETV > TDF	£57,995	13.441	£6,247
Peg IFN > TDF > TDF + LAM	£59,503	13.444	£502,667
Genotype C (-ve)			
No treatment	£49,337	12.055	-
Peg IFN > ETV > TDF	£58,171	13.633	£5,598
Peg IFN > TDF > TDF + LAM	£59,826	13.636	£551,667
Genotype D (-ve)			
No treatment	£49,337	12.054	-
Peg IFN > ETV > TDF	£57,652	13.336	£6,486
ETV > TDF	£57,773	13.349	£9,308

Figure 5: Results of Probabilistic analysis of the cost effectiveness of ETV > TDF compared with Peg IFN > ETV > TDF in negative patients with genotype A.



9.5 Evidence statements

9.5.1 Clinical evidence statements

For people who are HBeAg positive receiving pegylated interferon alfa:

- One study compared the effect of pegylated interferon alfa 2a versus lamivudine, and of peginterferon plus lamivudine versus lamivudine, on HBeAg seroconversion after 48 weeks treatment and 24 weeks follow up in a post-hoc subgroup analysis of people who had different genotypes. There was no significant difference in the relative effects across the different genotypes, or between A and non-A genotypes, but the evidence quality was low.
- Moderate and low quality evidence in two studies showed in multivariable analyses that pegylated interferon is significantly more clinically effective in people with genotype A compared with genotype C, either for HBeAg loss or for combined HBeAg loss/HBV DNA undetectable levels.
- Moderate and very low quality evidence in two studies suggested that pegylated interferon is more clinically effective in people with genotype A compared with genotype D.

- Very low quality evidence in one study showed in multivariate analysis that there is no significant difference between genotypes A and B in the effectiveness of pegylated interferon.
- Moderate quality evidence for three studies showed in multivariable analyses that pegylated interferon is significantly more clinically effective in people with genotype B compared with genotype C, either for HBeAg clearance or for combined outcomes.

In people who are HBeAg negative receiving pegylated interferon:

- One study compared the effect of pegylated interferon alfa 2a versus lamivudine, and of peginterferon plus lamivudine versus lamivudine, on the combined response (HBV DNA <20,000 and ALT normal) after 48 weeks treatment and 24 weeks follow up in a post-hoc subgroup analysis of people who had different genotypes. There was no significant difference in the relative effects across the different genotypes for the comparison of pegylated interferon versus lamivudine. However, there was a significant difference for pegylated interferon plus lamivudine versus lamivudine, with the former being more clinically effective than lamivudine for all non-B genotypes (low quality evidence), but the reverse being true for genotype B (very low quality evidence).
- Moderate quality evidence in one study showed in multivariable analysis that pegylated interferon is clinically more effective in people with genotype C compared with genotype D, for the outcome undetectable HBV DNA levels and normal ALT.
- The same study showed in multivariable analysis that the combination of pegylated interferon plus lamivudine was clinically more effective than pegylated interferon monotherapy in people with genotype B, but the reverse was true in people with genotype D.

In people who are HBeAg positive and receiving lamivudine treatment:

- Findings were mixed across studies conducting multivariable analyses comparing people with genotypes B and C: moderate quality evidence in one study showed a significantly greater combined response rate in people with genotype B, but there was no significant difference in HBeAg seroconversion in another study (very low quality). Four studies with low quality evidence suggested that virological breakthrough or emergence of resistance was not significantly different between genotypes B and C.
- Low quality evidence in one study in people with mixed HBeAg positivity suggested that people with genotype A were significantly more likely to have emerging resistance than people with genotype B, although there were few patients with genotype A.

In people treated with adefovir:

- Low quality evidence in three studies suggested there was no significant difference in virological response between people with genotype B versus C (one study) and A versus D (two studies)

9.5.2 Economic evidence statements

- The Economic evidence shows that it is unlikely that genotyping is cost effective in HBeAg positive patients however it is possible that it could be cost effective in negative patients but there is a lot of uncertainty in this result.

9.6 Recommendations and link to evidence

Recommendations	26. Do not offer genotype testing to determine initial treatment in people with chronic hepatitis B.
Relative values of different outcomes	HBeAg seroconversion HBeAg loss Undetectable HBV DNA The GDG considered HBeAg seroconverision as the most important outcome for this question. If HBeAg seroconversion is not achieved with interferon based treatment, patients are considered non-responders.
Trade off between clinical benefits and no benefits	Clinical evidence from multivariable analysis of cohort studies identifies whether genotype is an independent predictor of response to treatment. The evidence in people who are HBeAg positive suggests that genotype A may be associated with a better response to pegylated interferon treatment (as measured by undetectable HBV DNA and HBeAg loss) than genotypes C or D. One study of pegylated interferon suggested no significant difference in response between genotypes A and B. However, a post-hoc subgroup analysis by genotype of the comparison of pegylated interferon versus lamivudine showed no significant difference in effectiveness between any of the genotypes, including genotypes A versus non-A. Evidence from 3 studies suggested pegylated interferon is more effective in people with genotype B versus genotype C. In people who are HBeAg negative receiving pegylated interferon or peginterferon plus lamivudine, the treatment was significantly more effective in people with genotype C compared with genotype D. A post-hoc subgroup analysis by genotype of the comparison of pegylated interferon versus lamivudine showed no significant difference in effectiveness between any of the genotypes. However, for the comparison of peginterferon versus lamivudine versus lamivudine there appeared to be a significant reversal in the direction of effect for genotype B compared to the other genotypes. This was regarded with caution in view of small numbers and the non-randomised and post-hoc nature of the comparisons. Multivariable analysis in studies of HBeAg positive people being treated with lamivudine had mixed conclusions; there may have been a better response in people with genotype B compared with genotype C; there was no significant difference between genotypes B and C for resistance, but there may have been more resistance in genotype A compared with B. In people treated with adefovir, there were no significant differences in virological response between genotypes B versus C or A versus D.
Economic considerations	The original model on treatment modified for the question on genotype testing shows that the same treatment is likely to be cost-effective in every HBeAg positive patients, independently from their genotype. For this reason, genotype testing in HBeAg positive patients would not add any useful information to guide management and would not be cost-effective. In HBeAg negative patients, the model shows that for patients with genotype A and D the most cost-effective treatment is entecavir followed by tenofovir rather than Peg IFN; however the difference in costs and QALY between the strategies ETV > TDF and Peg IFN > ETV > TDF is marginal and very uncertain. The GDG felt that in light of this uncertainty and because genotyping is not widely available or regularly done,

	the increased investment in genotyping equipment for this indication would not be a worthwhile use of NHS resources.
Quality of evidence	Focussing on the evidence from multivariable analyses – the prognostic ability of the various genotypes in people being treated with specific interventions - the quality for this type of review was moderate to low mainly. Two studies reported the preferred analysis – investigating the comparison of the treatments for different genotype groups, however, the analysis in both instances was a post-hoc subgroup analysis, which was regarded with caution. It would have been preferable to have stratified by genotype and then randomise to treatments. No studies were found for children.
Other considerations	The GDG felt that the prevalence of genotype highly depends upon country of origin of the virus. For example, genotype B and C are more prevalent in people of Asian family origin, whereas A and D are more prevalent in people of white European origin. The GDG noted that patients receiving treatment would be monitored for effectiveness; therefore if pegylated interferon was found to be ineffective in any patient, this would be picked up. There may be additional circumstances that patients would like to find out their genotype as a source of information and genotype testing could be offered, but this is outside the scope of this guideline, which is concerned with whether genotyping could affect treatment choices. There may also be additional prognostic reasons for the clinician wishing for genotype testing to be carried out.

10 Thresholds for treatment

10.1 Introduction

Decisions regarding hepatitis B treatment are usually made based on clinical features, levels of serum ALT and HBV DNA, and when available, liver histology.

Prospective studies have provided reliable estimates of the rate of progression of HBV-related liver disease. Age, gender, alanine aminotransferase (ALT) levels, viral factors including serum HBV DNA level, HBV genotype and HBV precore/core promoter variants have been shown to influence disease progression. Quantifying serum HBV DNA levels, a key measure of the success of antiviral therapy for chronic hepatitis B, has also been revolutionised. A decade ago, non-PCR based assays with lower limit of detection (LLOD) >100,000 copies/ml (~20,000 IU/ml) were still used in many countries and PCR assays available at that time had LLOD around 1,000 copies/ml (~200 IU/ml). Real-time PCR assays with LLOD of 10-30 IU/ml are now widely used for monitoring response to antiviral therapy. In comparative studies of anti-viral potency we have used the Dakin formula [22] to correct for differences in LLOD.

The past decade has also witnessed studies questioning the definition and meaning of normal ALT level. Studies of blood donors and persons being evaluated for living liver donation found that healthy persons who test negative for hepatitis B and C and who denied regular alcohol drinking and use of potentially hepatotoxic medications, have ALT levels well below the upper limit of normal (ULN) determined by clinical diagnostic laboratories[57,84] . . Support for lowering the ULN for ALT has also derived from studies showing that CHB patients with ALT levels within the normal range defined by diagnostic laboratories, can have inflammation and fibrosis on liver biopsy[48] .

The decision to initiate antiviral therapy is clear in patients who present with life-threatening liver disease: acute liver failure, decompensated cirrhosis, and severe exacerbations of chronic hepatitis B (defined as ALT flares accompanied by jaundice and/or coagulopathy). In these patients treatment acts as a bridge to liver transplantation. Additionally, starting antiviral treatment early in advanced liver failure will prevent recurrence of HBV infection in patients who ultimately need a liver transplant. The decision to initiate antiviral therapy is also obvious in patients with compensated cirrhosis although the recommended HBV DNA cutoff levels for initiating treatment across professional society guidelines differ[25,59,63] .

In patients who have not progressed to cirrhosis, decision regarding when to start treatment is based on levels of ALT, HBV DNA and liver histology. Not all patients with CHB will have elevated ALT. In particular, during the immune tolerant phase of the disease there will be HBeAg positivity and high levels of HBV replication but normal or low levels of aminotransferases. Patients are highly infectious during this stage but will have little or no liver necroinflammation and very slow progression to fibrosis[27,61] . Only later in the course of the disease will patients enter the immune reactive HBeAg positive phase with continuing HBeAg positivity but with the immune response leading to a reduction in HBV replication at the risk of increased necroinflammation. During this phase of disease the risk of fibrosis progression will be much higher but with an associated higher predilection for HBeAg loss and seroconversion. Targeting treatment, to the correct phase of CHB disease is important to ensure that treatment is delivered when the chance of seroconversion is maximal or when the risks of progression to fibrosis are greatest during immune clearance or immune escape phase. Appropriate longitudinal follow-up is crucial in evaluating the starting point for treatment. This includes the assessment of the severity of liver disease, measurements of viral load, the incidence of co-infections with viruses such as hepatitis D, hepatitis C or HIV, and the degree of liver necroinflammation and fibrosis.

See also Chapter 7 'Assessment and referral'.

10.2 Review question: What are the thresholds (e.g. HBV DNA, ALT levels) for starting treatment after initial diagnosis and pre-therapeutic tests of CHB?

For full details see review protocol in Appendix C. The GDG's original question concerned referral to specialist services, but they later revised the question to address directly which thresholds determine when further assessment is required (e.g. through invasive or non-invasive diagnostic techniques) or when treatment should be initiated.

The review investigates several aspects of thresholds, depending on the phase of hepatitis B:

- For people who are in the immune-tolerant phase or people who are inactive carriers, ALT and HBV DNA levels are used to indicate changes in phase and the likely existence of fibrosis (i.e. diagnosis).
- For people who are in the immune active phase (HBeAg positive) or in the immune escape phase (HBeAg negative), ALT and HBV DNA levels are used to determine likely future progression of liver disease and therefore indications for treatment (i.e. prognosis)

The question can thus be considered to be about both diagnostic and prognostic predictors, but the reviewing framework is similar.

Table 63: Predictor framework of review question

Protocol	
Population	Children, young people and adults with CHB infection
Predictive factor(s)	• Thresholds of detectable HBV DNA • Thresholds of normal or abnormal ALT levels
Outcomes	Indication for management of CHB (treatment and further investigations)

The following test outcomes were considered to represent indications for management:

- Histology
  - Fibrosis on liver biopsy (F≥2 by METAVIR; or 3 or more on Knodell/Ishak)
  - Inflammation on liver biopsy (Knodell index >1
- Biological markers
  - Combination of markers indicating active disease

We note at the outset of this review that HBV DNA thresholds may be reported as copies/ml or IU/ml. The conversion factor is 1 IU/ml ≈5.3 copies/ml, but generally a threshold of 2000 IU/ml is taken to correspond to 10,000 copies/ml (or 4 log10 copies/ml).

The upper limit of normal (ULN) for ALT values is understood to mean a threshold of 40 IU/L or, more recently, 30 IU/L for males and 19 IU/L for females.

10.3 Clinical evidence

We searched for studies examining different thresholds of HBV DNA and ALT for management of CHB. Sixteen studies were identified and included in this review. The majority of the studies carried out multivariable analyses; however, some did not report covariates included in the models. Multivariable analyses allow the independent predictors to be determined and so more reliance is placed on the results from these analyses.

The evidence is reviewed separately for people in different phases of CHB, although some studies report results for a mixed population of HBeAg positive and negative.

10.3.1 Adults with CHB infection in the immune tolerance phase (HBeAg positive, ALT normal, HBV DNA levels high, liver biopsy normal)

Table 64: Summary characteristics of included studies

Study design	Patient Characteristics	Predictive factors	Outcomes
Chu 2007 Prospective N=133 Taiwan	Immune-tolerance phase HBeAg (+) patients with normal ALT levels (0-36IU/L) Majority were genotype B	• Maximal ALT levels during immune-clearance phase	Hepatitis reactivation following HBeAg seroconversion (defined as >2xULN ALT + HBV DNA >1.4x10^5 copies/ml)

10.3.1.1 Summary results

Thresholds: ALT

One prospective cohort study (Chu et al 2007) was conducted in 133 HBeAg positive patients with normal ALT (≤36IU/L) (in the immune-tolerant phase). Cox proportional hazards multivariable analysis was carried out based on variables that had p-values ≤ 0.1 on univariate analysis; there were 5 covariates and 26 events, giving a ratio of events to covariates of 5.2.
The study found that people with an ALT level above 5 x ULN during the immune-tolerance phase, in comparison with people below 2 x ULN, were significantly associated with hepatitis reactivation (defined as ALT >2xULN and HBV DNA >1.4x10^5 copies/ml) at a minimum of one year following HBeAg seroconversion (mean follow up 5.8 years (SD 4.2)) (Table 65). The category 2-5 x ULN was not significantly associated with reactivation, in comparison with <2 x ULN; there were similar numbers of patients in each category. Other significant factors on multivariable analysis were male gender, genotype B (versus C) and age at HBeAg seroconversion). The evidence was considered to be of moderate quality.

Table 65: Thresholds of ALT levels for hepatitis reactivation during immune tolerance phase at a minimum of 1 year follow up

	Multivariable analysis*▪	
Threshold of ALT during HBeAg positive (immune clearance) phase	Hazard ratio (95% CI)	P value
<2 x ULN 2-5 x ULN >5 x ULN	– 1 (referent) 2.75 (95%CI 0.89 to 8.47) 3.57 (95%CI 1.22 to 10.46)	 0.08 **0.02**

**Cox proportional hazards regression models.*

▪ *Multivariable model included gender, genotype, two ALT categories and age at HBeAg seroconversion, factors significant (p<0.1) on univariate analysis.*

10.3.2 Adults with CHB infection in the inactive carrier phase (immune control phase) (HBeAg negative, ALT normal, low HBV DNA levels, normal liver biopsy)

10.3.2.1 Summary characteristics of included studies

Table 66: Included studies in HBeAg negative patients in the inactive carrier phase

Included studies Study design	Patient characteristics	Predictive factors	Outcomes
Nakazawa 2011 Prospective N=104 Japan	HBeAg (-), HBeAb positive with normal ALT levels (<40IU/L) for at least 6 months	• ALT • HBV DNA Length of follow up: mean 6.4 years	Hepatic reactivation (defined as ≥60IU/L, or at least >1.5xULN)
Chu 2010 Retrospective N=250 Taiwan	HBeAg (-), anti-HBe (+), persistently normal ALT (≤36IU/L) at least once every 6-12mo for ≥10y	• HBV DNA (lowest limit of detection = 200copies/ml)	Active hepatitis (defined as HBsAg (+), anti-HBe (+), persistently abnormal ALT 2xULN, HBV DNA >10^4 copies/ml)
Papatheodoridis 2008A Retrospective N= 434 Greece	HBeAg (-) Inactive: persistently normal ALT and HBV DNA 2,000-20,000 IU/ml	• HBV DNA (lowest limit of detection = 400 copies/ml)	Histological indication for treatment (grade ≥7 and/or stage ≥, according to the Ishak scoring)
Lin 2007A Prospective N=414 Taiwan	HBeAg (-), anti-HBe (+), persistently normal ALT (<40 and <30IU/L for men and women) for ≥2y Majority (~78%) genotype B	• HBV DNA (lowest limit of detection = 100 copies/ml) Length of follow up: regular follow up >1 year after enrolment.	High normal ALT (0.5-1xULN)
Montazeri 2010 Prospective N=132 Iran	HBeAg (-), anti-HBe (+), persistently normal ALT (<40IU/L) for 12 mo Majority Asians	• HBV DNA (lowest limit of detection = 5.8IU/ml) • ALT Length of follow up: followed 3 months after baseline liver biopsy	Knodell scoring: Histological disease (defined as total HAI score ≥5) Significant fibrosis (defined as stage ≥2) Significant inflammation (defined as grade ≥4)

Included studies Study design	Patient characteristics	Predictive factors	Outcomes
Park 2012B Prospective N=104 Korea	HBeAg negative; inactive carriers or HBeAg negative chronic hepatitis (reactivation)	• HBV DNA a)<850 IU/ml b)>850 IU/ml • HBsAg levels a)<850 IU/ml • b)>850 IU/ml	Viral reactivation (DNA over 2000 IU/ml and/or ALT over 40 U/L)

10.3.2.2 Summary Results

Threshold: HBV DNA

One retrospective study (Chu et al 2010) was conducted in 250 asymptomatic HBeAg negative, anti-HBe positive patients with persistently normal ALT (≤36IU/L)(inactive carrier phase) to investigate predictors of the presence of active hepatitis (persistently abnormal ALT 2xULN and HBV DNA >10,000 copies/ml); 36% of the inactive carriers had HBV DNA levels above 10,000 copies/ml. A total of 75 carriers (52 men and 23 women) had persistently normal ALT levels, according to the AASLD revised criteria of ALT of ≤30IU/L in men and ≤19IU/L in women and 43% of them had HBV DNA levels >10,000 copies/ml (Table 67).

Multivariable logistic regression analysis was carried out in the subset of the population with HBV DNA levels above 10,000 copies/ml (n=90), based on variables that had p-values < 0.1 on univariate analysis; there were 4 covariates but it was unclear how many patients had active hepatitis. Other significant predictors were male gender and basal core promoter T1762/A1764.

Table 67: Thresholds of HBV DNA levels in anti-HBe positive carriers with HBV DNA >10^4 copies/ml for active infection*

N=90	Adjusted OR (95%CI)	P value
HBV DNA levels		
10^4-10^5 copies/ml	1.0	
>10^5 copies/ml	21.5 (8.4-55.4)	<0.0001

**multiple logistic regression – covariates gender, genotype C versus B, Basal core promoter.*

Another prospective study (Lin et al 2007A) was conducted in 414 HBeAg negative/anti-HBe positive carriers (majority with genotype B) who had persistently normal ALT (40IU/L for men and 30 IU/L for women) (inactive carriers) at least 2 years. Multivariable logistic regression analysis was conducted based on 8 covariates to predict the presence of high normal ALT, which was considered a surrogate marker of progression (and therefore constituting high risk of bias); there were 238 events. The results showed that the threshold of HBV DNA ≥10,000 copies/ml was significantly associated with high normal ALT (defined as 0.5-1xULN).

Table 68: Results of a multivariable analysis of HBV DNA levels with high-normal ALT (0.5-1xULN) status at follow up

	OR (95%CI)	P value

	OR (95%CI)	P value
HBV DNA level <4log10 ≥4log10	 1.0 (referent) 1.83 (1.07-3.13)	 0.027
Age < 30 years 30-39 years 40-49 years ≥ 50 years	 – 1 2.43 (95%CI 1.18 to 5.03) 4.22 (95%CI 1.99 to 8.93) 4.06 (95%CI 1.69 to 9.78)	 0.016 <0.001 0.002

**adjusted for gender, age, genotype (C versus B), precore 1896, basal core promoter 1762/1764*

Other significant predictors were: male gender and age over 30 years (**Table 68**),

Another prospective study (Montazeri et al 2010) was conducted in 132 HBeAg negative, anti-HBe positive patients (majority Asians) with persistently normal ALT (<40IU/L) (inactive carriers) for 12 months. Multivariable analysis found that the threshold of HBV DNA ≥2.9 log10 copies/ml at baseline was significantly associated with the presence of histological disease (HAI ≥5 (n=50), necroinflammation (n=53), fibrosis (n=40)) (Table 69) The threshold of 2.9 log10 IU/ml was chosen based on the observed median values of the data, and this was confirmed by analysis of the receiver operating characteristics curve (optimal value 2.94 log IU/ml). There were 3 covariates, so the ratio of events/covariates is more than 10 for each outcome.

Table 69: Thresholds of HBV DNA for identifying histological disease, based on the Knodell scoring system*

	Adjusted OR (95%CI)					
HBV DNA (log10 IU/ml)	**Total score (HAI) ≥5 (n=50, 38%)**	**P value**	**Necro inflammation (grade ≥4) (n=53, 40.2%)**	**P value**	**Fibrosis (stage≥2) (n=40, 30.3%)**	**P value**
<2.9 (4,467 copies) ≥2.9	1.0 5.43 (2.4-12.3)	 <0.0001	1.0 3.47 (1.58-7.47)	 0.02	1.0 4.23(1.81-9.85)	 <0.0001

**multivariable binary regression analysis – covariates were age (above and below 36 years), gender and HBV DNA level*

None of the other predictors were significant; age above versus below 36 years (the median) had an odds ratio of: 1.98 (95%CI 0.89 to 4.38).

The study also followed 132 patients for a median of 57 months (range 18 to 106); 61 patients had a repeat biopsy. Unadjusted odds ratios for an increase from baseline in total HAI of ≥2 were:

- Change from baseline in HBV DNA above versus below the median of 2.67 log IU/ml: OR 4.65 (95%CI 1.5 to 14.6)
- Increase from baseline of HBV DNA log score of ≥1 unit: OR 4.53 (95%CI 1.2 to 17.5).

It is noted that for this outcome the patients were selected – those who agreed to have a second biopsy.

A prospective study (Nakazawa et al 2011)in 104 asymptomatic HBeAg negative carriers with persistently normal ALT (<40IU/L) found that hepatitis reactivation (ALT ≥60IU/L or ≥1.5xULN) occurred in 13.5% of the patients (n=14) during a mean follow up time of 6.4 years. Multivariable

analysis showed that a threshold of HBV DNA ≥100,000 copies/ml was significantly related to future hepatitis reactivation, and there were 2 covariates. This was still a small number of events, so likely to be at high risk of bias.

Table 70: Thresholds of HBV DNA for future hepatitis reactivation*

	Hazard ratio (95%CI)	P value
HBV DNA (log10 copies/ml)		
<5 (n=93)	1.0	
≥5 (n=11)	3.43 (1.14-10.31)	**0.028**

** Multivariable Cox proportional hazards regression analysis – the other covariate was ALT level*

A prospective study (Park 2012B) was conducted in 104 adult treatment-naive patients with chronic HBV infection (HBsAg positive for at least 6 months); patients were HBeAg negative/anti-HBe positive, HBV genotype C, and had had normal ALT (≤40 IU/ml) and HBV viral loads <2000 IU/ml for at least 12 months. The study examined the association between HBV DNA levels and reactivation of HBV replication (defined as DNA >2000 IU/ml and ALT > 40 IU/L). At the end of follow up (median 39 (range 36-42) months), there were 31 people with HBeAg negative chronic hepatitis (reactivation) whose HBV DNA or ALT levels had ever exceeded the previous standards.
On multivariable analysis, HBV DNA (>850 IU/ml versus <850) had an OR of 14.90 (95% CI 5.00 to 44.41), p<0.001; there were 31 events. HBsAg (log $_{10}$ IU/ml) was also a significant predictor. The quality of the study was rated as at moderate risk of bias.

Table 71: Thresholds of HBV DNA for future hepatitis reactivation*

	Odds ratio (95%CI)	P value
HBV DNA (log10 copies/ml)		
<850 IU/ml (n=73)	1.0	
≥ 850 IU/ml (n=31)	14.90 (95% CI 5.00 to 44.41)	**0.01**

** Multivariable logistic regression analysis*

Threshold: ALT

One prospective study (Montazeri et al 2010) in 132 HBeAg negative, anti-HBe positive patients with persistently normal ALT (<40IU/L) for 12 months (in inactive carrier phase) only reported univariate analyses: the threshold of ALT levels at 23 IU/l at baseline was not significantly associated with either type of histological disease progression (HAI>=5, necroinflammation, fibrosis) at baseline. The threshold of 23 IU/ml was selected based on the observed median values of the data.

A prospective study (Nakazawa et al 2011) of 104 asymptomatic HBeAg negative carriers with persistently normal ALT (<40IU/L) (in inactive carrier phase) examined the association between high normal ALT versus low normal ALT and future hepatitis reactivation (ALT ≥60IU/L or ≥1.5xULN). During a mean follow up time of 6.4 years, hepatitis reactivation occurred in 13.5% of the patients (n=14). Multivariable analysis showed that the threshold of ALT level at 21-40IU/ml could significantly identify patients who experienced quicker future hepatitis reactivation (Table 72). The small number of events is likely to put the study at higher risk of bias, but the use of a time dependent analysis is good.

Table 72: Thresholds of ALT for future hepatitis reactivation*

	Hazard ratio (95%CI)	P value

	Hazard ratio (95%CI)	P value
ALT (IU/L)		
≤20 (n=60)	1.0	
21-40 (n=44)	18.43 (95%CI 2.38 to 142.7)	<0.005

** Multivariable Cox proportional hazards regression analysis – covariates are HBV DNA and ALT*

10.3.3 Adults with CHB infection in the immune active phase (HBeAg positive, ALT elevated or fluctuating, HBV DNA levels moderate, liver biopsy – active inflammation)

10.3.3.1 Summary characteristics of included studies

Table 73: Included studies in HBeAg positive patients

Study design	Population	Predictive factors	Outcomes
Lai 2007 Retrospective N=193 USA	HBeAg (+), with HBV DNA >10,000 copies/ml	• ALT levels: a) Persistently normal (<40IU/L) b)1-1.5xULN c)>1.5xULN Further subgroups: Low normal (0-25IU/L) High normal (26-40IU/L)	Fibrosis (defined as stage 2-4 by METAVIR) Significant inflammation (defined as grade 2-3)
Kumar 2008 Prospective N=1387 India	HBeAg (+) >50% genotype D	• ALT levels a) persistently normal (≤40IU/L) b) Persistently elevated ALT (>40IU/L) c) Intermittently elevated ALT (>40IU/L)	Significant fibrosis (defined as F≥2)/ inflammation (Knodell index)

10.3.3.2 Summary results

Threshold ALT

A retrospective cross-sectional study (Lai et al 2007) was conducted in 110 HBeAg positive patients (and 82 HBeAg negative patients) with HBV DNA ≥10,000 copies/ml. Stratified multivariable analysis for the HBeAg positive patients was based on variables that were significant on univariate analysis; there were 4 covariates but the number of events was unclear in this population.
Patients were divided into 3 ALT groups: persistently normal (< 1 x ULN), ALT 1 to 1.5 x ULN and ALT > 1.5 ULN.
The analysis showed that higher ALT levels were significantly associated with a diagnosis of both significant fibrosis (METAVIR ≥F2) and inflammation (METAVIR grade 2-3) (Table 74). The study stated that the predictive factor was 'increasing ALT' or 'moving from one ALT category to the next' which suggests it may be a continuous variable, but this was not clear.

Table 74: Thresholds of ALT levels for identifying significant fibrosis and inflammation (Lai et al 2007)*

	Significant fibrosis	Multivariable OR (95% CI)	P values
ALT group	Increase in ALT group	1.77 (95%CI 1.02 to 3.07)	**0.04**
	Significant inflammation		
ALT group	Increase in ALT group	1.89 (95%CI 1.08 to 3.29)	**0.026**

**Multivariable logistic regression model adjusted for age, grade of inflammation, ALT group and alcohol intake*
The study appeared to be a retrospective cross-sectional study, i.e. predicting current liver disease. The population was from chart records of patients who had HBV DNA > 10,000 copies/ml. It was considered to be at high risk of bias.
Other significant predictors were: grade of fibrosis / stage of inflammation and age: OR 1.07 (95%CI 1.01 to 1.14) per year.

A prospective cohort study (Kumar et al 2008) included 603 asymptomatic HBeAg positive patients who had been followed for at least 1 year. Patients were divided into 3 categories: those who had persistently normal ALT levels (at least 3 ALT values ≤40IU/L in the previous year and normal at the last follow up); those with intermittently elevated ALT (at least 3 ALT values >40 IU/L at any time during the previous year) and persistently elevated ALT (at least 3 ALT values > 40IU/L during the previous year and elevated at the last follow up or on starting treatment. Categorisation was also carried out using updated criteria: threshold of 30 IU/L for males and 19 IU/L for females. The study investigated the effect of ALT group on the diagnosis of fibrosis.

- 39.7% of those with persistently normal ALT had fibrosis stage ≥2;
- 65.1% of those with persistently or intermittently elevated ALT (>40IU/L) had fibrosis stage ≥2.

Table 75: Distribution of fibrosis stages in persistently normal and persistently/intermittently elevated ALT levels

HBeAg (+)	F≥2 (n=360)	F<2	P value
Persistently/intermittently elevated ALT (>40IU/L) (n=508)	331 (65.1%)	177 (34.9%)	
Persistently normal ALT (<40 IU/L) (n=73)	29 (39.7%)	44 (60.3%)	≤0.001

This gives an unadjusted odds ratio of 2.84 (95%CI 1.72 to 4.69) for the prediction of fibrosis in people with persistently or intermittently elevated ALT versus persistently normal ALT for a risk of 40% in people with persistently normal ALT levels

Multivariable logistic regression was reported for people who were HBeAg positive and negative, based on 5 factors significant on univariate analysis and there were 360/603 patients with fibrosis levels of F2 and above. Further details are given in section 10.3.5.

10.3.4 Adults with CHB infection in the immune escape phase (HBeAg negative, ALT elevated or fluctuating, HBV DNA levels moderate, liver biopsy – active inflammation)

10.3.4.1 Summary characteristics of included studies

Study design	Patient characteristics	Predictive factors	Outcomes
Papatheodoridis 2008A Retrospective N= 434 Greece	HBeAg (-) Active: elevated ALT and detectable HBV DNA	• HBV DNA (lowest limit of detection = 400 copies/ml)	Histological indication for treatment (grade ≥7 and/or stage ≥, according to the Ishak scoring)
Lai 2007 Retrospective N=193 USA	HBeAg (-), with HBV DNA >10,000 copies/ml	• ALT levels a) Persistently normal (<40IU/L) b) 1-1.5xULN c) >1.5xULN Further subgroups: Low normal (0-25IU/L) High normal (26-40IU/L)	Significant fibrosis (stage 2-4 by METAVIR) Significant inflammation (grade 2-3)
Kumar 2008 Prospective N= 1387 India	HBeAg (-) >50% genotype D	• ALT a) persistently normal (≤40IU/L) b) Persistently/ intermittently elevated ALT (>40IU/L) Length of follow up: • ≥1 year	Significant fibrosis (defined as F≥2)/ inflammation (Knodell index)
Lee 2011 Retrospective N=136 Taiwan	HBeAg (-)	• HBV DNA >20,000 IU/ml • HBV DNA >1,000,000 IU/ml • ALT >80 IU/L	Significant fibrosis (defined as ≥2 on Ishak scoring system) Significant inflammation (Ishak grade ≥7)

10.3.4.2 Summary results

Thresholds: HBV DNA

A retrospective study (Papatheodoridis et al 2008A) was conducted in 399 treatment naïve HBeAg negative patients with detectable HBV DNA and elevated ALT (on at least 2 occasions) and investigated the predictive ability of HBV DNA levels for determining histological indication for treatment (defined as Ishak grading ≥7 and/or stage ≥2 by liver biopsy). 333/399 patients showed histological indication for treatment and the proportion was lowest in those with HBV DNA <2,000 IU/ml (10.5%). Multivariable logistic regression analysis based on at least 3 covariates, indicated that the threshold of HBV DNA of 200,000IU/ml was found to be significantly associated with histological indication for treatment compared with <2000 IU/ml; however, the thresholds of 2000 to 20,000 and 20,000 to 200,000 were not significantly associated (Table 76).

Table 76: Thresholds of HBV DNA levels for histological indication for treatment (Ishak grading score ≥7 and/or stage ≥2)*

	Frequency, (%) (N=399)	Adjusted OR(95%CI)	P value
HBV DNA (IU/ml)			Trend <0.001
80-<2,000	42 (10.5)	1 (referent)	
2,000 to <20,000	63 (15.8)	1.6 (95%CI 0.6 to 4.2)	0.30
20,000 to <200,000	91 (22.8)	2.2 (95%CI 0.9 to 5.4)	0.098
>200,000	203 (50.9)	4.9 (95%CI 2.0 to 11.6)	<0.001
Abnormal ALT on the day of biopsy(>40 IU/L)		2.1 (95%CI 1.1 to 4.2)	0.037
Age, years			Trend <0.001
<30		– 1 (referent)	
30 to 44		2.9 (95%CI 1.3 to 6.4)	0.008
45 to59		10.5 (95%CI 4.3 to 25.8)	<0.001
≥ 60 years		20.5 (95%CI 6.6 to 63.4)	<0.001

**multivariable logistic regression – covariates included age and higher ALT levels..*

Other significant factors were abnormal ALT on the day of liver biopsy and age (see table).

Subgroup of patients with persistently normal ALT

In an additional group of 35 treatment naïve HBeAg negative patients with detectable HBV DNA (2,000-20,000 IU/ml) and persistently normal ALT, it was found that 82.9% (29/35) of those with HBV DNA 2,000-20,000IU/ml showed histological indication for treatment (Ishak grading ≥7 and/or stage ≥2 by liver biopsy).

Table 77: Distribution of fibrosis according to HBV DNA level among a subgroup of patients with persistently normal ALT based on the 40IU/L cut off and the updated cut off criteria

HBeAg (-)	HBV DNA <5 log copies		HBV DNA <4 log copies	
	<40IU/L (n=75)	M: <30IU/L F: <19IU/L (n=27)	<40IU/L (n=52)	M: <30IU/L F: <19IU/L (n=19)
n with liver biopsy	29 (38.7%)	12 (44.5%)	9 (17.3%)	4 (21%)
Any fibrosis, n (%)	15 (51.7)	8 (66.7)	6 (66.7)	2 (50)
Inactive liver disease (HAI <3 and fibrosis stage ≤1), n (%)	23 (79.3)	9 (75)	7 (77.8)	3 (75)
Active liver disease (HAI ≥3 and fibrosis stage ≥2), n (%)	6 (20.7)	3 (25)	2 (22.2)	1 (25)

A retrospective study (Lee 2011) of 136 treatment-naive patients with chronic HBV infection (HBsAg positive), who were negative for HBeAg for at least 6 months and had elevated serum ALT (≥40U/L, 1 x ULN) recorded at least 1 month apart and HBV DNA >2000 IU/ml found a significant relationship between raised HBV DNA levels and both hepatic fibrosis (defined as ≥2 on Ishak scoring system; cut off >20,000 IU/ml) and hepatic necro-inflammation (Ishak grade ≥7; cut off $>10^9$ IU/ml) in

multivariable analysis. Raised ALT (>80U/L) was also associated with necro-inflammation in multivariable analysis. The study is of moderate quality (retrospective; appropriate multivariable analysis).

Table 78: Thresholds of HBV DNA levels for identifying significant fibrosis and inflammation (Lee 2011)*

	Significant fibrosis	Multivariable OR (95% CI)	P values
HBV DNA level	>20,000 versus ≤ 20,000 IU/ml	4.60 (95%CI 1.39 to 15.17)	**0.012**
	Significant inflammation		
HBV DNA level	> 10^9 versus ≤10^9 IU/ml	3.21 (95%CI 1.26 to 8.17)	**0.014**
ALT level	>80 IU/L versus < 80 IU/L	9.92 (95%CI 1.21 to 81.63)	**0.033**

**Multivariable logistic regression model adjusted for BMI, AST and platelets.*

Thresholds: ALT

A prospective study (Kumar et al 2008) was conducted in 784 asymptomatic HBeAg negative patients (majority were genotype D) with a follow up time of at least 1 year. Patients were divided into 3 categories: those who had persistently normal ALT levels (at least 3 ALT values ≤40IU/L in the previous year and normal at the last follow up); those with intermittently elevated ALT (at least 3 ALT values >40 IU/L at any time during the previous year) and persistently elevated ALT (at least 3 ALT values > 40IU/L during the previous year and elevated at the last follow up or on starting treatment. Categorisation was also carried out using updated criteria: threshold of 30 IU/L for males and 19 IU/L for females. The study investigated the effect of ALT group on the diagnosis of fibrosis.

- 13.8% of those with persistently normal ALT had fibrosis stage ≥2;
- 19.2% of those with persistently normal ALT, defined by the updated cut off criteria (M: 30IU/L; F: 19IU/L) (N=26), had fibrosis stage ≥2;
- 63.9% of those with persistently or intermittently elevated ALT (>40IU/L) had fibrosis stage ≥2.

Table 79: Distribution of fibrosis stages according to different ALT groups, based on the 40IU/L cut off

HBeAg (-)	F≥2	F<2	P value
Persistently/ intermittently elevated ALT (>40 IU/L) (n=634)	405 (63.9)	229 (36.1)	
Persistently normal ALT (<40 IU/L) (n=58)	8 (13.8)	50 (86.2)	**<0.001**

This gives an unadjusted odds ratio of 11.05 (95%CI 5.15 to 23.72), risk for normal ALT levels = 14% (8/58). It is noted that 34 (5%) liver biopsy specimens were not available for the persistently elevated group, but half were missing (58) in the persistently normal group. This puts this analysis at high risk of bias.
Multivariable logistic regression was reported for people who were HBeAg positive and negative, based on 5 factors significant on univariate analysis and there were 360/603 patients with fibrosis levels of F2 and above. Further details are given in section 10.3.5.

A retrospective cross-sectional study (Lai et al 2007) was conducted in 110 HBeAg positive patients (and 82 HBeAg negative patients) with HBV DNA ≥10,000 copies/ml. Stratified multivariable analysis for the HBeAg negative patients was based on variables that were significant on univariate analysis; there were 4 covariates but the number of events was unclear in this population.

Patients were divided into 3 ALT groups: persistently normal (< 1 x ULN), ALT 1 to 1.5 x ULN and ALT > 1.5 ULN. The analysis showed that higher ALT levels were not significantly associated with a diagnosis of either significant fibrosis (METAVIR ≥F2) or inflammation (METAVIR grade 2-3) but no data were given.
The study appeared to be a retrospective cross-sectional study, i.e. predicting current liver disease. The population was from chart records of patients who had HBV DNA > 10,000 copies/ml. It was considered to be at high risk of bias.

10.3.5 Summary characteristics of included studies in mixed HBeAg adults with CHB infection,

Table 80: Included studies in mixed HBeAg patients

Study design	Patient characteristics	Predictive factors	Outcomes
Chen 2010B Retrospective N=228 China	Mixed HBeAg status	• ALT a)Normal ALT (≤1xULN) b)Slightly elevated ALT (>1xULN but <2xULN) • HBV DNA a)<100,000 copies/ml b)≥100,000 copies/ml	Scheuer scoring: Significant fibrosis (defined as stage ≥2) Significant inflammation (defined as grade ≥2)
Lai 2007 Retrospective N=193 USA	Mixed HBeAg status, HBV DNA >10,000 copies/ml	• ALT levels a) Persistently normal (<40IU/L) b) 1-1.5xULN c) >1.5xULN Further subgroups: Low normal (0-25IU/L) High normal (26-40IU/L)	Significant fibrosis (defined as stage 2-4 by METAVIR) Significant inflammation (defined as grade 2-3)
Kumar 2008 Prospective N=1387 India	Mixed HBeAg status >50% genotype D	• ALT a) persistently normal (≤40IU/L) b) Persistently/ intermittently elevated ALT (>40IU/L) Length of follow up: ≥1 year	Significant fibrosis (defined as F≥2)/ inflammation (Knodell index)
Seo 2005 Retrospective N=64 Japan	Mixed HBeAg status	• HBV DNA Various cut-off levels	Classification as inactive carrier or reactivation phase
Malik 2011 Cross-sectional N=140 UK	Mixed HBeAg status	• Viral load: HBV DNA level >6 log	Significant fibrosis (modified Ishak scoring system: 0-2 defined as mild disease, 3-4 moderate disease, 5-6 severe disease)

Study design	Patient characteristics	Predictive factors	Outcomes
Göbel 2011 Retrospective N=253 Germany	Mixed HBeAg status	• ALT (normal; 1-2 x ULN; > 2 x ULN)	Significant fibrosis (Desmet/Scheuer score ≥F2) Significant inflammation (grade ≥G2)
Zheng 2012 Cross-sectional N=13637 people without risk factors for liver disease (derivation cohort for new definition of ULN ALT. Same 13637 people plus 3523 people with chronic hepatitis B plus 5598 with non-alcoholic fatty liver disease (NAFLD)	Mixed HBeAg status	Defining the new upper limit of normal in the group (n=13637) without risk factors for liver disease: 95th percentile of ALT 35.2 IU/L in men and 23.4 IU/L in women. These values used as the new upper limits of normal in the next part of the study.	Prediction of chronic hepatitis B status (diagnosis of CHB known at same time as biochemistry)

10.3.6 Summary result findings in adults with mixed HBeAg positivity with CHB infection

10.3.6.1 Thresholds: HBV DNA

One retrospective study (Chen 2010B) was conducted in 228 HBsAg mixed positivity patients (104 HBeAg positive and 124 HBeAg negative) who had ALT levels below 2 x ULN to examine the effect of HBV DNA thresholds for predicting the presence of fibrosis (stage ≥ 2, by Scheuer scoring) and inflammation (grade ≥2). Multivariable analysis across all patients included HBeAg status as a variable, alongside 6 other covariates; there were 112 events; 51.4% and 47% of patients with baseline HBV DNA below 100,000 copies/ml and above 100,000 copies/ml had significant fibrosis (stage ≥2) (Scheuer scoring), respectively. The threshold of 100,000 copies/ml was not a significant predictor in multivariable analysis. The study was considered to be at high risk of bias.

Table 81: Significant fibrosis or inflammation according to HBV DNA levels*

	Significant fibrosis	Multivariable OR (95% CI)	P values
HBV DNA	<100,000 copies/ml (n=56) >100,000 copies/ml (n=56)	1 1.03 (95%CI 0.48 to 2.23)	**0.936**
	Significant inflammation		
HBV DNA	<100,000 copies/ml (n=46) >100,000 copies/ml (n=37)	0.73 (95%CI 0.36 to 1.52)	**0.405**

**Multivariable logistic regression model adjusted for ALT, age, HBeAg positivity, hepatitis B positive family history, inflammation grade*

Significant predictors for fibrosis were age (which was possibly categorical or above and below 30 years), a positive family history of HBV and inflammation grade.

A prospective study (Kumar et al 2008) of 1387 asymptomatic patients (majority were genotype D) with a follow up time of at least 1 year found that a baseline HBV DNA of ≥10,000 copies/ml was significantly associated with significant fibrosis (Knodell scoring). Patients were divided into 3 categories: those who had persistently normal ALT levels (at least 3 ALT values ≤40IU/L in the previous year and normal at the last follow up); those with intermittently elevated ALT (at least 3 ALT values >40 IU/L at any time during the previous year) and persistently elevated ALT (at least 3 ALT values > 40IU/L during the previous year and elevated at the last follow up or on starting treatment. Categorisation was also carried out using updated criteria: threshold of 30 IU/L for males and 19 IU/L for females. The study investigated the effect of ALT group on the diagnosis of fibrosis.

Multivariable logistic regression was reported for people who were HBeAg positive and negative, based on 5 factors significant on univariate analysis; 773 patients had significant fibrosis. This outcome was considered to be at low risk of bias.

Table 82: Results of a multivariable analysis of HBV DNA levels for identifying significant fibrosis

Significant fibrosis (F≥2)	Adjusted OR (95% CI)	P values
Baseline HBV DNA		
<10,000 copies	1.0	
≥10,000 copies	1.86 (95%CI 1.18 to 2.92)	0.007
Age / years		
< 30	1	
30-39	0.93 (95%CI 0.70 to 1.25)	0.640
40-49	1.13 (95%CI 0.82 to 1.57)	0.447
≥ 50	1.66 (95%CI 1.13 to 2.45)	0.010

**multiple logistic regression – covariates are not stated explicitly by the study, but significant results were reported for three age categories and ALT status, as well as HBV DNA level.*
The results for age are also included in the table.

A retrospective study (Seo et al 2005) of 64 patients who were followed for a mean of 51.5 months (range 5-157 months) found that a cut off score of 5 log copies/ml (10^5 copies/ml) was differentiated between the inactive carrier phase of the disease and the reactivation phase (especially if patients were tested twice with an interval of 4 months). There was no multivariable analysis.

A cross-sectional study (Malik et al 2011) of 140 adult treatment-naive patients with chronic HBV infection (HBsAg positive for more than 6 months) examined whether viral load (HBV DNA level >6 log) was associated with moderate/severe liver fibrosis (defined by a modified Ishak scoring system: 0-2 defined as mild disease, 3-4 moderate disease, 5-6 severe disease) in a multivariable logistic regression analysis, which was based on factors that were significant on univariate analysis. There were six covariates and 70 events across both HBeAg positive and negative patients; there were 74 patients with HBV DNA levels above 6 log10 copies and all the HBeAg positive patients were above this level. The study reported that HBV DNA at a threshold of 6 log10 copies was not significant, but did not give any odds ratios.

A retrospective study (Göbel et al 2011) of 253 adult treatment-naive patients with chronic HBV infection (HBsAg + for >6 months) found that ALT level was associated with significant fibrosis (Desmet/Scheuer score ≥F2; p= 0.02) and significant inflammation (grade ≥G2; p= 0.002) but multivariable analyses were not done for these outcomes.

A cross-sectional study (Zheng et al 2012) of 13,637 people without risk factors for liver disease was used to derive a new definition of the ULN for ALT. The same 13637 people plus 3523 people with chronic hepatitis B plus 5598 with non-alcoholic fatty liver disease (NAFLD) were used to predict chronic hepatitis B status or NAFLD (separately). Using the newly defined cut off values (35.2 IU/L in men and 23.4 IU/L in women), sensitivity (95% CI) was 39.35 (37.0-41.7) in men (compared with 15.84 (14.2-17.7) using the old cut off values) and 35.27 (32.6-38.0) in women (compared with 6.61 (5.3-8.2) using the old cut off values); specificity was 94.84 (94.2-95.4) in men (compared with 98.68 (98.3-99.0) using the old cut off values) and 94.61 (94.1-95.1) in women (compared with 99.39 (99.2-99.5) using the old cut off values). There was no multivariable analysis and the same normal cohort was used for derivation of the new cut off score and testing of these cut offs against a population including patients with chronic hepatitis B).

10.3.6.2 Thresholds: ALT

One retrospective study (Lai 2007) was conducted in 192 patients (with about 50% HBeAg positive) with HBV DNA ≥10,000 copies/ml and persistently normal ALT (<40IU/L) (inactive carriers); 18% of patients in the normal ALT group had significant fibrosis (≥2). 62% and 78% of patients with >1.5xULN (N=107) had significant fibrosis and necro-inflammation, respectively (Table 25).

When the normal ALT group was further categorised as low normal (0-25IU/L) (n=20) and high normal (26-40IU/L) (n=39), 5% of patients with low normal ALT had significant fibrosis, compared to 25% with high normal ALT (Table 26).

ALT groups were stratified into subgroups: <1x, >1x, >1.5x, >2x, >3x and >5x ULN; and the distribution of stage and grade was not significantly different between the groups.

Table 83: Distribution of fibrosis or grade of necro-inflammation according to different ALT thresholds (Lai et al 2007)

	Significant fibrosis (F2-4)	Significant inflammation (A2-3)
Normal ALT levels	18%	34%
1-1.5xULN	34%	54%
>1.5xULN	62%	78%

Table 84: Distribution of fibrosis or grade of necro-inflammation stratified by normal ALT subgroups (Lai et al 2007)

	Significant fibrosis (F2-4)	Significant inflammation (A2-3)
Low normal ALT group(0-25 IU/l)	5%	20%
High normal ALT group (26-40 IU/L)	25%	41%

A retrospective study (Chen 2010B) of 228 HBsAg positive patients (104 HBeAg positive and 124 HBeAg negative) found that 33% and 41% of patients with normal (≤1xULN) and mildly elevated ALT levels (>1-<2xULN) had significant fibrosis (stage ≥2) (Scheuer scoring) respectively (Table 85). The definition of ULN used in this study was not specified and there was inadequate information on patients' characteristics.

Table 85: Distribution of fibrosis or grade of inflammation according to different ALT thresholds

	Significant fibrosis (stage ≥2)	Significant inflammation (grade ≥2)
Normal ALT (≤1xULN) (n=141)	47 (33.3%)	67 (47.5%)
Slightly elevated ALT (>1xULN but <2xULN) (n=187)	77 (41.4%)	97 (51.7%)

A prospective study (Kumar et al 2008) of 1387 asymptomatic patients (majority were genotype D) with a follow up time of at least 1 year found that persistently or intermittently elevated ALT >40IU/L was significantly associated with significant fibrosis (Knodell scoring).

Table 86: Thresholds of ALT for significant fibrosis *

Sig. fibrosis (F≥2)	Adjusted OR (95% CI)	P value
ALT group		
<40IU/L persistently normal	1.0	
>40IU/L persistently/ intermittently elevated	4.3 (95%CI 2.87 to 6.45)	<0.001

**multiple logistic regression – covariates are not stated explicitly by the study, but significant results were reported for three age categories, ALT status and HBV DNA level.*

Predictive factor: HBV DNA levels

A retrospective study (Arai 2012) of 423 HBsAg carriers (treatment naïve) (240 HBeAg negative and 183 HBeAg positive) investigated baseline measurements of serum HBV DNA in predicting future HBsAg seroclearance, defined as HBsAg level <0.03IU/ml. Multivariable Cox proportional hazards analysis based on at least 4 covariates for 25 events, suggested that HBV DNA at baseline (with a threshold of 5 log10 copies/ml) was not a predictor for future HBsAg seroclearance (average follow up of 6 years).

Table 87: Cox regression analysis – predictive models for HBsAg future spontaneous seroclearance

	Multivariable analysis*▪	
Predictive factors (at baseline)	Hazard ratio (95% CI)	P value
HBV DNA		
>5 log10 copies/ml	1.0	
< 5 log10 copies/ml	0.94 (0.66-1.35)	NS

*covariates in multivariable analysis included age (not significant and not defined), HBeAg positivity status and HBsAg level.

10.3.7 Summary result findings in children with CHB infection

No relevant studies have been identified.

10.4 Summary table of evidence

The evidence is summarised here for the multivariable analyses only, unless unadjusted analyses provide the only comparative data. Evidence is provided for thresholds for HBV DNA levels and ALT levels; and age dependence is reported where this was available.

Table 88: Summary table of evidence

	HBV DNA and ALT thresholds
HBeAg positive Immune-tolerance phase	**ALT >5 x ULN (36IU/L)** – future hepatitis reactivation • HR 3.57 (95%CI 1.22 to 10.46) for ALT > 5 ULN versus <2 ULN • HR 2.75 (95%CI 0.89 to 8.47) for ALT 2-5 ULN versus <2ULN In multivariable analyses for the prediction of reactivation following seroconversion; moderate quality evidence. [Age at HBeAg seroconversion: ≥ 40 years versus < 40 years: HR 4.40 (95%CI 1.69 to 11.36)]
HBeAg negative Inactive carriers	**HBV DNA for predicting future active CHB (all had multivariable analyses):** • >10^5 copies/ml versus 10^4-10^5 copies/ml for predicting active CHB (persistently abnormal ALT 2xULN and HBV DNA >10,000 copies/ml): o OR 21.5 (95%CI 8.4 to 55.4) (high risk of bias) • ≥5 log10copies/ml versus <5log10 copies/ml for reactivation (ALT ≥60IU/L or ≥1.5xULN): o HR 3.43(95%CI 1.14 to 10.31); (high risk of bias) • ≥4log10 versus <4log10 copies/ml for high normal ALT (0.5-1 x ULN): o OR 1.83(95%CI 1.07 to 3.13); risk for <10^4 copies/ml (high risk of bias) • > 850 IU/ml (4500 copies/ml) versus ≤ 850 IU/ml for reactivation (DNA >2000 IU/ml and ALT > 40 IU/L): o OR 14.90 (95% CI 5.00 to 44.41) (moderate risk of bias) • ≥2.9 log10 versus <2.9 log10 copies/ml: o for future fibrosis: OR 5.43 (95%CI 2.4 to 12.3); (moderate risk of bias) o for future necroinflammation: OR 3.47 (95%CI 1.58 to 7.47); (moderate risk of bias) o for future HAI≥5: OR 5.42(95%CI 2.4 to 12.3); (moderate risk of bias) **ALT for predicting future active CHB** • 21-40IU/l versus ≤20 IU/l for future reactivation (ALT ≥60IU/L or ≥1.5xULN): o HR 18.43 (95%CI 2.38 to 142.7) (high risk of bias) [Age for predicting reactivation: • 30-39 years versus <30 years: OR 2.43 (95%CI 1.18 to 5.03) (high risk of bias) • >36 years versus <36 years for identifying fibrosis: OR 1.98 (95%CI 0.89 to 4.38) (moderate risk of bias)]
HBeAg positive Immune active phase	**ALT for predicting current fibrosis and inflammation** • Increase in ALT group (e.g. normal -> 1-1.5 → >1.5 ULN: o For significant fibrosis: OR 1.77 (95%CI 1.02 to 3.07) in multivariable analysis (high risk of bias) o For significant inflammation: OR 1.89 (95%CI 1.08 to 3.29) in multivariable analysis (high risk of bias)

	HBV DNA and ALT thresholds
	• >40 IU/l persistently/intermittently (over 3 measurements) versus < 40 IU/l for significant fibrosis: o **Unadjusted** OR 2.84 (95%CI 1.72 to 4.69); risk for <40 IU/l =40% (29/73) (high risk of bias) [Age: continuous variable per year for significant fibrosis: OR 1.072 (95%CI 1.013 to 1.136) (high risk of bias)
HBeAg negative immune escape phase (reactivated)	**HBV DNA levels for predicting current fibrosis** • Categorical comparison of DNA levels for Ishak fibrosis (moderate risk of bias), o >200,000 IU/ml versus <2000 IU/ml : OR 4.9 (95%CI 2.0 to 11.6) o 20,000 to <200,000 IU/ml versus <2000 IU/ml : OR 2.2 (95%CI 0.9 to 5.4) o 2,000 to <20,000 IU/ml versus <2000 IU/ml: OR 1.6 (95%CI 0.6 to 4.2) o Study 2: >20,000 IU/ml versus <20,000 IU/ml: OR 4.60 (95% CI 1.39 to 15.17), for 5/21 (24%) in below threshold group; Ishak scoring system (moderate risk of bias) • Categorical comparison of DNA levels for necro-inflammation: o $>10^9$ versus $\leq 10^9$ copies/ml: OR 3.21 (95% CI 1.26 to 8.17), for 11/66 (17%) in below threshold group (moderate risk of bias) **ALT levels for predicting current fibrosis** • >40 IU/l versus <40 IU/l: o Abnormal ALT on day of biopsy (Ishak score): OR 2.1 (95%CI 1.1 to 4.2) (moderate risk of bias) • Increase in ALT group (e.g. normal -> 1-1.5 → >1.5 ULN: o For significant fibrosis: not significant in multivariable analysis (high risk of bias) • **unadjusted odds ratio:** 11.05 (95%CI 5.15 to 23.72), risk for normal ALT levels = 14% (8/58) ALT for predicting necro-inflammation • >80 IU/L versus < 80 IU/L: OR 9.92 (95%CI 1.21 to 81.63) (high risk of bias) [Age: 30-44 years versus <30 years for predicting current fibrosis (Ishak score): OR 2.9 (95%CI 1.3 to 6.4) (moderate risk of bias)
Mixed HBeAg status	**HBV DNA as a predictor of current fibrosis:** • > 6 log10 copies/ml versus < 6 log10 copies/ml: not significant on multivariable analysis but no numbers (high risk of bias) • >100,000 copies/ml versus <100,000 copies/ml: o OR 1.03 (95%CI 0.48 to 2.23) (moderate risk of bias) o OR 1.86 (95%CI 1.18 to 2.92) (low risk of bias) **HBV DNA as a predictor of current inflammation:** • >100,000 copies/ml versus <100,000 copies/ml: o OR 0.73 (95%CI 0.36 to 1.52) (moderate risk of bias) **ALT as a predictor of current fibrosis:** • > 40 IU/L persistently/intermittently (over 3 measurements) versus < 40 IU/L (persistently normal over 3 measurements): o OR 4.3 (95%CI 2.87 to 6.45) (low risk of bias)

	HBV DNA and ALT thresholds
	[Age for predicting current fibrosis: • 30-39 years versus <30 years: OR 0.93 (95%CI 0.70 to 1.25) (low risk of bias) • 40-49 years versus <30 years: OR 1.13 (95%CI 0.82 to 1.57) • ≥ 50 years versus <30 years: OR 1.66 (95%CI 1.13 to 2.45)]

10.5 Economic evidence

Published literature

No published cost-effectiveness analyses were identified.

Economic considerations

When considering the most appropriate threshold at which a patient requires further assessment or treatment , it is important to consider both the costs and quality of life associated with treating a greater number of patients than is necessary as well as the costs and quality of life associated with excluding those who may benefit from treatment. In other words, it is important to consider the trade-off between setting too inclusive and too exclusive threshold. Any increased costs (in terms of inappropriate treatment) must be justified by the benefits of identifying those who may have been inappropriately managed.

10.6 Evidence statements

10.6.1 Clinical evidence statements

10.6.1.1 Adults with CHB infection

One study in patients who were HBeAg positive and in the immune tolerance phase showed that ALT levels above 5 x ULN was a significant independent predictor of future reactivation in comparison with levels below 2 x ULN; intermediate levels (2 to 5 x ULN) were not significant. The evidence was moderate quality. Age above 40 years in comparison with below 40 years was also a significant independent predictor.

Five studies investigated independent predictors of future active hepatitis in people who were HBeAg negative inactive carriers. Values of HBV DNA above thresholds ranging from 5 log10 copies/ml (20,000 IU/ml) to 2.9 log10 copies/ml (4200 IU/ml) were significant independent predictors. The evidence quality was moderate. Only one study gave data on ALT, in which 21-40 IU/L in comparison with below20 IU/L was a significant independent predictor; the evidence was of low quality. The evidence was inconsistent for age as a predictor: one study reported age above 30 years was an independent predictor; another study found age above 36 years not to be significant; the evidence quality was low.

Two studies investigated predictors of current fibrosis in people who were HBeAg positive in the immune active phase. One showed an increase in ALT group to 1-1.5 xULN was a significant independent predictor; the other showed a level above 40 IU/L to be a significant predictor on univariate analysis; the evidence was low quality. Age, as a continuous variable, was an independent predictor (low quality evidence).

Two studies investigated predictors of current fibrosis in people who were HBeAg negative in the immune escape phase: both showed that HBV DNA levels above 20,000 IU/ml were independent predictors of current fibrosis, but one study showed levels between 2000 and 20,000 IU/ml were not significant predictors; the evidence was of moderate quality. One study showed that 9 log10 copies/ml was an independent predictor of necro-inflammation (moderate quality). For ALT as predictors, two studies gave conflicting information: in one, an ALT level above a threshold of 40 IU/L was a significant independent predictor, in another a change to 1-1.5 x ULN was not significant (low quality evidence). Age above 30 years was a significant independent predictor in one study (moderate quality).

In two studies in people with mixed HBeAg status, HBV DNA levels above 100,000 copies/ml (20,000 IU/ml) had conflicting results, one showed this threshold was an independent predictor of current fibrosis, the other did not (moderate quality evidence). An ALT threshold of 40 IU/L was a significant independent predictor (persistently or intermittently above the threshold on at least 3 occasions) compared with persistently normal (high quality evidence). Age above 30 years was not a significant predictor of current fibrosis, but age above 50 years was in comparison with age below 30 years (high quality evidence).

There was no evidence in children.

10.6.2 Economic evidence statements

No published cost-effectiveness analyses were identified.

10.7 Recommendations and links to evidence

Recommendations	**27. Offer antiviral treatment to adults aged 30 years and older who have HBV DNA greater than 2000 IU/ml and abnormal ALT (greater than or equal to 30 in males and greater than or equal to 19 in females) on 2 consecutive tests conducted 3 months apart.** **28. Offer antiviral treatment to adults who have HBV DNA greater than 20,000 IU/ml and abnormal ALT (greater than or equal to 30 in males and greater than or equal to 19 in females) on 2 consecutive tests conducted 3 months apart regardless of age or the extent of liver disease.** **29. Offer antiviral treatment to adults with cirrhosis and detectable HBV DNA, regardless of HBeAg status, HBV DNA and ALT levels.** **Children and young people with chronic hepatitis B compensated liver disease** **30. Offer antiviral treatment if there is evidence of significant fibrosis (METAVIR stage greater than F2 or Ishak stage greater than or equal to 3) or abnormal ALT (greater than or equal to 30 IU/ml for males and greater than or equal to 19 IU/ml for females) on 2 consecutive tests conducted 3 months apart.**
Relative values of different outcomes	The presence of an immune reactive phase evident by HBV DNA replication and hepatitis, leading to significant fibrosis (defined as METAVIR stage ≥F2) were considered the most important outcomes, as these patients are at the greatest risk of progression to cirrhosis, decompensation, liver failure and hepatocellular carcinoma. Therefore, these patients should be assessed and treated if necessary.
Trade off between clinical benefits and harms	The evidence review is concerned with determining which patients should be offered antiviral treatment, based on the patient's HBV DNA and ALT levels, and which patients have no need of treatment at that stage of their disease. High levels of these predictive factors either indicate that a patient in an inactive phase is likely to change sooner to a more active phase or that the patient has underlying fibrosis that needs treatment to prevent further liver disease. The objective of the review was to determine the thresholds of HBV DNA and ALT that discriminate between people requiring treatment and people who do not. Therefore all the analyses reported are based on the *relative* likelihood of biochemical reactivation (defined as rising ALT) or fibrosis. Results from multivariable analyses are summarised in order to determine the independent predictor thresholds. The evidence is reported by phase of hepatitis B, but the GDG considered the wider picture across all phases when determining thresholds for initiation of treatment. The most evidence for HBV DNA thresholds was in the HBeAg negative inactive carrier phase and it was found that thresholds for HBV DNA as low as 4200 IU/ml could still discriminate between people with and without risk of biochemical reactivation of hepatitis B. On the other hand, HBV DNA levels below 20,000 IU/ml were not significant predictors of fibrosis in people in the

	immune escape phase and sometimes not in a mixed population. The GDG decided that it was preferable to treat at a lower threshold in order to avoid development of advanced liver disease (avoiding false negatives), but to monitor the patients effectively. There are currently two thresholds in current use, 20,000 and 2000 IU/ml and the GDG decided to recommend the latter. A relatively small minority of mainly HBeAg positive people also requiring treatment are those with necroinflammation or fibrosis on biopsy with HBV DNA >20,000 IU/mL and abnormal ALT. Generally, ALT levels above 1 x ULN were significant predictors of fibrosis, but a more rigorous threshold described in one of the best studies was that of being persistently or intermittently above the 40 IU/L threshold on at least three occasions. The GDG stated that this was particularly important when ALT levels are fluctuating and used this threshold for all phases. The GDG decided to recommend the more recent definition of ULN (30 IU/L for men and 19 IU/L for women) in preference to 40 IU/L. Age as a predictor was not reported widely in these studies, but where it was included in multivariable analyses, the lowest age threshold was 30 years. People above 30 years were at greater risk of having underlying fibrosis or were at risk of progressing to a more active phase. Therefore, the GDG decided to recommend differently for people above and below this age threshold.
Economic considerations	The GDG considered the costs, efficacy and availability of non-invasive tests for patients with CHB. The GDG stated that if: The ALT level was persistently abnormal over two tests at a level of ≥30IU/ml for men and ≥19IU/ml for women and/or The HBV DNA level was persistently ≥2000 IU/ml This would represent the most cost effective threshold for treatment. The GDG thought that the cost of testing all patients at this threshold would be justified by the increase in quality of life and reduction in mortality associated with prompt and early initiation of appropriate treatment. They agreed that based on the review of the clinical evidence in chapter 4 on diagnostic test accuracy, transient elastography represents the most clinically and cost-effective non-invasive test for people with CHB.
Quality of evidence	The evidence reviewed was restricted to prospective and retrospective studies investigating predictors either for future reactivation or for existing fibrosis. Most studies reported multivariable analyses and these were used wherever possible and assessed for quality. Studies reporting unadjusted or univariate analyses were regarded as being at high risk of bias and potentially confounded. Some studies had few events and were regarded as at high risk of bias. The retrospective studies were considered less reliable than prospective studies because of risk of recall bias. The studies reported different thresholds and had different definitions of outcome, particularly for reactivation, but an important consideration was consistency across the studies. Generally, the evidence quality was low or moderate. No studies were found for children in relation to HBV DNA and ALT thresholds indicating the need for further investigation. However, the GDG considered that the thresholds of 2,000 IU/ml for HBV DNA levels and abnormal ALT level (≥30 for men and ≥19 for women) for adults with CHB could be extrapolated for children with chronic hepatitis B.
Other considerations	The GDG concluded that the original question posed on what were the thresholds to indicate referral to specialist services was not the correct one. Because of the complexity of the anticipated serological results of the tests done in primary care, the GDG agreed that all CHB patients should be referred to a specialist for assessment of liver disease. What the thresholds determine are when a further assessment of liver disease

	and fibrosis is required through either noninvasive or invasive methods or for when antiviral treatment should begin, and this, the group believed was best undertaken within a specialist service. However the group agreed the results for the outcomes of indication for treatment or further investigation provided information to inform recommendations. Although the evidence on thresholds was reviewed by phase of hepatitis B, the GDG took into consideration the evidence across all phases when determining treatment thresholds. Evidence on age as a predictor was extracted from the studies in this review if it was reported. We did not search for evidence on this predictor, but there was sufficient evidence to support the recommendation. These recommendations were based on the evidence reviewed and on the experience and opinion of the GDG. The GDG was mindful that thresholds for treatment recommendations should be considered in conjunction with the recommendations for treatment, monitoring and stopping, and patient information on the different types of treatment for CHB, including awareness of the potential for short term (one-off) treatment with peg interferon versus potential for lifetime treatment with nucleo(t)sides, and side effects of drugs including resistance, and with reference to the patient's personalised care plan (Chapter 6).

11 Antiviral therapies

11.1 Pharmacological therapies

11.1.1 Introduction

The ultimate goal of the pharmacological treatment of chronic hepatitis B (CHB) is to prevent liver fibrosis, cirrhosis, hepatic failure and hepatocellular carcinoma. CHB cannot be cured; the ultimate aim is resolution of the chronic infection measured by the loss and/or seroconversion of HBsAg. The hepatitis B virus synthesises covalently closed circular DNA (cccDNA) shortly after infection which then remains permanently in the liver. Seroreversion to HBsAg positivity has been observed the most in patients undergoing immunosuppression for cancer chemotherapy or post organ transplantation.

Surrogate goals and measures of treatment response therefore need to be used. Normalisation of serum ALT is the main biochemical measure that acts as a proxy for the resolution of necroinflammation in the liver. The main virologic responses are a decrease in serum HBV DNA viral load, loss and/or seroconversion of HBeAg and, ultimately, loss and/or seroconversion of HBsAg. Resolution of necroinflammation and the resolution or slowing of fibrosis can also be measured directly through liver histology.

Interferon (IFN)-alfa and lamivudine were recommended for the treatment of chronic hepatitis B in the 1990's (TA96). During the last decade, two formulations of pegylated IFN (PEG-IFN) and four additional nucleos(t)ide analogues (NUCs) have been licensed. PEG-IFN has replaced conventional IFN allowing weekly dosing instead of thrice weekly injections with improved tolerance and increased rates of response. Although IFN has weak anti-viral activity, it has immune stimulating properties and enhances clearance of HBV infected cells. The advantages of IFN therapy are a finite duration of therapy, more durable HBeAg seroconversion, and a higher rate of HBsAg loss, especially in patients with genotype A infection. NUCs have potent inhibitory effect on HBV DNA replication. The advantages of NUCs are convenience (once daily oral administration) and tolerability. Because of the long half-life of the virus infected hepatocytes[75] viral relapse is common when NUCs are discontinued thus a long duration and often lifelong therapy is required with resultant risk of drug resistance and high cumulative costs. The guideline makes recommendations on the sequence in which the available licensed drugs should be used when treatment for HBV is indicated. IFN should not be used in patients with decompensated cirrhosis, acute liver failure, those receiving immunosuppressive therapy for co-existing conditions, pregnancy or psychiatric contraindications. Patients with cirrhosis and no evidence of portal hypertension may be treated with PEG-IFN.

A major concern with long-term NA treatment is the production of and selection for drug resistance mutations. HBV has a high rate of replication with 10^{12} virions being produced per day and a mutational rate of 10^{-5} substitutions per base per cycle[75]. This means that up to $10^{10\text{-}12}$ mutations can be produced every day; for such a small genome this means that all possible nucleotide changes can occur in one day. The rate at which drug resistance conferring mutations can be selected for is therefore dependent upon the overall HBV DNA level, the speed with which viral suppression is achieved and the duration of treatment (including any previous treatment)[62] . Lamivudine is the NA that is associated with the highest rate of drug resistance, with very low rates recorded in entecavir. Currently no induced drug resistance mutations caused by tenofovir treatment have been clearly identified. To begin with drug resistant viruses tend to have decreased replication fitness compared to the wild-type virus, leading to lower HBV DNA levels [76]. However viral fitness generally improves as the virus accumulates compensatory mutations during continued treatment. The increase in HBV DNA level may exceed pre treatment levels leading to virologic breakthrough. This breakthrough of

the virus is likely to be followed by biochemical breakthrough when the ALT begins to rise again as the patient's immune system detects the accumulating viral particles. In some cases this emergence of antiviral resistance can lead to hepatitis flares and progress to hepatic decompensation.

Some drug resistance mutations reduce efficacy to more than one NA – leading to cross-resistance and therefore limiting the future options for treatment. This may be a particular risk in patients treated with sequential NA therapy using only single agents [31,106]. Once drug resistance mutations have developed they are archived within the virus population and will re-surface if the same, or a cross-reacting, drug is re-introduced.

11.1.2 Overview of the evidence

This chapter consists of two review questions:

- In people with CHB, what is the clinical and cost effectiveness of pharmacological monotherapies and combinations in achieving remission of the activity of CHB?
- In people with CHB, what is the clinical and cost-effectiveness of sequential drug therapy (add-on or switching monotherapies) in achieving remission of the activity of CHB

Both reviews address interventions for different populations: people who are treatment naïve (first line treatments), and people who have already received particular treatments for CHB and have become resistant to them (second line treatments). All evidence is presented separately for people who are HBeAg positive and negative.

The reviews are intended to determine which is the best single therapy (monotherapy), whether anything can be gained by adding a second treatment to the first (combination therapy) and whether it is useful either to add a different treatment to the first at a later stage or to switch from treatment 1 to treatment 2 (sequential therapies).

Within each treatment-naïve and resistant population, the interventions in these two reviews are *alternative* treatments for patients, even if that treatment is a strategy of first line and second line, and therefore the interventions can be compared across both reviews. This chapter seeks to bring together all the evidence in one place.

To aid the process, five network meta-analyses on two outcomes – the proportion of patients with undetectable HBV DNA and the proportion of patients achieving HBeAg seroconversion - have been conducted, comparing treatments across both reviews. Full details on the NMA is in appendix J

Network meta-analysis for a particular outcome allows the evidence from all comparisons to be combined statistically, and outputs include the relative effectiveness of each intervention compared with a common comparator and also allows the ranking of interventions. The results of the NMAs are used in the de-novo health economic models described in Appendix H and I.

The health economic model evaluates the cost-effectiveness of switching to different monotherapy and combination nucleos(t)ide treatments, usually after a prescribed course of peg-IFN or following the development of drug resistance to initial NA therapy.

The objective of treating people with CHB is to prevent the progression of liver disease to decompensated cirrhosis and liver failure, to hepatocellular carcinoma and to death. The drug therapies aim to do this by reducing the activity of the DNA virus to negligible proportions or, in the best case scenario, to achieve "cure" (HBsAg seroconversion). People in this latter state are assumed to be at no greater risk of developing progressive liver disease than in those without CHB.

Generally there is very little evidence from trials on the effect of drug treatments on the incidence of advanced liver disease, hepatocellular carcinoma and death, and so various markers are used as surrogate outcomes: undetectable levels of HBV DNA, HBeAg seroconversion and ALT normalisation. These outcomes have been examined in trials at the end of 12 months treatment and also after a follow up period on or off treatment following seroconversion in order to determine whether the virus re-activates. The reviews also examine whether or not people become drug resistant and examine adverse drug events.

The evidence is presented firstly as head-to-head (or "pairwise" or "direct") comparisons of all pairs of interventions, and then the results of a network meta-analysis are given.

The direct evidence is divided into the following sections and sub-sections:

11. Antiviral monotherapies in adults and children (2-16 years old) infected with CHB
12. Antiviral combination therapies in adults and children (2-16 years old) infected with CHB
13. Antiviral sequential therapies (add-on or switching monotherapies) in adults and children (2-16 years old) infected with CHB (section 11.1.5.1)
14. Antiviral therapy (monotherapies and combination therapies) in CHB adults and children co-infected with hepatitis delta or C virus (section 11.1.2)

All evidence is presented separately for people who are HBeAg positive and negative, and the evidence is further stratified into nucleos(t)ide naïve, and lamivudine resistant populations.

11.1.3 Antiviral monotherapies, combination therapies and sequential therapies in adults infected with CHB

Below is a matrix showing where evidence was identified. A box filled with numbers represents where evidence was found and is reviewed in this chapter; the numbers are the number of studies found (n) and the total number of patients (N).

Figure 6: Monotherapies, combination therapies and sequential treatments for HBeAg positive treatment-naïve adults with CHB infection

Entecavir	n=6[#] (Zhao 2011A N=389 including Leung 2009 N=65)			
Lamivudine		n=4~ N= 1344 (Chang 2006 N=715+ Ren 2007 N=42 + Shindo 2009A N=68 + Yao 2007A N=519)		
Pegylated Interferon α 2a				n=1 (Lau 2005* N=543)

Interferon α 2a/ 2b				N=1 (Schalm 2000** N=151)							
Telbivudine	n=1 (Chan 2007) N=90	n=2 N=175 Suh 2010 N=44 + Zheng 2010?	n=3 N=1274	n=3 (Lai 2005) N=63~ + Hou 2008A N=290 + Lai 2007 N=291)							
Tenofovir	n=1 (Marcellin 2008 Study 103) N=266										
Placebo	n=1 (Marcellin 2003) N=338 (10mg vs. placebo arms only)†	n=1 (Yao 2007) N=145 (LAM resistant but HBeAG + or -)		n=5 N= (Dienstag 1999 N=137 + Lai 1998 N=215: Liaw 2004 N=651+ Schiff 2003** N=175+ Yao 1999 N=429)							
ADF + LAM				n=1 (Sung 2008) N=115							
PEG α 2a + LAM				n=1 (Lau 2005* N=543)	n=1 (Lau 2005* N=542)						
PEG α 2b + LAM				n=1 (Chan 2005) N=100		n=1 (Janssen 2005) N=307					
Emtricitabine + tenofovir								n=1 (Berg 2010) N=105			
Interferon α 2a/ 2b + LAM			n=6 N=515 n=4 (Schalm 2000** N=144+ Ayaz 2006 N=68 + Cindoruk 2002 N=100 + Yalcin 2003 N=49)	n=7 (Hasan 2003 N=61 + Sarin 2005 N=75 + Schiff 2003** N=182+ Schalm 2000** N=157+ Barbaro 2001 N=151+ Jang 2004 N=83 +					n=1 (Schiff 2003**) N=119		

				Yuki 2008 N=64)								
TBV+ LAM				n=1~ (Lai 2005) N=60			n=1~ (Lai 2005) N=85					
LAM followed by PEG α 2b						n=1 Sarin 2007 N=63					n=1 N=59	
Switch LAM to LAM + IF α 2a/ 2b				n=2[+] N=157								
Switch LAM to telbivudine				n=1 (Safadi 2011) N=162								
ETV + TDF		n=1 (Lok 2012) N=379										
Switch LAM to entecavir										n=1 (Ryu 2010) N=92		
Sequential adefovir then telbivudine	n=1 (Chan 2007 N=91)											n=1 (Chan 2007 N=91
	ADF	**ETV**	**IF α 2a/ 2b**	**LAM**	**PEG 2a**	**PEG 2b**	**TBV**	**TNF**	**Placebo**	**ADF + LAM**	**Placebo followed by PEG α 2b**	**Telbivudine**

*3 arm trial ~3 arm trial +3 arm trial [+]3 arm trial (third arm non-standard dose)

** 3 arm trial

[#]from meta-analysis

Figure 7: Monotherapies, combination therapies and sequential treatments for HBeAg negative adults with CHB infection

Lamivudine			n=2 (Lai 2006 N=638 + Yao 2007A N=73)			
Pegylated Interferon α 2a		n=1 (Piccolo 2009) N=60		n=1 (Marcellin 2004 N=358)		
Telbivudine				n=2 (Hou 2008A N=42 + Lai 2007 N=446)		
Tenofovir	n=1 (Marcellin 2008 Study 102) N=375					
Placebo	n=1			n=2		

	(Hadziyannis 2003) N=185			(Tassopoulos 1999, Chan 2007C N=125+139)		
PEG α 2a + LAM				n=1 (Marcellin 2004 N=360)	n=1 (Marcellin 2004 N=356)	
PEG α 2b + LAM						n=2 (Kaymakoglu 2007 N=48 + Papadopoulos 2009 N=126)
Interferon α 2b + LAM				— n =5 (Akarca 2004 N=80 + Economou 2005 N=50 + Santantonio 2002 N=50 + Shi 2006 N=162 + Yurdaydin 2005 N=78)		
Switch entecavir to lamivudine			n=1 Fung 2011 N=50			
Switch LAM to entecavir				n=1 (Matsuura 2011 N=27)		
Switch LAM to telbivudine				n=1 (Safadi 2011) N=84		
	ADF	**– P eg IFN alpha 2a + adefovir**	**Entecavir**	**LAM**	**PEG 2a**	**PEG 2b**

Figure 8: Monotherapies, combination therapies and sequential treatments for Lamivudine-resistant HBeAg positive adults with CHB infection

Adefovir			
Lamivudine			
Adefovir + lamivudine		n=2 (Perrillo 2004 N=95 + Peters 2004* N=39)	
Switch lamivudine to entecavir		n=2 (Chang 2005A N=182 + Sherman 2006 N=286)	
Switch lamivudine + adefovir to entecavir + adefovir			n=1 (Lim 2012) N=90
	Adefovir	**Lamivudine**	**Adefovir + lamivudine**

* three armed study

Figure 9: Monotherapies, combination therapies and sequential treatments for Lamivudine-resistant HBeAg negative adults with CHB infection

Adefovir			
Lamivudine			
Adefovir + lamivudine	n=2 (Rapti 2007 N=42+ Vassiliadis 2010 N=60)		
Switch lamivudine to adefovir only			n=1 (Akyildiz 2007) N=54
Switch lamivudine + adefovir to adefovir only			n=1 (Aizawa 2010) N=29
	Adefovir	**Lamivudine**	**Adefovir + lamivudine**

Figure 10: Monotherapies, combination therapies and sequential treatments for previously Lamivudine-treated (some resistant) mixed HBeAg positive and HBeAg negative adults with CHB infection

Switch lamivudine to adefovir	**n=1 (Hann 2010) N=18**
	Overlap lamivudine + adefovir for three months then adefovir monotherapy

Figure 11: Monotherapies, combination therapies and sequential treatments for co-infected adults with CHB infection

Pegylated Interferon α 2a	n=1 (Wedemeyer 2001A) N=59			
Tenofovir	n=1 (Peters 2006) N=52			
Placebo		n=1 (Niro 2005) N=31		

Pegylated Interferon α 2a + adefovir	n=1 (Wedemeyer 2001A) N=61		n=1 (Wedemeyer 2001A) N=60	
Interferon alfa-2b plus lamivudine				n=1 (Canbakan 2006) N=26
	Adefovir	**Lamivudine**	**Pegylated Interferon α 2a**	**Interferon alfa-2b**

Figure 12: Monotherapies, combination therapies and sequential treatments for adults with decompensated CHB infection

Placebo				
Entecavir	n=1 (Liaw 2011)		n=1 (Liaw2011A)*	n=1 (Liaw2011A)*
Telbivudine		n=1 (Chan 2012) N=232		
Tenofovir				n=1 (Liaw2011A)*
	Adefovir	**Lamivudine**	**Tenofovir**	**Tenofovir + emtricitabine**

*** 3 arm trial**

Figure 13: Monotherapies, combination therapies and sequential treatments for children with CHB infection

Placebo or no treatment	n=1 (Jonas 2008) N=173	n=1 (Sokal 1998) N=149	n=1 (Jonas 2002) N=288			
IFN α + LAM then LAM alone		n=1 (Dikici 2004* N=122)		n=2 (Dikici 2002 N=32 and Dikici 2004* N=120)		
Lam then IFN α + LAM then LAM		n=1 (Dikici 2004* N=122)				
Interferon α2a + LAM					nn=1 (Ozgenc 2004) N=63	n=1 (Kansu 2006) N=177
IFN α 2b + LAM (12 months)					n=1 (Dikici 2001) N=57	
	ADF	**IF α 2a/ 2b**	**LAM**	**Lam then IFN α + LAM then LAM**	**Interferon α 2b + LAM (6 months)**	**LAM then IFN-α 2a+ LAM**

Dikici 2004 3-armed trial total n=182

11.1.4 Review question: In people with CHB, what is the clinical and cost effectiveness of pharmacological monotherapies and combinations in achieving remission of the activity of CHB?

Table 89: Protocol

Protocol	
Population	Children (2-16years), young people and adults with chronic hepatitis B virus

Protocol	
	infection
Intervention	• Interferon/Pegylated alpha-interferon 2a/2b (will be tested as a monotherapy intervention only for children) • Tenofovir • Entecavir • Adefovir • Lamivudine • Telbivudine • Emtricitabine (in combination with tenofovir)
Comparison	• Intefon/Pegylated alpha-interferon (2a and 2b) • Tenofovir • Entecavir • Adefovir • Lamivudine • Telbivudine • Emtricitabine (in combination with tenofovir) • Placebo or no treatment
Outcomes	• Log reduction of HBV DNA • Proportion of people with undetectable serum hepatitis B virus DNA • Proportion of people with with ALT normalisation • Proportion of people with with HBeAg loss and/or seroconversion • Proportion of people with with HBsAg loss and/or seroconversion • Quality of life measures (EQ-5, SF-35, liver disease specific) • Proportion of people withdrawn due to adverse events • Incidence of resistance

Note: The standard dose of the intervention will be data extracted where available; where a study assesses another dose only, the study will be downgraded in terms of directness; where a three-arm study assesses the standard dose and another dose, only the standard dose data will be used. The standard doses used will be:

- Pegylated alpha-interferon 2a –180microg once a week, reduced to 135 microg if patients have CrCL less than 30 mL/min
- Pegylated alpha-interferon 2b – in combination treatments 1.5 micrograms per kilogram body weight, or on its own at 0.5 or 1.0 micrograms/kg
- Tenofovir – 245mg once daily
- Entecavir - Compensated liver disease not previously treated with nucleoside analogues, adult over 18 years, 500 micrograms once daily; compensated liver disease with lamivudine-resistant chronic hepatitis B, adult over 18 years, 1 mg once daily; decompensated liver disease, adult over 18 years, 1 mg once daily
- Telbivudine - 600 mg once daily
- Emtricitabine (in combination with tenofovir) - tenofovir disoproxil (as fumarate) 245 mg, emtricitabine 200 mg

Searches were conducted for systematic reviews of randomized clinical trials (RCTs) and RCTs comparing the effectiveness of monotherapies and combinations as interventions for achieving the remission of chronic Hepatitis B for children, young people and adults with chronic Hepatitis B. We did not search for RCTs in adults comparing pegylated interferon alpha-2a versus placebo. This guideline was asked to incorporate the TA 96 recommendation of pegylated interferon alpha-2a as an option for initial treatment of CHB for adults so the decision of not searching for comparative

RCTs of pegylated interferon a-2a versus placebo was made for pragmatic reasons due to time and resource constraints. No RCTs were found comparing pegylated interferon alpha-2b versus placebo.

11.1.4.1 Summary characteristics of included studies

There were 34 trials comparing antiviral monotherapies or combination treatments in patients who were HbsAg positive; the review included 24 direct comparisons, for which most were represented by one trial.

Table 90: Monotherapies and combination therapies for HBeAg positive treatment-naïve adults with CHB infection

Comparison	Included studies (N=)	Setting	Study population	Outcomes: times reported and thresholds
Nucleoside naïve population				
Adefovir versus placebo	Marcellin 2003 (N=338)	Multicentre, International (incl N America, Europe, Australia and SE Asia)	Treatment naïve and previously treated with IFN-alpha (24%)	End of 48 weeks
Lamivudine versus placebo	Dienstag 1999 (N=137)	USA (34 centres)	Treatment naïve	End of 52 weeks and 16 weeks follow up
Lamivudine versus placebo	Yao 1999 (N=429)	China	Unclear whether the study was based on treatment naïve or previously treated population	End of 12 weeks
Lamivudine (100mg dose only) versus placebo	Lai 1998 (N=215)	South east Asia	Treatment naïve and previously treated people (but not LAM treated during the last 6 months)	End of 52 weeks
Lamivudine versus placebo	Schiff 2003 (N=175)	Multinational	Hepatitis B e antigen (HBeAg) positive chronic hepatitis B who had failed interferon therapy previously	End of 52 weeks
Lamivudine versus placebo	Liaw 2004 N=651	Multinational	Largely HBeAg (+) (58%) patients with histologically confirmed cirrhosis or advanced fibrosis (98% Asian) (without evidence of liver decompensation)	End of follow up mean 32 months of treatment
Entecavir versus adefovir	Leung 2009 (N=65)	Asia	Nucleos(t)ide naïve adults	End of 48 weeks
Entecavir versus lamivudine	Chang 2006 N=715	Multicentre; international (incl. Europe, N and S America, Asia, Australia)	99% HBeAg positive; Treatment naïve and previously treated (16%) adults	End of 48 weeks
Entecavir versus lamivudine	Ren 2007 N=42	China	Nucleoside analogue naïve	End of 48 weeks
Entecavir versus	Yao 2007A	Multicentre;	Mixed population: HBeAg (+)	End of 48 weeks

Comparison	Included studies (N=)	Setting	Study population	Outcomes: times reported and thresholds
lamivudine	N=519	China	and (-) (largely positive; >85%); nucleos(t)ide naïve adults; reported separately	
Entecavir versus lamivudine	Shindo 2009A N=68	Japan	Mixed population: HBeAg (+) and (-) (largely positive; >85%); nucleos(t)ide naïve adults	End of 22 weeks
Entecavir plus tenofovir versus entecavir	Lok 2012-11-22 N=379	Multicetnre; international	70% HBeAg +; treatment naive	End of 96 weeks treatment
Lamivudine (52 weeks) versus Interferon alpha 2a/2b (placebo 8 weeks then IFN 16 weeks) versus lamivudine 8 weeks then Lam + IFN 16 weeks	Schalm 2000 Lam N=82; IFN N=69 and IFN+Lam N=75	Multicentre (51 centres in 15 countries)	Mixed population: HBeAg (+) and (-) (largely positive; 99%); not treated with IFN or antiviral in the last 6 months	End of 52 weeks treatment and week 64 (follow up)
Lamivudine (N=272) versus pegylated alpha 2a (N=271) versus Pegylated alpha 2a + LAM (N=271)	Lau 2005 N=814	Multicentre; international (67 sites in 16 countries)	Treatment naïve and previously treated people (12% prior IFN and 13% prior LAM treatment)	End of 48 weeks and 24 weeks follow up
Telbivudine versus adefovir	Chan 2007 N=90	16 outpatient clinics in HK, Australia, Canada, France, Korea, Singapore, Taiwan, Thailand the USA	Treatment naïve	End of 52 weeks
Telbivudine versus entecavir	Suh 2010 N=44	Multicentre; Korea	Treatment naïve	End of 12 weeks of treatment
Telbivudine versus entecavir	Zheng 2010 N=131	China	Nucleos(t)ide naïve Chinese people	End of 24 weeks
Telbivudine versus lamivudine	Liaw 2009 and Lai 2007 (52 weeks) N=921	Multi centre (112 centres in 20 countries)	Nucleos(t)ide naïve people	52 weeks and End of 104 weeks
Telbivudine versus	Hou 2008 A N= 290	China	Nucleos(t)ide naïve people	End of 52 weeks

– Telbivudine + lamivudine (N=41) vs telbivudine (N=44) vs lamivudine (N=19)	Lai 2005 N=104	International	Nucleos(t)ide naïve people	End of 52 weeks
– Interferon alpha 2a + lamivudine versus interferon alpha 2a	Ayaz 2006 (IFN alpha 2a, 9 MU) N=68	Turkey	Treatment naïve	End of 1 year treatment and 6 months follow up
Comparison	**Included studies (N=)**	**Setting**	**Study population**	**Outcomes: times reported and thresholds**
lamivudine				
Tenofovir versus adefovir	Marcellin 2008 N=266 (Study 103)	Multicentre; international (106 clinical sites in 15 countries)	Majority Nucleos(t)ide naïve people (4.5% previously treated people with nucleos(t)ides)	End of 48 weeks
Emtricitabine + tenofovir versus tenofovir	Berg 2010 N=105	International multi-centre	Mixed population of HBeAg (+) and (-) (largely positive (>70%)); 58% of the sample had previous LAM use	End of 48 weeks
Adefovir + lamivudine versus lamivudine	Sung 2008 N=115	International multicentre	Nucleos(t)ide naïve adults	End of 52 weeks and 104 weeks treatment
Interferon alpha 2a/ 2b + lamivudine versus interferon alpha 2a/2b	Cindoruk 2002 (IFN alpha, 9MU) N=100	Turkey	Treatment naïve	End of 6 months treatment and 6 months follow up
Interferon alpha 2b + lamivudine versus interferon alpha 2b	Yalcin 2003 (IFN a2b, 10 MU) N=49	Turkey	Treatment naïve	End of 1 year treatment and min. 1 year follow up

– Interferon alpha 2b + lamivudine versus lamivudine	Jang 2004 – long term therapy (IFN alpha, 5MU) N=83	Korea	Unresponsive to IFN alpha 2b treatment	6, 12, 24 and 36 months follow up
– Interferon alpha 2a /2b + lamivudine versus lamivudine	Yuki 2008 (IFN alpha, 6 MU) N=64	Japan	Perinatally transmitted people with genotype B and C. Mixed HBeAg (+) and (-) people – largely HBeAg (+). Small % previously treated with IFN.	End of 1 year treatment
– Peg Interferon alpha 2b + lamivudine versus lamivudine	Chan 2005 (Chan 2005A long term follow up study) N=100	Hong Kong, China	Treatment naïve people	At end of 52 weeks treatment, 24 weeks follow up and long term follow up (mean 117 weeks for combination therapy and 124 weeks for monotherapy)
– Peg Interferon alpha 2b + lamivudine versus peg IFN alpha 2b	Janssen 2005 N=307	Multinational	Some people had received previous IFN (21%) or lamivudine (13%) therapy Mixed ethnicity	At end of 52 weeks treatment and 26 weeks follow up
Interferon alpha 2b + lamivudine (24 weeks) versus lamivudine (52 weeks)	Barbaro 2001 (IFNα2b) N=151	Italy	Some were non-responders to previous treatment with IFNα2b. 4-5% in each group had cirrhosis at baseline	At 24/52 weeks treatment and 12 months follow up
Lamivudine (24 weeks) + interferon α 2b (16 weeks from week 9) versus placebo (52 weeks)	Schiff 2003 N=119	Multinational	Hepatitis B e antigen (HBeAg) positive chronic hepatitis B who had failed interferon therapy previously	At 52 weeks
Lamivudine (24 weeks) + interferon α 2b (16 weeks from week 9) versus lamivudine (52 weeks)	Schiff 2003 N=182	Multinational	Hepatitis B e antigen (HBeAg) positive chronic hepatitis B who had failed interferon therapy previously	At 52 weeks

Table 91: HBeAg positive or negative or mixed population lamivudine refractory or resistant patients with chronic hepatitis B

Comparison	Included studies (N=)	Setting	Study population	Outcomes: times reported
Entecavir versus placebo	Yao 2007 N=145	China (5 centres)	Mixed population: HBeAg (+) and (-) (largely positive; 90%); previously treated with lamivudine with 42% of the sample with lamivudine resistance	End of 12 weeks
Adefovir + Lamivudine versus Adefovir versus lamivudine	Peters 2004 N=39	International multi-centre	Lamivudine resistant HBeAg positive Some patient were previously treated with lamivudine	End of 48 weeks treatment
Lamivudine + adefovir versus lamivudine + placebo	Perrillo 2004 N=95	International multi-centre	Lamivudine resistant HBeAg positive Previously treated with lamivudine	End of 52 weeks treatment:
Lamivudine + adefovir versus lamivudine + placebo	Perillo 2011 (follow up study of Perrillo 2004) N=116	International multi-centre	Lamivudine resistant Previously treated with lamivudine	Additional 52 weeks treatment
Lamivudine + adefovir versus adefovir	Vassiliadis 2010	Greece	Lamivudine resistant HBeAg negative	12, 24, 36 and 48 months of treatment

Table 92: Monotherapies and combination therapies for HBeAg negative people with chronic Hepatitis B

Comparison	Included studies (N=)	Setting	Study population	Outcomes
Adefovir versus placebo	Hadziyannis 2003 N=185	Multicentre, International (incl. Canada, Europe, Israel, Australia, Taiwan and Singapore)	Treatment naïve and previously treated with IFN-alpha (41%)	End of 48 weeks
Lamivudine versus placebo	Tassopoulos 1999 N=125	Multinational	Treatment naïve and previously treated people	End of 24 weeks
	Chan 2007c N=139	Hong Kong and China	Treatment naïve people	Outcomes reported at the end of 104 weeks and 6 months post-treatment follow up
Entecavir versus lamivudine	Lai 2006 N=638	Multicentre; international	Nucleoside analogue naïve	Outcomes reported at the end of 48 weeks

Comparison	Included studies (N=)	Setting	Study population	Outcomes
		(incl. Europe, Middle East, Asia, Australia, N and S America)	people	
Entecavir versus lamivudine	Yao 2007A	Multicentre; China	Mixed population: HBeAg (+) and (-) (largely positive; >85%); nucleos(t)ide naïve adults; reported separately	End of 48 weeks
Lamivudine versus pegylated interferon-alpha versus Pegylated interferon-alpha + lamivudine	Marcellin 2004 N=537	Multicentre; 54 sites in 13 countries	Treatment naïve and a minority previously treated people	End 48 weeks and 24 weeks follow up
Telbivudine versus lamivudine	Hou 2008 A N= 44	China	Nucleos(t)ide naïve people	End of 52 weeks
Telbivudine versus lamivudine	Lai 2007 (same study as Liaw 2009) N=446	Multi centre (112 centres in 20 countries)	Nucleos(t)ide naïve people	Outcomes reported at the end of 52 weeks and 104 weeks
Tenofovir versus adefovir	Marcellin 2008 N=375 (Study 102)	Multicentre; international (106 clinical sites in 15 countries)	Predominantly White and Asian Minority previously treated people	Outcomes reported at the end of 48 weeks

– Interferon alpha 2b + lamivudine versus lamivudine	Akarca 2004 N=80	Turkey	Minority had received previous interferon but nucleos(t)ide analogue naive	24 weeks of randomised therapy, then interferon stopped in combination group; follow up up to 96 weeks (both groups still on lamivudine through 96 weeks)
– Interferon alpha 2b + lamivudine versus lamivudine	Economou 2005	Multicentre; Greece	Some (around 50%) previously treated with IFN; none had received other antivirals	Outcomes reported at end of 24 months of treatment and 6 months follow up afterwards
– Interferon alpha + lamivudine versus lamivudine	Santantonio 2002 N=50	Italy	Some (around 40%) previously treated with interferon	Outcomes reported at end of 12 months of treatment and 6 months follow up
– Interferon alpha 2a + lamivudine versus lamivudine	Yurdaydin 2005	Turkey	Treatment naive	12 months treatment
Pegylated interferon alpha 2a + adefovir versus pegylated interferon alpha 2a	Piccolo 2008	Italy	HBeAg negative	End of treatment at 48 weeks and follow up 24 weeks later
Pegylated interferon alpha 2b + lamivudine versus pegylated interferon alpha 2b	Kaymakoglu 2007 N=48	Turkey	HBeAg negative	End of treatment at 48 weeks and follow up 24 weeks later
Pegylated interferon alpha 2b + lamivudine versus pegylated interferon alpha 2b	Papadopoulos 2009 N=126	Greece	HBeAg negative	End of treatment at 48 weeks and follow up 24 weeks later

Table 93: Monotherapies and combination therapies for people with chronic Hepatitis B coinfected with hepatitis delta virus or HIV

Comparison	Included studies (N=)	Setting	Study population	Outcomes
Nucleos(t)ide naïve population				
Interferon alpha- 2a versus no treatment	Farci 1994 N=42			Outcomes reported at the end of 48 weeks and at 6 months, 32 months and 12 years follow up. Threshold <400 copies/ml
Interferon alpha -2b versus no treatment	Rosina 1991 N=61			Outcomes reported at the end of 12 months and after 12 months follow up
Peginterferon alfa-2a plus adefovir versus adefovir versus peginterferon alfa-2a	Wedemeyer 2011 N=31	not stated (abstract only)	HBV and HDV coinfection	Outcomes reported at the end of 48 weeks and after 24 weeks follow up
Interferon alfa-2b plus lamivudine versus interferon alfa-2b	Canbakan 2006 N=26			Outcomes reported at the end of 48 weeks and at 96 weeks follow up
Interferon alfa-2a plus lamivudine versus lamivudine	Yurdaydn 2008 N=26			Outcomes reported at end of 12 months and 6 months follow up
Lamivudine versus placebo	Niro 2005	Italy and Germany	HBV and HDV coninfected, most HBeAg negative	End of 52 weeks randomised treatment

Table 94: Monotherapies and combination therapies for children with chronic Hepatitis B

Comparison	Included studies (N=)	Setting	Study population	Outcomes
Adefovir versus placebo	Jonas 2008 N=173	USA and Europe	Predominantly White and Asian children; around 50% previously treated	Outcomes reported at the end of 48 weeks' treatment: HBV DNA, ALT, seroconversion
Lamivudine versus placebo	Jonas 2002 N=288	North America, South America and Europe	Predominantly White and Asian children; around	Outcomes reported at the end of 52 weeks' treatment: HBV DNA, ALT,

– Interferon alpha 2a + lamivudine versus Interferon alpha 2b + lamivudine	Ozgenc 2004 N=63	Turkey	Ethnicity not stated	Outcomes reported at the end of 6 months combination treatment then 6 months lamivudine alone: HBV DNA, ALT, HBeAg clearance and anti-HBe seroconversion, Anti-HBs seroconversion
Comparison	**Included studies (N=)**	**Setting**	**Study population**	**Outcomes**
			45% no response to previous treatment with interferon	seroconversion
Interferon alpha 2b versus no treatment	Sokal 1998 N=149	Belgium, France, Canada, and the United States	Predominantly White children; no antivirals in last 12 months	Outcomes reported at the end of 24 weeks' treatment and follow up 24 weeks later (week 48): HBV DNA, ALT, loss of HBeAG, loss of HBsAg
Interferon alpha 2b + lamivudine for 6 months versus Interferon alpha 2b + lamivudine for 12 months	Dikici 2001 N=57	Turkey	Ethnicity not stated	Outcomes reported at the end of combination treatment (6 or 12 months) and after 6 months follow up with no treatment: HBeAg/Anti-HBe seroconversion, clearance of HBV DNA and normalization of ALT

11.1.4.2 Pharmacological monotherapies and combination therapies in achieving remission of the activity of CHB infection for HBeAg positive adults

Nucleos(t)ide naïve adults with HBeAg positive CHB

Comparison of adefovir versus placebo

Table 95: Adefovir versus placebo - clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Adefovir Frequency (%)/ mean (SD)	Placebo Frequency (%)/ mean (SD)	Relative Risk (95% CI)	Absolute	
HBV DNA reduction (log10 copies/mL) (assessed at the end of 48 weeks treatment)										
Marcellin 2003	1 RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	3.57 (1.64)	0.98 (1.32)		MD 2.59 higher (2.27 to 2.91 higher)	HIGH
% of people with undetectable HBV DNA (<400 copies/mL) (assessed at the end of 48 weeks treatment)										
Marcellin 2003	1 RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	36/171 (21.1%)	0/167 (0%)	Peto OR 9.08 (4.55 to 18.10)	210 more per 1000 (from 150 more to 270 more)	HIGH
% of people with HBeAg loss (assessed at the end of 48 weeks treatment)										
Marcellin 2003	1 RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	41/171 (24%)	17/161 (10.6%)	RR 2.27 (1.35 to 3.83)	134 more per 1000 (from 37 more to 299 more)	HIGH

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Adefovir Frequency (%)/ mean (SD)	Placebo Frequency (%)/ mean (SD)	Relative Risk (95% CI)	Absolute	
% of people with HBeAg seroconversion (assessed at the end of 48 weeks treatment)										
Marcellin 2003	1 RCT- double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision [(a)]	20/171 (11.7%)	9/161 (5.6%)	RR 2.09 (0.98 to 4.46)	61 more per 1000 (from 1 fewer to 193 more)	MODERATE
% of people with ALT normalisation (assessed at the end of 48 weeks treatment)										
Marcellin 2003	1 RCT- double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	81/168 (48.2%)	26/164 (15.9%)	RR 3.04 (2.07 to 4.47)	323 more per 1000 (from 170 more to 550 more)	HIGH
% of people with histologic improvement (assessed at the end of 48 weeks treatment)										
Marcellin 2003	1 RCT- double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	89/168 (53%)	41/161 (25.5%)	RR 2.08 (1.54 to 2.81)	275 more per 1000 (from 138 more to 461 more)	HIGH

[(a)] *Confidence interval is consistent with two clinical decisions; no appreciable harm or benefit, appreciable benefit*

[(b)] *Confidence interval is consistent with three clinical decisions; no appreciable harm or benefit, appreciable benefit, appeciable harm.*

Comparison of lamivudine versus placebo

Table 96: Lamivudine versus placebo - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamivudine	placebo	Relative (95% CI)	Absolute	Quality
% of patients with undetectable HBV DNA (<1.6 pg/ml) at end of treatment											
4: Dienstag 1999, Lai 1998, Schiff 2003, Yao 1999	RCTs	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	380/606 (62.7%)	37/292 (12.7%)	RR 4.63 (3.37 to 6.36)	460 more per 1000 (from 300 more to 679 more)	MODERATE
% of patients with undetectable HBV DNA (<1.6 pg/ml) at end of treatment - 52 week treatment											
3: Dienstag 1999, Lai 1998, Schiff 2003	RCTs	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	110/313 (35.1%)	23/193 (11.9%)	RR 3.14 (2.08 to 4.75)	255 more per 1000 (from 129 more to 447 more)	MODERATE
% of patients with undetectable HBV DNA (<1.6 pg/ml) at end of treatment - 12 week treatment											
1: Yao 1999	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	270/293 (92.2%)	14/99 (14.1%)	RR 6.52 (4.01 to 10.6)	781 more per 1000 (from 426 more to 1000 more)	MODERATE
Loss of serum HBeAg (end of treatment)											
4: Dienstag 1999, Lai	RCTs	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	104/606 (17.2%)	23/289 (8%)	RR 2.5 (1.64 to 3.83)	119 more per 1000 (from 51 more to 225 more)	MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamivudine	placebo	Relative (95% CI)	Absolute	
1998, Schiff 2003, Yao 1999											
Loss of serum HBeAg (end of treatment) - 52-week treatment											
3: Dienstag 1999, Lai 1998, Schiff 2003	RCTs	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	81/322 (25.2%)	18/195 (9.2%)	RR 2.85 (1.76 to 4.61)	171 more per 1000 (from 70 more to 333 more)	MODERATE
Loss of serum HBeAg (end of treatment) - 12-week treatment											
1: Yao 1999	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23/284 (8.1%)	5/94 (5.3%)	RR 1.52 (0.6 to 3.89)	28 more per 1000 (from 21 fewer to 154 more)	LOW
HBeAg seroconversion (end of treatment)											
4: Dienstag 1999, Lai 1998, Schiff 2003, Yao 1999	RCTs	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	81/595 (13.6%)	20/286 (7%)	RR 2.02 (1.27 to 3.23)	71 more per 1000 (from 19 more to 156 more)	MODERATE
HBeAg seroconversion (end of treatment) - 52-week treatment											
3: Dienstag 1999, Lai 1998,	RCTs	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	52/311 (16.7%)	14/192 (7.3	RR 2.25 (1.28 to 3.93)	91 more per 1000 (from 20 more to 214 more)	MODERATE

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamivudine	placebo	Relative (95% CI)	Absolute	Quality
Schiff 2003								%)			
HBeAg seroconversion (end of treatment) - 12-week treatment											
1: Yao 1999	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29/284 (10.2%)	6/94 (6.4 %)	RR 1.6 (0.69 to 3.73)	38 more per 1000 (from 20 fewer to 174 more)	LOW
HBsAg seroconversion (end of treatment)											
1: Yao 1999	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/293 (5.1%)	4/99 (4%)	RR 1.27 (0.43 to 3.73)	11 more per 1000 (from 23 fewer to 110 more)	LOW
HBsAg seroconversion (end of treatment) - 12-week treatment											
1: Yao 1999	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/293 (5.1%)	4/99 (4%)	RR 1.27 (0.43 to 3.73)	11 more per 1000 (from 23 fewer to 110 more)	LOW
Histologic improvement (end of treatment)											
3: Dienstag 1999, Lai 1998, Schiff 2003	RCTs	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	176/328 (53.7%)	48/199 (24.1%)	RR 2.2 (1.68 to 2.88)	289 more per 1000 (from 164 more to 453 more)	MODERATE
Histologic improvement (end of treatment) - 52-week treatment											
3: Dienstag 1999, Lai 1998, Schiff	RCTs	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	176/328 (53.7%)	48/199 (24.1%)	RR 2.2 (1.68 to 2.88)	289 more per 1000 (from 164 more to 453 more)	MODERATE

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamivudine	placebo	Relative (95% CI)	Absolute	Quality
2003											
Genotypic mutation (end of treatment)											
2: Dienstag 1999, Lai 1998	RCTs	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	34/187 (18.2%)	0/143 (0%)	RR 30.18 (4.33 to 210.19)	-	MODERATE
Genotypic mutation (end of treatment) - 52-week treatment											
2: Dienstag 1999, Lai 1998	RCTs	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	34/187 (18.2%)	0/143 (0%)	RR 30.18 (4.33 to 210.19)	-	MODERATE
ALT normalization (end of treatment)											
4: Dienstag 1999, Lai 1998, Schiff 2003, Yao 1999	RCTs	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	237/427 (55.5%)	39/223 (17.5%)	RR 2.91 (2.18 to 3.89)	334 more per 1000 (from 206 more to 505 more)	MODERATE
ALT normalization (end of treatment) - 52 week treatment											
3: Dienstag 1999, Lai 1998, Schiff 2003	RCTs	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	146/276 (52.9%)	25/172 (14.5%)	RR 3.39 (2.34 to 4.9)	347 more per 1000 (from 195 more to 567 more)	MODERATE
ALT normalization (end of treatment) - 12-week treatment											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamivudine	placebo	Relative (95% CI)	Absolute	Quality
1: Yao 1999	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	91/151 (60.3%)	14/51 (27.5%)	RR 2.2 (1.38 to 3.49)	329 more per 1000 (from 104 more to 684 more)	MODERATE
HBeAg seroconversion (16 weeks follow up)											
1: Dienstag 1999	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/63 (17.5%)	6/69 (8.7%)	RR 2.01 (0.79 to 5.11)	88 more per 1000 (from 18 fewer to 357 more)	LOW
Loss of serum HBeAg (16 weeks follow up)											
1: Dienstag 1999	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	19/66 (28.8%)	11/71 (15.5%)	RR 1.86 (0.96 to 3.6)	133 more per 1000 (from 6 fewer to 403 more)	LOW
Loss of serum HBsAg (16 weeks follow up)											
1: Dienstag 1999	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/66 (1.5%)	0/71 (0%)	OR 3.27 (0.13 to 81.81)	-	LOW
% of patients with undetectable HBV DNA (<1.6 pg/ml) 16 weeks follow up											
1: Dienstag 1999	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/52 (32.7%)	16/53 (30.2%)	RR 1.08 (0.62 to 1.91)	24 more per 1000 (from 115 fewer to 275 more)	LOW
% of patients with undetectable HBV DNA (<1.6 pg/ml) 16 weeks follow up											
1: Dienstag 1999	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/52 (32.7%)	16/53 (30.2%)	RR 1.08 (0.62 to 1.91)	24 more per 1000 (from 115 fewer to 275 more)	LOW

[1] Randomisation and allocation concealment not stated
[2] Confidence interval compatible with three treatment decisions: benefit, no benefit or harm, or harm
[3] Confidence interval compatible with two clinical decisions: no benefit or harm, or benefit

Follow up studies (Leung, 2001, Chang 2004A)

People with chronic Hepatitis B HBeAg positive who received lamivudine 100 mg daily in the 1 year double blinded trial (Lai, 1998) entered a follow up study for up to 4 years treatment with lamivudine. 58 and 49 people entered the 3 and 4 year follow ups respectively.

The following table shows the comparative analysis of outcomes assessed at the end of 1 year of double blinded trial, at 3 and 4- year follow ups.

Table 97: Outcomes assessed at the end of first year RCT and at the end of 3 and 4 year follow ups with lamivudine

Outcomes	People received lamivudine for 1 year	People received lamivudine up to 3 years	People received lamivudine up to 4 years
% of people with detectable HBV DNA (>=1000 copies/mL)	55/117 (47%)	41/51 (80%)	Not reported
% of people with HBeAg seroconversion	33/303 (10.9%)	23/58 (40%)	27/58 (46.6%)
% of people with HBeAg loss	21/66 (31.8%)	0%	0%
% of people with ALT normalisation	95/161 (59%)	29/45 (64%)	31/45 (69%)
% of people with improvement in liver histology (>= point decrease in Knodell HAI score)		9/13 (69%)a	9/13 (69%)a
Incidence of resistance	-	27/51 (53%)	39/51 (76.4%)

[a] *Only 13 people had available biopsies at baseline*
[b] *The figures in this column include the people who experienced these outcomes during the 4 year follow up, so the values are cumulative of the experience of people after 4 year of treatment with lamivudine*

Table 98: Lamivudine versus placebo (severe cirrhosis but not decompensation)- clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamivudine versus placebo**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
Resistance mutation at end of follow up											
1: Liaw 2004	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	209/430 (48.6%)	11/214 (5.1%)	RR 9.46 (5.27 to 16.95)	435 more per 1000 (from 219 more to 820 more)	LOW

Comparison of interferon versus lamivudine

Table 99: Interferon versus lamivudine - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interferon**	**lamivudine**	**Relative (95% CI)**	**Absolute**	**Quality**	
HBeAg seroconversion at week 52												
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/64 (18.8 %)	14/80 (17.5%)	RR 1.07 (0.53 to 2.15)	12 more per 1000 (from 82 fewer to 201 more)	LOW	
Histological response at week 52												
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25/54 (46.3 %)	31/63 (49.2%)	RR 0.94 (0.64 to 1.38)	30 fewer per 1000 (from 177 fewer to 187 more)	LOW	
HBeAg loss at week 52												
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/56 (23.2 %)	14/60 (23.3%)	RR 0.99 (0.51 to 1.93)	2 fewer per 1000 (from 114 fewer to 217 more)	LOW	
Undetectable HBV DNA at week 52												
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/55 (29.1 %)	36/60 (60%)	RR 0.48 (0.31 to 0.77)	312 fewer per 1000 (from 138 fewer to 414 fewer)	MODERATE	
ALT normalisation at week 52												
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/55 (29.1 %)	33/58 (56.9%)	RR 0.51 (0.32 to 0.82)	279 fewer per 1000 (from 102 fewer to 387 fewer)	MODERATE	

Quality assessment							No of patients		Effect		Quality	
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interferon**	**lamivudine**	**Relative (95% CI)**	**Absolute**		
HBeAg seroconversion at week 64												
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/64 (21.9 %)	16/80 (20%)	RR 1.09 (0.58 to 2.07)	18 more per 1000 (from 84 fewer to 214 more)	LOW	
HBeAg loss at week 64												
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/48 (29.2 %)	13/62 (21%)	RR 1.39 (0.72 to 2.68)	82 more per 1000 (from 59 fewer to 352 more)	LOW	
Undetectable HBV DNA at week 64												
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/49 (28.6 %)	20/63 (31.7%)	RR 0.9 (0.51 to 1.59)	32 fewer per 1000 (from 156 fewer to 187 more)	LOW	
ALT normalisation at week 64												
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16/50 (32%)	13/63 (20.6%)	RR 1.55 (0.83 to 2.91)	113 more per 1000 (from 35 fewer to 394 more)	LOW	

[1] Incomplete allocation concealment. The lamivudine group was single blinded after week 8.
[2] The confidence interval is consistent with three clinical decisions (appreciable benefit, appreciable harm, no appreciable benefit or harm)

Comparison of pegylated interferon alfa-2a versus lamivudine

Table 100: Pegylated interferon alfa-2a versus Lamivudine - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peg	Lam	Relative (95% CI)	Absolute	Quality
% of people with undetectable HBV DNA (<400 copies/ml) (end of 48 weeks)											
1: Lau 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68/243 (28%)	108/230 (47%)	RR 0.6 (0.47 to 0.76)	188 fewer per 1000 (from 113 fewer to 249 fewer)	MODERATE
% of people with HBV DNA <100,000 copies/ml (end of 48 weeks)											
1: Lau 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	142/243 (58.4%)	169/230 (73.5%)	RR 0.8 (0.7 to 0.91)	147 fewer per 1000 (from 66 fewer to 220 fewer)	MODERATE
HBeAg seroconversion (48 weeks of treatment)											
1: Lau 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	72/243 (29.6%)	55/230 (23.9%)	RR 1.24 (0.92 to 1.67)	57 more per 1000 (from 19 fewer to 160 more)	LOW
HBeAg loss (48 weeks of treatment)											
1: Lau 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	81/243 (33.3%)	59/230 (25.7%)	RR 1.3 (0.98 to 1.72)	77 more per 1000 (from 5 fewer to 185 more)	LOW
Normalisation of ALT (48 weeks of treatment)											
1: Lau	randomis	seriou	no serious	no serious	no serious	none	105/	168/	RR 0.59 (0.5	299 fewer per 1000	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peg	Lam	Relative (95% CI)	Absolute	Quality
2005	ed trials	s[1]	inconsistency	indirectness	imprecision		243 (43.2%)	230 (73 %)	to 0.7)	(from 219 fewer to 365 fewer)	MODERATE
% of people withdrawn due to adverse events											
1: Lau 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/243 (3.3 %)	2/272 (0.7 %)	RR 4.48 (0.96 to 20.88)	26 more per 1000 (from 0 fewer to 146 more)	LOW
% of people with undetectable HBV DNA (<400 copies/ml) (24 weeks follow up)											
1: Lau 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39/243 (16 %)	14/230 (6.1 %)	RR 2.64 (1.47 to 4.73)	100 more per 1000 (from 29 more to 227 more)	MODERATE
% of people with HBV DNA <100,000 copies/ml (24 weeks follow up)											
1: Lau 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	86/243 (35.4%)	60/230 (26.1%)	RR 1.36 (1.03 to 1.79)	94 more per 1000 (from 8 more to 206 more)	MODERATE
HBeAg seroconversion (24 weeks follow up)											
1: Lau 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	87/243 (35.8%)	52/230 (22.6%)	RR 1.58 (1.18 to 2.12)	131 more per 1000 (from 41 more to 253 more)	MODERATE
HBeAg loss (24 weeks follow up)											
1: Lau 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	91/243 (37.	57/230 (24.	RR 1.51 (1.14 to 1.99)	126 more per 1000 (from 35 more to 245 more)	MODERATE

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Peg**	**Lam**	**Relative (95% CI)**	**Absolute**	**Quality**
							4%)	8%)			
Normalisation of ALT (24 weeks follow up)											
1: Lau 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	111/243 (45.7%)	76/230 (33%)	RR 1.38 (1.1 to 1.74)	126 more per 1000 (from 33 more to 245 more)	MODERATE

[1] Partially double blind study with no further details
[2] The confidence interval is consistent with two clinical decisions: appreciable benefit and no appreciable benefit or harm

Comparison of telbivudine versus adefovir

Table 101: Telbivudine versus adefovir - clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Telbivudine Frequency (%)/mean	Adefovir Frequency (%)/mean (SD)/mean	Relative Risk (95% CI)	Absolute	
Log reduction in HBV DNA (copies/ml) (assessed at the end of 52 weeks treatment)										
Chan 2007	1 RCT-unblinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Not assessed	6.56	6.44	0.84 (0.19, 1.49)*	-	-
% of people with undetectable HBV DNA (<300 copies/mL) (assessed at the end of 52 weeks treatment)										
Chan 2007	1 RCT-unblinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [c]	26/43 (60.5%)	17/42 (40.5%)	RR 1.49 (0.96 to 2.32)	198 more per 1000 (from 16 fewer to 534 more)	LOW
% of people with HBeAg loss (assessed at the end of 52 weeks)										
Chan 2007	1 RCT-unblinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [b]	13/43 (30.2%)	9/42 (21.4%)	RR 1.41 (0.68 to 2.94)	88 more per 1000 (from 69 fewer to 416 more)	VERY LOW

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Telbivudine Frequency (%)/mean	Adefovir Frequency (%)/mean (SD)/mean	Relative Risk (95% CI)	Absolute	
% of people with HBeAg seroconversion (assessed at the end of 52 weeks)										
Chan 2007	1 RCT-unblinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Very serious imprecision [(b)]	12/43 (27.9%)	8/42 (19%)	RR 1.47 (0.67 to 3.22)	90 more per 1000 (from 63 fewer to 423 more)	VERY LOW
% of people with ALT normalisation (assessed at the end of 52 weeks)										
Chan 2007	1 RCT-unblinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(c)]	35/43 (81.4%)	36/42 (85.7%)	RR 0.95 (0.79 to 1.15)	43 fewer per 1000 (from 180 fewer to 129 more)	LOW
% of people withdrawn due to adverse events										
Chan 2007	1 RCT-unblinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	0/42 (0%)	0/43 (0%)	not pooled	not pooled	MODERATE

(a) Investigators blinded to HBV serologic data from baseline to week 52. Unclear blinding in people/ staff from 3rd party agency that collected and analysed data
(b) Confidence interval is consistent with three clinical decision; appreciable benefit, no appreciable benefit or harm, appreciable harm.
(c) Confidence interval is consistent with two clinical decisions, no appreciable benefit or harm, appreciable harm.

*Based on the adjusted effect for baseline covariates (baseline HBV DNA leve, age, body mass index, sex and study site)

Comparison of telbivudine versus lamivudine

Table 102: Telbivudine versus lamivudine - clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Telbivudine Frequency (%)/ mean (SD)	Lamivudine Frequency (%)/ mean (SD)	Relative Risk (95% CI)	Absolute	
% of people with undetectable HBV DNA (<300 copies/ml) (assessed at the end of 52 weeks treatment)										
Hou, 2008A Lai 2007*	3 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	373/605 (61.7%)	241/606 (39.8%)	RR 1.55 (1.38 to 1.74)	219 more per 1000 (from 151 more to 294 more)	HIGH
% of people with undetectable HBV DNA (<200 copies/ml) (assessed at the end of 52 weeks treatment)										
Lai 2005	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision [(a)]	27/44 (61.4%)	6/19 (31.6%)	RR 1.94 (0.96 to 3.92)	297 more per 1000 (from 13 fewer to 922 more)	MODERATE
% of people with undetectable HBV DNA (<300 copies/ml) (assessed at the end of 104 weeks treatment)										
Liaw 2009	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	255/458 (55.7%)	178/463 (38.4%)	RR 1.45 (1.26 to 1.67)	173 more per 1000 (from 100 more to 258 more)	HIGH
% of people with HBeAg seroconversion (assessed at the end of 52 weeks treatment)										

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Telbivudine Frequency (%)/ mean (SD)	Lamivudine Frequency (%)/ mean (SD)	Relative Risk (95% CI)	Absolute	
Hou, 2008A Lai 2005 Lai 2007*	3 RCTs-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision [a]	153/649 (23.7%)	130/625 (20.8%)	RR 1.13 (0.92 to 1.39)	27 more per 1000 (from 17 fewer to 81 more)	MODERATE
% of people with HBeAg seroconversion (assessed at end of 104 weeks)										
Liaw 2009	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision [a]	136/458 (29.7%)	114/463 (24.6%)	RR 1.21 (0.97 to 1.49)	52 more per 1000 (from 7 fewer to 121 more)	MODERATE
% of people with HBeAg loss (assessed at the end of 52 weeks treatment)										
Hou, 2008A Lai 2005 Lai 2007*	3 RCTs-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision [a]	179/649 (27.6%)	142/625 (22.7%)	RR 1.2 (0.99 to 1.46)	45 more per 1000 (from 2 fewer to 105 more)	MODERATE
% of people with HBeAg loss (assessed at end of 104 weeks)										
Liaw 2009	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[a]	161/458 (35.2%)	135/463 (29.2%)	RR 1.21 (1 to 1.46)	61 more per 1000 (from 0 more to 134 more)	MODERATE
% of people with HBsAg loss (assessed at end of 104 weeks)										
Hou, 2008A Lai 2005	3 RCTs-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision [b]	6/458 (1.3%)	6/463 (1.3%)	RR 1.01 (0.33 to 3.11)	0 more per 1000 (from 9 fewer to	LOW

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Telbivudine Frequency (%)/ mean (SD)	Lamivudine Frequency (%)/ mean (SD)	Relative Risk (95% CI)	Absolute	
Lai 2007*									27 more)	
% of people with HBsAg seroconversion (assessed at end of 104 weeks)										
Liaw 2009	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision [(b)]	2/458 (0.44%)	3/463 (0.65%)	RR 0.67 (0.11 to 4.01)	2 fewer per 1000 (from 6 fewer to 20 more)	LOW
% of people with ALT normalisation (assessed at the end of 52 weeks treatment)										
Hou, 2008A Lai 2005 Lai 2007*	3 RCTS-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	510/649 (78.6%)	466/625 (74.6%)	RR 1.05 (0.99 to 1.12)	37 more per 1000 (from 7 fewer to 89 more)	HIGH
% of people with ALT normalisation (assessed at end of 104 weeks)										
Liaw 2009	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	318/458 (69.4%)	286/463 (61.8%)	RR 1.12 (1.02 to 1.23)	74 more per 1000 (from 12 more to 142 more)	HIGH
Incidence of resistance (viral breakthrough accompanied by genotypic mutation) (assessed at the end of 52 weeks treatment)										
Hou, 2008A Lai 2005 Lai 2007*	3 RCTS-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	36/649 (5.5%)	74/625 (11.8%)	RR 0.47 (0.32 to 0.69)	63 fewer per 1000 (from 37 fewer to 81 fewer)	HIGH
Incidence of resistance (viral breakthrough accompanied with genotypic mutation) (assessed at end of 104 weeks)										

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Telbivudine Frequency (%)/ mean (SD)	Lamivudine Frequency (%)/ mean (SD)	Relative Risk (95% CI)	Absolute	
Liaw 2009	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	115/458 (25.1%)	183/463 (39.5%)	RR 0.64 (0.52 to 0.77)	142 fewer per 1000 (from 91 fewer to 190 fewer)	HIGH
Viral breakthrough (assessed at the end of 52 weeks treatment)										
Lai 2005	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	2/44 (4.5%)	3/19 (15.8%)	RR 0.29 (0.05 to 1.59)	112 fewer per 1000 (from 150 fewer to 93 more)	LOW
% of people with histologic improvement (assessed at the end of 52 weeks treatment)										
Lai 2007*	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (a)	296/458 (64.6%)	261/463 (56.4%)	RR 1.15 (1.03 to 1.27)	85 more per 1000 (from 17 more to 152 more)	MODERATE
% of people withdrawn due to adverse events										
Lai 2005 Lai 2007*	2 RCTs-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	1/731 (0.14%)	1/699 (0.14%)	RR 0.99 (0.06 to 15.79)	0 fewer per 1000 (from 1 fewer to 21 more)	VERY LOW

(a) Confidence interval is consistent with two clinical decisions; no appreciable harm or benefit, appreciable benefit.
(b) Confidence interval is consistent with three clinical decisions ; appreciable harm, no appreciable harm or benefit, appreciable benefit.
**Lai 2007 is the same RCT as Liaw 2009, but reported outcomes at week 52.*

Comparison of tenofovir versus adefovir

Table 103: Tenofovir versus adefovir - clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Tenofovir Frequency (%)/ mean (SD)	Adefovir Frequency (%)/ mean (SD)	Relative Risk/ Mean difference (95% CI)	Absolute	
Log reduction HBV DNA (assessed at the end of 48 weeks treatment)										
Marcellin 2008	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	6.18 (0.9)	3.9 (1.6)	2.25 (1.88 TO 2.62)	MD 2.25 higher (1.88 to 2.62 higher)	HIGH
% of people with HBV DNA <400 copies/mL (assessed at the end of 48 weeks treatment)										
Marcellin 2008	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	133/160 (83.1%)	12/84 (14.3%)	RR 5.82 (3.43 to 9.87)	689 more per 1000 (from 347 more to 1000 more)	HIGH
% people with HBeAg seroconversion (assessed at the end of 48 weeks treatment)										
Marcellin 2008	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision[a]	32/153 (20.9%)	14/80 (17.5%)	RR 1.2 (0.68 to 2.11)	35 more per 1000 (from 56 fewer to 194 more)	LOW
% of people with HBsAg loss (assessed at the end of 48 weeks treatment)										
Marcellin 2008	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision[a]	5/158 (3.2%)	0/82 (0%)	Peto OR 4.69 (0.73 to 30.22	30 more per 1000 (from 0 fewer to 60 more)	LOW

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Tenofovir Frequency (%)/ mean (SD)	Adefovir Frequency (%)/ mean (SD)	Relative Risk/ Mean difference (95% CI)	Absolute	
% of people with ALT normalisation (assessed at the end of 48 weeks treatment)										
Marcellin 2008	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[b]	115/169 (68%)	49/90 (54.4%)	RR 1.25 (1.01 to 1.55)	136 more per 1000 (from 5 more to 299 more)	MODERATE
% of people with histologic improvement (assessed at the end of 48 weeks treatment)										
Marcellin 2008	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (b)	131/176 (74.4%)	61/90 (67.8%)	RR 1.1 (0.93 to 1.3)	68 more per 1000 (from 47 fewer to 203 more)	MODERATE
Incidence of resistance (assessed at the end of 48 weeks treatment)										
Marcellin 2008	1 RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness (c)	No serious imprecision	0/426 (0%)	0/215 (0%)	not pooled	not pooled	MODERATE
% of people withdrawn due to adverse events										
Marcellin 2008	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	0/176 (0%)	0/90 (0%)	not pooled	not pooled	HIGH

(a) *The confidence interval is consistent with three clinical decisions; appreciable clinical harm, no appreciable clinical harm or benefit and appreciable clinical benefit.*
(b) *The confidence interval is consistent with two clinical decisions; no appreciable clinical benefit or harm and appreciable clinical benefit*
(c) *Results were reported for a mixed group of HBeAg positive and negative adults with CHB.*

Comparison of entecavir versus lamivudine

Table 104: Entecavir versus lamivudine - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Entecavir	Lamivudine (HBeAg positive)	Relative (95% CI)	Absolute	Quality
Log reduction of HBV DNA (end of treatment) (Better indicated by higher values)											
3: Chang 2006; Shindo 2009A; Yao 2007A	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	597	575	-	MD 1.46 higher (1.25 to 1.66 higher)	LOW
% with undetectable HBV DNA (<300 copies/mL) (end of treatment week 48)											
3: Chang 2006; Ren 2007; Yao 2007A	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	417/586 (71.2%)	220/563 (39.1%)	RR 1.82 (1.62 to 2.04)	320 more per 1000 (from 242 more to 406 more)	MODERATE
% with undetectable HBV DNA (<0.7MEq/mL) (end of treatment week 48)											
2: Chang 2006; Shindo 2009A	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	354/372 (95.2%)	263/354 (74.3%)	RR 1.28 (1.2 to 1.37)	208 more per 1000 (from 149 more to 275 more)	LOW

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Entecavir	Lamivudine (HBeAg positive)	Relative (95% CI)	Absolute	Quality
% with HBeAg loss (end of treatment week 48)											
3: Chang 2006; Shindo 2009A; Yao 2007A	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	120/593 (20.2%)	115/572 (20.1%)	RR 1 (0.8 to 1.26)	0 fewer per 1000 (from 40 fewer to 52 more)	MODERATE
% with HBeAg seroconversion (end of treatment week 48)											
4: Chang 2006; Ren 2007; Shindo 2009A; Yao 2007A	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	111/614 (18.1%)	108/593 (18.2%)	RR 0.99 (0.78 to 1.25)	2 fewer per 1000 (from 40 fewer to 46 more)	MODERATE
% with ALT normalisation (end of treatment week 48)											
4: Chang 2006; Ren 2007; Shindo 2009A;	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	484/616 (78.6%)	426/595 (71.6%)	RR 1.1 (1.03 to 1.17)	72 more per 1000 (from 21 more to 122 more)	MODERATE
% with HBsAg loss (end of treatment week 48)											
1: Chang 2006	randomised	no serious	no serious inconsi	no serious	very seriou	none	6/340 (1.8%)	4/321 (1.2%)	OR 1.42 (0.4	5 more per 1000 (from 7	LOW

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Entecavir	Lamivudine (HBeAg positive)	Relative (95% CI)	Absolute	Quality
	trials	risk of bias	stency	indirectness	s[3]				to 5.09)	fewer to 48 more)	
% discontinuation due to adverse events (end of treatment week 48)											
2: Chang 2006; Shindo 2009A	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/386 (0.5%)	11/388 (2.8%)	OR 0.18 (0.04 to 0.81)	23 fewer per 1000 (from 5 fewer to 27 fewer)	MODERATE
Histologic improvement											
1: Chang 2006	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	226/292 (77.4%)	195/269 (72.5%)	RR 1.07 (0.97 to 1.18)	51 more per 1000 (from 22 fewer to 130 more)	HIGH
Viral breakthrough											
1: Chang 2006	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/340 (1.8%)	63/321 (19.6%)	RR 0.09 (0.04 to 0.2)	179 fewer per 1000 (from 157 fewer to 188 fewer)	HIGH

[1] One or two of the studies did not report details of randomisation or allocation concealment
[2] Heterogeneity
[3] Confidence interval compatible with three clinical decisions: harm, no harm or benefit, or benefit

Comparison of entecavir versus adefovir

Table 105: Entecavir versus adefovir - clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Frequency (%)	Frequency (%)	Relative Risk (95% CI)	Absolute	
% of people with undetectable DNA (<300 copies/ml) (assessed at the end of 48 weeks)										
Leung 2009	RCT-unblinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	19/33 (57.6%)	6/32 (18.8%)	RR 3.07 (1.41 to 6.69)	388 more per 1000 (from 77 more to 1000 more)	MODERATE
% of people with HBeAg seroconversion (assessed at the end of 48 weeks)										
Leung 2009	RCT-unblinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Very serious imprecision [(b)]	5/33 (15.2%)	7/32 (21.9%)	RR 0.69 (0.24 to 1.96)	68 fewer per 1000 (from 166 fewer to 210 more)	VERY LOW
% of people with loss of HBeAg (assessed at the end of 48 weeks)										
Leung 2009	RCT-unblinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Very serious imprecision [(b)]	6/33 (18.2%)	7/32 (21.9%)	RR 0.83 (0.31 to 2.21)	37 fewer per 1000 (from 151 fewer to 265 more)	VERY LOW
% of people with ALT normalisation (assessed at the end of 48 weeks)										
Leung 2009	RCT-unblinded	Serious limitations [(a)]	No serious inconsistenc	No serious indirectness	Serious imprecision	25/33 (75.8%)	20/32 (62.5%)	RR 1.21 (0.87 to	131 more per 1000	LOW

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Frequency (%)	Frequency (%)	Relative Risk (95% CI)	Absolute	
			y		(c)			1.69)	(from 81 fewer to 431 more)	
% of people withdrawn due to adverse events										
Leung 2009	RCT-unblinded	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	1/33 (3%)	0/36 (0%)	PETO OR 8.09 (0.16 to 409.34)	30 more per 1000 (from 50 fewer to 110 more)	VERY LOW

(a) *Unblinded study with no information on randomization or allocation concealment.*
(b) *Confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable benefit.*
(c) *Confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm*

Table 106: Comparison of entecavir plus tenofovir versus entecavir alone

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Entecavir + tenofovir**	**Entecavir alone**	**Relative (95% CI)**	**Absolute**	**Quality**
HBV DNA <50 IU/mL at 48 weeks											
1 Lok 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	158/197 (80.2%)	128/182 (70.3%)	RR 1.14 (1.01 to 1.28)	98 more per 1000 (from 7 more to 197 more)	LOW
								70.3%		98 more per 1000 (from 7 more to 197 more)	
ALT normalisation at 48 weeks											
1 Lok 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	143/197 (72.6%)	151/182 (83%)	RR 0.87 (0.79 to 0.97)	108 fewer per 1000 (from 25 fewer to 174 fewer)	LOW
								83%		108 fewer per 1000 (from 25 fewer to 174 fewer)	
HBeAg loss at 48 weeks											
1 Lok 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	27/138 (19.6%)	32/126 (25.4%)	RR 0.77 (0.49 to 1.21)	58 fewer per 1000 (from 130 fewer to 53 more)	VERY LOW
								25.4%		58 fewer per 1000 (from 130 fewer to 53 more)	
HBeAg seroconversion at 48 weeks											
1 Lok	randomis	seriou	no serious	serious[2]	serious4	none	25/138	28/126	RR 0.82	40 fewer per 1000	

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Entecavir + tenofovir**	**Entecavir alone**	**Relative (95% CI)**	**Absolute**	
2012	ed trials	s[1]	inconsistency				(18.1%)	(22.2%)	(0.5 to 1.32)	(from 111 fewer to 71 more)	VERY LOW
								22.2%		40 fewer per 1000 (from 111 fewer to 71 more)	
HBsAg loss at 48 weeks											
1 Lok 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious4	none	2/197 (1%)	4/182 (2.2%)	RR 0.46 (0.09 to 2.49)	12 fewer per 1000 (from 20 fewer to 33 more)	VERY LOW
								2.2%		12 fewer per 1000 (from 20 fewer to 33 more)	
HBsAg seroconversion at 48 weeks											
1 Lok 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious4	none	1/197 (0.5%)	1/182 (0.5%)	RR 0.92 (0.06 to 14.66)	0 fewer per 1000 (from 5 fewer to 75 more)	VERY LOW
								0.6%		0 fewer per 1000 (from 6 fewer to 82 more)	
HBV DNA <50 IU/mL at 96 weeks											
1 Lok 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	164/197 (83.2%)	139/182 (76.4%)	RR 1.09 (0.98 to 1.21)	69 more per 1000 (from 15 fewer to 160 more)	LOW
								76.4%		69 more per 1000 (from 15 fewer to 160 more)	
ALT normalisation at 96 weeks											

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Entecavir + tenofovir**	**Entecavir alone**	**Relative (95% CI)**	**Absolute**	**Quality**
1 Lok 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	136/197 (69%)	149/182 (81.9%)	RR 0.84 (0.75 to 0.95)	131 fewer per 1000 (from 41 fewer to 205 fewer)	LOW
								81.9%		131 fewer per 1000 (from 41 fewer to 205 fewer)	
HBeAg loss at 96 weeks											
1 Lok 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	41/138 (29.7%)	49/126 (38.9%)	RR 0.76 (0.55 to 1.07)	93 fewer per 1000 (from 175 fewer to 27 more)	VERY LOW
								38.9%		93 fewer per 1000 (from 175 fewer to 27 more)	
HBeAg seroconversion at 96 weeks											
1 Lok 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	30/138 (21.7%)	41/126 (32.5%)	RR 0.67 (0.45 to 1)	107 fewer per 1000 (from 179 fewer to 0 more)	VERY LOW
								32.5%		107 fewer per 1000 (from 179 fewer to 0 more)	
HBsAg loss at 96 weeks											
1 Lok 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	7/197 (3.6%)	5/182 (2.7%)	RR 1.29 (0.42 to 4)	8 more per 1000 (from 16 fewer to 82 more)	VERY LOW
								2.8%		8 more per 1000 (from 16 fewer to 84 more)	
HBsAg seroconversion at 96 weeks											

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Entecavir + tenofovir**	**Entecavir alone**	**Relative (95% CI)**	**Absolute**	
1 Lok 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	4/197 (2%)	2/182 (1.1%)	RR 1.85 (0.34 to 9.97)	9 more per 1000 (from 7 fewer to 99 more)	VERY LOW
								1.1%		9 more per 1000 (from 7 fewer to 99 more)	
Virologic breakthrough at 96 weeks											
1 Lok 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	7/197 (3.6%)	2/182 (1.1%)	RR 3.23 (0.68 to 15.36)	25 more per 1000 (from 4 fewer to 158 more)	VERY LOW
								1.1%		25 more per 1000 (from 4 fewer to 158 more)	
Discontinued due to adverse events											
1 Lok 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	5/197 (2.5%)	2/182 (1.1%)	RR 2.31 (0.45 to 11.76)	14 more per 1000 (from 6 fewer to 118 more)	VERY LOW
								1.1%		14 more per 1000 (from 6 fewer to 118 more)	

[1] Open label study
[2] Not standard dose of tenofovir
[3] Confidence interval compatible with two decisions: harm, or neither harm nor benefit
[4] Confidence interval compatible with three clinical decisions: harm, neither benefit nor harm, or benefit

Table 107: Comparison of of interferon alpha plus lamivudine versus placebo

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamivudine + IFN	placebo	Relative (95% CI)	Absolute	Quality
% of patients with undetectable HBV DNA (<1.6 pg/ml) at 52 weeks											
1: Schiff 2003	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	13/57 (22.8%)	9/54 (16.7%)	RR 1.37 (0.64 to 2.94)	62 more per 1000 (from 60 fewer to 323 more)	MODERATE
Loss of serum HBeAg - 52-weeks											
1: Schiff 2003	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	13/63 (20.6%)	7/54 (13%)	RR 1.59 (0.68 to 3.7)	76 more per 1000 (from 41 fewer to 350 more)	MODERATE
HBeAg seroconversion - 52-weeks											
1: Schiff 2003	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	7/57 (12.3%)	7/53 (13.2%)	RR 0.93 (0.35 to 2.47)	9 fewer per 1000 (from 86 fewer to 194 more)	MODERATE
Histologic improvement - 52-weeks											
1: Schiff 2003	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20/63 (31.7%)	14/56 (25%)	RR 1.27 (0.71 to 2.27)	67 more per 1000 (from 73 fewer to 317 more)	MODERATE
ALT normalization (end of treatment) - 52 weeks											
1: Schiff 2003	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	11/62 (17.7%)	8/54 (14.8%)	RR 1.2 (0.52 to 2.76)	30 more per 1000 (from 71 fewer to 261 more)	MODERATE

[1] Confidence interval compatible with three clinical decisions: benefit, no benefit or harm, or harm

Comparison of interferon alpha plus lamivudine versus interferon alpha

Table 108: Interferon alpha plus lamivudine versus interferon alpha- clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamivudine + Interferon alpha**	**IFN alone**	**Relative (95% CI)**	**Absolute**	**Quality**
Undetectable HBV DNA - 24 weeks of treatment											
2: Cindoruk 2002; Yalcin 2003	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	58/83 (69.9%)	30/65 (46.2%)	RR 1.43 (1.03 to 1.98)	198 more per 1000 (from 14 more to 452 more)	LOW
Undetectable HBV DNA - 52 weeks of treatment											
2: Ayaz 2006; Yalcin 2003	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	61/64 (95.3%)	31/48 (64.6%)	RR 1.47 (1.17 to 1.85)	304 more per 1000 (from 110 more to 549 more)	MODERATE
Undetectable HBV DNA - After 6 months of follow up											
2: Ayaz 2006; Cindoruk 2002	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	51/81 (63%)	31/83 (37.3%)	RR 1.69 (1.22 to 2.35)	258 more per 1000 (from 82 more to 504 more)	LOW
Undetectable HBV DNA - After 12 months of follow up											
1: Yalcin 2003	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	15/33 (45.5%)	3/15 (20%)	RR 2.27 (0.77 to 6.69)	254 more per 1000 (from 46 fewer to 1000 more)	LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamivudine + Interferon alpha	IFN alone	Relative (95% CI)	Absolute	
HBeAg seroconversion - At 6 months of treatment											
1: Yalcin 2003	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	18/33 (54.5%)	5/15 (33.3%)	RR 1.64 (0.75 to 3.57)	213 more per 1000 (from 83 fewer to 857 more)	LOW
HBeAg seroconversion - At 12 months of treatment											
2: Ayaz 2006; Yalcin 2003	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	26/64 (40.6%)	11/94 (22.4%)	RR 1.39 (0.8 to 2.43)	88 more per 1000 (from 45 fewer to 321 more)	LOW
HBeAg seroconversion - After 1 year of follow up											
1: Yalcin 2003	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	18/33 (54.5%)	3/15 (20%)	RR 2.73 (0.95 to 7.86)	346 more per 1000 (from 10 fewer to 1000 more)	LOW
HBsAg loss at end of treatment											
2: Ayaz 2006; Yalcin 2003	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	2/62 (3.2%)	0/48 (0%)	RR 2.5 (0.13 to 49.05)	-	LOW
ALT normalisation - At 6 months of treatment											
2: Cindoruk 2002; Yalcin 2003	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	61/83 (73.5%)	33/65 (50.8%)	RR 1.56 (1.19 to 2.03)	284 more per 1000 (from 96 more to 523 more)	MODERATE
ALT normalisation - At 12 months of treatment											
2: Ayaz	randomis	serio	no serious	no serious	serious[4]	none	48/64	28/4	RR 1.21	123 more per	

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamivudine + Interferon alpha**	**IFN alone**	**Relative (95% CI)**	**Absolute**	
2006; Yalcin 2003	ed trials	us[1]	inconsistency	indirectness			(75%)	8 (58.3 %)	(0.92 to 1.59)	1000 (from 47 fewer to 344 more)	LOW
ALT normalisation - After 6 months of follow up											
2: Ayaz 2006; Cindoruk 2002	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	45/81 (55.6%)	33/83 (39.8 %)	RR 1.39 (1.01 to 1.91)	155 more per 1000 (from 4 more to 362 more)	MODERATE
ALT normalisation - After 1 year of follow up											
1: Yalcin 2003	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	16/33 (48.5%)	3/15 (20%)	RR 2.42 (0.83 to 7.08)	284 more per 1000 (from 34 fewer to 1000 more)	LOW
Histological response											
1: Yalcin 2003	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[4]	none	26/31 (83.9%)	4/15 (26.7 %)	RR 3.15 (1.34 to 7.38)	573 more per 1000 (from 91 more to 1000 more)	VERY LOW

[1] Randomisation/allocation concealment unclear or incomplete
[2] Heterogeneity
[3] Confidence interval compatible with three clinical decisions: harm; no harm or benefit; benefit
[4] Confidence interval compatible with two clinical decisions: no harm or benefit; or benefit

Comparison of of pegylated interferon alpha-2a plus lamivudine versus pegylated interferon alpha-2a

Table 109: Pegylated interferon alpha-2a plus lamivudine versus pegylated interferon alpha-2a- plus placebo: clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				Quality
							No of people		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pegIFNa2a + LAM	pegIFNa2a (HBeAg positive)	Relative (95% CI)	Absolute	
HBV DNA log reduction (copies/ml) (assessed at the end of 48 week treatment)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	none	7.2 (2.4)	4.5 (3.2)		MD 2.7 higher (2.2 to 3.2 higher)	MODERATE
% of people with undetectable HBV DNA (<400 copies/ml) (assessed at the end of 48 week treatment)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	none	186/246 (75.6%)	68/243 (28%)	RR 2.7 (2.18 to 3.35)	476 more per 1000 (from 330 more to 658 more)	MODERATE
% of people with HBeAg loss (assessed at the end of 48 week treatment)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	73/246 (29.7%)	81/243 (33.3%)	RR 0.89 (0.69 to 1.16)	37 fewer per 1000 (from 103 fewer to 53 more)	LOW
% of people with HBeAg seroconversion (assessed at the end of 48 week treatment)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [c]	none	64/246 (26%)	72/243 (29.6%)	RR 0.88 (0.66 to 1.17)	36 fewer per 1000 (from 101 fewer to 50 more)	LOW
% of people with ALT normalisation (assessed at the end of 48 week treatment)											
1 Lau	RCT-	Serious	No serious	No serious	Serious	none	126/246	105/243	RR 1.19 (0.98	82 more per 1000	

Quality assessment							Summary of findings				Quality
2005	partially double blinded	limitations [a]	inconsistency	indirectness	imprecision [b]		(51.2%)	(43.2%)	to 1.43)	(from 9 fewer to 186 more)	LOW
HBV DNA log reduction (copies/ml) (assessed at the end of 24 week follow up)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [d]	none	2.7 (3.66)	2.4 (3.2)	-	MD 0.3 higher (0.3 lower to 0.9 higher)	LOW
% of people with HBV DNA < 100,000 copies/ml (assessed at the end of 24 week follow up)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision	none	91/246 (37%)	86/243 (35.4%)	RR 1.05 (0.83 to 1.32)	18 more per 1000 (from 60 fewer to 113 more)	LOW
% of people with HBeAg loss (assessed at the end of 24 week follow up)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [c]	none	77/246 (31.3%)	91/243 (37.4%)	RR 0.84 (0.65 to 1.07)	60 fewer per 1000 (from 131 fewer to 26 more)	LOW
% of people with HBeAg seroconversion (assessed at the end of 24 week follow up)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [c]	none	74/246 (30.1%)	87/243 (35.8%)	RR 0.84 (0.65 to 1.08)	57 fewer per 1000 (from 125 fewer to 29 more)	LOW
% of people with ALT normalisation (assessed at the end of 24 week follow up)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [c]	none	106/246 (43.1%)	111/243 (45.7%)	RR 0.94 (0.77 to 1.15)	27 fewer per 1000 (from 105 fewer to 69 more)	LOW
% of people with histologic improvement (assessed at the end of 24 week follow up)											
1 Lau 2005	RCT-partially double	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	112/215 (52.1%)	102/207 (49.3%)	RR 1.06 (0.88 to 1.28)	30 more per 1000 (from 59 fewer to 138 more)	LOW

Quality assessment							Summary of findings				Quality
	blinded										
Incidence of resistance (genotypic mutation)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(c)]	none	9/256 (3.5%)	0/243 (0%)	PETO OR 7.25 (1.94 to 27.08)	40 more per 1000 (from 10 more to 60 more)	LOW
% of people withdrawn due to adverse events											
1 Lau 2005	RCT-partially double blinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	none	12/271 (4.4%)	2/272 (0.74%)	RR 6.02 (1.36 to 26.65)	37 more per 1000 (from 3 more to 189 more)	MODERATE

(a) Partially double blind study with no further details.
(b) The confidence interval is consistent with two clinical decisions: appreciable benefit and no appreciable benefit or harm.
(c) (c) The confidence interval is consistent with two clinical decisions: appreciable harm and no appreciable benefit or harm. .

(d) The confidence interval is consistent with three clinical decisions: appreciable benefit, no appreciable benefit or harm and appreciable harm

Comparison of pegylated interferon alpha-2b plus lamivudine versus pegylated interferon alpha-2b

Table 110: Comparison of pegylated interferon alpha-2b plus lamivudine versus pegylated interferon alpha-2b - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Peg IFN alpha 2b + lam**	**peg IFN alpha 2b alone**	**Relative (95% CI)**	**Absolute**	
HBV DNA <200,000 copies/mL at end treatment											
1: Janssen	randomised trials	no serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	96/130 (73.8%)	40/136 (29.4%)	RR 2.51 (1.9 to	444 more per 1000 (from 265 more to	HIGH

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Peg IFN alpha 2b + lam**	**peg IFN alpha 2b alone**	**Relative (95% CI)**	**Absolute**	
2005		risk of bias							3.32)	682 more)	
Undetectable HBV DNA (<400 copies/mL) at end treatment											
1: Janssen 2005	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/130 (33.1%)	13/136 (9.6%)	RR 3.46 (1.95 to 6.13)	235 more per 1000 (from 91 more to 490 more)	HIGH
ALT normalisation at end treatment											
1: Janssen 2005	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	66/130 (50.8%)	46/136 (33.8%)	RR 1.5 (1.12 to 2.01)	169 more per 1000 (from 41 more to 342 more)	HIGH
HBeAg loss at end treatment											
1: Janssen 2005	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	57/130 (43.8%)	40/136 (29.4%)	RR 1.49 (1.08 to 2.06)	144 more per 1000 (from 24 more to 312 more)	HIGH
HBeAg seroconversion at end treatment											
1: Janssen 2005	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	33/130 (25.4%)	30/136 (22.1%)	RR 1.15 (0.75 to 1.77)	33 more per 1000 (from 55 fewer to 170 more)	MODERATE
HBsAg loss at end treatment											
1: Janssen 2005	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	9/130 (6.9%)	7/136 (5.1%)	RR 1.35 (0.52 to 3.51)	18 more per 1000 (from 25 fewer to 129 more)	LOW

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Peg IFN alpha 2b + lam**	**peg IFN alpha 2b alone**	**Relative (95% CI)**	**Absolute**	
HBsAg seroconversion at end treatment											
1: Janssen 2005	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/130 (6.2%)	6/136 (4.4%)	RR 1.39 (0.5 to 3.91)	17 more per 1000 (from 22 fewer to 128 more)	LOW
HBV DNA <200,000 copies/mL after 6 months follow up											
1: Janssen 2005	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	41/114 (36%)	37/118 (31.4%)	RR 1.15 (0.8 to 1.65)	47 more per 1000 (from 63 fewer to 204 more)	MODERATE
Undetectable HBV DNA (<400 copies/mL) after 6 months follow up											
1: Janssen 2005	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	12/114 (10.5%)	9/118 (7.6%)	RR 1.38 (0.6 to 3.15)	29 more per 1000 (from 31 fewer to 164 more)	LOW
ALT normalisation after 6 months follow up											
1: Janssen 2005	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	46/114 (40.4%)	44/118 (37.3%)	RR 1.08 (0.78 to 1.5)	30 more per 1000 (from 82 fewer to 186 more)	MODERATE
HBeAg loss after 6 months follow up											
1: Janssen 2005	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	46/114 (40.4%)	49/118 (41.5%)	RR 0.97 (0.71 to 1.32)	12 fewer per 1000 (from 120 fewer to 133 more)	LOW
HBeAg seroconversion after 6 months folllow up											

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Peg IFN alpha 2b + lam**	**peg IFN alpha 2b alone**	**Relative (95% CI)**	**Absolute**	
1: Janssen 2005	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	38/114 (33.3%)	39/118 (33.1%)	RR 1.01 (0.7 to 1.45)	3 more per 1000 (from 99 fewer to 149 more)	LOW
HBsAg loss after 6 months follow up											
1: Janssen 2005	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	9/114 (7.9%)	9/118 (7.6%)	RR 1.04 (0.43 to 2.51)	3 more per 1000 (from 43 fewer to 115 more)	LOW
HBsAg seroconversion after 6 months follow up											
1: Janssen 2005	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	9/114 (7.9%)	7/118 (5.9%)	RR 1.33 (0.51 to 3.45)	20 more per 1000 (from 29 fewer to 145 more)	LOW

[1] Confidence interval compatible with two clinical decisions: no harm or benefit, or benefit
[2] Confidence interval compatible with three clinical decisions: benefit, no harm or benefit, or harm

(a) The confidence interval is consistent with two clinical decisions; appreciable benefit and no appreciable benefit or harm.
(b) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.

Comparison of of interferon alpha plus lamivudine versus lamivudine

Table 111: Interferon alpha plus lamivudine versus lamivudine - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamivudine + Interferon alpha	lamivudine alone	Relative (95% CI)	Absolute	Quality
Undetectable HBV DNA - 24 weeks of treatment											
2: Barbaro 2001; Jang 2004	randomised trials	serious[1]	serious2	no serious indirectness	serious[3]	none	93/117 (79.5%)	84/117 (71.8%)	RR 1.11 (0.97 to 1.27)	79 more per 1000 (from 22 fewer to 194 more)	VERY LOW
Undetectable HBV DNA - 52 weeks of treatment											
4: Barbaro 2001; Jang 2004; Schiff 2003; Yuki 2008	randomised trials	serious[1]	serious2	no serious indirectness	serious[3]	none	102/204 (50%)	144/261 (55.2%)	RR 0.87 (0.74 to 1.03)	72 fewer per 1000 (from 143 fewer to 17 more)	LOW
Undetectable HBV DNA - 24 months of treatment											
1: Jang 2004	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/41 (100%)	42/42 (100%)	RR 1 (0.95 to 1.05)	0 fewer per 1000 (from 50 fewer to 50 more)	LOW
Viral breakthrough during treatment - At 6 months of treatment											
1: Jang 2004	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	2/41 (4.9%)	2/42 (4.8%)	RR 1.02 (0.15 to 6.93)	1 more per 1000 (from 40 fewer to 282 more)	VERY LOW
Viral breakthrough during treatment - At 1 year of treatment											
2: Barbaro 2001; Jang 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	5/117 (4.3%)	6/117 (5.1%)	RR 0.84 (0.26 to 2.68)	8 fewer per 1000 (from 38 fewer to 86	LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamivudine + Interferon alpha	lamivudine alone	Relative (95% CI)	Absolute	
										more)	
Viral breakthrough during treatment - At 24 months of treatment											
1: Jang 2004	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/41 (19.5%)	23/42 (54.8%)	RR 0.36 (0.18 to 0.7)	350 fewer per 1000 (from 164 fewer to 449 fewer)	LOW
HBeAg loss - At 6 months of treatment											
1: Jang 2004	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	9/41 (22%)	9/42 (21.4%)	RR 1.02 (0.45 to 2.32)	4 more per 1000 (from 118 fewer to 283 more)	VERY LOW
HBeAg loss - At 12 months of treatment											
2: Jang 2004; Schiff 2003	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[4]	none	32/104 (30.8%)	50/158 (31.6%)	RR 0.93 (0.63 to 1.38)	22 fewer per 1000 (from 117 fewer to 120 more)	VERY LOW
HBeAg loss - At 24 months of treatment											
1: Jang 2004	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	25/41 (61%)	17/42 (40.5%)	RR 1.51 (0.97 to 2.34)	206 more per 1000 (from 12 fewer to 542 more)	VERY LOW
HBeAg seroconversion - At 12 months of treatment											
4: Barbaro 2001; Schiff 2003; Yuki 2008	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	40/163 (24.5%)	44/217 (20.3%)	RR 1.11 (0.76 to 1.62)	22more per 1000 (from 49 fewer to 126 more)	LOW
HBeAg seroconversion - After 1 year of follow up											

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamivudine + Interferon alpha**	**lamivudine alone**	**Relative (95% CI)**	**Absolute**	**Quality**
1: Barbaro 2001	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/76 (32.9%)	11/75 (14.7%)	RR 2.24 (1.19 to 4.23)	182 more per 1000 (from 28 more to 474 more)	MODERATE
HBsAg loss at end of treatment											
2: Barbaro 2001; Schiff 2003	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	4/139 (2.9%)	2/194 (1%)	RR 3.78 (0.71 to 20.06)	29 more per 1000 (from 3 fewer to 196 more)	LOW
ALT normalisation - At 6 months of treatment											
1: Jang 2004	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/41 (90.2%)	41/42 (97.6%)	RR 0.92 (0.83 to 1.03)	78 fewer per 1000 (from 166 fewer to 29 more)	LOW
ALT normalisation - At 12 months of treatment											
3: Jang 2004; Schiff 2003; Yuki 2008	randomised trials	serious[1]	serious2	no serious indirectness	serious[3]	none	78/133 (58.6%)	111/191 (58.1%)	RR 0.89 (0.75 to 1.05)	64 fewer per 1000 (from 145 fewer to 29 more)	VERY LOW
ALT normalisation - At 24 months of treatment											
1: Jang 2004	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/41 (100%)	42/42 (100%)	RR 1 (0.95 to 1.05)	0 fewer per 1000 (from 50 fewer to 50 more)	LOW
ALT normalisation - 1 year follow up											
1: Barbaro 2001	randomised trials	serious[1]	no serious inconsistenc	no serious indirectnes	serious[3]	none	28/76 (36.8%)	17/75 (22.7%)	RR 1.63 (0.97 to	143 more per 1000 (from 7	LOW

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamivudine + Interferon alpha**	**lamivudine alone**	**Relative (95% CI)**	**Absolute**	
			y	s					2.71)	fewer to 388 more)	
Genotypic resistance during treatment											
3: Barbaro 2001; Jang 2004; Yuki 2008	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	16/105 (15.2%)	38/120 (31.7%)	RR 0.6 (0.37 to 0.99)	127 fewer per 1000 (from 3 fewer to 200 fewer)	LOW
Histological response - 52 weeks of treatment											
1: Schiff 2003	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/63 (31.7%)	62/119 (52.1%)	RR 0.61 (0.41 to 0.91)	203 fewer per 1000 (from 47 fewer to 307 fewer)	MODERATE

[1] Blinding/randomisation/allocation concealment unclear or incomplete
[2] Heterogeneity
[3] Confidence interval compatible with two clinical decisions: no harm or benefit, or benefit
[4] Confidence interval compatible with three clinical decisions: harm; no harm or benefit; or benefit

Comparison of pegylated interferon alpha-2a plus lamivudine versus lamivudine

Table 112: Pegylated interferon alpha-2a plus lamivudine versus lamivudine - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				Quality
							No of people		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**pegIFNa2a + LAM**	**LAM**	**Relative (95% CI)**	**Absolute**	

Quality assessment							Summary of findings				Quality
HBV DNA log reduction (copies/ml) (assessed at the end of 48 week treatment) (Better indicated by lower values)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	7.2 (2.4)	5.8 (2.8)	1.4 (0.94 to 1.86)	MD 1.4 higher (0.94 to 1.86 higher)	MODERATE
% of people with undetectable HBV DNA (<400 copies/ml) (assessed at the end of 48 week treatment))											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	186/246 (75.6%)	108/230 (47%)	RR 1.61 (1.38 to 1.88)	286 more per 1000 (from 178 more to 413 more)	MODERATE
% of people with HBeAg loss (assessed at the end of 48 week treatment)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	None	73/246 (29.7%)	59/230 (25.7%)	RR 1.16 (0.86 to 1.55)	41 more per 1000 (from 36 fewer to 141 more)	LOW
% of people with HBeAg seroconversion (assessed at the end of 48 week treatment)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	None	64/246 (26%)	55/230 (23.9%)	RR 1.09 (0.8 to 1.49)	22 more per 1000 (from 48 fewer to 117 more)	LOW
% of people with ALT normalisation (assessed at the end of 48 week treatment)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [c]	None	126/246 (51.2%)	168/230 (73%)	RR 0.7 (0.61 to 0.81)	219 fewer per 1000 (from 139 fewer to 285 fewer)	LOW
HBV DNA log reduction (copies/ml) (assessed at the end of 24 week follow up)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [d]	None	2.7 (3.6)	1.9 (3.2)	MD 0.8 (0.2 to 1.49)	MD 0.8 higher (0.2 to 1.4 higher)	LOW
% of people with HBV DNA (< 100,000 copies/ml) (assessed at the end of 24 week follow up)											

Quality assessment							Summary of findings				Quality
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	None	91/246 (37%)	60/230 (26.1%)	RR 1.42 (1.08 to 1.86)	110 more per 1000 (from 21 more to 224 more)	LOW
% of people with HBeAg loss (assessed at the end of 24 week follow up)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	None	77/246 (31.3%)	57/230 (24.8%)	RR 1.26 (0.94 to 1.69)	64 more per 1000 (from 15 fewer to 171 more)	LOW
% of people with HBeAg seroconversion (assessed at the end of 24 week follow up)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	None	74/246 (30.1%)	52/230 (22.6%)	RR 1.33 (0.98 to 1.81)	75 more per 1000 (from 5 fewer to 183 more)	LOW
% of people with ALT normalisation (assessed at the end of 24 week follow up)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	None	106/246 (43.1%)	76/230 (33%)	RR 1.3 (1.03 to 1.65)	99 more per 1000 (from 10 more to 215 more)	LOW
% of people with Histologic improvement (assessed at the end of 24 week follow up)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	None	112/215 (52.1%)	93/184 (50.5%)	RR 1.03 (0.85 to 1.25)	15 more per 1000 (from 76 fewer to 126 more)	LOW
Resistance (genotypic mutation)											
1 Lau 2005	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	9/256 (3.5%)	69/254 (27.2%)	RR 0.13 (0.07 to 0.25)	236 fewer per 1000 (from 204 fewer to 253 fewer)	MODERATE
% of people withdrawn due to adverse events											
1 Lau	RCT-partially	Serious limitations	No serious	No serious	No serious	None	12/271	2/272	RR 6.02 (1.36 to	37 more per 1000 (from 3 more to 189	MODERATE

Quality assessment							Summary of findings				Quality
2005	double blinded	[a]	inconsistency	indirectness	imprecision		(4.4%)	(0.74%)	26.65)	more)	

(a) Partially double blind study with no follow uprther details.
(b) The confidence interval is consistent with two clinical decisions: appreciable benefit and no appreciable benefit or harm.
(c) The confidence interval is consistent with two clinical decisions: appreciable harm and appreciable benefit or harm.
(d) The mean difference did not reach default MID.

Comparison of pegylated interferon alpha-2b plus lamivudine versus lamivudine

Table 113: Pegylated interferon alpha-2b plus lamivudine versus lamivudine - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		Quality	
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PegIFN alpha-2b + lam**	**lamivudine alone**	**Relative (95% CI)**	**Absolute**		
HBV DNA <100 copies/mL at end treatment												
1: Chan 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[s2]	none	5/48 (10.4%)	2/48 (4.2%)	RR 2.5 (0.51 to 12.26)	63 more per 1000 (from 20 fewer to 469 more)	VERY LOW	
Resistance at end treatment												
1: Chan 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	10/48 (20.8%)	19/48 (39.6%)	RR 0.53 (0.27 to 1.01)	186 fewer per 1000 (from 289 fewer to 4 more)	LOW	
ALT normalisation at end treatment												
1: Chan 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	45/50 (90%)	39/50 (78%)	RR 1.15 (0.97 to 1.37)	117 more per 1000 (from 23 fewer to 289 more)	LOW	
Histological improvement at end treatment												
1: Chan 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/40 (10%)	4/44 (9.1%)	RR 1.1 (0.29 to 4.11)	9 more per 1000 (from 65 fewer to 283 more)	VERY LOW	

Quality assessment							No of patients		Effect		Quality	
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PegIFN alpha-2b + lam**	**lamivudine alone**	**Relative (95% CI)**	**Absolute**		
HBeAg loss at end treatment												
1: Chan 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/48 (62.5%)	14/48 (29.2%)	RR 2.14 (1.31 to 3.51)	333 more per 1000 (from 90 more to 732 more)	MODERATE	
HBeAg seroconversion at end treatment												
1: Chan 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/48 (62.5%)	14/48 (29.2%)	RR 2.14 (1.31 to 3.51)	333 more per 1000 (from 90 more to 732 more)	MODERATE	
HBsAg loss at end treatment												
1: Chan 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/48 (2.1%)	0/48 (0%)	OR 3.06 (0.12 to 77.09)	-	VERY LOW	
HBV DNA <100 copies/mL at 24 weeks follow up												
1: Chan 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/43 (7%)	2/37 (5.4%)	OR 1.31 (0.21 to 8.31)	16 more per 1000 (from 42 fewer to 268 more)	VERY LOW	
ALT normalisation at 24 weeks follow up												
1: Chan 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	25/50 (50%)	15/50 (30%)	RR 1.67 (1 to 2.76)	201 more per 1000 (from 0 more to 528 more)	LOW	

[1] Unblinded study
[2] Confidence interval compatible with three clinical decisions: harm, no harm or benefit, or benefit
[3] Confidence interval compatible with two clinical decisions: benefit, or no harm or benefit

Comparison of adefovir plus lamivudine versus lamivudine

Table 114: Adefovir plus lamivudine versus lamivudine - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamivudine plus adefovir versus lamivudine**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**
HBV DNA < 10000 copies/mL at 52 weeks											
1: Sung 2008	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31/53 (58.5%)	29/56 (51.8%)	RR 1.13 (0.8 to 1.59)	67 more per 1000 (from 104 fewer to 306 more)	LOW
Undetectable HBV DNA < 200 copies/mL at 52 weeks											
1: Sung 2008	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	21/53 (39.6%)	23/56 (41.1%)	RR 0.96 (0.61 to 1.52)	16 fewer per 1000 (from 160 fewer to 214 more)	VERY LOW
ALT normalisation at 52 weeks											
1: Sung 2008	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/51 (47.1%)	39/56 (69.6%)	RR 0.68 (0.48 to 0.95)	223 fewer per 1000 (from 35 fewer to 362 fewer)	MODERATE
HBeAg loss at 52 weeks											
1: Sung 2008	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/52 (11.5%)	12/54 (22.2%)	RR 0.52 (0.21 to 1.28)	107 fewer per 1000 (from 176 fewer to 62 more)	VERY LOW
HBeAg seroconversion at 52 weeks											
1: Sung 2008	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/52 (9.6%)	9/54 (16.	RR 0.58 (0.21 to 1.61)	70 fewer per 1000 (from 132 fewer to 102 more)	VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamivudine plus adefovir versus lamivudine	Control	Relative (95% CI)	Absolute	
								7%)			
Resistance mutation at 52 weeks											
1: Sung 2008	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/58 (8.6%)	10/51 (19.6%)	RR 0.44 (0.16 to 1.2)	110 fewer per 1000 (from 165 fewer to 39 more)	LOW

[1] Randomisation and allocation concealment unclear
[2] Confidence interval compatible with two clinical decisions: benefit, or no harm or benefit
[3] Confidence interval compatible with three clinical decisions: harm, no harm or benefit, or benefit

11.1.4.3 Lamivudine resistant adults with HBeAg positive CHB

Comparison of entecavir versus placebo

Table 115: Entecavir versus placebo- clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Entecavir Frequency (%)/ mean (SD)	Placebo Frequency (%)/ mean (SD)	Relative Risk (95% CI)	Absolute	
Log reduction in HBV DNA (copies/mL) (assessed at the end of 12 weeks treatment)										
Yao 2007	1 RCT- double blinded	Serious limitations[a]	No serious inconsistenc	Serious indirectness[b]	No serious imprecision	4.3 (1.18)	0.15 (1.08)		MD 4.15	LOW

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Entecavir Frequency (%)/ mean (SD)	Placebo Frequency (%)/ mean (SD)	Relative Risk (95% CI)	Absolute	
			y						higher (3.70 to 4.60 higher)	
% of people with undetectable HBV DNA (<300 copies/mL) (assessed at the end of 12 weeks treatment)										
Yao 2007	1 RCT- double blinded	Serious limitations[a]	No serious inconsistency	Serious indirectness[b]	No serious imprecision	9/116 (7.8%)	0/29	PETO OR 3.76 (0.70, 20.17)	8 more per 1000 (from 1 to 15 more)	LOW
% of people with ALT normalisation (≤1 x ULN) (assessed at the end of 12 weeks treatment)										
Yao 2007	1 RCT- double blinded	Serious limitations[a]	No serious inconsistency	Serious indirectness[b]	No serious imprecision	40/59 (67.8%)	1/16 (6.3%)	RR 10.85 (1.61 to 72.95)	616 more per 1000 (from 38 more to 4497 more	LOW
Incidence of adverse events leading to withdrawal										
Yao 2007	1 RCT- double blinded	Serious limitations[a]	No serious inconsistency	Serious indirectness[b]	Serious imprecision [(c)]	0/116 (0%)	1/29 (3.4%)	RR 0.09 (0 to 2.05)	--	LOW

(a) *Unclear randomisation method and allocation concealment.*
(b) *Mixed population: 90% of the participants were HBeAg positive.*
(c) *Confidence interval consistent with two clinical decisions (no appreciable clinical harm or benefit, appreciable clinical benefit*

Comparison of adefovir plus lamivudine versus lamivudine

Table 116: Adefovir plus lamivudine versus lamivudine - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamivudine + adefovir	lamivudine	Relative (95% CI)	Absolute	Quality
Undetectable HBV DNA at end of treatment											
2: Perrillo 2004; Peters 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/62 (25.8%)	0/64 (0%)	OR 9.88 (3.47 to 28.17)	-	MODERATE
ALT normalisation at end of treatment											
2: Perrillo 2004; Peters 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/61 (39.3%)	4/65 (6.2%)	OR 9.72 (3.15 to 30.02)	328 more per 1000 (from 110 more to 602 more)	MODERATE
HBeAg loss at end of treatment											
2: Perrillo 2004; Peters 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/58 (15.5%)	1/61 (1.6%)	OR 7.74 (1.33 to 45.11)	98 more per 1000 (from 5 more to 413 more)	MODERATE
HBeAg seroconversion at end of treatment											
2: Perrillo 2004; Peters 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/58 (6.9%)	1/61 (1.6%)	OR 3.33 (0.51 to 21.91)	36 more per 1000 (from 8 fewer to 251 more)	VERY LOW
Resistance at end of treatment											
1: Perrillo	randomis	serio	no serious	no serious	very	none	26/42	44/46	RR 0.65	335 fewer per	

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamivudine + adefovir	lamivudine	Relative (95% CI)	Absolute	
2004;	ed trials	us[1]	inconsistency	indirectness	serious[2]		(61.9%)	(95.7%)	(0.51 to 0.83)	1000 (from 163 fewer to 469 fewer)	VERY LOW

[1] No information on randomisation/allocation concealment in one study
[2] Confidence interval is compatible with three clinical decisions: harm, no harm or benefit, or benefit

Comparison of adefovir plus lamivudine versus adefovir

Table 117: Adefovir plus lamivudine versus adefovir - clinical study characteristics and clinical summary of findings

Quality assessment							No of people		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adefovir + lamivudine	Adefovir	Relative (95% CI)	Absolute	
Reduction in HBV DNA (assessed at the end of 48 weeks treatment)											
1 Peters 2004	RCT-double blinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(b)]	None	20	19	-	MD 0.54 lower (1.34 lower to 0.26 higher)	LOW
% of people with undetectable HBV DNA (<1000 copies/ml) (assessed at the end of 48 weeks treatment)											
1 Peters 2004	RCT-double blinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Very serious imprecision [(c)]	None	7/20 (35%)	5/18 (26.3%)	RR 1.33 (0.51 to 3.48)	87 more per 1000 (from 129 fewer to 653 more)	VERY LOW
% of people with HBeAg loss (assessed at the end of 48 weeks treatment)											
1:	RCT-	Serious	No serious	No serious	Very	None	3/18	3/19	RR 1.06	9 more per 1000 (from	VERY LOW

Quality assessment							No of people		Effect		Quality
Peters 2004	double blinded	limitations [a]	inconsistency	indirectness	serious imprecision [c]		(16.7%)	(15.8%)	(0.24 to 4.57)	120 fewer to 564 more)	
% of people with HBeAg seroconversion (assessed at the end of 48 weeks treatment)											
1 Peters 2004	RCT-double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [c]	None	1/18 (5.6%)	2/18 (10.5%)	RR 0.53 (0.05 to 5.33)	49 fewer per 1000 (from 100 fewer to 456 more)	VERY LOW
% of people with ALT normalisation (assessed at the end of 48 weeks treatment)											
1 Peters 2004	RCT-double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [c]	None	10/19 (52.6%)	9/18 (47.4%)	RR 1.11 (0.59 to 2.1)	52 more per 1000 (from 194 fewer to 521 more)	VERY LOW
% of people withdrawn due to adverse events											
1 Peters 2004	RCT-double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/20 (0%)	0/19 (0%)	not pooled	not pooled	MODERATE

(a) Unclear allocation concealment.
(b) The mean difference did not reach the default MID.
(c) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm

Comparison of adefovir versus lamivudine

Table 118: Adefovir versus lamivudine- clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Adefovir**	**lamivudine**	**Relative (95% CI)**	**Absolute**	**Quality**

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Adefovir**	**lamivudine**	**Relative (95% CI)**	**Absolute**	
Undetectable HBV DNA at end of treatment											
1: Peters 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/18 (27.8 %)	0/18 (0%)	OR 9.56 (1.48 to 61.61)	-	MODERATE
ALT normalisation at end of treatment											
1: Peters 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/19 (47.4 %)	1/19 (5.3%)	OR 16.2 (1.78 to 147.07)	421 more per 1000 (from 37 more to 838 more)	MODERATE
HBeAg loss at end of treatment											
1: Peters 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/19 (15.8 %)	0/19 (0%)	OR 8.27 (0.4 to 172.05)	-	VERY LOW
HBeAg seroconversion at end of treatment											
1: Peters 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/19 (10.5 %)	0/19 (0%)	OR 7.81 (0.47 to 129.75)	-	VERY LOW

[1] Unclear allocation concealment
[2] Confidence interval compatible with three clinical decisions: harm, no harm or benefit, or benefit

Comparison of emtricitabine plus tenofovir versus tenofovir

Table 119: Emtricitabine plus tenofovir versus tenofovir - clinical study characteristics and clinical summary of findings

Quality assessment	No of patients	Effect	Quality

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Emtricitabine + tenofovir	tenofovir	Relative (95% CI)	Absolute	
HBV DNA <400 copies/mL at 24 weeks of therapy											
1: Berg 2010	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	36/52 (69.2%)	35/53 (66%)	RR 1.05 (0.8 to 1.37)	33 more per 1000 (from 132 fewer to 244 more)	MODERATE

[1] Confidence interval compatible with two clinical decisions: benefit, or no benefit or harm

11.1.4.4 Pharmacological monotherapies and combination therapies in achieving remission of the activity of CHB for HBeAg negative adults

11.1.4.5 Comparison of adefovir versus placebo

Table 120: Adefovir versus placebo - clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Adefovir Frequency (%)/ mean (Sd) or median	Placebo Frequency (%) or median	Relative Risk (95% CI)	Absolute	
Median HBV DNA reduction (log10 copies/mL) (assessed at the end of 48 weeks treatment)										
Hadziyannis 2003	1 RCT- double blinded	No serious limitations	No serious inconsistency	No serious indirectness	[a]	3.91	1.35	[b]	[b]	HIGH
% of people with undetectable HBV DNA (<400 copies/mL) (assessed at the end of 48 weeks treatment)										
Hadziyannis 2003	1 RCT- double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	63/123 (51.2%)	0/61 (0%)	Peto OR 9.61 (5.04 to 18.31)	510 more per 1000 (from 420 more to 600 more)	HIGH
% of people with ALT normalisation (assessed at the end of 48 weeks treatment)										
Hadziyannis 2003	1 RCT- double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	84/116 (72.4%)	17/59 (28.8%)	RR 2.51 (1.66 to 3.81)	435 more per 1000 (from 190 more to 810 more)	HIGH
% of people with histologic improvement (assessed at the end of 48 weeks treatment)										
Hadziyannis 2003	1 RCT- double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	77/121 (63.6%)	19/57 (33.3%)	RR 1.91 (1.29 to	303 more per 1000	HIGH

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Adefovir Frequency (%)/ mean (Sd) or median	Placebo Frequency (%) or median	Relative Risk (95% CI)	Absolute	
								2.82)	(from 97 more to 607 more)	

(a) *Imprecision cannot be assessed as median was reported and forest plot cannot be generated.*
(b) *Relative risk and absolute effect could not be obtained because median was reported.*

Follow up study (Hadziyannis 2006)

People with chronic Hepatitis B HBeAg negative who participated in a 48 week double blinded trial (Hadziyannis 2003) entered a follow up study up to 204 weeks treatment with adefovir. 125 people treated with adefovir continued therapy in the follow up study; 70 people had adefovir all this period (240 weeks in total) and 50 people received placebo the first 48 weeks and then adefovir (people in this group received adefovir for 192 weeks).

The following table shows the comparative analysis of outcomes assessed at the end of 48 weeks of the double blinded trial, and at the end of 192 and 204 weeks of adefovir exposure.

Table 121: Outcomes assessed at the end of 48, 192 and 204 weeks of adefovir exposure

Outcomes	People received adefovir for 48 weeks (N=117)	People received adefovir for 192 weeks (N=125)	People received adefovir for 204 weeks (N=70)a
% of people with undetectable DNA (< 1000 copies/ml)	62/117 (53%)	62% b	53% b
% of people with ALT normalisation (ITT analysis with missing data perceived as failures)	84/116 (72.4%)	63% b	59% b
% of people with improvement in at least one score in Ishak score c	29/46 (63%)		
Incidence of resistance d	29/125 (23.2%)		

[a] *Includes only people received adefovir for all the period of 240 weeks*
[b] *ITT analysis with missing data perceived as failure*
[c] *Available case analysis*
[d] *ITT analysis*

11.1.4.6 Comparison of lamivudine versus placebo

Table 122: Lamivudine versus placebo - clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lamivudine Frequency (%)/ median (range)	Placebo Frequency (%) or median (range)	Relative Risk/Absolute median difference (95% CI)	Absolute	
% of people with undetectable HBV DNA (<2.5pg/ml) (assessed at the end of 24 weeks treatment)										
1 Tassopoulos 1999	RCT- double blinded	Serious limitations[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	49/54 (90.7%)	14/54 (25.9%)	RR 3.5 (2.21 to 5.54)	648 more per 1000 (from 314 more to 1000 more)	MODERATE
% of people with undetectable HBV DNA (<10,000copies/ml) (assessed at the end of 24 months treatment)										
1 Chan 2007c	RCT- double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	52/89 (58.4%)	9/47 (19.1%)	RR 3.05 (1.65 to 5.63)	393 more per 1000 (from 124 more to 887 more)	HIGH
% of people with undetectable HBV DNA (<10,000copies/ml) (assessed at 6 months follow up)										
1 Chan 2007c	RCT- double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision [(b)]	29/89 (32.6%)	12/47 (25.5%)	RR 1.28 (0.72 to 2.26)	71 more per 1000 (from 71 fewer to 322 more)	MODERATE
% of people with HBsAg loss										

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lamivudine Frequency (%)/ median (range)	Placebo Frequency (%) or median (range)	Relative Risk/Absolute median difference (95% CI)	Absolute	
Chan 2007c Tassopoulos 1999	RCT- double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision [(c)]	1/1084 (0.9%)	1/84 (1.2%)	RR 0.74 (0.09 to 5.87)	3 fewer per 1000 (from 11 fewer to 58 more)	LOW
% of people with ALT normalisation (assessed at the end of 24 months treatment)										
1 Chan 2007c	RCT- double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	66/89 (74.2%)	17/47 (36.2%)	RR 2.05 (1.38 to 3.06)	380 more per 1000 (from 137 more to 745 more)	HIGH
% of people with ALT normalisation (assessed at 6 months follow up)										
1 Chan 2007c	RCT- double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	53/89 (59.6%)	18/47 (38.3%)	RR 1.55 (1.04 to 2.32)	211 more per 1000 (from 15 more to 506 more)	HIGH
Incidence of resistance (genotypic YMDD mutation) (assessed at the end of 24 months treatment)										
1 Chan 2007c	RCT- double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	22/70 (31.4%)	1/35 (2.9%)	RR 11 (1.55 to 78.29)	286 more per 1000 (from 16 more to 2208 more)	HIGH
Incidence of resistance (phenotypic resistance or viral breakthrough) (assessed at the end of 24 months treatment)										

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lamivudine Frequency (%)/ median (range)	Placebo Frequency (%) or median (range)	Relative Risk/Absolute median difference (95% CI)	Absolute	
1 Chan 2007c	RCT- double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	16/70 (23%)	0/35 (0%)	RR 16.73 (1.03 to 271)	--	HIGH
% of people with histologic improvement (assessed at the end of 24 months treatment)										
1 Chan 2007c	RCT- double blinded	Serious limitations [(e)]	No serious inconsistency	No serious indirectness	Serious imprecision [(d)]	14/18 (77.8%)	2/8 (25%)	RR 3.11 (0.91 to 10.59)	527 more per 1000 (from 22 fewer to 1000 more)	LOW

(a) Unclear allocation concealment.
(b) The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm.
(c) The confidence interval is consistent with three clinical decisions; appreciable harm, no appreciable harm or benefit, appreciable benefit.
(d) The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm.
(e) The second liver biopsy was an optional examination and 26 people had paired biopsy. Unclear when the second liver biopsy was done.

Comparison of lamivudine versus Peg-IFN-alpha

Table 123: Lamivudine versus pegylated interferon alfa-2a - clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lamivudine Frequency (%)/ mean (SD)	Peginterferon alfa-2a Frequency (%)/mean (SD)	Relative Risk/Mean Difference (95% CI)	Absolute	
HBV DNA reduction (log copies/mL) (assessed at the end of 48 weeks treatment)										
Marcellin 2004	1 RCT- partially double blinded	Serious limitations[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	4.2 (0.15)	4.1 (0.18)	MD 1.3 (1.27 to 1.33	MD 1.3 higher (1.27 to 1.33 higher)	MODERATE
HBV DNA log reduction (log copies/ml) (assessed at 24 weeks follow up)										
Marcellin 2004	1 RCT- partially double blinded	Serious limitations[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	1.6 (0.2)	2.3 (0.2)	MD -0.5 (-0.54 to -0.46)	MD 0.5 lower (0.54 to 0.46 lower)	MODERATE
% of people with undetectable HBV DNA (<400 copies/ml) (assessed at the end of 48 weeks treatment)										
Marcellin 2004	1 RCT- partially double blinded	Serious limitations[(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(c)]	133/155 (85.8%)	112/165 (67.9%)	RR 1.26 (1.12 to 1.43)	176 more per 1000 (from 81 more to 292 more)	LOW
% of people with undetectable HBV DNA (<400 copies/ml) (assessed at 24 weeks follow up)										

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lamivudine Frequency (%)/ mean (SD)	Peginterferon alfa-2a Frequency (%)/mean (SD)	Relative Risk/Mean Difference (95% CI)	Absolute	
Marcellin 2004	1 RCT- partially double blinded	Serious limitations[a]	No serious inconsistency	No serious indirectness	Serious imprecision [c]	53/155 (34.2%)	76/165 (43%)	RR 0.74 (0.56 to 0.98)	120 fewer per 1000 (from 9 fewer to 203 fewer)	LOW
% of people with HBsAg loss (assessed at 24 weeks follow up)										
Marcellin 2004	1 RCT- partially double blinded	Serious limitations[a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	0/155 (0%)	7/165 (4.2%)	RR 0.07 (0 to 1.23)	39 fewer per 1000 (from 42 fewer to 10 more)	LOW
% of people with HBsAg seroconversion (assessed at 24 weeks follow up)										
Marcellin 2004	1 RCT- partially double blinded	Serious limitations[a]	No serious inconsistency	No serious indirectness	Very serious imprecision [b]	0/155 (0%)	5/165 (3%)	RR 0.1 (0.01 to 1.74)	27 fewer per 1000 (from 30 fewer to 22 more)	VERY LOW
% of people with ALT normalisation (assessed at the end of 48 weeks treatment)										
Marcellin 2004	1 RCT- partially double blinded	Serious limitations[a]	No serious inconsistency	No serious indirectness	No serious imprecision	132/155 (85.2%)	67/165 (40.6%)	RR 2.1 (1.72 to 2.55)	447 more per 1000 (from 292 more to 629 more)	MODERATE

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lamivudine Frequency (%)/ mean (SD)	Peginterferon alfa-2a Frequency (%)/mean (SD)	Relative Risk/Mean Difference (95% CI)	Absolute	
% of people with ALT normalisation (assessed at 24 weeks follow up)										
Marcellin 2004	1 RCT- partially double blinded	Serious limitations[a]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	80/155 (51.6%)	105/165 (63.6%)	RR 0.81 (0.67 to 0.98)	121 fewer per 1000 (from 13 fewer to 210 fewer)	LOW
Resistance – genotypic YMDD mutation (assessed at 48 weeks treatment**)**										
Marcellin 2004	1 RCT- partially double blinded	Serious limitations[a]	No serious inconsistency	No serious indirectness	No serious imprecision	32/179 (18%)	0/165 (0%)	RR 59.94 (3.70 to 971.16)	--	MODERATE
% of people with histologic improvement (assessed at 24 weeks follow up)										
Marcellin 2004	1 RCT- partially double blinded	Serious limitations[a]	No serious inconsistency	No serious indirectness	No serious imprecision	72/125 (57.6%)	85/143 (59.4%)	RR 0.97 (0.79 to 1.19)	18 fewer per 1000 (from 125 fewer to 113 more)	MODERATE

[a] *Partially double blinded study with no further details.*
[b] *The confidence interval is consistent with three clinical decisions; appreciable harm, no appreciable harm or benefit, appreciable benefit.*
[c] *The confidence interval is consistent with two clinical decisions; appreciable harm, no appreciable harm or benefit.*

Comparison of telbivudine versus lamivudine

Table 124: Telbivudine versus lamivudine - clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Telbivudine Frequency (%)/ mean (SD)	Lamivudine Frequency (%)/ mean (SD)	Relative Risk/Mean difference (95% CI)	Absolute	
HBV DNA Reduction (log10 copies/mL) (assessed at the end of 52 weeks treatment)										
Lai 2007*	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	5.23	4.40	MD 2.29 (1.58 to 3.33)	MD 2.29 higher (1.58 to 3.33 higher)	HIGH
% of people with undetectable HBV DNA (assessed at the end of 52 weeks treatment)										
Hou 2008 A Lai 2007*	2 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision [(a)]	213/242 (88%)	177/246 (72%)	RR 1.22 (1.12 to 1.34)	158 more per 1000 (from 86 more to 245 more)	MODERATE
% of people with undetectable HBV DNA (<300 copies/ml) (assessed at the end of 104 weeks)										
Liaw 2009	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	182/222 (82%)	127/224 (56.7%)	RR 1.45 (1.27 to 1.65)	255 more per 1000 (from 153 more to 369 more)	HIGH
% of people with HBsAg loss (assessed at the end of 104 weeks)										

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Telbivudine Frequency (%)/ mean (SD)	Lamivudine Frequency (%)/ mean (SD)	Relative Risk/Mean difference (95% CI)	Absolute	
Liaw 2009	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	1/222 (0.45%)	2/224 (0.89%)	RR 0.5 (0.05 to 5.52)	4 fewer per 1000 (from 8 fewer to 40 more)	LOW
% of people with HBsAg seroconversion (assessed at the end of 104 weeks)										
Liaw 2009	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision[b]	1/222 (0.45%)	1/224 (0.45%)	RR 1.01 (0.06 to 16.03)	0 more per 1000 (from 4 fewer to 67 more)	LOW
% of people with ALT normalisation (assessed at the end of 52 weeks treatment)										
Hou 2008 A Lai 2007*	2 RCT-double blinded	No serious limitations	Very serious inconsistency [(b)]	No serious indirectness	No serious imprecision	312/369 (84.6%)	290/367 (79%)	RR 1.07 (1 to 1.14)	55 more per 1000 (from 0 more to 111 more)	LOW
% of people with ALT normalisation (assessed at the end of 104 weeks)										
Liaw 2009	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	173/222 (77.9%)	157/224 (70.1%)	RR 1.11 (1 to 1.24)	77 more per 1000 (from 0 more to 168 more)	HIGH
Incidence of resistance (assessed at the end of 52 weeks treatment)										
Lai 2007*	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	5/222 (2.3%)	24/224 (10.7%)	RR 0.21 (0.08 to 0.54)	85 fewer per 1000 (from 49 fewer to 99	HIGH

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Telbivudine Frequency (%)/ mean (SD)	Lamivudine Frequency (%)/ mean (SD)	Relative Risk/Mean difference (95% CI)	Absolute	
									fewer)	
% of people with histologic improvement (assessed at the end of 52 weeks)										
Lai 2007*	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	148/222 (66.7%)	148/224 (66.1%)	RR 1.01 (0.88 to 1.15)	7 more per 1000 (from 79 fewer to 99 more)	HIGH

[(a)] *Confidence interval is consistent with two clinical decisions – appreciable benefit and no appreciable benefit or harm*
[(b)] *Confidence interval is consistent with three clinical decisions – appreciable harm, no appreciable harm or benefit, appreciable benefit.*
[(c)] *Substantial heterogeneity (I^2=96%; p=<0.0001).*
**Lai 2007 is the same RCT as Liaw 2009, but reported outcomes at week 52.*

Comparison of tenofovir versus adefovir

Table 125: Tenofovir versus adefovir - clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Tenofovir Frequency (%)/ mean (SD)	Adefovir Frequency (%)/ mean (SD)	Relative Risk/ Mean difference(95% CI)	Absolute	
Log reduction HBV DNA (assessed at the end of 48 weeks treatment)										
Marcellin 2008	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	4.55 (0.99)	4.07 (1.23)	MD 0.48 (0.22 to 0.74)	MD 0.48 higher (0.22 to 0.74 higher)	HIGH
% of people with HBV DNA <400 copies/mL (assessed at the end of 48 weeks treatment)										
Marcellin 2008	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	233/241 (96.7%)	79/117 (67.5%)	RR 1.43 (1.26 to 1.63)	290 more per 1000 (from 176 more to 425 more)	HIGH
% of people with HBsAg loss (assessed at the end of 48 weeks treatment)										
Marcellin 2008	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	0/250 (0%)	0/125 (0%)	not pooled	not pooled	HIGH
% of people with ALT normalisation (assessed at the end of 48 weeks treatment)										
Marcellin 2008	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	180/236 (76.3%)	91/118 (77.1%)	RR 0.99 (0.88 to 1.12)	8 fewer per 1000 (from 93 fewer to 93 more)	HIGH

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Tenofovir Frequency (%)/ mean (SD)	Adefovir Frequency (%)/ mean (SD)	Relative Risk/ Mean difference(95% CI)	Absolute	
% of people with histologic improvement (assessed at the end of 48 weeks treatment)										
Marcellin 2008	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	181/250 (72.4%)	86/125 (68.8%)	RR 1.05 (0.91 to 1.21)	34 more per 1000 (from 62 fewer to 144 more)	HIGH

Comparison of entecavir versus lamivudine

Table 126: Entecavir versus lamivudine - clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Entecavir Frequency (%)/ mean (SD)	Lamivudine Frequency (%)/ mean (SD)	Relative Risk/ Mean difference (95% CI)	Absolute	
Log reduction HBV DNA (assessed at the end of 48 weeks treatment)										
Lai 2006, Yao 2007	2 RCTs-double blinded	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)	5.0 (1.7), 5.2 (1.32)	4.5 (1.9), 4.5 (1.78)	MD 0.53 (0.26 to 0.8)	MD 0.53 higher (0.26 to 0.8 higher)	LOW
% of people with undetectable HBV DNA (<300 copies/mL) (assessed at the end of 48 weeks treatment)										
Lai 2006, Yao 2007	2 RCTs-double blinded	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision(b)	324/344 (94.2%)	254/336 (75.6%)	RR 1.25 (1.17 to 1.33)	189 more per 1000 (from 129 more to 249 more)	LOW
% of people with undetectable HBV DNA (<0.7MEq/mL) (assessed at the end of 48 weeks treatment)										
Lai 2006	1 RCT-double blinded	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision	309/311 (99.4%)	279/296 (94.3%)	RR 1.05 (1.02 to 1.09)	47 more per 1000 (from 19 more to 85 more)	MODERATE
% of people with ALT normalisation (assessed at the end of 48 weeks treatment)										
Lai 2006, Yao 2007	2 RCTs-double blinded	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision	284/344 (82.6%)	253/336 (75.3%)	RR 1.1 (1.02 to 1.19)	75 more per 1000 (from 15 more to 143 more)	MODERATE

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Entecavir Frequency (%)/ mean (SD)	Lamivudine Frequency (%)/ mean (SD)	Relative Risk/ Mean difference (95% CI)	Absolute	
Viral breakthrough (assessed at the end of 48 weeks treatment)										
Lai 2006	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	5/265 (2%)	25/313 (8%)	RR 0.24 (0.09 to 0.61)	61 fewer per 1000 (from 31 fewer to 73 fewer)	HIGH
Incidence of resistance – viral breakthrough and genotypic YMDD mutation* (assessed at the end of 48 weeks treatment)										
Lai 2006	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	--	20/25 (80%)	Not pooled	Not pooled	--
% of people with histologic improvement (assessed at the end of 48 weeks treatment)										
Lai 2006	1 RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	208/265 (78.5%)	174/250 (69.6%)	RR 1.13 (1.02 to 1.25)	90 more per 1000 (from 14 more to 174 more)	HIGH

(f) One study did not report details on randomisation and allocation concealment.

(g) Mean difference did not reach the minimal clinically important difference.

*Subgroup analysis among those who developed viral breakthrough (N=25) in the lamivudine group. There was no evidence of resistance to ETV at week 48 in paired samples from 211 randomly selected people in the ETV group.

Follow up study (Yao, 2010)

People with chronic Hepatitis B HBeAg positive who participated in the double blinded trial (Yao 2007) and partially responded (defined as HBV DNA<0.7 Meq/mL by bDNA but ALT >1.25 x ULN) or no responded to treatment with either entecavir or lamivudine for 48 weeks, were opted to receive entecavir (0.5 mg/daily) for up to 3 years (N=160).

The following table shows the comparative analysis of outcomes assessed at the end of 48 weeks treatment and at the end of 3 year follow up.

Table 127: Outcomes assessed at the end of 3 year follow up with entecavir

Outcomes	People received entecavir up to 48 weeks	People received entecavir up to 3 years
% of people with detectable HBV DNA (>300 copies/ml)	168/586 (28.7%) [a]	16/149 (11%)
% of people with HBeAg seroconversion	110/586 (18.8%) [a]	60/225 (27%)
% of people with HBeAg loss	119/565 (21.1%) [b]	80/225 (36%)
% of people with ALT normalisation	460/586 (78.5%) [a]	129/150 (86%)
Incidence of resistance	-	5/195 (2.6%)

[a] *Meta-analyzed results from 3 studies (Chang 2006, Yao 2007, Ren 2007). Please refer to Table 18.*
[b] *Results from Chang study. Please refer to Table 18.*

Comparison of of pegylated interferon alpha-2a plus lamivudine versus pegylated interferon alpha-2a

Table 128: Pegylated interferon alpha-2a plus lamivudine versus pegylated interferon alpha-2a (HBeAg negative people) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				Quality
							No of people		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PegIFNa-2a + lamivudine Frequency (%)	PegIFNa-2a Frequency (%)	Relative Risk/ Mean difference (95% CI)	Absolute	
HBV DNA log reduction (copies/ml) (assessed at the end of 48 week treatment)											
1 Marcellin 2004	RCT-partially double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	5 (1.97)	4.1 (2.3)	0.9 (0.44 to 1.36)	MD 0.9 higher (0.44 to 1.36 higher)	LOW
% of people with HBV DNA <20,000 copies/ml (assessed at the end of 48 week treatment)											
1 Marcellin 2004	RCT-partially double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	149/162 (92%)	134/165 (81.2%)	RR 1.13 (1.04 to 1.23)	106 more per 1000 (from 32 more to 187 more)	MODERATE
% of people with ALT normalisation (assessed at the end of 48 week treatment)											
1 Marcellin 2004	RCT-partially double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	None	87/162 (53.7%)	67/165 (40.6%)	RR 1.32 (1.05 to 1.67)	130 more per 1000 (from 20 more to 272 more)	LOW
HBV DNA log reduction (copies/ml) (assessed at the end of 24 week follow up)											
1 Marcellin	RCT-partially	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision	none	2.4 (2.99)	2.3 (2.62)	0.1 (-0.5 to 0.7)	MD 0.1 higher (0.5 lower to 0.7 higher)	LOW

Quality assessment							Summary of findings				Quality
2004	double-blinded				[b]						
% of people with HBV DNA <20,000 copies/ml (assessed at the end of 24 week follow up)											
1 Marcellin 2004	RCT-partially double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	72/162 (44.4%)	71/165 (43%)	RR 1.03 (0.81 to 1.32)	13 more per 1000 (from 82 fewer to 138 more)	LOW
% of people with HBsAg loss (assessed at the end of 24 week follow up)											
1 Marcellin 2004	RCT-partially double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [d]	none	5/162 (3.1%)	7/165 (4.2%)	RR 0.73 (0.24 to 2.25)	11 fewer per 1000 (from 32 fewer to 53 more)	VERY LOW
% of people with HBsAg seroconversion (assessed at the end of 24 week follow up)											
1 Marcellin 2004	RCT-partially double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [d]	none	3/162 (1.9%)	5/165 (3%)	RR 0.61 (0.15 to 2.52)	12 fewer per 1000 (from 26 fewer to 46 more)	VERY LOW
% of people with ALT normalisation (assessed at the end of 24 week follow up)											
1 Marcellin 2004	RCT-partially double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	none	107/162 (66%)	105/165 (63.6%)	RR 1.04 (0.88 to 1.22)	25 more per 1000 (from 76 fewer to 140 more)	MODERATE
% of people with Histologic improvement (assessed at the end of 24 week follow up)											
1 Marcellin 2004	RCT-partially double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [e]	none	68/143 (47.6%)	85/143 (59.4%)	RR 0.8 (0.64 to 1)	119 fewer per 1000 (from 214 fewer to 0 more)	LOW
Resistance (genotypic mutation)											
1 Marcellin 2004	RCT-partially double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [d]	none	1/173 (0.58%)	0/165 (0%)	PETO OR 7.06 (0.14 to 355.95)	10 more per 1000 (from 10 fewer to 20 more)	VERY LOW

(a) Partially double blind study with no follow up details.
(b) The confidence interval did not reach default MID.
(c) The confidence interval is consistent with two clinical decisions: appreciable benefit, no appreciable benefit or harm.
(d) The confidence interval is consistent with three clinical decisions: appreciable benefit, no appreciable benefit or harm and appreciable harm.
(e) The confidence interval is consistent with two clinical decisions: appreciable harm and no appreciable benefit or harm.

Comparison of pegylated interferon alpha-2b plus lamivudine versus pegylated interferon alpha-2b

Table 129: Pegylated interferon alpha-2b plus lamivudine versus pegylated interferon alpha-2b (HBeAg negative people) - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peg IFN alpha 2b + lam	Peg IFN alpha 2b	Relative (95% CI)	Absolute	Quality
Normalisation of ALT end of 48 weeks treatment											
1: Kaymakoglu 2007	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/29 (65.5%)	10/19 (52.6%)	RR 1.24 (0.75 to 2.06)	126 more per 1000 (from 132 fewer to 558 more)	LOW
Normalisation of ALT after 24 weeks follow up											
2: Kaymakoglu 2007; Papadopoulos 2009	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	38/115 (33%)	22/51 (43.1%)	RR 0.8 (0.54 to 1.19)	86 fewer per 1000 (from 198 fewer to 82 more)	LOW
Undetectable HBV DNA at end of 48 weeks treatment											
2: Kaymakoglu 2007; Papadopoulos 2009	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	96/117 (82.1%)	36/54 (66.7%)	RR 1.22 (0.99 to 1.5)	147 more per 1000 (from 7 fewer to 333 more)	LOW
Undetectable HBV DNA after 24 weeks follow up											
2: Kaymakoglu 2007; Papadopoulos 2009	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	62/115 (53.9%)	22/51 (43.1%)	RR 1.22 (0.85 to 1.76)	95 more per 1000 (from 65 fewer to 328 more)	LOW
HBsAg seroconversion after 24 weeks follow up											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peg IFN alpha 2b + lam	Peg IFN alpha 2b	Relative (95% CI)	Absolute	Quality
1: Kaymakoglu 2007	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/27 (3.7%)	2/16 (12.5%)	RR 0.3 (0.03 to 3.01)	87 fewer per 1000 (from 121 fewer to 251 more)	LOW

[1] Unblinded; randomisation and allocation concealment unclear
[2] Confidence interval compatible with two clinical decisions: no harm or benefit, or benefit
[3] Confidence interval compatible with two clinical decisions, no harm or benefit, or harm

Comparison of pegylated interferon alpha plus adefovir versus pegylated interferon alpha

Table 130: Pegylated interferon alpha plus adefovir versus pegylated interferon alpha (HBeAg negative people) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				Quality
							No of people		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peg INFa + ADF	Peg INF a	Relative (95% CI)	Absolute	
% of people with ALT normalisation (assessed at the end of 48 weeks treatment)											
1 Piccolo 2009	RCT-unclear blinding	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(b)]	none	17/30 (56.7%)	10/30 (33.3%)	RR 1.7 (0.94 to 3.08)	233 more per 1000 (from 20 fewer to 693 more)	LOW
% of people with ALT normalisation (assessed at the end of 24 weeks follow up)											
1 Piccolo 2009	RCT-unclear blinding	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Very serious imprecision [(c)]	none	10/30 (33.3%)	10/30 (33.3%)	RR 1 (0.49 to 2.05)	0 fewer per 1000 (from 170 fewer to 350 more)	VERY LOW
% of people with undetectable HBV DNA (assessed at the end of 48 weeks treatment)											

Quality assessment							Summary of findings				Quality
1 Piccolo 2009	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	20/30 (66.7%)	11/30 (36.7%)	RR 1.82 (1.07 to 3.1)	301 more per 1000 (from 26 more to 770 more)	LOW
% of people with undetectable HBV DNA (assessed at the end of 24 weeks follow up)											
1 Piccolo 2009	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision	none	3/30 (10%)	1/30 (3.3%)	RR 3 (0.33 to 27.23)	67 more per 1000 (from 22 fewer to 874 more)	VERY LOW
% of people with HBsAg loss (assessed at the end of 24 weeks follow up)											
1 Piccolo 2009	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [c]	none	1/30 (3.3%)	0/30 (0%)	PETO OR 7.39 (0.15 to 372.38)	30 more per 1000 (from 50 fewer to 120 more)	VERY LOW

[a] *Unclear blinding.*
[b] *The confidence interval is consistent with two clinical decisions: appreciable benefit and no appreciable benefit or harm.*
[c] *The confidence interval is consistent with three clinical decisions: appreciable benefit, no appreciable benefit or harm and appreciable harm.*

Comparison of interferon alpha plus lamivudine versus lamivudine

Table 131: Interferon alpha plus lamivudine versus lamivudine (HBeAg negative people) - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interferon alpha + lamivudine**	**lamivudine**	**Relative (95% CI)**	**Absolute**	
Undetectable HBV DNA - At 6 months of treatment											
1: Akarca 2004	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	34/40 (85%)	37/40 (92.5%)	RR 0.92 (0.79 to 1.08)	74 fewer per 1000 (from 194 fewer to 74 more)	LOW
Undetectable HBV DNA - At 12 months of treatment											

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interferon alpha + lamivudine**	**lamivudine**	**Relative (95% CI)**	**Absolute**	
2: Santantonio 2002; Yurdaydin 2005	randomised trials	serious[1]	serious[3]	no serious indirectness	no serious imprecision	none	57/63 (90.5%)	46/60 (76.7%)	RR 1.19 (1.01 to 1.4)	146 more per 1000 (from 8 more to 307 more)	LOW
Undetectable HBV DNA - At 24 months of treatment											
1: Economou 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/21 (85.7%)	13/26 (50%)	RR 1.71 (1.12 to 2.61)	355 more per 1000 (from 60 more to 805 more)	MODERATE
Undetectable HBV DNA - After 6 months of follow up											
2: Economou 2005; Yurdaydin 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	25/60 (41.7%)	26/65 (40%)	RR 0.99 (0.67 to 1.45)	4 fewer per 1000 (from 132 fewer to 180 more)	VERY LOW
Undetectable HBV DNA - After 27 months of follow up											
1: Yurdaydin 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious4	none	9/36 (25%)	9/34 (26.5%)	RR 0.94 (0.43 to 2.09)	16 fewer per 1000 (from 151 fewer to 289 more)	VERY LOW
ALT normalisation - At 6 months of treatment											
1: Akarca 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/40 (42.5%)	30/40 (75%)	RR 0.57 (0.38 to 0.85)	322 fewer per 1000 (from 112 fewer to 465 fewer)	MODERATE
ALT normalisation - At 12 months of treatment											
2: Santantonio 2002; Yurdaydin	randomised trials	serious[1]	no serious inconsistenc	no serious indirectnes	no serious imprecisio	none	41/63 (65.1%)	50/65	RR 0.85 (0.69 to	115 fewer per 1000 (from 238	MODERAT

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interferon alpha + lamivudine	lamivudine	Relative (95% CI)	Absolute	Quality
2005			y	s	n			(76.9%)	1.05)	fewer to 38 more)	E
ALT normalisation - At 24 months of treatment											
1: Economou 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/21 (90.5%)	16/26 (61.5%)	RR 1.47 (1.05 to 2.05)	289 more per 1000 (from 31 more to 646 more)	MODERATE
ALT normalisation - After 6 months of follow up											
2: Economou 2005; Yurdaydin 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	26/60 (43.3%)	21/65 (32.3%)	RR 1.3 (0.84 to 2.03)	97 more per 1000 (from 52 fewer to 333 more)	LOW
ALT normalisation - After 27 months of follow up											
1: Yurdaydin 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	9/36 (25%)	7/34 (20.6%)	RR 1.21 (0.51 to 2.9)	43 more per 1000 (from 101 fewer to 391 more)	VERY LOW
Virological breakthrough											
2: Economou 2005; Yurdaydin 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/60 (6.7%)	13/63 (20.6%)	RR 0.34 (0.12 to 0.95)	136 fewer per 1000 (from 10 fewer to 182 fewer)	MODERATE
Virological breakthrough - At 12 months of treatment											

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interferon alpha + lamivudine**	**lamivudine**	**Relative (95% CI)**	**Absolute**	
1: Yurdaydin 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/39 (2.6%)	2/39 (5.1%)	RR 0.5 (0.05 to 5.29)	26 fewer per 1000 (from 49 fewer to 220 more)	VERY LOW
Virological breakthrough - At 24 months of treatment											
1: Economou 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/21 (14.3%)	11/24 (45.8%)	RR 0.31 (0.1 to 0.97)	316 fewer per 1000 (from 14 fewer to 412 fewer)	MODERATE
Discontinued due to adverse events - At 24 months of treatment											
1: Economou 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	3/24 (12.5%)	0/26 (0%)	RR 7.56 (0.41 to 139.17)	-	VERY LOW
Virological resistance											
3: Economou 2005; Santantonio 2002; Yurdaydin 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/78 (12.8%)	34/84 (40.5%)	RR 0.32 (0.17 to 0.59)	275 fewer per 1000 (from 166 fewer to 336 fewer)	MODERATE
Virological resistance - At 12 months of treatment											
2: Santantonio 2002; Yurdaydin 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/57 (14%)	22/58 (37.9%)	RR 0.37 (0.19 to 0.73)	239 fewer per 1000 (from 102 fewer to 307 fewer)	MODERATE
Virological resistance - After 6 months of follow up											
1: Economou 2005	randomised trials	serious[1]	no serious inconsistenc	no serious indirectnes	no serious imprecisio	none	2/21 (9.5%)	12/26	RR 0.21 (0.05 to	365 fewer per 1000 (from 83	MODERAT

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interferon alpha + lamivudine	lamivudine	Relative (95% CI)	Absolute	
			y	s	n			(46.2%)	0.82)	fewer to 438 fewer)	E
Histological improvement - At 12 months of treatment											
1: Yurdaydin 2005	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	17/25 (68%)	19/25 (76%)	RR 0.89 (0.63 to 1.27)	84 fewer per 1000 (from 281 fewer to 205 more)	VERY LOW

[1] Randomisation/allocation concealment unclear
[2] Not standard dose of lamivudine
[3] Heterogeneity
[4] Confidence interval compatible with three clinical decisions: benefit, no harm or benefit, or harm
[5] Confidence interval compatible with two clinical decisions: benefit, or no harm or benefit

Comparison of of pegylated interferon alpha-2a plus lamivudine versus lamivudine

Table 132: Pegylated interferon alpha-2a plus lamivudine versus lamivudine (HBeAg negative people) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				Quality
							No of people		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	pegIFNa2a + LAM	LAM	Relative (95% CI)	Absolute	
HBV DNA log reduction (copies/ml) (assessed at the end of 48 week treatment) (Better indicated by higher values)											
1 Marcellin 2004	RCT-partially double	Serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (b)	None	5 (1.97)	4.2 (2.02)	-	MD 0.8 higher (0.38 to 1.22 higher)	LOW

Quality assessment							Summary of findings				Quality
	blinded	[a]									
% of people with HBV DNA < 20,000 copies/ml (assessed at the end of 48 week treatment)											
1 Marcellin 2004	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	149/162 (92%)	132/155 (85.2%)	RR 1.08 (1 to 1.17)	68 more per 1000 (from 0 more to 145 more)	MODERATE
% of people with ALT normalisation (assessed at the end of 48 week treatment)											
1 Marcellin 2004	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	none	87/162 (53.7%)	132/155 (85.2%)	RR 0.63 (0.54 to 0.74)	315 fewer per 1000 (from 221 fewer to 392 fewer)	MODERATE
HBV DNA log reduction (copies/ml) (assessed at the end of 24 week follow up)											
1 Marcellin 2004	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	None	2.4 (2.99)	2.3 (2.62)	-	MD 0.1 higher (0.5 lower to 0.7 higher)	LOW
% of people with HBV DNA < 20,000 copies/ml (assessed at the end of 24 week follow up)											
1 Marcellin 2004	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [c]	None	72/162 (44.4%)	45/155 (29%)	RR 1.53 (1.13 to 2.07)	154 more per 1000 (from 38 more to 311 more)	LOW
% of people with HBsAg loss (assessed at the end of 24 week follow up)											
1 Marcellin 2004	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [d]	None	5/162 (3.1%)	0/155 (0%)	PETO OR 7.26 (1.24 to 42.37)	30 more per 1000 (from 0 to 60 more)	VERY LOW
% of people with HBsAg seroconversion (assessed at the end of 24 week follow up)											
1 Marcellin 2004	RCT-partially double blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [d]	None	3/162 (1.9%)	0/155 (0%)	PETO OR 7.17 (0.74 to 69.42)	20 more per 1000 (from 10 fewer to 40 more)	VERY LOW

Quality assessment							Summary of findings				Quality
% of people with ALT normalisation (assessed at the end of 24 week follow up)											
1 Marcellin 2004	RCT-partially double blinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(c)]	None	107/162 (66%)	80/155 (51.6%)	RR 1.28 (1.06 to 1.54)	145 more per 1000 (from 31 more to 279 more)	LOW
% of people with histologic improvement (assessed at the end of 24 week follow up)											
1 Marcellin 2004	RCT-partially double blinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(e)]	None	68/143 (47.6%)	72/125 (57.6%)	RR 0.83 (0.66 to 1.04)	98 fewer per 1000 (from 196 fewer to 23 more)	LOW
Resistance (genotypic mutation)											
1 Marcellin 2004	RCT-partially double blinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	none	1/173 (0.58%)	32/179 (17.9%)	RR 0.03 (0 to 0.23)	173 fewer per 1000 (from 138 fewer to 179 fewer)	MODERATE

(a) Partially double blind study with no further details.
(b) The confidence interval did not reach default MID.
(c) The confidence interval is consistent with two clinical decisions: appreciable benefit and no appreciable benefit or harm.
(d) The confidence interval is consistent with three clinical decisions: appreciable benefit, no appreciable benefit or harm and appreciable harm.
(e) The confidence interval is consistent with two clinical decisions: appreciable harm and no appreciable benefit or harm.

Comparison of adefovir plus lamivudine versus adefovir

Table 133: Adefovir plus lamivudine versus adefovir (HBeAg negative people) - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamivudine plus adefovir**	**switching lamivudine to adefovir monotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**
Undetectable HBV DNA <1000 copies/mL - After 12 months of treatment											

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamivudine plus adefovir**	**switching lamivudine to adefovir monotherapy**	**Relative (95% CI)**	**Absolute**	
2: Rapti 2007; Vassiliadis 2010	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	42/73 (57.5%)	20/29 (69%)	RR 0.86 (0.63 to 1.17)	97 fewer per 1000 (from 255 fewer to 117 more)	LOW
Undetectable HBV DNA <1000 copies/mL - After 24 months of treatment											
2: Rapti 2007; Vassiliadis 2010	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	54/73 (74%)	20/29 (69%)	RR 1.09 (0.83 to 1.45)	62 more per 1000 (from 117 fewer to 310 more)	LOW
ALT normalisation - After 12 months of treatment											
2: Rapti 2007; Vassiliadis 2010	randomised trials	serious[1]	serious4	no serious indirectness	serious[3]	none	56/73 (76.7%)	20/29 (69%)	RR 1.15 (0.87 to 1.51)	103 more per 1000 (from 90 fewer to 352 more)	VERY LOW
ALT normalisation - After 24 months of treatment											
2: Rapti 2007; Vassiliadis 2010	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64/73 (87.7%)	18/29 (62.1%)	RR 1.43 (1.06 to 1.93)	267 more per 1000 (from 37 more to 577 more)	MODERATE

[1] Randomisation and allocation concealment unclear
[2] Confidence interval compatible with two clinical decisions: harm, or no harm or benefit

11.1.4.7 Pharmacological monotherapies and combination therapies in achieving remission of the activity of CHB for people co-infected with hepatitis D or C virus

Comparison of interferon alfa-2a versus no treatment

Table 134: Interferon alpha- 2a versus no treatment for people co-infected with chronic hepatitis B and D- clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Interferon alfa-2a Frequency (%)/ median	No treatment Frequency (%)/ median	Relative Risk (95% c.i)	Absolute	
% of people with detectable HDV DNA (assessed at the end of 48 weeks treatment)										
Farci 1994	1 RCT- blinding unclear	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	4/14 (28.6%)	13/13 (100%)	RR 0.31 (0.14 to 0.68)	690 fewer per 1000 (from 320 fewer to 860 fewer)	MODERATE
% of people with detectable HBV DNA (>400 copies/ml)(assessed at the end of 48 weeks treatment)										
Farci 1994	1 RCT- blinding unclear	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [b]	0/14 (0%)	2/13 (15.4%)	RR 0.19 (0.01 to 3.56)	125 fewer per 1000 (from 152 fewer to 394 more)	VERY LOW
% of people with ALT normalization (assessed at the end of 48 weeks treatment)										
Farci 1994	1 RCT- blinding unclear	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	10/14 (71.4%)	1/13 (7.7%)	RR 9.29 (1.37 to 62.83)	638 more per 1000 (from 28 more to	MODERATE

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Interferon alfa-2a Frequency (%)/ median	No treatment Frequency (%)/ median	Relative Risk (95% c.i)	Absolute	
									4756 more)	
% of people with detectable HDV DNA (assessed at 6 months follow up)										
Farci 1994	1 RCT- blinding unclear	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)	8/14 (57.1%)	12/13 (92.3%)	RR 0.62 (0.38 to 1)	351 fewer per 1000 (from 572 fewer to 0 more)	LOW
% of people with detectable HBV DNA (>=400 copies/ml) (assessed at 6 months follow up)										
Farci 1994	1 RCT- blinding unclear	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	2/14 (14.3%)	2/13 (15.4%)	RR 0.93 (0.15 to 5.67	11 fewer per 1000 (from 131 fewer to 718 more)	VERY LOW
% of people with ALT normalization (assessed at 6 months follow up)										
Rosina 1991	1 RCT- blinding unclear	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	7/14 (50%)	1/13 (7.7%)	RR 6.5 (0.92 to 45.9)	423 more per 1000 (from 6 fewer to 3454 more)	VERY LOW
% of people with detectable HDV DNA (assessed at 12 years follow up)										
Farci 1994	1 RCT- blinding unclear	Serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	12/12 (100%)	3/3 (100%)	RR 1 (0.68 to 1.47)	0 fewer per 1000 (from	LOW

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Interferon alfa-2a Frequency (%)/ median	No treatment Frequency (%)/ median	Relative Risk (95% c.i)	Absolute	
		(a)			(c)				320 fewer to 470 more)	
% of people with detectable HBV DNA (>400 copies/ml) (assessed at 12 years follow up)										
Farci 1994	1 RCT- blinding unclear	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	1/12 (8.3%)	0/3 (0%)	RR 0.92 (0.05 to 18.5)	0 fewer per 1000 (from 0 fewer to 0 more)	VERY LOW
% of people with ALT normalization (assessed at 12 years follow up)										
Farci 1994	1 RCT- blinding unclear	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	7/12 (58.3%)	0/3 (0%)	RR 4.62 (0.33 to 64.31)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
% of people underwent liver transplantation (assessed at 12 years follow up)										
Farci 1994	1 RCT- blinding unclear	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	1/14 (7.1%)	5/13 (38.5%)	RR 0.19 (0.02 to 1.39)	312 fewer per 1000 (from 377 fewer to 150 more)	VERY LOW
Survival rate (assessed at 12 years follow up)										
Farci 1994	1 RCT- blinding unclear	Serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	12/14 (85.7%)	3/13 (23.1%)	RR 3.71 (1.35 to	625 more per 1000	MODERATE

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Interferon alfa-2a Frequency (%)/ median	No treatment Frequency (%)/ median	Relative Risk (95% c.i)	Absolute	
		(a)						10.25)	(from 81 more to 2135 more)	

(a) *Unclear blinding and allocation concealment.*
(b) *Confidence interval is consistent with three clinical decisions; appreciable harm, no appreciable harm or benefit, appreciable benefit.*
(c) *Confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm.*

Comparison of interferon alfa-2b versus no treatment

Table 135: Interferon alpha -2b versus no treatment for people co-infected with chronic hepatitis B and D- clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Interferon alfa-2a Frequency (%)	No treatment Frequency (%)	Relative Risk (95% c.i)	Absolute	
% of patient with ALT normalisation (assessed at the end of 1 year treatment)										
Rosina 1991	1 RCT- blinding unclear	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)	8/26 (30.8%)	0/22 (0%)	RR 14.48 (0.88 to 237.53)	-	LOW
% of patient with histologic improvement (definition unclear) (assessed at the end of 1 year treatment)										

Quality assessment						Summary of findings				
								Effect		Quality
Authors	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Interferon alfa-2a Frequency (%)**	**No treatment Frequency (%)**	**Relative Risk (95% c.i)**	**Absolute**	
Rosina 1991	1 RCT- blinding unclear	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	11/19 (57.9%)	5/14 (35.7%)	RR 1.62 (0.73 to 3.61)	221 more per 1000 (from 96 fewer to 932 more)	LOW

[a] *No details on allocation sequence and blinding.*
[b] *The confidence interval is consistent with two clinical decisions; appreciable benefit and no appreciable benefit or harm*

Comparison of peginterferon alfa-2a plus adefovir versus adefovir

Table 136: Peginterferon alfa-2a plus adefovir versus adefovir for people co-infected with chronic hepatitis B and D- clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Peginterferon alfa-a plus adefovir Frequency (%)/ median	Adefovir Frequency (%)/ median	Relative Risk (95% c.i)	Absolute	
Clearance of HDV RNA end of 48 weeks treatment										
1	randomised trials	no serious risk of bias	no serious inconsistency	serious indirectness[(a)]	no serious imprecision	6/26 (23.1%)	0/28 (0%)	OR 9.91 (1.84 to 53.3)	-	MODERATE
Clearance of HDV RNA after 24 weeks follow up										
1	randomised trials	no serious risk of bias	no serious inconsistency	serious indirectness[(a)]	no serious imprecision	7/26 (26.9%)	0/28 (0%)	OR 10.4 (2.15 to 50.22)	-	MODERATE
Log reduction HBV DNA (copies/ml) (assessed at the end of 48 weeks treatment)										
Wedemeyer, 2011	1 RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness [(a)]	-	0	1.46	-	-	-
Log reduction HBV DNA (copies/ml) (assessed at the end of 24 week follow up)										
Wedemeyer, 2011	1 RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness [(a)]	-	1.30	1.40	-	-	-
% of people with ALT normalisation (assessed at the end of 48 weeks treatment)										

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Peginterferon alfa-a plus adefovir Frequency (%)/ median	Adefovir Frequency (%)/ median	Relative Risk (95% c.i)	Absolute	
Wedemeyer, 2011	1 RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness (a)	No serious imprecision	10/26 (38.5%)	2/28 (7.1%)	RR 5.38 (1.3 to 22.3)	313 more per 1000 (from 21 more to 1521 more)	MODERATE
% of people with ALT normalisation (assessed at the end of 24 week follow up)										
Wedemeyer, 2011	1 RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness (a)	Serious imprecision (b)	11/26 (42.3%)	3/28 (10.7%)	RR 3.95 (1.24 to 12.59)	316 more per 1000 (from 26 more to 1242 more)	LOW

(a) A mixed population of HBeAg positive (15.5%) and negative people (84.5%)
(b) Confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm.

Table 137: Peginterferon alfa-2a plus adefovir versus peginterferon alfa-2a for people co-infected with chronic hepatitis B and D- clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Peginterferon alfa-a plus adefovir Frequency (%)/ median	Peginterferon alfa-2a Frequency (%)/ median	Relative Risk (95% c.i)	Absolute	
Clearance of HDV RNA end of 48 weeks treatment										

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Peginterferon alfa-a plus adefovir Frequency (%)/ median	Peginterferon alfa-2a Frequency (%)/ median	Relative Risk (95% c.i)	Absolute	
1: Wedemeyer 2001A	randomised trials	no serious risk of bias	no serious inconsistency	serious indirectness[(a)]	no serious imprecision	6/26 (23.1%)	6/26 (23.1%)	RR 1 (0.37 to 2.7)	0 fewer per 1000 (from 145 fewer to 392 more)	MODERATE
Clearance of HDV RNA after 24 weeks follow up										
1: Wedemeyer 2001A	randomised trials	no serious risk of bias	no serious inconsistency	serious indirectness[(a)]	no serious imprecision	7/26 (26.9%)	7/26 (26.9%)	RR 1 (0.41 to 2.45)	0 fewer per 1000 (from 159 fewer to 390 more)	MODERATE
Log reduction HBV DNA (copies/ml) (assessed at the end of 48 weeks treatment)										
Wedemeyer, 2011	1 RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness [(a)]	-	0	1.46	-	-	-
Log reduction HBV DNA (copies/ml) (assessed at the end of 24 week follow up)										
Wedemeyer, 2011	1 RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness [(a)]	-	1.30	2.10	-	-	-
% of people with ALT normalisation (assessed at the end of 48 weeks treatment)										
Wedemeyer, 2011	1 RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness [(a)]	Very serious imprecision [(b)]	10/26 (38.5%)	8/26 (30.8%)	RR 1.25 (0.59 to 2.66)	77 more per 1000 (from 126 fewer to 511 more)	MODERATE
% of people with ALT normalisation (assessed at the end of 24 week follow up)										

Quality assessment						Summary of findings				
								Effect		Quality
Authors	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Peginterferon alfa-a plus adefovir Frequency (%)/ median**	**Peginterferon alfa-2a Frequency (%)/ median**	**Relative Risk (95% c.i)**	**Absolute**	
Wedemeyer, 2011	1 RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness (a)	Very serious imprecision (b)	11/26 (42.3%)	13/26 (50%)	RR 0.85 (0.47 to 1.53)	75 fewer per 1000 (from 265 fewer to 265 more)	VERY LOW

(a) A mixed population of HBeAg positive (15.5%) and negative people (84.5%).
(b) The confidence interval is consistent with three clinical decisions; appreciable harm, no appreciable harm or benefit, appreciable benefit.

Table 138: Adefovir versus peginterferon alfa-2a for people co-infected with chronic hepatitis B and D- clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Adefovir Frequency (%)/ median	Peginterferon alfa-2a Frequency (%)/ median	Relative Risk (95% c.i)	Absolute	
1: Wedemeyer 2001A	randomised trials	no serious risk of bias	no serious inconsistency	serious indirectness[(a)]	no serious imprecision	0/28 (0%)	6/26 (23.1%)	OR 0.1 (0.02 to 0.54)	202 fewer per 1000 (from 91 fewer to 225 fewer)	MODERATE

1: Wedemeyer 2001A	randomised trials	no serious risk of bias	no serious inconsistency	serious indirectness(a)	no serious imprecision	0/28 (0%)	7/26 (26.9%)	OR 0.1 (0.02 to 0.46)	234 fewer per 1000 (from 124 fewer to 262 fewer)	MODERATE
Log reduction HBV DNA (copies/ml) (assessed at the end of 48 weeks treatment)										
Wedemeyer, 2011	1 RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness (a)	-	0	1.46	-	-	-
Log reduction HBV DNA (copies/ml) (assessed at the end of 24 weeks follow up)										
Wedemeyer, 2011	1 RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness (a)	-	1.40	2.10	-	-	-
% of people with ALT normalisation (assessed at the end of 48 weeks treatment)										
Wedemeyer, 2011	1 RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness (a)	Serious imprecision (b)	2/28 (7.1%)	8/26 (30.8%)	RR 0.23 (0.05 to 0.99)	237 fewer per 1000 (from 3 fewer to 292 fewer)	LOW
% of people with ALT normalisation (assessed at the end of 24 weeks follow up)										
Wedemeyer, 2011	1 RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness (a)	No serious imprecision	3/28 (10.7%)	13/26 (50%)	RR 0.21 (0.07 to 0.67)	395 fewer per 1000 (from 165 fewer to 465 fewer)	MODERATE

(a) A mixed population of HBeAg positive (15.5%) and negative people (84.5%)
(b) The confidence interval is consistent with two clinical decisions; appreciable harm, no appreciable benefit or harm

Comparison of interferon alfa-2b plus lamivudine versus interferon alfa-2b

Table 139: Interferon alfa-2b plus lamivudine versus interferon alfa-2b for people co-infected with chronic hepatitis B and D- clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Interferon alfa-2b plus lamivudine Frequency (%)	Interferon alfa-2b Frequency (%)	Relative Risk (95% c.i)	Absolute	
% of people with detectable HDV DNA (assessed at the end of 48 weeks treatment)										
Canbakan 2006	1 RCT- blinding unclear	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	7/12 (58.3%)	5/14 (35.7%)	RR 1.63 (0.7 to 3.82)	225 more per 1000 (from 107 fewer to 1007 more)	VERY LOW
% of people with ALT normalization (assessed at the end of 48 weeks treatment)										
Canbakan 2006	1 RCT- blinding unclear	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	5/12 (41.7%)	8/14 (57.1%)	RR 0.73 (0.32 to 1.64)	154 fewer per 1000 (from 389 fewer to 366 more)	VERY LOW
% of people with ALT normalization (assessed at the end of 96 weeks follow up)										
Canbakan 2006	1 RCT- blinding unclear	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)	2/12 (16.7%)	6/14 (42.9%)	RR 0.39 (0.1 to 1.58)	261 fewer per 1000 (from 386 fewer to 249 more)	LOW
Mortality (96 weeks follow up)										

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Interferon alfa-2b plus lamivudine Frequency (%)	Interferon alfa-2b Frequency (%)	Relative Risk (95% c.i)	Absolute	
Canbakan 2006	1 RCT- blinding unclear	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	4/12 (33.3%)	1/14 (7.1%)	RR 4.67 (0.6 to 36.29)	262 more per 1000 (from 29 fewer to 2521 more)	VERY LOW
% of people who underwent liver transplantation (assessed at the end of 96 weeks follow up)										
Canbakan 2006	1 RCT- blinding unclear	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	1/12 (8.3%)	1/14 (7.1%)	RR 1.17 (0.08 to 16.72)	12 more per 1000 (from 66 fewer to 1123 more)	VERY LOW

(a) Unclear randomisation, blinding and allocation concealment.
(b) Confidence interval is consistent with three clinical decisions; appreciable harm, appreciable harm or benefit, appreciable benefit.
(c) Confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm.
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Comparison of interferon alfa-2a plus lamivudine versus lamivudine

Table 140: Interferon alfa-2a plus lamivudine versus lamivudine for people co-infected with chronic hepatitis B and D- clinical study characteristics and clinical summary of findings

Quality assessment	Summary of findings		
		Effect	Quality

Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Interferon alfa-2a plus lamivudine Frequency (%)	Lamivudine Frequency (%)	Relative Risk (95% c.i)	Absolute	
% of people with detectable HDV DNA (assessed at the end of 12 months treatment)										
Yurdaydn 2008	1 RCT-unblinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	serious imprecision [b]	7/14 (50%)	15/17 (88.2%)	RR 0.57 (0.33 to 0.98)	379 fewer per 1000 (from 18 fewer to 591 fewer)	LOW
% of people with ALT normalization (assessed at the end of 12 months treatment)										
Yurdaydn 2008	1 RCT-unblinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	9/14 (64.3%)	3/17 (17.6%)	RR 3.64 (1.21 to 10.93)	466 more per 1000 (from 37 more to 1752 more)	LOW
% of people with detectable HDV DNA (assessed at the end of 6 months follow up)										
Yurdaydn 2008	1 RCT-unblinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	9/14 (64.3%)	15/17 (88.2%)	RR 0.73 (0.48 to 1.12)	238 fewer per 1000 (from 459 fewer to 106 more)	LOW
% of people with ALT normalization (assessed at the end of 6 months follow up)										
Yurdaydn 2008	1 RCT-unblinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [c]	3/14 (21.4%)	4/17 (23.5%)	RR 0.91 (0.24 to 3.41)	21 fewer per 1000 (from 179 fewer to 567 more)	VERY LOW

[a] *Unblinded study with no details on randomisation.*
[b] *Confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm.*
[c] *Confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.*

Comparison of lamivudine versus placebo for people co-infected with chronic hepatitis B and D

Table 141: Lamivudine versus placebo for people co-infected with chronic hepatitis B and D - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamivudine versus placebo (coinfected with HDV)	Control	Relative (95% CI)	Absolute	Quality
HDV RNA clearance at end of 52 weeks treatment											
1: Niro 2005	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/20 (0%)	0/11 (0%)	not pooled	not pooled	LOW
ALT U/L at end of 52 weeks treatment (Better indicated by lower values)											
1: Niro 2005	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	20	11	-	MD 12 lower (48.11 lower to 24.11 higher)	LOW

[1] Small sample size; no events
[2] Small sample size; wide confidence intervals consistent with benefit or no effect

11.1.4.8 Pharmacological monotherapies and combination antiviral therapies in achieving remission of the activity of CHB for children

Adefovir versus placebo

Table 142: Adefovir versus placebo (HBeAg positive children) - clinical study characteristics and clinical summary of findings

Quality assessment							No of children		Effect		Quality
No of studies	Design	Rik of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adefovir Frequency (%)	Placebo Frequency (%)	Relative (95% CI)	Absolute	
% of children with ALT normalisation - all ages (assessed at the end of 48 weeks treatment)											
1 Jonas 2008	1 RCT-double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	64/115 (55.7%)	12/58 (20.7%)	RR 2.68 (1.57 to 4.55)	348 more per 1000 (from 118 more to 734 more)	MODERATE
% of children with ALT normalisation - children aged 12-17 years (assessed at the end of 48 weeks treatment)											
1 Jonas 2008	1 RCT-double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	36/56 (64.3%)	6/27 (22.2%)	RR 2.89 (1.39 to 6.02)	420 more per 1000 (from 87 more to 1000 more)	MODERATE
% of children with ALT normalisation - children aged 7-11 years (assessed at the end of 48 weeks treatment)											
1 Jonas 2008	1 RCT-double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	21/36 (58.3%)	3/19 (15.8%)	RR 3.69 (1.26 to 10.82)	425 more per 1000 (from 41 more to 1000 more)	MODERATE
% of children with ALT normalisation - children aged 2-6 years (assessed at the end of 48 weeks treatment)											
1 Jonas 2008	1 RCT-double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [b]	None	7/23 (30.4%)	3/12 (25%)	RR 1.22 (0.38 to 3.88)	55 more per 1000 (from 155 fewer to 720 more)	VERY LOW
% of children with undetectable HBV DNA (<169 copies/ml) – all ages (assessed at the end of 48 weeks treatment)											
1 Jonas 2008	1 RCT-double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	13/115 (11%)	1/58 (2%)	RR 3.64 (0.86 to 15.44)	46 more (2 fewer to 249 more)	MODERATE
% of children with undetectable HBV DNA (<169 copies/ml) - children aged 12-17 years (assessed at the end of 48 weeks treatment)											
1 Jonas 2008	1 RCT-double-	Serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	4/56 (7%)	0/27 (0%)	RR 4.42 (0.25 to 79.27)	-	MODERATE

Quality assessment							No of children		Effect		Quality
	blinded	[a]									
% of children with undetectable HBV DNA (<169 copies/ml) - children aged 7-11 years (assessed at the end of 48 weeks treatment)											
1 Jonas 2008	1 RCT-double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [c]	None	6/36 (17%)	0/19 (0%)	RR 7.03 (0.42 to 118.43)	-	LOW
% of children with undetectable HBV DNA (<169 copies/ml) - children aged 2-6 years (assessed at the end of 48 weeks treatment)											
1 Jonas 2008	1 RCT-double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	3/23 (13%)	1/12 (8%)	RR 1.57 (0.18 to 13.48)	48 more (68 fewer to 1000 more)	MODERATE
% of children with HBsAg seroconversion (assessed at the end of 48 weeks treatment)											
1 Jonas 2008	1 RCT-double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [b]	None	1/115 (0.87%)	0/58 (0%)	PETO OR 4.50 (0.07 to 286.03)	10 more per 1000 (from 20 fewer to 40 more)	VERY LOW
% of children with HBeAg seroconversion (assessed at the end of 48 weeks treatment)											
1 Jonas 2008	1 RCT-double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [d]	None	18/113 (15.9%)	3/57 (5.3%)	RR 3.03 (0.93 to 9.85)	107 more per 1000 (from 4 fewer to 466 more)	LOW
Incidence of resistance											
1 Jonas 2008	1 RCT-double-blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/115 (0%)	0/58 (0%)	RR 1.0	0 fewer per 1000 (from 0 fewer to 0 more)	MODERATE

[a] *No details of allocation concealment.*
[b] *The confidence interval is consistent with three clinical decisions; appreciable harm, no appreciable harm or benefit, appreciable benefit.*
[c] *The confidence interval is consistent with two clinical decisions; appreciable harm, no appreciable harm or benefit.*
[d] *The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable harm or benefit.*

Interferon alpha-2a plus lamivudine versus interferon alpha-2b plus lamivudine

Table 143: Interferon alpha-2a plus lamivudine versus interferon alpha-2b plus lamivudine (HBeAg positive children)- clinical study characteristics and clinical summary of findings

Quality assessment							No of children		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interferon-alpha 2a + lamivudine Frequency (%)**	**Interferon-alpha 2b + lamivudine Frequency (%)**	**Relative (95% CI)**	**Absolute**	
% of children with ALT normalisation (assessed at the end of 12 months treatment)											
1 Ozgenc 2004	RCT-unblinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious limitations [b]	None	24/29 (82.8%)	32/34 (94.1%)	RR 0.88 (0.73 to 1.06)	113 fewer per 1000 (from 254 fewer to 56 more)	LOW
% of children with HBeAg seroconversion (assessed at the end of 12 months treatment)											
1 Ozgenc 2004	RCT-unblinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious limitations [c]	None	15/29 (51.7%)	16/34 (47.1%)	RR 1.1 (0.67 to 1.81)	47 more per 1000 (from 155 fewer to 381 more)	VERY LOW
% of children with response (DNA clearance, HBeAg seroconversion and ALT normalization) (assessed at 6 months follow up)											
1 Ozgenc 2004	RCT-unblinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious limitations [c]	None	13/29 (44.8%)	16/34 (47.1%)	RR 0.95 (0.56 to 1.63)	24 fewer per 1000 (from 207 fewer to 296 more)	VERY LOW
% of children with HBs seroconversion (assessed at the end of 12 months treatment)											
1 Ozgenc 2004	RCT-unblinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious limitations [c]	None	3/29 (10.3%)	0/34 (0%)	PETO OR 9.44 (0.94 to 94.89)	100 more per 1000 (from 20 fewer to 220 more)	VERY LOW
% of children with undetectable DNA (assessed at the end of 12 months treatment)											
1 Ozgenc 2004	RCT-unblinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious limitations [c]	None	26/29 (89.7%)	33/34 (97.1%)	RR 0.92 (0.81 to 1.06)	78 fewer (184 fewer to 58 more)	VERY LOW

[a] *Unblinded study with no details of randomisation and allocation concealment.*
[b] *The confidence interval is consistent with two clinical decisions; appreciable harm, no appreciable benefit or harm.*
[c] *The confidence interval is consistent with three clinical decisions; appreciable harm, no appreciable harm or benefit, appreciable benefit.*

Interferon alpha-2b versus no treatment

Table 144: Interferon alpha-2b verus no treatment (HBeAg positive childen)- clinical study characteristics and clinical summary of findings

Quality assessment							No of children		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interferon-alpha 2b Frequency (%)	No treatment Frequency (%)	Relative (95% CI)	Absolute	
% of children with ALT normalisation (assessed at week 48 (24 weeks after end of treatment))											
1 Sokal 1998	RCT-un blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [b]	none	12/70 (17.1%)	13/74 (17.6%)	RR 0.98 (0.48 to 1.99)	4 fewer per 1000 (from 91 fewer to 174 more)	VERY LOW
% of children with undetectable HBV DNA (assessed at week 24: end of treatment))											
1 Sokal 1998	RCT-un blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [c]	none	18/70 (25.7%)	8/74 (10.8%)	RR 2.38 (1.11 to 5.12)	149 more (12 more to 445 more)	LOW
% of children with undetectable HBV DNA (assessed at week 48 (24 weeks after end of treatment))											
1 Sokal 1998	RCT-un blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [c]	none	23/70 (32.9%)	8/74 (10.8%)	RR 3.04 (1.46 to 6.34)	221 more (50 more to 577 more)	LOW
% of children with HBeAg loss (assessed at week 48 (24 weeks after end of treatment))											
1 Sokal 1998	RCT-un blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	none	23/70 (32.9%)	8/74 (10.8%)	RR 3.04 (1.46 to 6.34)	221 more per 1000 (from 50 more to 577 more)	MODERATE
% of children with HBsAg loss (assessed at week 48 (24 weeks after end of treatment))											
1 Sokal 1998	RCT-un blinded	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [c]	none	7/70 (10%)	1/74 (1.4%)	RR 7.4 (0.93 to 58.62)	86 more per 1000 (from 1 fewer to 779 more)	LOW

[a] *Allocation concealment not reported. Unblinded study.*
[b] *The confidence interval is consistent with three clinical decisions; appreciable harm, no appreciable harm or benefit, appreciable benefit.*
[c] *The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm*

Lamivudine versus placebo

Table 145: Lamivudine versus placebo (HBeAg positive children)- clinical study characteristics and clinical summary of findings

Quality assessment							No of children		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamivudine Frequency (%)	Placebo Frequency (%)	Relative (95% CI)	Absolute	
% of children with ALT normalisation (assessed at the end of 52 weeks treatment)											
Jonas 2002	1 RCT-double blinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	none	100/191 (55%)	11/95 (12%)	RR 4.52 (2.55 to 8.01)	408 more (179 more to 812 more)	MODERATE
% of children with loss of HBeAg (assessed at the end of 52 weeks treatment)											
Jonas 2002	1 RCT-double blinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(b)]	none	50/191 (26%)	14/95 (15%)	RR 1.78 (1.04 to 3.05)	115 more (6 more to 302 more	LOW
% of children with undetectable HBV DNA (assessed at the end of 52 weeks treatment)											
Jonas 2002	1 RCT-double blinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	none	117/191 (61%)	15/95 (16%)	RR 3.88 (2.41 to 6.26)	455 more (223 more to 831 more)	MODERATE
% of children with loss of HBsAg (assessed at the end of 52 weeks treatment)											
Jonas 2002	1 RCT-double blinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	none	3/191 (2%)	0/95 (0%)	PETO OR 4.52 (0.41 to 50.35)		MODERATE
Incidence of resistance (assessed at the end of 52 weeks treatment)											
Jonas 2002	1 RCT-double blinded	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	No serious imprecision	none	31/166 (18.7%)	0/86 (0%)	PETO OR 5.61 (2.54 to 12.37)	190 more per 1000 (from 130 to 250 more)	MODERATE

[(a)] *Allocation concealment not reported.*

[(b)] *The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm*

Interferon alpha 2b + Lamivudine 6 months versus Interferon alpha 2b + Lamivudine 12 months

Table 146: Interferon alpha 2b + Lamivudine 6 months versus Interferon alpha 2b + Lamivudine 12 months (HBeAg positive children)- clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interferon alpha 2b + lamivudine 6 months	Interferon alpha 2b + lamivudine 12 months	Relative (95% CI)	Absolute	Quality
ALT normalization at end of therapy											
Dikici 2001	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/30 (60%)	21/27 (77.8%)	RR 0.77 (0.54 to 1.1)	179 fewer per 1000 (from 358 fewer to 78 more)	LOW
HBeAg clearance at end of therapy											
Dikici 2001	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/30 (33.3%)	16/27 (59.3%)	RR 0.56 (0.31 to 1.02)	261 fewer per 1000 (from 409 fewer to 12 more)	LOW
HBeAg seroconversion at end of therapy											
Dikici 2001	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/30 (16.7%)	10/27 (37%)	RR 0.45 (0.18 to 1.15)	204 fewer per 1000 (from 304 fewer to 56 more)	LOW
HBsAg clearance at end of therapy											
Dikici 2001	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/30 (3.3%)	5/27 (18.5%)	RR 0.18 (0.02 to 1.45)	152 fewer per 1000 (from 181 fewer to 83 more)	VERY LOW
HBsAg seroconversion at end of therapy											

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interferon alpha 2b + lamivudine 6 months**	**Interferon alpha 2b + lamivudine 12 months**	**Relative (95% CI)**	**Absolute**	**Quality**
Dikici 2001	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/30 (6.7%)	2/27 (7.4%)	RR 0.9 (0.14 to 5.96)	7 fewer per 1000 (from 64 fewer to 367 more)	VERY LOW
Undetectable HBV DNA at end of therapy											
Dikici 2001	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/30 (96.7%)	27/27 (100%)	RR 0.97 (0.88 to 1.06)	30 fewer per 1000 (from 120 fewer to 60 more)	MODERATE
ALT normalization 6 months after end of therapy											
Dikici 2001	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/30 (76.7%)	27/27 (100%)	RR 0.77 (0.63 to 0.95)	230 fewer per 1000 (from 50 fewer to 370 fewer)	MODERATE
HBeAg clearance 6 months after end of therapy											
Dikici 2001	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/30 (36.7%)	15/27 (55.6%)	RR 0.66 (0.37 to 1.18)	189 fewer per 1000 (from 350 fewer to 100 more)	LOW
HBeAg seroconversion 6 months after end of therapy											
Dikici 2001	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/30 (20%)	10/27 (37%)	RR 0.54 (0.23 to 1.29)	170 fewer per 1000 (from 285 fewer to 107 more)	VERY LOW
HBsAg clearance 6 months after end of therapy											
Dikici	randomi	serio	no serious	no serious	very	none	2/30	5/27	RR 0.36	119 fewer per	

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interferon alpha 2b + lamivudine 6 months**	**Interferon alpha 2b + lamivudine 12 months**	**Relative (95% CI)**	**Absolute**	**Quality**
2001	sed trials	us[1]	inconsistency	indirectness	serious[3]		(6.7%)	(18.5%)	(0.08 to 1.7)	1000 (from 170 fewer to 130 more)	VERY LOW
HBsAg seroconversion 6 months after end of therapy											
Dikici 2001	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/30 (3.3%)	2/27 (7.4%)	RR 0.45 (0.04 to 4.69)	41 fewer per 1000 (from 71 fewer to 273 more)	VERY LOW
Undetectable HBV DNA 6 months after end of therapy											
Dikici 2001	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/30 (96.7%)	26/27 (96.3%)	RR 1 (0.91 to 1.11)	0 fewer per 1000 (from 87 fewer to 106 more)	MODERATE

[1] No details of randomisation or allocation concealment
[2] The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm
[3] The confidence interval is consistent with three clinical decisions; appreciable harm, no appreciable harm or benefit, appreciable benefit.

11.1.4.9 Economic evidence

Monotherapies

Literature review

Three studies[6,89,95] were included that compared two or more of the interventions of interest.

Two studies[6,89] evaluated therapeutic options for the treatment of individuals with HBeAg positive chronic hepatitis B and two studies [6,95]evaluated treatment options for individuals with HBeAg negative chronic hepatitis B.

These studies are summarised in the economic evidence profiles below (Table 147 and Table 148for HBeAg positive patients and Table 149 and Table 150 for HBeAg negative patients). See also the full study evidence tables in Appendix F.

Given the availability of more applicable and better quality evidence, fifteen studies[1,7,20,45,50,51,64,78,90,96-98,103,108,109] were selectively excluded due to poor applicability and/or methodological limitations. Excluded studies are summarised in Appendix M.

HBeAg positive

Table 147: First line pharmacological therapies – Economic study characteristics

Study	Limitations	Applicability	Other comments
Spackman 2008	Potentially serious limitations [(a)]	Partially applicable [(b)]	Decision analytic model; comparators included no treatment, lamivudine, entecavir, adefovir, Pegylated INF α 2a and telbivudine; treatment effects estimated from some RCTs[13,52,54,67,69,81] included in the NCGC clinical review
Buti 2009	Potentially serious limitations [(c)]	Partially applicable [(d)]	Decision analytic model; comparators included no treatment, lamivudine, entecavir, adefovir, tenofovir and telbivudine; treatment effects estimated from some RCTs[13,52,53,68,83] included in the NCGC clinical review.

(a) Unclear how closely treatment effect estimates match NCGC clinical review; no health state to capture outcome of HBsAg loss; study funded by Bristol Meyers Squibb (makers of entecavir)
(b) Does not include all relevant comparators (e.g. tenofovir); treatment duration maximum 4 years; Costing perspective is US third-party payer: some uncertainty about applicability of US unit costs and estimates of resource use
(c) Unclear how closely treatment effect estimates match NCGC clinical review; no health state to capture outcome of HBsAg loss; study funded by Gilead Sciences (makers of tenofovir)
(d) Does not include all relevant comparators (e.g. Peg INF); costing perspective is Spanish NHS: some uncertainty about applicability of Spanish unit costs and estimates of resource use; utilities based on estimates from a Spanish population.

Table 148: First line pharmacological therapies – Economic summary of findings

Intervention	Incremental cost	Incremental effects (QALYs)	ICER (cost per QALY gained)	Uncertainty
Spackman 2008(a)				
No treatment				Results were sensitive to deterministic sensitivity analysis
Lamivudine	£11,612	0.5	extendedly	

Intervention	Incremental cost	Incremental effects (QALYs)	ICER (cost per QALY gained)	Uncertainty
			dominated	around variables: • Seroconversion rates with entecavir in years 2-4 • seroconversion rates in years 3-4 in patients treated first with peg INF and then entecavir • Decreasing RR of cirrhosis associated with entecavir after peg INF At extremes, these variables made peg INF more effective and potentially cost-effective. Entecavir was more cost-effective when viral suppression decreased the risk of cirrhosis for all years of treatment not just first year. Entecavir was not cost-effective when the baseline seroconversion rate for no treatment increased.
Entecavir	£14,227	0.82	£17,350 compared to no treatment	
Adefovir	£1,055	-0.45	dominated by entecavir	
Peg INF α 2a	£2,058	-0.06	dominated by entecavir	
Telbivudine	£2,145	-0.15	dominated by entecavir	
Buti 2009(b)				
No treatment				In the base case, adefovir + lamivudine was used as the salvage therapy. In a sensitivity analysis, tenofovir+entecavir was used as salvage therapy. This increased both costs and QALYs, but did not change the incremental results. Results of the probabilistic analysis state that tenofovir dominates adefovir, entecavir and telbivudine in 100% of simulations and dominates lamivudine and no treatment in 56% and 14% respectively.
Lamivudine	£3,314	0.98	extendedly dominated	
Tenofovir	£3,741	1.74	£2,150 compared to no treatment	
Entecavir	£2,363	-0.22	dominated by tenofovir	
Telbivudine	£2,761	-0.47	dominated by entecavir and tenofovir	
Adefovir	£3,186	-0.75	dominated by entecavir, tenofovir and telbivudine	

(a) Converted from 2006 US Dollars to 2008 UK Pounds using 2008 Purchasing Power Parities
(b) Converted from 2008 Spanish Euros to 2008 UK Pounds using 2008 Purchasing Power Parities

HBeAg negative

Table 149: First line pharmacological therapies – Economic study characteristics

Study	Limitations	Applicability	Other comments
Buti 2009	Potentially serious limitations [(a)]	Partially applicable [(b)]	Decision analytic model; comparators included no treatment, lamivudine, entecavir, adefovir, tenofovir and telbivudine; treatment effects estimated from some RCTs[13,52,53,68,83] included in

Study	Limitations	Applicability	Other comments
			the NCGC clinical review.
Veenstra 2008	Potentially serious limitations [c]	Partially applicable [d]	Decision analytic model; comparators included lamivudine, entecavir and adefovir given for 5 years, 10 years, lifetime or 5 years on and 1 year off; treatment effects estimated from some RCTs[35-37,53] included in the NCGC clinical review.

(a) Unclear how closely treatment effect estimates match NCGC clinical review; no health state to capture outcome of HBsAg loss; study funded by Gilead Sciences (makers of tenofovir)
(b) Does not include all relevant comparators (e.g. Peg INF); costing perspective is Spanish NHS: some uncertainty about applicability of Spanish unit costs and estimates of resource use; utilities based on estimates from a Spanish population.
(c) Unclear how closely treatment effect estimates match NCGC clinical review; funded by Bristol Meyers Squibb (makers of entecavir)
(d) Does not include all relevant comparators (e.g. Peg INF, tenofovir); costing perspective is US third-party payer: some uncertainty about applicability of US unit costs and estimates of resource use

Table 150: First line pharmacological therapies – Economic summary of findings

Study	Incremental cost	Incremental effects (QALYs)	ICER (cost per QALY gained)	Uncertainty
Buti 2009(a)				
No treatment				Results of the probabilistic analysis state that tenofovir dominates lamivudine in 1%; adefovir in 44%, entecavir in 90%; telbivudine in 98%; no treatment in 2% of simulations.
Lamivudine	£4,161	1.82	£2,286	
Adefovir	£7,439	-0.09	dominated	
Tenofovir	£9,193	1.98	£4,643	
Telbivudine	£4,629	-0.81	dominated	
Entecavir	£8,070	-0.17	dominated	
Veenstra 2008(b)				
Lamivudine (5)				Results were sensitive to the following variables: • rate of resistance with lamivudine • baseline risk of cirrhosis • cost of entecavir • response to salvage therapy When durability of response was decreased (i.e. risk of relapse increased), then strategies involving cessation of therapy increased costs and reduced QALYs. Only when risk of relapse was 90%, lifetime treatment with adefovir was more effective than 5 on-1 off treatment with lamivudine.
Entecavir (5)	£6,528	0.64	£10,200	
Adefovir (5)	£1,442	-0.86	dominated	
Lamivudine (10)	£9,351	0.28	extended dom	
Entecavir (10)	£15,131	1.52	extended dom	
Adefovir (10)	£3,163	-0.9	dominated	
Lamivudine (5/1)	22,129	0.9	extended dom	
Entecavir (5/1)	£37,744	3.14	£15,098	
Adefovir (5/1)	£14,206	-1.21	dominated	
Lamivudine (lifetime)	£21,423	-0.38	dominated	
Entecavir (lifetime)	£23,445	0.25	£93,779	
Adefovir (lifetime)	£16,522	-1.04	dominated	

(a) Converted from 2008 Euros to 2008 UK Pounds using 2008 Purchasing Power Parities
(b) Converted from 2006 US Dollars to 2006 UK Pounds using 2006 Purchasing Power Parities

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 151: Unit cost of interventions

Item	Cost	Notes
Lamivudine (Zeffix)	Tablets, 100 mg net price 28-tab pack = £78.09	ca. £1,015 per year
Adefovir (Hepsera)	Tablets, 10 mg net price 30-tab pack = £296.73	ca. £3,610 per year
Entecavir (Baraclude)	Tablets, 500 micrograms net price 30-tab pack = £363.26; Tablets, 1 mg net price 30-tab pack = £363.26. Oral solution, 50 micrograms/mL net price 210-mL pack = £423.80.	ca. £4,420 per year
Tenofovir (Viread)	Tablets, 245 mg net price 30-tab pack = £240.46.	ca. £2,925 per year
Telbivudine (Sebivo)	Tablets, 600 mg net price 28-tab pack = £290.33	ca. £3,774 per year
Peg INF α 2a (Pegasys)	Injection, peginterferon alfa-2a, net price 135-microgram prefilled syringe = £107.76, 180-microgram prefilled syringe = £124.40.	

Source: BNF 62[41]

New cost-effectiveness analysis

Note that this area was prioritised for new cost-effectiveness analysis. The results of this analysis can be found in section 11.1.8. There is also a full write-up of the methods and results in Appendix I. The results show a sequential analysis of the different treatment options. The analysis shows that Pegylated Interferon a2α is the cost effective first line therapy. If this is not effective however or is badly tolerated then Tenofovir is the favoured treatment.

Combinations

Literature review

Two studies[21,96] were included that compared two or more of the interventions of interest. One study[96] evaluated the cost-effectiveness of antiviral therapies, used alone and in combination, in the treatment of individuals with non-cirrhotic HBeAg positive chronic hepatitis B. The other study[21] compared antiviral therapies, used alone and in combination, in the treatment of a mixed population, including individuals with HBeAg positive and negative chronic hepatitis B, with and without cirrhosis.

These studies are summarised in the economic evidence profiles below. See also the full study evidence tables in Appendix F.

No relevant economic evaluations of combination therapy options for individuals with HBeAg negative chronic hepatitis B were identified.

No studies were selectively excluded.

HBeAg positive CHB patients

Table 152: Combination antiviral therapy versus Monotherapy – Economic study characteristics

Study	Limitations	Applicability	Other comments
Veenstra 2007	Very serious limitations [(a)]	Partially applicable [(b)]	Decision analytic model; comparators included lamivudine and entecavir, with combination lamivudine+adefovir evaluated in a sensitivity analysis; treatment effects estimated from some RCTs[13,81] included in the NCGC clinical review

(a) Unclear how closely treatment effect estimates match NCGC clinical review; study funded by Bristol Meyers Squibb (makers of entecavir)

(b) Does not include all relevant comparators; treatment duration maximum 2 years; Costing perspective is US third-party payer: some uncertainty about applicability of US unit costs and estimates of resource use

Table 153: Combination antiviral therapy versus Monotherapy – Economic summary of findings

Study	Incremental cost	Incremental effects	ICER
Veenstra 2007 (a)			
Lamivudine	least cost	least effective	
Lamivudine+Adefovir	£2,257	0.05	dominated by entecavir
Entecavir [(b)]	£1,380	0.28	£4,929

(a) Converted from 2006 US Dollars to 2008 UK Pounds using 2008 Purchasing Power Parities

(b) Incremental results presented for comparison with lamivudine

It is worth noting that the analysis by Veenstra and colleagues was not included in the review of antiviral therapies used alone because of its methodological limitations and the availability of better quality, more applicable evidence. It has been included for the review of combination therapies largely due a lack of better quality data. The combination of lamivudine+adefovir was only evaluated as part of a sensitivity analysis and therefore neither inputs for the strategy nor results (costs and QALYs) were reported in any detail. This makes validation of the comparison very difficult.

Mixed population of cirrhotic and non-cirrhotic HBeAg positive and negative CHB patients

Table 154: Combination antiviral therapy versus Monotherapy – Economic study characteristics

Study	Limitations	Applicability	Other comments
Dakin 2010	Minor limitations (a)	Directly applicable (b)	Decision analytic model; comparators included sequences of lamivudine, adefovir, entecavir, tenofovir, best supportive care and combinations of adefovir and lamivudine and entecavir and adefovir; treatment effects estimated from a network meta-analysis of RCTs[22]

(a) Unclear how closely effect estimates match the clinical evidence review; estimates of resource use associated with severe liver disease taken from costing study among hepatitis C patients; potential conflict of interest.
(b) Study population is appropriate and may be reflective of the case mix seen in clinical practice, but difficult to know if therapies are more, less or equally cost-effective in both HBeAg positive and negative, with and without compensated cirrhosis

Table 155: Combination antiviral therapy versus Monotherapy – Economic summary of findings

Study	Incremental cost	Incremental effects	ICER	Uncertainty
Dakin 2010				
TDF then TDF+LAM (a)	-	-	dominates	
ADV+LAM then TDF+LAM (b)	£14,125	- 0.41	dominated by TDF then TDF+LAM	
ETV+ADV then LAM (b)	£47,596	- 0.1		

(a) TDF then TDF+LAM was the most cost-effective strategy when all comparators are considered.
(b) Compared to TDF then TDF+LAM

The analysis by Dakin looks to be a publication of the analysis that was submitted as evidence to inform NICE TA 173. Although the results presented here are for a mixed population, the analysis critically appraised in the Evidence Review Group Report for TA 173[42] was stratified by HBeAg status. Unfortunately, full incremental results of the combination antiviral strategies were not presented by HBeAg status in the ERG Report; however, the authors state that this was because combination strategies were clearly dominated (more costly and less effective) by strategies starting with tenofovir alone for both patients with HBeAg positive and negative chronic hepatitis B.

Combination strategies in NA-naïve patients were found to be more effective than some single agent strategies, generally those starting with lamivudine or adefovir alone; however, they were very unlikely to be considered cost-effective given a NICE willingness to pay threshold of £20,000 per QALY compared to any single antiviral therapy option.

Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 156: Unit cost of interventions

Item	Cost	Notes
Lamivudine (Zeffix)	Tablets, 100 mg net price 28-tab pack = £78.09	ca. £1,015 per year
Adefovir (Hepsera)	Tablets, 10 mg net price 30-tab pack = £296.73	ca. £3,610 per year
Entecavir (Baraclude)	Tablets, 500 micrograms net price 30-tab pack = £363.26; Tablets, 1 mg net price 30-tab pack = £363.26. Oral solution, 50 micrograms/mL net price 210-mL pack = £423.80.	ca. £4,420 per year
Tenofovir (Viread)	Tablets, 245 mg net price 30-tab pack = £240.46.	ca. £2,925 per year
Telbivudine (Sebivo)	Tablets, 600 mg net price 28-tab pack = £290.33	ca. £3,774 per year

Item	Cost	Notes
Peg INF α 2a (Pegasys)	Injection, peginterferon alfa-2a, net price 135-microgram prefilled syringe = £107.76, 180-microgram prefilled syringe = £124.40.	
Adefovir + Lamivudine	10 mg + 100 mg	ca. £4,610
Adefovir + Entecavir	10 mg + 500 micrograms (NA naïve) 10 mg + 1 mg (resistant)	ca. £8,030
Emtricitabine plus tenofovir (Tenofovir + emtricitabine)	Tablets, 225 mg tenofovir+200 mg emtricitabine net price 30-tab pack = £418.50	ca. £5,092

Source: BNF 62[41]

New cost-effectiveness analysis

This area was prioritised for new cost-effectiveness analysis. The results of this analysis can be found in section **Error! Reference source not found.**. There is also a full write-up of the methods and results in Appendix I. The results show a sequential analysis of the different treatment options. The analysis shows that Pegylated Interferon a2α is the cost effective first line therapy. If this is not effective however or is badly tolerated then Tenofovir is the favoured treatment. In terms of combinations, if Tenofovir is not tolerated or ineffective, then a combination of tenofovir and Lamivudine is the cost effective option. However, if concerns about the use of lamivudine exist, then switching to entecavir would be cost effective.

11.1.4.10 Clnical Evidence statements

Adults

Monotherapy for nucleos(t)ide naïve HBeAg positive adults

One randomized trial of 338 nucleos(t)ide naïve HBeAg positive adults with CHB showed that adefovir treatment is beneficial compared to placebo for the following outcomes assessed at the end of 48 weeks of treatment:

- Log reduction in HBV DNA (HIGH QUALITY)
- Proportion of adults with undetectable HBV DNA (<400 copies/ml) (HIGH QUALITY)
- Proportion of adults with HBeAg loss (HIGH QUALITY)
- Proportion of adults with ALT normalization (HIGH QUALITY)
- Proportion of adults with histological improvement (HIGH QUALITY)

One randomized trial of 338 nucleos(t)ide naïve HBeAg positive adults with CHB showed that adefovir treatment is neither beneficial nor harmful on increasing the proportion of people with HBeAg secoroconversion at the end of 48 weeks of treatment compared to placebo (MODERATE QUALITY)

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Three randomised studies of sample size ranging from 440-527 HBeAg positive adults with CHB found a benefit of lamivudine compared with placebo on the following outcomes at the end of 52 weeks treatment :

- proportion of adult with undetectable HBV DNA(MODERATE QUALITY)
- Proportion of adults with HBeAg loss (end of treatment) (MODERATE QUALITY)
- Proportion of adults with ALT normalization (MODERATE QUALITY)
- Proportion of adults with histological improvement (MODERATE QUALITY)

Two randomised studies of 330 people found a benefit of lamivudine compared with placebo on the following outcomes:

Genotypic mutation (end of treatment) (MODERATE QUALITY)

One randomised study of 392 people found no benefit of lamivudine compared with placebo on the following outcomes:

HBsAg seroconversion (end of treatment) (LOW QUALITY)

One randomised study of 132 people found no benefit of lamivudine compared with placebo on the following outcomes:

HBeAg seroconversion (16 weeks follow up) (LOW QUALITY)

Loss of serum HBeAg (16 weeks follow up) (LOW QUALITY)

% of patients with undetectable HBV DNA (<1.6 pg/ml) 16 weeks follow up (LOW QUALITY)

……..

One randomised study of 151 patients found a benefit of lamivudine compared with interferon on the following outcomes:

- Undetectable HBV DNA at week 52 (MODERATE QUALITY)
- ALT normalisation at week 52 (MODERATE QUALITY)

One randomised study of 151 patients found no benefit of lamivudine compared with interferon on the following outcomes:

- HBeAg seroconversion at week 52 (LOW QUALITY)
- Histological response at week 52 (LOW QUALITY)
- HBeAg loss at week 52 (LOW QUALITY)
- HBeAg seroconversion at week 64 (LOW QUALITY)
- HBeAg loss at week 64 (LOW QUALITY)
- Undetectable HBV DNA at week 64 (LOW QUALITY)
- ALT normalisation at week 64 (LOW QUALITY)

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One randomized trial of 543 nucleos(t)ide naïve HBeAg positive adults with CHB showed that lamivudine treatment is beneficial compared to pegylated interferon alpha-2a on the following outcomes at the end of 48 weeks of treatment:

- the proportion of people with undetectable HBV DNA (<400 copies/ml) (MODERATE QUALITY)
- the proportion of people with ALT normalization (MODERATE QUALITY)

One randomized trial of 543 nucleos(t)ide naïve HBeAg positive adults with CHB suggested that lamivudine treatment may be neither beneficial nor harmful compared to pegylated interferon alpha-2a on the following outcomes at the end of of 48 weeks of treatment:

- the proportion of people with HBeAg seroconversion (LOW QUALITY)

- the proportion of people withdrawn due to adverse events (LOW QUALITY)

One randomized trial of 543 nucleos(t)ide naïve HBeAg positive adults with CHB showed that pegylated interferon alpha-2a is beneficial compared to lamivudine treatment on the following outcomes:

- the proportion of people with HBeAg loss at the end of 48 weeks of treatment (MODERATE QUALITY)
- the proportion of people with undetectable HBV DNA (<400 copies/ml) at the end of 24 weeks of follow up (MODERATE QUALITY)
- the proportion of people with HBeAg seroconversion at the end of 24 weeks of follow up (MODERATE QUALITY)
- the proportion of people with HBeAg loss at the end of 24 weeks of follow up (MODERATE QUALITY)
- the proportion of people with ALT normalization at the end of 24 weeks of follow up (MODERATE QUALITY)

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One randomized trial of 85 nucleos(t)ide naïve HBeAg positive adults with CHB suggested that telbivudine treatment may be beneficial compared to adefovir on the proportion of people with undetectable HBV DNA (<300 copies/ml) at the end of 52 weeks of treatment (LOW QUALITY).

One randomized trial of 85 nucleos(t)ide naïve HBeAg positive adults with CHB showed that telbivudine treatment is neither beneficial nor harmful compared to adefovir on the proportion of people withdrawn due to adverse events at the end of 52 weeks of treatment (MODERATE QUALITY).

One randomized trial of 85 nucleos(t)ide naïve HBeAg positive adults with CHB suggested that telbivudine treatment may be neither beneficial nor harmful compared to adefovir the following outcomes at the end of 52 weeks of treatment:

- the proportion of people with HBeAg loss (VERY LOW QUALITY)
- the proportion of people with HBeAg seroconversion (VERY LOW QUALITY)
- the proportion of people with ALT normalization (LOW QUALITY)

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Three randomized trials of 1274 nucleos(t)ide naïve HBeAg positive adults with CHB showed that telbivudine treatment is beneficial compared to lamivudine on the log reduction in the HBV DNA at the end of 52 weeks of treatment (MODERATE QUALITY).

One randomized trial of 1211 nucleos(t)ide naïve HBeAg positive adults with CHB showed that telbivudine treatment is beneficial compared to lamivudine on the proportion of people with undetectable HBV DNA (<300 copies/ml) at the end of 52 weeks of treatment (HIGH QUALITY).

One randomized trial of 63 nucleos(t)ide naïve HBeAg positive adults with CHB showed that telbivudine treatment is beneficial compared to lamivudine on the proportion of people with undetectable HBV DNA (<200 copies/ml) at the end of 52 weeks of treatment (MODERATE QUALITY).

One randomized trial of 921 nucleos(t)ide naïve HBeAg positive adults with CHB showed that telbivudine treatment is beneficial compared to lamivudine on the proportion of people with undetectable HBV DNA (<200 copies/ml) and incidence of resistance at the end of 104 weeks of treatment (HIGH QUALITY).

Three randomized trials of 1274 nucleos(t)ide naïve HBeAg positive adults with CHB showed that telbivudine treatment is neither beneficial nor harmful compared to lamivudine on the following outcomes at the end of 52 weeks of treatment:

- the proportion of people with HBeAg loss (MODERATE QUALITY)
- the proportion of people with HBeAg seroconversion (MODERATE QUALITY)
- the proportion of people with ALT normalization (HIGH QUALITY)

Three randomized trials of 921 nucleos(t)ide naïve HBeAg positive adults with CHB suggested that telbivudine treatment may be neither beneficial nor harmful compared to lamivudine on the proportion of people with HBsAg at the end of 104 weeks (LOW QUALITY).

One randomized trial of 921 nucleos(t)ide naïve HBeAg positive adults with CHB showed that telbivudine treatment is neither beneficial nor harmful compared to lamivudine on the following outcomes at the end of 104 weeks of treatment:

- the proportion of people with HBeAg loss (MODERATE QUALITY)
- the proportion of people with HBeAg seroconversion (MODERATE QUALITY)
- the proportion of people with ALT normalization (HIGH QUALITY)

One randomized trial of 921 nucleos(t)ide naïve HBeAg positive adults with CHB suggested that telbivudine treatment may be neither beneficial nor harmful compared to lamivudine on the proportion of people with HBsAg seroconversion at the end of 104 weeks of treatment (LOW QUALITY).

One randomized trial of 63 nucleos(t)ide naïve HBeAg positive adults with CHB suggested that telbivudine treatment may be beneficial compared to lamivudine on the proportion of people with viral breakthrough at the end of 52 weeks of treatment (LOW QUALITY).

One randomized trial of 921 nucleos(t)ide naïve HBeAg positive adults with CHB showed that telbivudine treatment is neither beneficial nor harmful compared to lamivudine on the proportion of people with histological improvement at the end of 52 weeks of treatment (MODERATE QUALITY).

Two randomized trials of 1430 nucleos(t)ide naïve HBeAg positive adults with CHB suggested that telbivudine treatment may be neither beneficial nor harmful compared to lamivudine on the proportion of people withdrawn due to adverse events at the end of 52 weeks of treatment (VERY LOW QUALITY).

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One randomized trial of 244 nucleos(t)ide naïve HBeAg positive adults with CHB showed that tenofovir treatment is beneficial compared to adefovir on the following outcomes at the end of 48 weeks of treatment:

- log reduction in HBV DNA (HIGH QUALITY)
- the proportion of people with undetectable HBV DNA (<400 copies/ml) (HIGH QUALITY)
- the proportion of people with ALT normalization (MODERATE QUALITY)

One randomized trial of 240 nucleos(t)ide naïve HBeAg positive adults with CHB suggested that tenofovir treatment may be neither beneficial nor harmful compared to adefovir on the following outcomes at the end of 48 weeks of treatment:

- the proportion of people with HBsAg loss (LOW QUALITY)
- the proportion of people with HBeAg seroconversion (LOW QUALITY)

One randomized trial of 268 nucleos(t)ide naïve HBeAg positive adults with CHB showed that tenofovir treatment may be neither beneficial nor harmful compared to adefovir on the following outcomes at the end of 48 weeks of treatment :

- the proportion of people with histological improvement (MODERATE QUALITY)
- the proportion of people withdrawn due to adverse events (HIGH QUALITY)

One randomized trial of 641 nucleos(t)ide naïve HBeAg positive and negative adults with CHB showed that tenofovir treatment may be neither beneficial nor harmful compared to adefovir on the incidence of resistance at the end of 48 weeks of treatment (MODERATE QUALITY).

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Two randomized trials of 1107 nucleos(t)ide naïve HBeAg positive adults with CHB showed that entecavir treatment is beneficial compared to lamivudine on log reduction in HBV DNA at the end of 48 weeks of treatment (HIGH QUALITY).

One randomized trial of 695 nucleos(t)ide naïve HBeAg positive adults with CHB showed that entecavir treatment is beneficial compared to lamivudine on the incidence of resistance at the end of 48 weeks of treatment (HIGH QUALITY)

Three randomized trial of 1149 nucleos(t)ide naïve HBeAg positive adults with CHB suggested that entecavir treatment may be beneficial compared to lamivudine on reducing the proportion of people with undetectable HBV DNA (<300 copies/ml) at the end of 48 weeks of treatment (LOW QUALITY).

Three randomized trials of 1149 nucleos(t)ide naïve HBeAg positive adults with CHB suggested that entecavir treatment may be neither beneficial nor harmful compared to lamivudine on the following outcomes at the end of 48 weeks of treatment:

- the proportion of people with HBeAg seroconversion (LOW QUALITY)
- the proportion of people with ALT normalization (LOW QUALITY).

One randomized trial of 661 nucleos(t)ide naïve HBeAg positive adults with CHB suggested that entecavir treatment may be neither beneficial nor harmful compared to lamivudine on the proportion of people with HBsAg loss at the end of 48 weeks of treatment (LOW QUALITY).

One randomized trial of 561 nucleos(t)ide naïve HBeAg positive adults with CHB showed that entecavir treatment is neither beneficial nor harmful compared to lamivudine on the proportion of people with histological improvement at the end of 48 weeks of treatment (HIGH QUALITY).

Two randomized trials of 1228 nucleos(t)ide naïve HBeAg positive adults with CHB showed that entecavir treatment is neither beneficial nor harmful compared to lamivudine on the proportion of people withdrawn due to adverse events at the end of 48 weeks of treatment (HIGH QUALITY).

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One randomized trial of 65 nucleos(t)ide naïve HBeAg positive adults with CHB showed that entecavir treatment is beneficial compared to adefovir on the proportion of people with undetectable HBV DNA (<300 copies/ml) at the end of 48 weeks of treatment (MODERATE QUALITY).

One randomized trial of 65 nucleos(t)ide naïve HBeAg positive adults with CHB suggested that entecavir treatment may be beneficial compared to adefovir on the proportion of people with ALT normalization at the end of 48 weeks of treatment (LOW QUALITY).

One randomized trial of 65 nucleos(t)ide naïve HBeAg positive adults with CHB suggested that entecavir treatment may be neither beneficial nor harmful compared to adefovir on the following outcomes at the end of 48 weeks of treatment:

- the proportion of people with HBeAg seroconversion (VERY LOW QUALITY)
- the proportion of people with HBeAg loss (VERY LOW QUALITY)
- the proportion of people withdrawn due to adverse events (VERY LOW QUALITY).

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One randomized trial of 131 nucleos(t)ide naïve HBeAg positive adults with CHB suggested that tenofovir treatment may be beneficial compared to entecavir on the following outcomes at the end of 24 weeks of treatment:

- the proportion of people with undetectable HBV DNA (LOW QUALITY)
- the proportion of people with HBeAg seroconversion (LOW QUALITY)

One randomized trial of 131 nucleos(t)ide naïve HBeAg positive adults with CHB suggested that tenofovir treatment may be neither beneficial nor harmful compared to entecavir on the following outcomes at the end of 24 weeks of treatment:

- log reduction in HBV DNA (VERY LOW QUALITY)
- the proportion of people with HBsAg (LOW QUALITY)
- the proportion of people with ALT normalization (LOW QUALITY)

One randomised trial of 379 nucleos(t)ide naive patients with CHB (70% HBeAg positive) found a benefit of entecavir plus tenofovir compared with entecavir monotherapy on the following outcomes:

- HBV DNA <50 IU/mL at 48 weeks (LOW QUALITY)

One randomised trial of 379 nucleos(t)ide naive patients with CHB (70% HBeAg positive) found neither benefit nor harm of entecavir plus tenofovir compared with entecavir monotherapy on the following outcomes:

- HBeAg loss at 48 and 96 weeks (LOW QUALITY)
- HBeAg seroconversion at 48 and 96 weeks (LOW QUALITY)
- HBsAg loss at 48 and 96 weeks (LOW QUALITY)
- HBsAg seroconversion at 48 and 96 weeks (LOW QUALITY)
- HBV DNA <50 IU/mL at 96 weeks (LOW QUALITY)
- Virological breakthrough at 96 weeks (LOW QUALITY)
- Discontinuation due to adverse events (LOW QUALITY)

One randomised trial of 379 nucleos(t)ide naive patients with CHB (70% HBeAg positive) found a harm of entecavir plus tenofovir compared with entecavir monotherapy on the following outcomes:

ALT normalisation at 48 and 96 weeks (LOW QUALITY)

Combination therapies for Nucleos(t)ide naïve HBeAg positive patients

One randomised trial of 119 people found no difference between lamivudine and interferon α 2b (for 24 weeks) and placebo at 52 weeks on the following outcomes:

- % of patients with undetectable HBV DNA (<1.6 pg/ml) (MODERATE QUALITY)

- Loss of serum HBeAg (MODERATE QUALITY)
- HBeAg seroconversion (MODERATE QUALITY)
- Histologic improvement (MODERATE QUALITY)
- ALT normalization (MODERATE QUALITY)

One randomised trial of 100 treatment naïve HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine may be neither beneficial nor harmful on the proportion of people with undetectable HBV DNA (undefined threshold) compared to interferon alpha at the end of 6 months treatment and 6 months follow up (VERY LOW AND LOW QUALITY).

One randomised trial of 64 treatment naïve HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine may be beneficial on achieving undetectable HBV DNA (<5pg/mL) compared to interferon alpha at the end of 12 months treatment (LOW QUALITY).

One randomised trial of 48 treatment naïve HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine may be beneficial on achieving undetectable HBV DNA (<1pg/mL) compared to interferon alpha at the end of 12 months treatment (VERY LOW QUALITY).

Two randomised trials of 152 treatment naïve HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine may be neither beneficial nor harmful on the proportion of people with undetectable HBV DNA ($<10^3$-10^4 copies/mL) compared to interferon alpha at the end of 12 months follow up (VERY LOW QUALITY).

One randomised trial of 100 treatment naïve HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine may be beneficial on the proportion of people with ALT normalisation compared to interferon alpha at the end of 6 months treatment and 6 months follow up (LOW QUALITY).

Two randomised trials of 152 treatment naïve HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine may be beneficial on the proportion of people with ALT normalisation compared to interferon alpha at the end of 12 months treatment and 6-12 months follow up (VERY LOW QUALITY).

Two randomised trials of 110 treatment naïve HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine may be neither beneficial nor harmful on the proportion of people with HBeAg seroconversion compared to interferon alpha at the end of 12 months treatment (VERY LOW QUALITY).

One randomised trial of 100 treatment naïve HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine may be neither beneficial nor harmful on the proportion of people with HBeAg seroconversion compared to interferon alpha at the end of 6 months follow up (VERY LOW QUALITY).

One randomised trial of 48 treatment naïve HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine may be beneficial on the proportion of people with HBeAg seroconversion compared to interferon alpha at the end of 12 months follow up (VERY LOW QUALITY).

One randomised trial of 46 treatment naïve HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine may be beneficial on the proportion of people with histological improvement compared to interferon alpha at the end of 12 months treatment (LOW QUALITY).

Two randomised trials of 298 treatment naïve HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine may be neither beneficial nor harmful on the proportion of people withdrawn due to adverse events compared to interferon alpha (VERY LOW QUALITY).

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One randomised trial of 542 treatment naïve HBeAg positive adults with CHB showed that pegylated interferon alpha 2a plus lamivudine combination therapy is beneficial on the proportion of people with undetectable HBV DNA (<400copies/mL) and log reduction of HBV DNA compared to pegylated interferon alone at the end of 48 weeks treatment (MODERATE QUALITY).

One randomised trial of 489 treatment naïve HBeAg positive adults with CHB showed that pegylated interferon alpha 2a plus lamivudine combination therapy may be neither beneficial nor harmful compared to pegylated interferon alone on the following outcomes:

- The proportion of people with HBeAg loss at the end of 48 weeks treatment and 24 weeks follow up (LOW QUALITY)
- The proportion of people with HBeAg seroconversion at the end of 48 weeks treatment and 24 weeks follow up (LOW QUALITY)
- ALT normalisation at the end of 48 weeks treatment and 24 weeks follow up (LOW QUALITY)
- The proportion of people with undetectable HBV DNA at the end of 24 weeks follow up (LOW QUALITY)
- proportion of people withdrawn due to adverse events compared to pegylated interferon alone (LOW QUALITY).

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One randomised trial of 266 HBeAg positive adults with CHB showed that pegylated interferon alpha 2b plus lamivudine combination therapy is beneficial on the proportion of people with undetectable HBV DNA (<400copies/mL) and incidence of resistance compared to pegylated interferon alpha 2b alone at the end of 52 weeks treatment (HIGH QUALITY).

One randomised trial of 266 HBeAg positive adults with CHB suggested that pegylated interferon alpha 2b plus lamivudine combination therapy may be neither beneficial nor harmful compared to pegylated interferon alpha 2b alone on the following outcomes:

- The proportion of people with undetectable HBV DNA (<400copies/mL) at the end of 6 months follow up (LOW QUALITY)
- The proportion of people with ALT normalisation at the end of 52 weeks treatment and 6 months follow up (MODERATE and LOW QUALITY)
- The proportion of people with HBeAg loss at the end of 6 months follow up (LOW QUALITY)
- The proportion of people with HBeAg seroconversion at the end of 52 weeks treatment and 6 months follow up (LOW QUALITY)
- The proportion of people with HBsAg loss and seroconversion at the end of 52 weeks treatment and 6 months follow up (LOW QUALITY)

One randomised trial of 266 HBeAg positive adults with CHB showed that pegylated interferon alpha 2b plus lamivudine combination therapy is beneficial on the incidence of resistance compared to pegylated interferon alpha 2b alone at the end of 52 weeks treatment (HIGH QUALITY).

One randomised trial of 266 HBeAg positive adults with CHB showed that pegylated interferon alpha 2b plus lamivudine combination therapy is harmful on the proportion of people with ALT normalisation and HBeAg loss compared to pegylated interferon alpha 2b alone at the end of 52 weeks treatment (MODERATE QUALITY).

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One randomised trial of 64 HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine combination therapy may be beneficial compared to lamivudine alone at the end of 52 weeks treatment on the following outcomes:

- The proportion of people with ALT normalisation (VERY LOW QUALITY)

- The proportion of people with undetectable HBV DNA (<2.6 log copies/mL) (LOW QUALITY)
- The proportion of people with HBeAg seroconversion (VERY LOW QUALITY)

One randomised trial of 151 HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine combination therapy may be beneficial compared to lamivudine alone on the following outcomes:

- The proportion of people with ALT normalisation at the end of 6 months follow up (LOW QUALITY)
- The proportion of people with undetectable HBV DNA (<1.6pg/mL) at the end of 24 weeks treatment (LOW QUALITY)
- The proportion of people with histological improvement at the end of 24 weeks treatment and 6 months follow up (LOW QUALITY)

One randomised trial of 151 HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine combination therapy may be neither beneficial nor harmful compared to pegylated interferon alpha 2b alone on the following outcomes:

- The proportion of people with undetectable HBV DNA at the end of 6 months follow up (LOW QUALITY)
- Incidence of resistance (VERY LOW QUALITY)

One randomised trial of 64 HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine combination therapy may be harmful on the incidence of resistance compared to pegylated interferon alpha 2b alone at the end of 52 weeks treatment (VERY LOW QUALITY).

One randomised trial of 52 HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine combination therapy may be harmful on the proportion of people with histological improvement (inflammation) compared to pegylated interferon alpha 2b alone at the end of 52 weeks treatment (VERY LOW QUALITY).

One randomised trial of 52 HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine combination therapy may be neither beneficial nor harmful on the proportion of people with histological improvement (fibrosis) compared to pegylated interferon alpha 2b alone at the end of 52 weeks treatment (VERY LOW QUALITY).

Two randomised trials of 298 HBeAg positive adults with CHB suggested that interferon alpha plus lamivudine combination therapy may be beneficial on the proportion of people withdrawn due to adverse events compared to pegylated interferon alpha 2b alone at the end of 52 weeks treatment (VERY LOW QUALITY).

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One randomised trial of 476 HBeAg positive adults with CHB showed that pegylated interferon alpha 2a plus lamivudine combination therapy is beneficial on the log reduction of HBV DNA and undetectable HBV DNA (<400copies/mL) compared to lamivudine alone at the end of 48 weeks treatment (MODERATE QUALITY).

One randomised trial of 543 HBeAg positive adults with CHB suggested that pegylated interferon alpha 2a plus lamivudine combination therapy may be beneficial compared to lamivudine alone on the following outcomes:

- The proportion of people with undetectable HBV DNA at the end of 48 weeks treatment (MODERATE QUALITY) and 24 weeks follow up (LOW QUALITY)
- The proportion of people with HBeAg loss at 24 weeks follow up (LOW QUALITY)
- The proportion of people with HBeAg seroconversion at 24 weeks follow up (LOW QUALITY)
- The proportion of people with ALT normalisation at 24 weeks follow up (LOW QUALITY)

One randomised trial of 476 HBeAg positive adults with CHB suggested that pegylated interferon alpha 2a plus lamivudine combination therapy may be neither beneficial nor harmful compared to lamivudine alone on the following outcomes at the end of 24 weeks follow up:

- The proportion of people with HBeAg loss at the end of 48 weeks treatment (LOW QUALITY)
- The proportion of people with HBeAg seroconversion at the end of 48 weeks treatment (LOW QUALITY)

One randomised trial of 543 HBeAg positive adults with CHB suggested that pegylated interferon alpha 2a plus lamivudine combination therapy may be harmful on

- the proportion of ALT normalisation compared to lamivudine alone at the end of 48 weeks treatment (LOW QUALITY).
- the proportion of people withdrawn due to adverse events compared to lamivudine alone on the following outcomes at the end of 24 weeks follow up (MODERATE QUALITY).

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Monotherapy for LAM resistant adults

One randomised trial of 145 LAM resistant adults (mixed population; 90% HBeAg + and 10% HBeAg -) found a benefit of entecavir over placebo for the following outcomes:

Mean reduction of HBV DNA from baseline to the end of 12 weeks of treatment (LOW QUALITY)

Proportion of patients with ALT normalisation at the end of 12 weeks of treatment (LOW QUALITY)

One randomised trial of 145 LAM resistant adults (mixed population; 90% HBeAg + and 10% HBeAg -) found no benefit of entecavir over placebo for the following outcomes:

Proportion of patients with undetectable HBV DNA at the end of 12 weeks of treatment (LOW QUALITY)

Adverse events leading to withdrawal at the end of 12 weeks of treatment (LOW QUALITY)

Combination therapy for LAM resistant adults

Monotherapy for HBeAg negative adults

One randomised trial of 185 HBeAg negative adults with CHB showed that adefovir is beneficial compared with placebo on the following outcomes:

- Proportion with undetectable HBV DNA at end of treatment (48 weeks) (HIGH QUALITY)
- ALT normalization at end of treatment (48 weeks) (HIGH QUALITY)
- Histological improvement at end of treatment (48 weeks) (HIGH QUALITY)

One randomised trial of 125 HBeAg negative patients with CHB showed that lamivudine is better than placebo on the following outcomes:

- Proportion with undetectable HBV DNA at end of treatment (24 weeks) (MODERATE QUALIT

One randomised trial of 139 HBeAg negative patients with CHB showed that lamivudine is better than placebo on the following outcomes:

- Proportion with undetectable HBV DNA at end of treatment (24 months) (HIGH QUALITY)
- ALT normalization at end of treatment (24 months) (HIGH QUALITY)
- ALT normalization at 6 months follow up (HIGH QUALITY)

One randomised trial of 139 HBeAg negative patients with CHB showed that lamivudine is no better than placebo on the following outcomes:

- Proportion with undetectable HBV DNA at 6 months follow up (MODERATE QUALITY)
- Histological improvement (time point unclear) (LOW QUALITY)

Two randomised trials of 264 HBeAg negative patients with CHB showed that lamivudine is no better than placebo on the following outcomes:

- HBsAg loss (LOW QUALITY)

In one randomised trial of 139 patients, lamivudine treatment was associated with a higher rate of resistance (genotypic resistance at 24 months: HIGH QUALITY; and viral breakthrough at 24 months; HIGH QUALITY).

Children

Monotherapy

Adefovir versus placebo

One randomised trial of 173 children with CHB found that adefovir was more effective than placebo as measured by the % of children with ALT normalisation at all ages (MODERATE QUALITY).

One randomised trial of 173 children with CHB found that adefovir was more effective than placebo as measured by the % of children with ALT normalisation: children aged 12-17 years (MODERATE QUALITY).

One randomised trial of 173 children with CHB found that adefovir was more effective than placebo as measured by the % of children with ALT normalisation: children aged 7-11 years (MODERATE QUALITY).

One randomised trial of 173 children with CHB found that adefovir was not more effective than placebo as measured by the % of children with ALT normalisation among children aged 2-6 years (VERY LOW QUALITY).

One randomised trial of 173 children with CHB found that adefovir was not more effective than placebo as measured by the % of children with undetectable HBV DNA: all ages (MODERATE QUALITY).

One randomised trial of 173 children with CHB found that adefovir was not more effective than placebo as measured by the % of children with undetectable HBV DNA: 12-17 years (MODERATE QUALITY).

One randomised trial of 173 children with CHB found that adefovir was not more effective than placebo as measured by the % of children with undetectable HBV DNA: 7-11 years (LOW QUALITY).

One randomised trial of 173 children with CHB found that adefovir was not more effective than placebo as measured by the % of children with undetectable HBV DNA: aged 2-6 years (MODERATE QUALITY).

One randomised trial of 173 children with CHB found that adefovir was not more effective than placebo as measured by the % of children with HBsAg seroconversion (VERY LOW QUALITY).

One randomised trial of 173 children with CHB found that adefovir was not more effective than placebo as measured by the % of children with HBeAg seroconversion (LOW QUALITY).

One randomised trial of 173 children with CHB found that adefovir was no worse than placebo as measured by the incidence of resistance (MODERATE QUALITY).

Lamivudine versus placebo

One randomised trial of 288 children with CHB found that lamivudine was more effective than placebo as measured by % of children with ALT normalisation (MODERATE QUALITY).

One randomised trial of 288 children with CHB found that lamivudine was more effective than placebo as measured by % of children with loss of HBeAg (LOW QULAITY).

One randomised trial of 288 children with CHB found that lamivudine was more effective than placebo as measured by % of children with undetectable HBV DNA (MODERATE QUALITY).

One randomised trial of 288 children with CHB found no difference between lamivudine and placebo as measured by % of children with loss of HBsAg (MODERATE QUALITY).

One randomised trial of 288 children with CHB found no difference between lamivudine and placebo as measured by the incidence of resistance (MODERATE QUALITY).

Interferon alpha 2b versus no treatment

One unblinded randomised trial of 149 children found no difference between Interferon alpha 2b and no treatment as measured by the % of children with ALT normalisation (VERY LOW QUALITY).

One unblinded randomised trial of 149 children found a benefit of Interferon alpha 2b over no treatment as measured by the % of children with undetectable HBV DNA (assessed at week 24: end of treatment) (LOW QUALITY).

One unblinded randomised trial of 149 children found a benefit of Interferon alpha 2b over no treatment as measured by the % of children with undetectable HBV DNA (assessed at week 48 (24 weeks after end of treatment)) (LOW QUALITY).

One unblinded randomised trial of 149 children found a benefit of Interferon alpha 2b over no treatment as measured by the % of children with HBeAg loss (assessed at week 48 (24 weeks after end of treatment)) (MODERATE QUALITY).

One unblinded randomised trial of 149 children found no difference between Interferon alpha 2b and no treatment as measured by the % of children with HBsAg loss (assessed at week 48 (24 weeks after end of treatment)) (LOW QUALITY).

Combination therapy

Interferon alpha 2a + lamivudine versus Interferon alpha 2b + lamivudine

One unblinded randomised trial of 63 children found no difference between Interferon alpha 2a + lamivudine (6 months combination then 6 months lamivudine alone) and Interferon alpha 2b + lamivudine (6 months combination then 6 months lamivudine alone) on the % of children with ALT normalisation (assessed at the end of 12 months treatment) (LOW QUALITY).

One unblinded randomised trial of 63 children found no difference between Interferon alpha 2a + lamivudine (6 months combination then 6 months lamivudine alone) and Interferon alpha 2b +

lamivudine (6 months combination then 6 months lamivudine alone) on the % of children with HBeAg seroconversion (assessed at the end of 12 months treatment) (VERY LOW QUALITY).

One unblinded randomised trial of 63 children found no difference between Interferon alpha 2a + lamivudine (6 months combination then 6 months lamivudine alone) and Interferon alpha 2b + lamivudine (6 months combination then 6 months lamivudine alone) on the % of children with response (DNA clearance, HBeAg seroconversion and ALT normalization) (assessed at 6 months follow up) (VERY LOW QUALITY).

One unblinded randomised trial of 63 children found no difference between Interferon alpha 2a + lamivudine (6 months combination then 6 months lamivudine alone) and Interferon alpha 2b + lamivudine (6 months combination then 6 months lamivudine alone) on the % of children with HBs seroconversion (assessed at the end of 12 months treatment) (VERY LOW QUALITY).

One unblinded randomised trial of 63 children found no difference between Interferon alpha 2a + lamivudine (6 months combination then 6 months lamivudine alone) and Interferon alpha 2b + lamivudine (6 months combination then 6 months lamivudine alone) on the % of children with undetectable DNA (assessed at the end of 12 months treatment) (VERY LOW QUALITY).

Interferon alpha 2b + lamivudine for 6 months versus same combination for 12 months

One randomised trial of 57 children found no difference between Interferon alpha 2b + lamivudine for 6 months versus the same combination for 12 months on ALT normalisation at the end of therapy (LOW QUALITY).

One randomised trial of 57 children found no difference between Interferon alpha 2b + lamivudine for 6 months versus the same combination for 12 months on HBeAg clearance at the end of therapy (LOW QUALITY).

One randomised trial of 57 children found no difference between Interferon alpha 2b + lamivudine for 6 months versus the same combination for 12 months on HBeAg seroconversion at the end of therapy (LOW QUALITY).

One randomised trial of 57 children found no difference between Interferon alpha 2b + lamivudine for 6 months versus the same combination for 12 months on HBsAg clearance at the end of therapy (VERY LOW QUALITY).

One randomised trial of 57 children found no difference between Interferon alpha 2b + lamivudine for 6 months versus the same combination for 12 months on HBsAg seroconversion at the end of therapy (VERY LOW QUALITY).

One randomised trial of 57 children found no difference between Interferon alpha 2b + lamivudine for 6 months versus the same combination for 12 months on undetectable HBV DNA at end of therapy (MODERATE QUALITY).

One randomised trial of 57 children found 12 months of therapy with Interferon alpha 2b + lamivudine was better than 6 months of the same combination on ALT normalization 6 months after end of therapy (MODERATE QUALITY).

One randomised trial of 57 children found no difference between Interferon alpha 2b + lamivudine for 6 months versus the same combination for 12 months on HBeAg clearance 6 months after the end of therapy (LOW QUALITY).

One randomised trial of 57 children found no difference between Interferon alpha 2b + lamivudine for 6 months versus the same combination for 12 months on HBeAg seroconversion 6 months after the end of therapy (VERY LOW QUALITY).

One randomised trial of 57 children found no difference between Interferon alpha 2b + lamivudine for 6 months versus the same combination for 12 months on HBsAg clearance 6 months after end of therapy (VERY LOW QUALITY).

One randomised trial of 57 children found no difference between Interferon alpha 2b + lamivudine for 6 months versus the same combination for 12 months on HBsAg seroconversion 6 months after end of therapy (VERY LOW QUALITY).

One randomised trial of 57 children found no difference between Interferon alpha 2b + lamivudine for 6 months versus the same combination for 12 months on undetectable HBV DNA 6 months after end of therapy (MODERATE QUALITY).

11.1.4.11 Economic Evidence statements

Monotherapies

- There is considerable uncertainty as to which therapy is the most cost-effective in the initial treatment of patients with HBeAg positive chronic hepatitis B.
  - No cost-utility analyses were identified comparing all interventions of interest in the treatment of patients with HBeAg positive chronic hepatitis B.
  - One study found that entecavir was likely to be cost effective in the initial treatment of patients with HBeAg positive chronic hepatitis B. This study was partially applicable and had potentially serious limitations.
  - One study found that tenofovir was likely to be cost effective in the initial treatment of patients with HBeAg positive chronic hepatitis B. This study was partially applicable and had potentially serious limitations.
- There is considerable uncertainty as to which therapy is the most cost-effective in the initial treatment of patients with HBeAg negative chronic hepatitis B.
  - No cost-utility analyses were identified comparing all interventions of interest in the treatment of patients with HBeAg negative chronic hepatitis B.
  - One study found that entacavir, given for 5 years with a 1 year break to check for durability, was likely to be cost effective in the initial treatment of patients with HBeAg negative chronic hepatitis B. The same study showed the lifetime treatment with entacavir, whilst most effective, was unlikely to represent a cost-effective use of healthcare resources. This study was partially applicable and had potentially serious limitations.
  - One study found that tenofovir was likely to be cost effective in the initial treatment of patients with HBeAg negative chronic hepatitis B. This study was partially applicable and had potentially serious limitations.
- The novel economic analysis shows that Pegylated Interferon a2α is the cost effective first line therapy. If this is not effective however or is badly tolerated then Tenofovir is the favoured treatment. In terms of combinations, if Tenofovir is not tolerated or ineffective, then a combination of tenofovir and Lamivudine is the cost effective option. However, if concerns about the use of lamivudine exist, then switching to entecavir would be cost effective.

Combinations

- No cost-utility analyses were identified comparing all combinations of interest in the treatment of patients with chronic hepatitis B.
- One study found that 2-year treatment with entecavir was likely to be less costly and more effective than a combination of lamivudine and adefovir in the initial treatment of patients with HBeAg positive chronic hepatitis B. This study was partially applicable and had very serious limitations.
- One study found that tenofovir was likely to be less costly and more effective than a combinations of both adefovir + lamivudine and entecavir + adefovir in the initial treatment of patients with HBeAg positive or negative chronic hepatitis B. This study was directly applicable and had minor limitations.
- The novel economic analysis shows that Pegylated Interferon a2α is the cost effective first line therapy. If this is not effective however or is badly tolerated then Tenofovir is the favoured treatment. In terms of combinations, if Tenofovir is not tolerated or ineffective, then a combination of tenofovir and Lamivudine is the cost effective option. However, if concerns about the use of lamivudine exist, then switching to entecavir would be cost effective.

11.1.5 Review question: In people with CHB, what is the clinical and cost-effectiveness of sequential drug therapy (add-on or switching monotherapies) in achieving remission of the activity of CHB?

Table 157: Protocol

Protocol	
Population	Children (2-16 years), young people and adults with chronic hepatitis B virus infection
Intervention	Add-on or switching from one drug to another • Pegylated alpha-interferon α • Tenofovir • Entecavir • Adefovir • Lamivudine • Telbivudine • Emtricitabine (in combination with tenofovir)
Comparison	• Pegylated alpha-interferon • Tenofovir • Entecavir • Adefovir • Lamivudine • Telbivudine • Emtricitabine (in combination with tenofovir)
Outcomes	• Log reduction of HBV DNA (indication of drug potency) • % with continuing undetectable serum hepatitis B virus DNA (potential for add on combination) • Incidence of resistance • % with ALT normalisation • % with HBeAg loss and/or seroconversion • % with HBsAg loss and/or seroconversion (long term outcome) • Quality of life

11.1.5.1 Clinical evidence

We searched for randomised trials comparing the clinical efficacy of different sequential antiviral treatments in HBeAg positive, HBeAg negative, lamivudine resistant adults and children with chronic hepatitis B. A total of fourteen studies have been identified and included in this review.

Summary characteristics of included studies

Table 158: HBeAg positive treatment naïve patients with chronic hepatitis B

Comparison	Included studies	Study population	Outcomes
Sequential treatment of lamivudine followed by pegylated interferon alpha-2b	Sarin 2007	Treatment naïve HBeAg positive patients	Assessed at the end of 28 weeks of treatment and 24 weeks follow up.

Comparison	Included studies	Study population	Outcomes
versus sequential treatment of placebo followed by pegylated interferon alpha-2b			
Sequential treatment of lamivudine followed by lamivudine plus interferon alpha combination therapy versus continuing lamivudine	Sarin 2005	Treatment naïve HBeAg positive patients with histologically proven chronic hepatitis B and ALT <1.5 x ULN	Assessed at 52 the end of weeks of treatment and 24 weeks follow up.
Sequential treatment with adfeovir then telbivudine versus telbivudine alone or adefovir alone	Chan 2007	Treatment naive	Assessed at end of 52 weeks treatment

Table 159: HBeAg positive interferon naïve patients with chronic hepatitis B

Comparison	Included studies	Study population	Outcomes
Sequential treatment of interferon alpha followed by interferon alpha plus lamivudine combination treatment followed by lamivudine alone versus lamivudine alone	Hasan 2003	HBeAg positive chronic hepatitis B infection. All patients were interferon naïve.	Assessed at the end of 48 weeks of treatment and 52 weeks follow up.

Table 160: HBeAg positive previously treated with lamivudine patients with chronic hepatitis B

Comparison	Included studies	Study population	Outcomes
Switching from lamivudine to adefovir monotherapy versus combination treatment of lamivudine plus adefovir for three months then adefovir monotherapy	Hann 2010	Patients with chronic hepatitis B receiving lamivudine therapy for ≥ 6 months; HBeAg positive or negative.	Assessed at the end of 12 months of treatment

Table 161: HBeAg positive lamivudine refractory or resistant patients with chronic hepatitis B

Comparison	Included studies	Study population	Outcomes
Switching from lamivudine to entecavir versus continuing lamivudine	Sherman 2006	Lamivudine-refractory patients, HBeAg positive	Assessed at the end of 52 weeks of treatment:
Switching from lamivudine to telbivudine versus continuing lamivudine	Safadi 2011	Chronic hepatitis B patients who exhibited persistent	Assessed at the end of 52 weeks of treatment.

Comparison	Included studies	Study population	Outcomes
		viraemia under lamivudine therapy, HBeAg positive	
Switching from lamivudine alone to combination treatment of lamivudine plus adefovir versus switching from lamivudine to entecavir	Ryu 2010	Lamvidune resistant patients, HBeAg positive	Assessed at the end of 12 months of treatment.
Switch from lamivudine to entecavir versus remain on lamivudine	Chang 2005A	Lamvidune resistant patients, majority HBeAg positive	24 and 48 weeks
Entecavir + adefovir or continue lamivudine + adefovir	Lim 2012	Lamvidune resistant patients, majority HBeAg positive	At end of 52 weeks treatment

Table 162: HBeAg negative antiviral naïve patients with chronic hepatitis B

Comparison	Included studies	Study population	Outcomes
Sequential treatment of lamivudine alone followed by combination treatment of lamivudine plus interferon alpha-2b followed by interferon alpha-2b alone versus lamivudine alone	Shi 2006	Chinese patients previously untreated with antiviral agents.	Assessed at the end of 48 weeks of treatment and 24 weeks of follow up.

Table 163: HBeAg negative lamivudine resistant patients with chronic hepatitis B

Comparison	Included studies	Study population	Outcomes
Switching from lamivudine to adefovir monotherapy versus combination treatment of lamivudine plus adefovir	Akyildiz 2007	Patients with lamivudine-resistant hepatitis B virus (HBV) infection.	Assessed at the end of 3 months of treatment and at 3 and 9 months follow up • undetectable HBV DNA levels (<2000 copies/ml) • ALT normalisation
Switching from lamivudine plus adefovir combination therapy to adefovir monotherapy versus continuing combination therapy of lamivudine plus	Aizawa 2010	Lamivudine resistant patients who responded to LAM plus ADV combination therapy	Assessed at 12, 24 and 30 months after randomization

Comparison	Included studies	Study population	Outcomes
adefovir			
Switching from lamivudine alone to combination treatment of lamivudine plus adefovir versus switching from lamivudine to adefovir monotherapy	Rapti 2007	Lamivudine resistant patients	Assessed at the end of 12 months treatment
Switching from lamivudine to telbivudine versus continuing lamivudine	Safadi 2011	Chronic hepatitis B patients who exhibited persistent viraemia under lamivudine therapy, HBeAg positive	Assessed at the end of 52 weeks of treatment

Table 164: HBeAg negative patients with chronic hepatitis B responders to previous treatment with lamivudine

Comparison	Included studies	Study population	Outcomes
Switching from lamivudine to entecavir versus continuing lamivudine	Matsuura 2011	Patients responded (HBV DNA of less than 2.6 log copies/m)l to previous treatment with lamivudine for more than 3 years	Assessed at the ened of mean 24 months follow-up

Table 165: HBeAg negative patients with chronic hepatitis B previously treated with entecavir and undetectable HBV DNA

Comparison	Included studies	Study population	Outcomes
Switching from entecavir to lamivudine alone versus continuing entecavir	Fung 2011	Patients previously treated with entecavir and undetectable HBV DNA	Assessed at the end of 96 weeks of treatment

Table 166: Children with chronic hepatitis B

Comparison	Included studies	Study population	Outcomes
Switching from interferon alpha plus lamivudine to lamivudine alone versus sequential treatment of lamivudine alone followed by interferon alpha plus lamivudine followed by lamivudine alone	Dikici 2002	Aged between 4-14 years	Assessed at the end of treatment and at 6 months follow up: • HBeAg loss • HBeAg seroconversion • Undetectable HBV DNA • HBsAg seroconversion • ALT normalisation

Comparison	Included studies	Study population	Outcomes
Interferon alpha versus sequential treatment of lamivudine alone followed by interferon alpha plus lamivudine	Dikici 2004	Aged between 3-15 years	Assessed at the end of 6 months of treatment and at 6 and 12 months follow up: • HBeAg loss • HBeAg seroconversion • Undetectable HBV DNA • HBsAg seroconversion • ALT normalisation
Switching from interferon alpha plus lamivudine to lamivudine alone versus sequential treatment of lamivudine alone followed by interferon alpha plus lamivudine followed by lamivudine alone			
Lamivudine + interferon simultaneously for 6 months, then continuing Lamivudine until seroconversion + 6 months, or to 24 months for breakthrough or nonresponse versus Lamivudine for 2 months, then add interferon for 6 months; lamivudine continued until seroconversion + 6 months, or to 24 months for breakthrough or nonresponse	Kansu 2006	Aged between 2 and 18 years	Assessed at 12, 18 and 24 months: • ALT normalisation • AntiHBe seroconversion • undetectable HBV DNA (<5pg/ml) • Breakthrough (serum HBV DNA >5pg/mL on two successive determinations after it had been undetectable, while still on treatment • Anti HBs • Incidence of resistance (YMDD mutations)

11.1.5.2 Sequential drug therapy (add-on or switching monotherapies) in achieving remission of the activity of CHB for HBeAg positive adults

Comparison of sequential treatment of lamivudine (LAM) followed by pegylated interferon alpha-2b versus placebo followed by pegylated interferon alpha-2b for treatment naïve patients

Table 167: Sequential treatment of lamivudine followed by pegylated interferon alpha-2b versus placebo followed by pegylated interferon alpha-2b (treatment naïve patients) - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAM followed by Peg IFN a-2b; Frequency (%)	Peg IFN a-2b; Frequency (%)	Relative; Risk Ratio (RR) (95% CI)	Absolute	
% of patients with undetectable HBV DNA (<4,700 copies/ml) (assessed at end of 28 weeks treatment)											
1Sarin 2007	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	16/34 (47.1%)	8/25 (32%)	RR 1.47 (0.75 to 2.88)	150 more per 1000 (from 80 fewer to 602 more)	VERY LOW
% of patients with undetectable HBV DNA (<4,700 copies/ml) (assessed at 24 weeks follow up)											
1Sarin 2007	RCT-unclear blinding	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	none	18/34 (52.9%)	4/25 (16%)	RR 3.31 (1.28 to 8.58)	370 more per 1000 (from 45 more to 1000 more)	MODERATE
% of patients with HBeAg loss (assessed at end of 28 weeks treatment)											
1Sarin 2007	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [c]	none	15/34 (44.1%)	8/25 (32%)	RR 1.38 (0.69 to 2.74)	122 more per 1000 (from 99 fewer to 557 more)	VERY LOW
% of patients with HBeAg loss (assessed at 24 weeks follow up)											
1Sarin 2007	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	14/34 (41.2%)	4/25 (16%)	RR 2.57 (0.96 to 6.88)	251 more per 1000 (from 6 fewer to 941 more)	LOW
% of patients with ALT normalisation (assessed at end of 28 weeks treatment)											

Quality assessment							No of patients		Effect		Quality
1Sarin 2007	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [c]	none	10/34 (29.4%)	5/25 (20%)	RR 1.47 (0.57 to 3.77)	94 more per 1000 (from 86 fewer to 554 more)	VERY LOW
% of patients with ALT normalisation (assessed at 24 weeks follow up)											
1Sarin 2007	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	13/34 (38.2%)	5/25 (20%)	RR 1.91 (0.78 to 4.67)	182 more per 1000 (from 44 fewer to 734 more)	VERY LOW

(a) Unclear blinding and allocation concealment.
(b) The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm
(c) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.

Comparison of switching from lamivudine (LAM) to lamivudine plus interferon alpha (LAM + INFa) versus lamivudine (LAM) for treatment naïve adults with CHB

Table 168: Switching from lamivudine to lamivudine plus interferon alpha versus lamivudine (treatment naïve adults) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching from LAM to LAM+IFN a; Frequency (%)**	**LAM; Frequency (%)**	**Relative; Risk Ratio (RR)/ Peto odds ratio (PETO OR) (95% CI)**	**Absolute**	
% of patients with undetectable HBV DNA (<1.4x10^{5}copies/mL) (assessed at the end of 52 weeks treatment)											
1 Sarin 2005	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	Very serious imprecision [d]	none	16/34 (47.1%)	13/35 (37.1%)	RR 1.27 (0.72 to 2.22)	100 more per 1000 (from 104 fewer to 453 more)	VERY LOW
% of patients with ALT normalization (assessed at the end of 52 weeks treatment)											

Quality assessment							Summary of findings				
1 Sarin 2005	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	Serious imprecision [c]	none	18/34 (52.9%)	15/35 (42.9%)	RR 1.24 (0.75 to 2.03)	103 more per 1000 (from 107 fewer to 441 more)	LOW
% of patients with HBeAg loss (assessed at the end of 52 weeks treatment)											
1 Sarin 2005	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	Very serious imprecision [d]	none	15/34 (44.1%)	14/35 (40%)	RR 1.1 (0.63 to 1.92)	40 more per 1000 (from 148 fewer to 368 more)	VERY LOW
% of patients with HBeAg seroconversion (assessed at the end of 52 weeks treatment)											
1 Sarin 2005	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	very serious imprecision [d]	none	10/34 (29.4%)	5/35 (14.3%)	RR 2.06 (0.78 to 5.4)	151 more per 1000 (from 31 fewer to 629 more)	VERY LOW
% of patients with histological improvement (≥2 points reduction in HAI score) (assessed at the end of 52 weeks treatment)											
1 Sarin 2005	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	very serious imprecision [d]	none	14/28 (50%)	12/26 (46.2%)	RR 1.08 (0.62 to 1.89)	37 more per 1000 (from 175 fewer to 411 more)	VERY LOW
Incidence of resistance											
1 Sarin 2005	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	very serious imprecision [d]	none	6/34 (14%)	3/35 (8.6%)	RR 1.63 (0.44 to 6.05)	54 more per 1000 (from 48 fewer to 433 more)	VERY LOW
% of patients with undetectable HBV DNA (<1.4x10^{5}copies/mL) (assessed at 24 weeks follow up)											
1 Sarin 2005	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	Serious imprecision [c]	none	15/34 (44.1%)	6/35 (17.1%)	RR 2.57 (1.13 to 5.85)	269 more per 1000 (from 22 more to 831 more)	LOW
% of patients with ALT normalisation (assessed at 24 weeks follow up)											
1 Sarin 2005	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/34 (44.1%)	5/35 (14.3%)	RR 3.09 (1.26 to 7.56)	299 more per 1000 (from 37 more to 937 more)	MODERATE
% of patients with HBeAg loss (assessed at 24 weeks follow up)											
1 Sarin 2005	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	Serious imprecision [c]	none	17/34 (50%)	7/35 (20%)	RR 2.5 (1.19 to 5.26)	300 more per 1000 (from 38 more to 852 more)	LOW

Quality assessment							Summary of findings				
% of patients with HBeAg seroconversion (assessed at 24 weeks follow up)											
1 Sarin 2005	RCT-unclear blinding	Serious limitations [(a)]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/34 (44.1%)	4/35 (11.4%)	RR 3.86 (1.42 to 10.46)	327 more per 1000 (from 48 more to 1081 more)	MODERATE
% of patients with HBsAg loss (assessed at 24 weeks follow up)											
1 Sarin 2005	RCT-unclear blinding	Serious limitations [(a)]	no serious inconsistency	no serious indirectness	very serious imprecision [(d)]	none	1/34 (2.9%)	0/35 (0%)	PETO OR 7.61 (0.15 to 383.66)	30 more per 1000 (from 50 fewer to 110 more)	

(a) Unclear blinding, no details on allocation concealment.
(b) The confidence interval is consistent with two clinical decisions; appreciable harm, no appreciable benefit or harm.
(c) The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm.
(d) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lam + IFN**	**Lam**	**Relative (95% CI)**	**Absolute**	
% of patients with HBeAg seroconversion at end treatment week 52											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/68 (29.4%)	14/80 (17.5%)	RR 1.68 (0.92 to 3.07)	119 more per 1000 (from 14 fewer to 362 more)	LOW
% of patients with HBeAg seroconversion at 12 week follow up											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	17/68 (25%)	16/80 (20%)	RR 1.25 (0.69 to 2.28)	50 more per 1000 (from 62 fewer to 256 more)	VERY LOW

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lam + IFN	Lam	Relative (95% CI)	Absolute	Quality
Histological response at end treatment week 52											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	21/57 (36.8%)	31/63 (49.2%)	RR 0.75 (0.49 to 1.14)	123 fewer per 1000 (from 251 fewer to 69 more)	VERY LOW
% of patients with HBeAg loss at end treatment week 52											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/55 (34.5%)	14/60 (23.3%)	RR 1.48 (0.82 to 2.66)	112 more per 1000 (from 42 fewer to 387 more)	LOW
% of patients with HBeAg loss at 12 week follow up											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	18/55 (32.7%)	13/62 (21%)	RR 1.56 (0.84 to 2.88)	117 more per 1000 (from 34 fewer to 394 more)	VERY LOW
Undetectable HBV DNA (<3pg/mL) at end treatment week 52											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/55 (36.4%)	36/60 (60%)	RR 0.61 (0.4 to 0.91)	234 fewer per 1000 (from 54 fewer to 360 fewer)	MODERATE
Undetectable HBV DNA (<3pg/mL) at 12 week follow up											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	17/55 (30.9%)	20/63 (31.7%)	RR 0.97 (0.57 to 1.66)	10 fewer per 1000 (from 137 fewer to 210 more)	VERY LOW
ALT normalisation at end treatment week 52											

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lam + IFN**	**Lam**	**Relative (95% CI)**	**Absolute**	
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	21/55 (38.2%)	33/58 (56.9%)	RR 0.67 (0.45 to 1.01)	188 fewer per 1000 (from 313 fewer to 6 more)	LOW
ALT normalisation at 12 week follow up											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/50 (36%)	13/63 (20.6%)	RR 1.74 (0.95 to 3.21)	153 more per 1000 (from 10 fewer to 456 more)	LOW
Genetic resistance at end treatment week 52											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/68 (0%)	19/61 (31.1%)	OR 0.09 (0.03 to 0.23)	272 fewer per 1000 (from 217 fewer to 298 fewer)	MODERATE
Genetic resistance at 12 week follow up											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/68 (0%)	12/57 (21.1%)	OR 0.09 (0.03 to 0.3)	187 fewer per 1000 (from 136 fewer to 203 fewer)	MODERATE
Adverse events leading to withdrawal											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/68 (2.9%)	3/80 (3.8%)	RR 0.78 (0.13 to 4.56)	8 fewer per 1000 (from 33 fewer to 134 more)	VERY LOW

[1] Incomplete blinding/allocation concealment
[2] Confidence interval compatible with two clinical decisions: benefit, or no harm or benefit
[3] Confidence interval compatible with three clinical decisions: benefit, no harm or benefit, or harm
[4] Confidence interval compatible with two clinical decisions: harm, or no harm or benefit

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lam + IFN**	**IFN**	**Relative (95% CI)**	**Absolute**	
% of patients with HBeAg seroconversion at end treatment week 52											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/68 (29.4 %)	12/64 (18.8%)	RR 1.57 (0.84 to 2.94)	107 more per 1000 (from 30 fewer to 364 more)	LOW
% of patients with HBeAg seroconversion at 12 week follow up											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	17/68 (25%)	14/64 (21.9%)	RR 1.14 (0.62 to 2.12)	31 more per 1000 (from 83 fewer to 245 more)	VERY LOW
Histological response at end treatment week 52											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	21/57 (36.8 %)	25/54 (46.3%)	RR 0.8 (0.51 to 1.24)	93 fewer per 1000 (from 227 fewer to 111 more)	VERY LOW
% of patients with HBeAg loss at end treatment week 52											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	19/55 (34.5 %)	13/56 (23.2%)	RR 1.49 (0.82 to 2.71)	114 more per 1000 (from 42 fewer to 397 more)	VERY LOW
% of patients with HBeAg loss at 12 week follow up											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	18/55 (32.7 %)	14/48 (29.2%)	RR 1.12 (0.63 to 2.01)	35 more per 1000 (from 108 fewer to 295 more)	VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lam + IFN**	**IFN**	**Relative (95% CI)**	**Absolute**	
Undetectable HBV DNA (<3pg/mL) at end treatment week 52											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	20/55 (36.4%)	16/55 (29.1%)	RR 1.25 (0.73 to 2.15)	73 more per 1000 (from 79 fewer to 335 more)	
Undetectable HBV DNA (<3pg/mL) at 12 week follow up											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	17/55 (30.9%)	14/49 (28.6%)	RR 1.08 (0.6 to 1.96)	23 more per 1000 (from 114 fewer to 274 more)	VERY LOW
ALT normalisation at end treatment week 52											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	21/55 (38.2%)	16/55 (29.1%)	RR 1.31 (0.77 to 2.23)	90 more per 1000 (from 67 fewer to 358 more)	VERY LOW
ALT normalisation at 12 week follow up											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	18/50 (36%)	16/50 (32%)	RR 1.12 (0.65 to 1.95)	38 more per 1000 (from 112 fewer to 304 more)	VERY LOW
Adverse events leading to withdrawal											
1: Schalm 2000	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/68 (2.9%)	0/64 (0%)	OR 7.07 (0.44 to 114.42)	-	VERY LOW

[1] Incomplete blinding/allocation concealment
[2] Confidence interval compatible with two clinical decisions: benefit, or no harm or benefit
[3] Confidence interval compatible with three clinical decisions: benefit, no harm or benefit, or harm

Comparison of switching from adefovir to telbivudine versus telbivudine for treatment naïve adults with CHB

Table 169: Switching from adefovir to telbivudine versus telbivudine (treatment naïve adults) - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adefovir then telbivudine	Telbivudine	Relative (95% CI)	Absolute	Quality	
Undetectable HBV DNA at end of 52 weeks treatment												
1: Chan2007	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	25/46 (54.3%)	26/43 (60.5%)	RR 0.9 (0.63 to 1.29)	60 fewer per 1000 (from 224 fewer to 175 more)	VERY LOW	
Viral breakthrough at end of 52 weeks treatment												
1: Chan2007	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/46 (0%)	3/43 (7%)	OR 0.12 (0.01 to 1.19)	61 fewer per 1000 (from 69 fewer to 12 more)	VERY LOW	
ALT normalisation at end of 52 weeks treatment												
1: Chan2007	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	39/46 (84.8%)	34/43 (79.1%)	RR 1.07 (0.88 to 1.31)	55 more per 1000 (from 95 fewer to 245 more)	LOW	
HBeAg loss at end of 52 weeks treatment												
1: Chan2007	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/46 (26.1%)	13/43 (30.2%)	RR 0.86 (0.44 to 1.68)	42 fewer per 1000 (from 169 fewer to 206 more)	VERY LOW	
HBeAg seroconversion at end of 52 weeks treatment												
1: Chan2007	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/46 (23.9%)	12/43 (27.9%)	RR 0.86 (0.42 to 1.73)	39 fewer per 1000 (from 162 fewer to 204 more)	VERY LOW	

[1] Investigators blinded to HBV serologic data from baseline to week 52. Unclear blinding in people/ staff from 3rd party agency that collected and analysed data
[2] Confidence interval is consistent with three clinical decision; appreciable benefit, no appreciable benefit or harm, appreciable harm.
[3] Confidence interval is consistent with two clinical decisions, no appreciable benefit or harm, appreciable benefit.

Comparison of switching from adefovir to telbivudine versus adefovir for treatment naïve adults with CHB

Table 170: Switching from adefovir to telbivudine versus adefovir (treatment naïve adults) - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Adefovir then telbivudine**	**Adefovir**	**Relative (95% CI)**	**Absolute**	**Quality**
Undetectable HBV DNA at end of 52 weeks treatment											
1: Chan 2007	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25/46 (54.3%)	17/42 (40.5%)	RR 1.34 (0.85 to 2.11)	138 more per 1000 (from 61 fewer to 449 more)	LOW
Viral breakthrough at end of 52 weeks treatment											
1: Chan 2007	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/46 (0%)	4/42 (9.5%)	OR 0.11 (0.02 to 0.84)	84 fewer per 1000 (from 14 fewer to 93 fewer)	MODERATE
ALT normalisation at end of 52 weeks treatment											
1: Chan 2007	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39/46 (84.8%)	36/42 (85.7%)	RR 0.99 (0.83 to 1.18)	9 fewer per 1000 (from 146 fewer to 154 more)	MODERATE
HBeAg loss at end of 52 weeks treatment											
1: Chan 2007	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	12/46 (26.1%)	9/42 (21.4%)	RR 1.22 (0.57 to 2.59)	47 more per 1000 (from 92 fewer to 341 more)	VERY LOW
HBeAg seroconversion at end of 52 weeks treatment											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adefovir then telbivudine	Adefovir	Relative (95% CI)	Absolute	Quality
1: Chan 2007	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/46 (23.9%)	8/42 (19%)	RR 1.26 (0.56 to 2.82)	50 more per 1000 (from 84 fewer to 347 more)	VERY LOW

[1] Investigators blinded to HBV serologic data from baseline to week 52. Unclear blinding in people/ staff from 3rd party agency that collected and analysed data
[2] Confidence interval is consistent with two clinical decisions, no appreciable benefit or harm, appreciable benefit.
[3] Confidence interval is consistent with three clinical decision; appreciable benefit, no appreciable benefit or harm, appreciable harm

Comparison of sequential treatment of interferon alpha (IFN alpha) followed by interferon alpha plus lamivudine (IFNa + LAM) followed by lamivudine versus lamivudine alone (LAM) for interferon treatment naïve patients

Table 171: Sequential treatment of interferon alpha followed by interferon alpha plus lamivudine followed by lamivudine versus lamivudine alone (interferon treatment naïve patients) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Rick of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFNa followed by IFNa +LAM followed by LAM	LAM	Relative (95% CI)	Absolute	
% of patients with undetectable HBV DNA (assessed at the end of 48 weeks treatment)											
1 Hasan 2003	RCT-unblinded	very serious limitations (a)	no serious inconsistency	no serious indirectness	No serious imprecision	none	31/31	29/29	RR 1.0	0 more per 1000 (from 0 fewer to 0 more)	LOW
% of patients with HBeAg seroconversion (assessed at the end of 48 weeks treatment)											
1 Hasan	RCT-	very	no serious	no serious	very serious	none	2/31 (6.5%)	0/29 (0%)	PETO OR	60 more per 1000	

Quality assessment							Summary of findings				
2003	unblinded	serious limitations [a]	inconsistency	indirectness	imprecision [b]				7.16 (0.44 to 117.45)	(from 40 fewer to 170 more)	VERY LOW
% of patients with HBeAg seroconversion (assessed at 52 weeks follow up)											
1 Hasan 2003	RCT-unblinded	very serious limitations [a]	no serious inconsistency	no serious indirectness	very serious imprecision [b0	none	2/31 (6.5%)	0/29 (0%)	PETO OR 7.16 (0.44 to 117.45)	60 more per 1000 (from 40 fewer to 170 more)	VERY LOW
% of patients with ALT normalisation (assessed at the end of 48 weeks treatment)											
1 Hasan 2003	RCT-unblinded	very serious limitations [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/31 (93.5%)	28/29 (96.6%)	RR 0.97 (0.86 to 1.09)	29 fewer per 1000 (from 135 fewer to 87 more)	LOW
% of patients with ALT normalisation (assessed at 52 weeks follow up)											
1 Hasan 2003	RCT-unblinded	very serious limitations [a]	no serious inconsistency	no serious indirectness	very serious imprecision [b]	none	3/31 (9.7%)	2/29 (6.9%)	RR 1.4 (0.25 to 7.81)	28 more per 1000 (from 52 fewer to 470 more)	VERY LOW

(a) Unblinded study with no details on randomisation and allocation concealment.
(b) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.

Comparison of switching from lamivudine (LAM) to entecavir (ETV) versus continuing lamivudine (LAM) for lamivudine refractory patients (persistent viraemia of documented resistance while receiving LAM)

Table 172: Switching from lamivudine to entecavir versus continuing lamivudine (lamivudine refractory patients) - clinical study characteristics and clinical summary of findings

Quality assessment	No of patients	Effect	Quality

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching lamivudine to entecavir	Continuing lamivudine	Relative (95% CI)	Absolute	
Log reduction in HBV DNA - 24 weeks of treatment (Better indicated by higher values)											
1: Chang 2005A	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	39	27	-	MD 3.26 higher (3.14 to 3.38 higher)	MODERATE
Log reduction in HBV DNA - 48 weeks of treatment (Better indicated by higher values)											
1: Sherman 2006	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	133	129	-	MD 4.63 higher (4.12 to 5.14 higher)	MODERATE
Undetectable HBV DNA											
2: Chang 2005A; Sherman 2006	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	126/173 (72.8%)	14/172 (8.1%)	RR 9.04 (5.42 to 15.08)	654 more per 1000 (from 360 more to 1000 more)	MODERATE
Undetectable HBV DNA - 24 weeks of treatment											
1: Chang 2005A	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	33/40 (82.5%)	6/43 (14%)	RR 5.91 (2.78 to 12.59)	685 more per 1000 (from 248 more to 1000 more)	MODERATE
Undetectable HBV DNA - 48 weeks of treatment											
1: Sherman 2006	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	93/133 (69.9%)	8/129 (6.2%)	RR 11.28 (5.71 to 22.26)	638 more per 1000 (from 292 more to 1000 more)	MODERATE
ALT normalisation - 24 weeks of treatment											
1: Chang	randomise	no	no serious	serious[1]	serious[2]	none	11/28	7/33	RR 1.85	180 more	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching lamivudine to entecavir	Continuing lamivudine	Relative (95% CI)	Absolute	Quality
2005A	d trials	serious risk of bias	inconsistency				(39.3%)	(21.2%)	(0.83 to 4.13)	per 1000 (from 36 fewer to 664 more)	LOW
ALT normalisation - 48 weeks of treatment											
1: Sherman 2006	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	86/133 (64.7%)	22/129 (17.1%)	RR 3.79 (2.54 to 5.66)	476 more per 1000 (from 263 more to 795 more)	MODERATE
HBeAG loss at 48 weeks of treatment											
1: Sherman 2006	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	14/133 (10.5%)	5/129 (3.9%)	RR 2.72 (1.01 to 7.32)	67 more per 1000 (from 0 more to 245 more)	MODERATE
HBeAG seroconversion at 48 weeks of treatment											
1: Sherman 2006	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	11/133 (8.3%)	4/129 (3.1%)	RR 2.67 (0.87 to 8.16)	52 more per 1000 (from 4 fewer to 222 more)	LOW
Histological improvement at 48 weeks of treatment											
1: Sherman 2006	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	68/124 (54.8%)	32/116 (27.6%)	RR 1.99 (1.42 to 2.78)	273 more per 1000 (from 116 more to 491 more)	MODERATE
Withdrawn due to adverse events at 48 weeks of treatment											
1:	randomise	no	no serious	serious[1]	no serious	none	2/141	10/145	RR 0.21	54 fewer per	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching lamivudine to entecavir	Continuing lamivudine	Relative (95% CI)	Absolute	Quality
Sherman 2006	d trials	serious risk of bias	inconsistency		imprecision		(1.4%)	(6.9%)	(0.05 to 0.92)	1000 (from 6 fewer to 66 fewer)	MODERATE

[1] Lamivudine resistant population
[2] Confidence interval compatible with two clinical decisions: benefit, or no harm or benefit

Comparison of switching from lamivudine plus adefovir to entecavir plus adefovir versus continuing lamivudine plus adefovir for lamivudine resistant patients

Table 173: Switching from lamivudine plus adefovir to entecavir plus adefovir versus continuing lamivudine plus adefovir for lamivudine resistant patients - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch lam+ade to ent+ade	Continue lam+ade	Relative (95% CI)	Absolute	Quality
Reduction of HBV DNA (log 10 IU/mL) at end 52 weeks treatment (Better indicated by lower values)											
1: Lim 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	45	45	-	MD 1.6 higher (1.15 to 2.05 higher)	LOW
Undetectable HBV DNA (60IU/mL) at end 52 weeks treatment											

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switch lam+ade to ent+ade**	**Continue lam+ade**	**Relative (95% CI)**	**Absolute**	**Quality**
1: Lim 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	13/45 (28.9%)	2/45 (4.4%)	RR 6.5 (1.56 to 27.17)	244 more per 1000 (from 25 more to 1000 more)	LOW
Virological breakthrough at end 52 weeks treatment											
1: Lim 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/45 (0%)	1/45 (2.2%)	OR 0.14 (0 to 6.82)	19 fewer per 1000 (from 22 fewer to 112 more)	VERY LOW
Resistance mutation to entecavir or adefovir at end 52 weeks treatment											
1: Lim 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	3/45 (6.7%)	15/45 (33.3%)	RR 0.2 (0.06 to 0.64)	267 fewer per 1000 (from 120 fewer to 313 fewer)	LOW
ALT normalisation at end 52 weeks treatment											
1: Lim 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	26/45 (57.8%)	20/45 (44.4%)	RR 1.3 (0.86 to 1.96)	133 more per 1000 (from 62 fewer to 427 more)	VERY LOW
HBeAg loss at end 52 weeks treatment											
1: Lim 2012	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/39 (5.1%)	0/41 (0%)	OR 7.99 (0.49 to 130.06)	-	VERY LOW

[1] Trial not blinded
[2] Lamivudine resistant
[3] Confidence interval compatible with three clinical decisions: benefit, no harm or benefit, or harm
[4] Confidence interval compatible with two clinical decisions: benefit, or no harm or benefit

Comparison of switching from lamivudine to telbivudine versus continuing lamivudine for previously treated patients with lamivudine and persistent viraemia (HBV DNA more than 3 log copies/ml)

Table 174: Switching from lamivudine to telbivudine versus continuing lamivudine (previously treated patients with lamivudine and persistant viraemia) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching from LAM to telbivudine; Frequency (%)/ Mean (SD)	Continuing LAM ; Frequency (%)/ Mean (SD)	Relative; Risk Ratio (RR)/ Mean difference (MD) (95% CI)	Absolute	
Log reduction HBV DNA (assessed at end of 52 weeks of treatment)											
1 Safadi 2011	RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	No serious imprecision	none	1.5 (3.02)	0.1 (3.34)	-	MD 1.4 higher (0.58 to 2.22 higher)	MODERATE
% of patients with undetectable HBV DNA (<300 copies/mL) (assessed at end of 52 weeks of treatment)											
1 Safadi 2011	RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	No serious imprecision	none	56/121 (46.3%)	38/124 (30.6%)	RR 1.51 (1.09 to 2.09)	156 more per 1000 (from 28 more to 334 more)	MODERATE
% of patients with HBeAg loss (assessed at end of 52 weeks of treatment)											
1 Safadi 2011	RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Very serious imprecision [c]	none	15/81 (18.5%)	11/81 (13.6%)	RR 1.36 (0.67 to 2.79)	49 more per 1000 (from 45 fewer to 243 more)	VERY LOW
% of patients with HBeAg seroconversion (assessed at end of 52 weeks of treatment)											
1 Safadi 2011	RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Very serious imprecision [c]	none	12/81 (14.8%)	8/81 (9.9%)	RR 1.5 (0.65 to 3.47)	49 more per 1000 (from 35 fewer to 244 more)	VERY LOW
% of patients with ALT normalisation (assessed at end of 52 weeks of treatment)											
1 Safadi 2011	RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Serious imprecision [b]	none	32/53 (60.4%)	27/53 (50.9%)	RR 1.19 (0.84 to 1.67)	97 more per 1000 (from 82 fewer to 341 more)	LOW

Quality assessment							Summary of findings				
Virological breakthrough - All patients (assessed at end of 52 weeks of treatment)											
1 Safadi 2011	RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Very serious imprecision [c]	none	18/116 (15.5%)	20/116 (17.2%)	RR 0.9 (0.5 to 1.61)	17 fewer per 1000 (from 86 fewer to 105 more)	VERY LOW
Virological breakthrough - Patients with wild type HBV at screening (assessed at end of 52 weeks of treatment)											
1 Safadi 2011	RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Very serious imprecision [c]	none	13/101 (12.9%)	12/101 (11.9%)	RR 1.08 (0.52 to 2.26)	10 more per 1000 (from 57 fewer to 150 more)	VERY LOW
Genotypic resistance - All patients (assessed at end of 52 weeks of treatment)											
1 Safadi 2011	RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Very serious imprecision [c]	none	15/101 (14.9%)	13/116 (11.2%)	RR 1.33 (0.66 to 2.65)	37 more per 1000 (from 38 fewer to 185 more)	VERY LOW
Genotypic resistance - Patients with wild type HBV at screening (assessed at end of 52 weeks of treatment)											
1 Safadi 2011	RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Very serious imprecision [c]	none	12/101 (11.9%)	13/106 (12.3%)	RR 0.97 (0.46 to 2.02)	4 fewer per 1000 (from 66 fewer to 125 more)	VERY LOW
Withdrawn due to adverse events by end of 52 weeks treatment											
1 Safadi 2011	RCT- double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Very serious imprecision [c]	none	1/122 (0.8%)	1/124 (0.8%)	OR 1.02 (0.06 to 16.44)	0 more per 1000 (from 8 fewer to 110 more)	VERY LOW

Mixed population; 66% and 65% were HBeAg positive in the telbivudine and continuing LAM groups respectively.
(a) The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm.
(b) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.

Comparison of switching from lamivudine (LAM) to adefovir (ADV) versus lamivudine plus adefovir (LAM + ADV) for patients previously treated with lamivudine

Table 175: Switching from lamivudine to adefovir versus lamivudine plus adefovir (patients previously treated with lamivudine) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Switching**	**LAM + ADV**	**Relative;**	**Absolute**	

Quality assessment							Summary of findings				
studies						considerations	from LAM to ADV; Frequency (%)	followed by ADV only; Frequency (%)	Risk Ratio (RR) (95% CI)		
% of patients with undetectable HBV DNA (<160 copies/ml) (assessed at the end of 12 months treatment)											
1 Hann 2010 B	RCT- unclear blinding	Serious limitations [a]	no serious inconsistency	Serious indirectness [b]	Very serious imprecision [c]	none	9/18 (50%)	7/17 (41.2%)	RR 1.21 (0.58 to 2.53)	86 more per 1000 (from 173 fewer to 630 more)	VERY LOW
% of patients with undetectable HBV DNA (<160 copies/ml) (assessed at the end of 12 months treatment)											
1 Hann 2010 B	RCT- unclear blinding	Serious limitations [a]	no serious inconsistency	Serious indirectness [b]	Very serious imprecision [c]	none	0/18 (0%)	2/17 (11.8%)	OR 0.12 (0.01 to 2.00)	102 fewer per 1000 (from 117 fewer to 93 more)	VERY LOW

(a) Unclear blinding, no details on randomization method or allocation concealment.
(b) Mixed population with the majority of patients being HBeAg.
(c) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.

Comparison of switching from lamivudine (LAM) to lamivudine plus adefovir (LAM+ADV) versus switching from lamivudine to entecavir (ETV) for lamivudine resistant adults with CHB

Table 176: Switching from lamivudine to lamivudine plus adefovir versus switching from lamivudine to entecavir (lamivudine resistant adults with CHB) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching from LAM to LAM+ADV; Frequency (%)/ mean (SD)	Switching from LAM to ETV; Frequency (%)/ mean (SD)	Relative; Risk Ratio (RR)/ Mean difference (MD) (95% CI)	Absolute	
Log reduction HBV DNA (assessed at the end of 12 months treatment) (Better indicated by lower values)											
1 Ryu	RCT-	very serious	no serious	Serious	no serious	none	3.8 (1.12)	2.72 (1.32)	-	MD 1.08 higher	

Quality assessment							Summary of findings				
2010	unblinded	limitations [a]	inconsistency	indirectness [b]	imprecision					(0.58 to 1.58 higher)	VERY LOW
% of patients with undetectable HBV DNA (<300copies/mL) (assessed at the end of 12 months treatment)											
1 Ryu 2010	RCT-unblinded	very serious limitations [a]	no serious inconsistency	Serious indirectness [b]	Serious imprecision [c]	none	18/47 (38.3%)	11/45 (24.4%)	RR 1.57 (0.84 to 2.94)	139 more per 1000 (from 39 fewer to 474 more)	VERY LOW
% of patients with ALT normalisation (assessed at the end of 12 months treatment)											
1 Ryu 2010	RCT-unblinded	very serious limitations [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39/41 (95.1%)	36/40 (90%)	RR 1.06 (0.93 to 1.2)	54 more per 1000 (from 63 fewer to 180 more)	LOW
% of patients with HBeAg loss (assessed at the end of 12 months treatment)											
1 Ryu 2010	RCT-unblinded	very serious limitations [a]	no serious inconsistency	Serious indirectness [b]	very serious imprecision [d]	none	4/39 (10.3%)	2/42 (4.8%)	RR 2.15 (0.42 to 11.11)	55 more per 1000 (from 28 fewer to 481 more)	VERY LOW
% of patients with HBeAg seroconversion (assessed at the end of 12 months treatment)											
1 Ryu 2010	RCT-unblinded	very serious limitations [a]	no serious inconsistency	Serious indirectness [b]	very serious imprecision [d]	none	2/39 (5.1%)	1/42 (2.4%)	RR 2.15 (0.2 to 22.82)	27 more per 1000 (from 19 fewer to 520 more)	VERY LOW
Incidence of resistance (YMDD mutation)											
1 Ryu 2010	RCT-unblinded	very serious limitations [a]	no serious inconsistency	Serious indirectness 9b)	very serious imprecision [d]	none	0/47 (0%)	2/45 (4.4%)	PETO OR 0.13 (0.01 to 2.06)	39 fewer per 1000 (from 44 fewer to 47 more)	VERY LOW

(a) Unblinded study with no details on randomization and allocation concealment.
(b) Mixed population with 88% HBeAg positive patients and 21.7% had cirrhosis.
(c) The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm.
(d) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.

11.1.5.3 Sequential drug therapy (add-on or switching monotherapies) in achieving remission of the activity of CHB for HBeAg negative adults

Comparison of switching from lamivudine (LAM) to lamivudine plus interferon alpha-2b versus lamivudine for antiviral treatment naïve adults with CHB

Table 177: Switching from lamivudine to lamivudine plus interferon alpha-2b versus lamivudine (antiviral treatment naïve adults with CHB) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching from LAM to LAM +IFNa; Frequency (%)	LAM ; Frequency (%)	Relative; Risk Ratio (RR) (95% CI)	Absolute	
% of patients with ALT normalisation (assessed at the end of 24 weeks treatment)											
1 Shi 2006	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	Serious imprecision [b]	none	28/64 (43.8%)	72/98 (73.5%)	RR 0.6 (0.44 to 0.81)	294 fewer per 1000 (from 140 fewer to 411 fewer)	LOW
% of patients with undetectable HBV DNA (<1000 copies/ml) (assessed at the end of 24 weeks treatment)											
1 Shi 2006	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	No serious imprecision	none	52/64 (81.3%)	76/98 (77.6%)	RR 1.05 (0.89 to 1.23)	39 more per 1000 (from 85 fewer to 178 more)	MODERATE
Incidence of resistance (assessed at the end of 24 weeks treatment)											
1 Shi 2006	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	very serious imprecision [c]	none	2/64 (3.1%)	6/98 (6.1%)	RR 0.51 (0.11 to 2.45)	30 fewer per 1000 (from 54 fewer to 89 more)	VERY LOW

(a) Unclear blinding, no details on randomisation method and allocation concealment.
(b) The confidence interval is consistent with two clinical decision; appreciable harm, no appreciable benefit or harm.
(c) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.

Comparison of sequential treatment of lamivudine (LAM) followed by lamivudine plus interferon alpha-2b (LAM + IFNa-2b) followed by interferon alpha-2b alone (IFNa-2b) versus lamivudine for antiviral treatment naïve adults with CHB

Table 178: Switching from lamivudine to lamivudine plus interferon alpha-2b to interferon alpha-2b alone versus lamivudine (antiviral treatment naïve adults with CHB) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAM followed by IFNa+LAM followed by IFNa; Frequency (%)	LAM; Frequency (%)	Relative; Risk Ratio (RR) (95% CI)	Absolute	
% of patients with ALT normalisation (assessed at end of 48 weeks treatment)											
1 Shi 2006	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	serious imprecision [b]	none	38/64 (59.4%)	54/98 (55.1%)	RR 1.08 (0.82 to 1.41)	44 more per 1000 (from 99 fewer to 226 more)	LOW
% of patients with undetectable HBV DNA (<1000 copies/ml) (assessed at end of 48 weeks treatment)											
1 Shi 2006	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	Serious imprecision [b]	none	36/64 (56.3%)	54/98 (55.1%)	RR 1.02 (0.77 to 1.35)	11 more per 1000 (from 127 fewer to 193 more)	VERY LOW
Incidence of resistance (assessed at end of 48 weeks treatment)											
1 Shi 2006	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/64 (0%)	22/98 (22.4%)	RR 0.03 (0 to 0.55)	218 fewer per 1000 (from 101 fewer to 224 fewer)	MODERATE
% of patients with ALT normalisation (end of 24 weeks follow up)											
1 Shi 2006	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	no serious indirectness	Serious imprecision [b]	none	34/64 (53.1%)	36/98 (36.7%)	RR 1.45 (1.02 to 2.05)	165 more per 1000 (from 7 more to 386 more)	LOW
% of patients with undetectable HBV DNA (<1000 copies/ml) (end of 24 weeks follow up)											
1: Shi	randomised	serious[1]	no serious	no serious	very serious[2]	none	9/64	18/98	RR 0.77 (0.37	42 fewer per 1000	

Quality assessment							Summary of findings				
2006	trials		inconsistency	indirectness			(14.1%)	(18.4%)	to 1.6)	(from 116 fewer to 110 more)	VERY LOW

(a) Unclear blinding, no details on randomisation method and allocation concealment.
(b) The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm.
(c) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.

Comparison of switching from lamivudine (LAM) to adefovir monotherapy (ADV) versus lamivudine plus adefovir (LAM + ADV) for lamivudine resistant adults with CHB

Table 179: Switching from lamivudine to adefovir monotherapy versus lamivudine plus adefovir (lamivudine resistant adults with CHB) - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching from LAM to ADV; Frequency (%)**	**LAM + ADV; Frequency (%)**	**Relative; Risk Ratio (RR) (95% CI)**	**Absolute**	
% of patients with undetectable HBV DNA (<2000 copies/ml) (assessed at end of 3 months treatment)											
1 Akyildiz 2007	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Very serious imprecision [c]	none	6/25 (24%)	6/29 (20.7%)	RR 1.16 (0.43 to 3.14)	33 more per 1000 (from 118 fewer to 443 more)	VERY LOW
% of patients with undetectable HBV DNA (<2000 copies/ml) (3 months follow up)											
1 Akyildiz 2007	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Very serious imprecision [c]	none	8/25 (32%)	13/29 (44.8%)	RR 0.71 (0.35 to 1.44)	130 fewer per 1000 (from 291 fewer to 197 more)	VERY LOW
% of patients with undetectable HBV DNA (<2000 copies/ml) (9 months follow up)											
1 Akyildiz	RCT-unclear	Serious limitations	No serious inconsistency	Serious indirectness	Serious imprecision	none	14/25 (56%)	27/29 (93.1%)	RR 0.6 (0.42 to 0.86)	372 fewer per 1000 (from 130 fewer to	VERY LOW

Quality assessment							No of patients		Effect		Quality
2007	blinding	[a]		[b]	[d]					540 fewer)	
% of patients with ALT normalisation (assessed at end of 3 months treatment)											
1 Akyildiz 2007	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Very serious imprecision [c]	none	10/25 (40%)	13/29 (44.8%)	RR 0.89 (0.48 to 1.67)	49 fewer per 1000 (from 233 fewer to 300 more)	VERY LOW
ALT normalisation (assessed at 3 months follow up)											
1 Akyildiz 2007	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Serious imprecision [d]	none	13/25 (52%)	20/29 (69%)	RR 0.75 (0.48 to 1.18)	172 fewer per 1000 (from 359 fewer to 124 more)	VERY LOW
ALT normalisation (assessed at 9 months follow up)											
1 Akyildiz 2007	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Serious imprecision [d]	none	18/25 (72%)	23/29 (79.3%)	RR 0.91 (0.67 to 1.23)	71 fewer per 1000 (from 262 fewer to 182 more)	VERY LOW

(a) Unclear blinding, randomisation method and allocation concealment.
(b) Mixed population; 68% and 62% in the ADV and combination (ADV + LAM) groups were HBeAg negative.
(c) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.
(d) The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm.
(e) The confidence interval is consistent with two clinical decisions; appreciable harm, no appreciable bevefit or harm.

Comparison of switching from lamivudine (LAM) plus adefovir (ADV) to adefovir monotherapy (ADV) versus continuing lamivudine plus adefovir (LAM + ADV) for lamivudine resistant adults with CHB

Table 180: Switching from lamivudine plus adefovir to adefovir monotherapy versus continuing lamivudine plus adefovir (lamivudine resistant adults with CHB) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching from LAM + ADV to ADV monotherapy;	LAM + ADV Frequency (%)	Relative; Risk Ratio (RR) (95% CI)	Absolute	

Quality assessment							Summary of findings				
							Frequency (%)				
% of patients with undetectable HBV DNA (<3.7 LGE/ml) (12 months after randomization)											
1 Aizawa 2010	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	No serious imprecision	none	13/13 (100%)	15/15 (100%)	RR 1 (0.87 to 1.14)	0 fewer per 1000 (from 130 fewer to 140 more)	LOW
% of patients with ALT normalisation (12 months after randomization)											
1 Aizawa 2010	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Serious imprecision [c]	none	13/13 (100%)	12/15 (80%)	RR 1.23 (0.93 to 1.63)	184 more per 1000 (from 56 fewer to 504 more)	VERY LOW
% of patients with HBeAg loss (12 months after randomization)											
1 Aizawa 2010	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Very serious imprecision [d]	none	3/6 (50%)	1/5 (20%)	RR 2.5 (0.36 to 17.17)	300 more per 1000 (from 128 fewer to 3234 more)	VERY LOW
% of patients with HBeAg seroconversion (12 months after randomization)											
1 Aizawa 2010	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Very serious imprecision [d]	none	1/6 (16.7%)	0/5 (0%)	PETO OR 6.25 (0.12 to 320.40)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
% of patients with undetectable HBV DNA (<3.7 LGE/ml) (24 months after randomization)											
1 Aizawa 2010	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	No serious imprecision	none	9/9 (100%)	10/10 (100%)	RR 1 (0.83 to 1.21)	0 fewer per 1000 (from 170 fewer to 210 more)	LOW
% of patients with ALT normalisation (24 months after randomization)											
1 Aizawa 2010	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Serious imprecision [c]	none	9/9 (100%)	8/10 (80%)	RR 1.23 (0.87 to 1.75)	184 more per 1000 (from 104 fewer to 600 more)	VERY LOW
% of patients with HBeAg loss (24 months after randomization)											
1 Aizawa 2010	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Very serious imprecision [d]	none	4/6 (66.7%)	1/5 (20%)	RR 3.33 (0.53 to 21.03)	466 more per 1000 (from 94 fewer to 4006 more)	VERY LOW
% of patients with undetectable HBV DNA (<3.7 LGE/ml) (30 months after randomization)											
1 Aizawa	RCT- unclear	Serious limitations	No serious inconsistency	Serious indirectness	Very serious imprecision	none	6/6 (100%)	7/7 (100%)	RR 1 (0.76 to 1.31)	0 fewer per 1000 (from 240 fewer to	VERY LOW

Quality assessment							Summary of findings				
2010	blinding	(a)		(b)	(d)					310 more)	
% of patients with ALT normalisation (30 months after randomization)											
1 Aizawa 2010	RCT-unclear blinding	Serious limitations (a)	No serious inconsistency	Serious indirectness (b)	Serious imprecision (c)	none	6/6 (100%)	7/7 (100%)	RR 1 (0.76 to 1.31)	0 fewer per 1000 (from 240 fewer to 310 more)	VERY LOW
% of patients with HBeAg loss (30 months after randomization)											
1 Aizawa 2010	RCT-unclear blinding	Serious limitations (a)	No serious inconsistency	Serious indirectness (b)	Very serious imprecision (d)	none	4/6 (66.7%)	2/5 (40%)	RR 1.67 (0.5 to 5.61)	268 more per 1000 (from 200 fewer to 1844 more)	VERY LOW

(a) Unclear blinding and randomisation method.
(b) Mixed population; 23% and 36% in the adefovir alone group and continuing adefovir and lamivudine group respectively were HBeAg positive. 23% and 36% in the switching to adefovir and continuing adefovir and lamivudine groups respectively had cirrhosis.
(c) The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm.
(d) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.

Comparison of switching from lamivudine (LAM) monotherapy to adefovir plus lamivudine (LAM+ADV) versus switching from lamivudine to adefovir (ADV) monotherapy in lamivudine resistant adults with CHB

Table 181: Switching from lamivudine to adefovir plus lamivudine versus switching from lamivudine to adefovir monotherapy - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Switching from LAM alone to LAM + ADV; Frequency (%)**	**ADV; Frequency (%)**	**Relative; Risk Ratio (RR) (95% CI)**	**Absolute**	
% of patients with undetectable HBV DNA (<1000 copies/ml) (assessed at the end of 12 months treatment)											
1 Rapti	RCT-	Very	No serious	Serious	Very serious	None	19/28	11/14	RR 0.86	110 fewer per 1000	

Quality assessment							No of patients		Effect		Quality
2007	unblinded	serious limitations (a)	inconsistency	indirectness (b)	imprecision (c)		(67.9%)	(78.6%)	(0.59 to 1.26)	(from 322 fewer to 204 more)	VERY LOW
% of patients with undetectable HBV DNA (<1000 copies/ml) (assessed at the end of 12 months follow up)											
1 Rapti 2007	RCT-unblinded	Very serious limitations (a)	No serious inconsistency	Serious indirectness (b)	Very serious imprecision (c)	None	23/28 (82.1%)	11/14 (78.6%)	RR 1.05 (0.76 to 1.44)	39 more per 1000 (from 189 fewer to 346 more)	VERY LOW
% of patients with ALT normalisation (assessed at the end of 12 months treatment)											
1 Rapti 2007	RCT-unblinded	Very serious limitations (a)	No serious inconsistency	Serious indirectness (b)	Serious imprecision (D)	None	25/28 (89.3%)	13/14 (92.9%)	RR 0.96 (0.79 to 1.17)	37 fewer per 1000 (from 195 fewer to 158 more)	VERY LOW
% of patients with ALT normalisation (assessed at the end of 12 months follow up)											
1 Rapti 2007	RCT-unblinded	Very serious limitations (a)	No serious inconsistency	Serious indirectness (b)	Serious imprecision (D)	None	25/28 (89.3%)	10/14 (71.4%)	RR 1.25 (0.88 to 1.78)	179 more per 1000 (from 86 fewer to 557 more)	VERY LOW

(a) Unblinded study with no details on randomisation and unclear allocation concealment.
(b) 38% of the patients had cirrhosis.
(c) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.
(d) The confidence interval is consistent with two clinical decisions; no appreciable benefit or harm, appreciable benefit.

Comparison of switching from lamivudine to entecavir versus continuing lamivudine for responders (HBV DNA less than 2.6 log copies/ml) treated with LAM for more than 3 years

Table 182: Switching from lamivudine to entecavir versus continuing lamivudine (responders treated with LAM for more than 3 years) - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch lamivudine to entecavir versus continue lamivudine	Control	Relative (95% CI)	Absolute	Quality
Undetectable HBV DNA (<2.6 log copies/mL) (mean 24 months treatment)											
1: Matsuura 2011	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	5/11 (45.5%)	5/17 (29.4%)	RR 1.55 (0.58 to 4.12)	162 more per 1000 (from 124 fewer to 918 more)	VERY LOW
Resistance (mean 24 months treatment)											
1: Matsuura 2011	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	0/11 (0%)	6/17 (35.3%)	OR 0.13 (0.02 to 0.81)	287 fewer per 1000 (from 47 fewer to 342 fewer)	LOW

[1] Unclear blinding, randomisation method and allocation concealment.
[2] Mixed population of lamivudine responders
[3] The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.

Comparison of switching from entecavir (ETV) to lamivudine (LAM) versus continuing entecavir for patients previously treated with entecavir with undetectableHBV DNA

Table 183: Switching from entecavir (ETV) to lamivudine (LAM) versus continuing entecavir for patients previously treated with entecavir with undetectableHBV DNA - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching from ETV to LAM; Frequency (%)	Continuing ETV; Frequency (%)	Relative; Risk Ratio (RR)/Peto odds ratio (PETO OR) (95% CI)	Absolute	
% of patients with undetectable HBV DNA (<100 copies/ml) (assessed at the end of 96 weeks treatment)											
1 Fung 2011	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	Serious indirectness [b]	No serious imprecision	none	19/25 (76%)	25/25 (100%)	RR 0.76 (0.61 to 0.96)	240 fewer per 1000 (from 40 fewer to 390 fewer)	LOW
% of patients with ALT normalisation (assessed at the end of 96 weeks treatment)											
1 Fung 2011	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	Serious indirectness [b]	no serious imprecision	none	20/20 (100%)	25/25 (100%)	RR 1 (0.92 to 1.09)	0 fewer per 1000 (from 80 fewer to 90 more)	LOW
Incidence of resistance (assessed at the end of 96 weeks treatment)											
1 Fung 2011	RCT-unclear blinding	Serious limitations [a]	no serious inconsistency	Serious indirectness [b]	Serious imprecision [c]	none	3/20 (15%)	0/25 (0%)	PETO OR 10.56 (1.03 to 108.64)	150 more per 1000 (from 20 fewer to 320 more)	VERY LOW

(a) Unclear blinding, no allocation concealment.
(b) Mixed population with the majority of patients (82%) being HBeAg negative and 8% having cirrhosis.
(c) The confidence interval is consistent with two clinical decisions; appreciable harm, no appreciable harm or benefit.

Comparison of switching from lamivudine to telbivudine versus continuing lamivudine for previously treated patients with lamivudine and persistent viraemia (HBV DNA more than 3 log copies/ml)

Table 184: Switching from lamivudine to telbivudine versus continuing lamivudine for previously treated patients with lamivudine and persistent viraemia - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching from LAM to telbivudine; Frequency (%)/ Mean (SD)	Continuing LAM ; Frequency (%)/ Mean (SD)	Relative; Risk Ratio (RR)/ Mean difference (MD) (95% CI)	Absolute	
% of patients with undetectable HBV DNA (only HBeAg negative) (assessed at week 52)											
1 Safadi 2011	RCT-double blinded	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision [(a)]	none	28/40 (70%)	26/40 (65%)	RR 1.08 (0.79 to 1.46)	52 more per 1000 (from 136 fewer to 299 more)	LOW

(a) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.

11.1.5.4 Sequential antiviral treatment for children with CHB

Comparison of interferon alpha versus sequential treatment of lamivudine followed by interferon plus lamivudine followed by lamivudine

Table 185: Interferon alpha (6 months) versus sequential treatment of lamivudine (2 months) followed by interferon plus lamivudine (6 months) followed by lamivudine (4 months) (HBeAg positive children) - clinical study characteristics and clinical summary of findings

Quality assessment							No of children		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFN-alpha Frequency	LAM followed by IFN+LAM	Relative (95% CI)	Absolute	

Quality assessment							No of children		Effect		Quality
							(%)	followed by LAM; Frequency (%)			
% of children with HBeAg loss (assessed at the end of 6 months treatment)											
1 Dikici 2004	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	16/62 (25.8%)	26/60 (43.3%)	RR 0.6 (0.36 to 0.99)	173 fewer per 1000 (from 4 fewer to 277 fewer)	VERY LOW
% of children with HBeAg seroconversion (assessed at the end of 6 months treatment)											
1 Dikici 2004	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	14/62 (22.6%)	21/60 (35%)	RR 0.65 (0.36 to 1.15)	123 fewer per 1000 (from 224 fewer to 52 more)	VERY LOW
% of children with undetectable HBV DNA (assessed at the end of 6 months treatment)											
1 Dikici 2004	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	none	21/62 (33.9%)	56/60 (93.3%)	RR 0.36 (0.25 to 0.52)	597 fewer per 1000 (from 448 fewer to 700 fewer)	LOW
% of children with HBsAg seroconversion (assessed at the end of 6 months treatment)											
1 Dikici 2004	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [c]	none	3/62 (4.8%)	5/60 (8.3%)	RR 0.58 (0.15 to 2.32)	35 fewer per 1000 (from 71 fewer to 110 more)	VERY LOW
% of children with HBeAg loss (assessed at 6 months follow up)											
1 Dikici 2004	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [c]	none	22/62 (35.5%)	25/60 (41.1%)	RR 0.85 (0.54 to 1.34)	92 fewer (192 fewer to 142 more)	VERY LOW
% of children with HBeAg seroconversion (assessed at 6 months follow up)											
1 Dikici 2004	RCT- unclear	Serious limitation	No serious inconsistency	No serious indirectness	Very serious imprecision	none	18/62 (29%)	21/60 (35%)	RR 0.83 (0.49 to 1.40)	60 fewer per 1000 (from 178 fewer to	VERY LOW

Quality assessment							No of children		Effect		Quality
	blinding	s [a]			[c]					140 more)	
% of children with undetectable HBV DNA (assessed at 6 months follow up)											
1 Dikici 2004	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	none	28/62 (45.2%)	52/60 (86.7%)	RR 0.52 (0.39 to 0.7)	416 fewer per 1000 (from 260 fewer to 529 fewer)	LOW
% of children with HBeAg loss (assessed at 12 months follow up)											
1 Dikici 2004	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [d]	none	29/62 (46.8%)	21/60 (35%)	RR 1.34 (0.86 to 2.07)	119 more per 1000 (from 49 fewer to 374 more)	VERY LOW
% of children with HBeAg seroconversion (assessed at 12 months follow up)											
1 Dikici 2004	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [c]	none	20/62 (32.3%)	21/60 (35%)	RR 0.92 (0.56 to 1.52)	28 fewer per 1000 (from 154 fewer to 182 more)	VERY LOW
% of children with undetectable HBV DNA (assessed at 12 months follow up)											
1 Dikici 2004	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [d]	none	38/62 (61.3%)	43/60 (71.7%)	RR 0.86 (0.66 to 1.1)	100 fewer per 1000 (from 244 fewer to 72 more)	VERY LOW
% of children with ALT normalisation (assessed at 12 months follow up)											
1 Dikici 2004	RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	30/62 (48.4%)	47/60 (78.3%)	RR 0.62 (0.46 to 0.83)	298 fewer per 1000 (from 133 fewer to 423 fewer)	LOW

[a] *No details of randomisation and allocation concealment. Blinding not reported.*

[b] *The confidence interval is consistent with two clinical decisions; appreciable harm, no appreciable benefit or harm.*

[c] *The confidence interval is consistent with three clinical decisions; appreciable harm, no appreciable harm or benefit, appreciable benefit.*

[d] The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm.

Comparison of switching interferon alpha plus lamivudine (IFN+LAM) to lamivudine alone (LAM) versus sequential treatment of lamivudine (LAM) followed by interferon plus lamivudine (IFN+LAM) followed by lamivudine (LAM) alone

Table 186: Interferon alpha plus lamivudine (6 months) followed by lamivudine alone (6 months) versus lamivudine (2 months) followed by interferon plus lamivudine (6 months) followed by lamivudine (4 months) - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFN-α + lamivudine (6 months), LAM alone (6-12 months)	Lamivudine (2 months), IFN+ lamivudine (6 months), lamivudine alone (4 months)	Relative (95% CI)	Absolute	Quality
Clearance of HBeAg (12 months)											
Dikici 2002, Dikici 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	42/77 (54.5%)	35/75 (46.7%)	RR 1.16 (0.85 to 1.59)	75 more per 1000 (from 70 fewer to 275 more)	LOW
Seroconversion to anti-HBe (12 months)											
Dikici 2002, Dikici 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34/77 (44.2%)	27/75 (36%)	RR 1.22 (0.83 to 1.81)	79 more per 1000 (from 61 fewer to 292 more)	LOW
Clearance of HBsAg (12 months)											
Dikici 2002, Dikici	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/77 (14.3%)	8/75 (10.7%)	RR 1.31 (0.56	33 more per 1000 (from 47 fewer to 219	VERY LOW

2004									to 3.05)	more)	
Seroconversion to anti-HBs (12 months)											
Dikici 2002, Dikici 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/77 (13%)	7/75 (9.3%)	RR 1.38 (0.55 to 3.42)	35 more per 1000 (from 42 fewer to 226 more)	VERY LOW
Undetectable HBV DNA (12 months)											
Dikici 2002, Dikici 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	69/77 (89.6%)	70/75 (93.3%)	OR 0.61 (0.19 to 1.96)	38 fewer per 1000 (from 207 fewer to 32 more)		
ALT normalisation (12 months)											
Dikici 2002	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/17 (82.4%)	11/15 (73.3%)	RR 1.12 (0.77 to 1.64)	88 more per 1000 (from 169 fewer to 469 more)	LOW
Clearance of HBeAg (18 months)											
Dikici 2002, Dikici 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40/77 (51.9%)	33/75 (44%)	RR 1.17 (0.84 to 1.64)	75 more per 1000 (from 70 fewer to 282 more)	LOW
Seroconversion to anti-HBe (18 months)											
Dikici 2002, Dikici 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37/77 (48.1%)	28/75 (37.3%)	RR 1.28 (0.88 to 1.86)	105 more per 1000 (from 45 fewer to 321 more)	LOW
Clearance of HBsAg (18 months)											

Dikici 2002	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/17 (23.5%)	3/15 (20%)	RR 1.18 (0.31 to 4.43)	36 more per 1000 (from 138 fewer to 686 more)	VERY LOW
Seroconversion to anti-HBs (18 months)											
Dikici 2002	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/17 (17.6%)	2/15 (13.3%)	RR 1.32 (0.25 to 6.88)	43 more per 1000 (from 100 fewer to 784 more)	VERY LOW
Undetectable HBV DNA (18 months)											
Dikici 2002, Dikici 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	69/77 (89.6%)	64/75 (85.3%)	OR 1.48 (0.56 to 3.89)	43 more per 1000 (from 88 fewer to 104 more)	VERY LOW
ALT normalisation (18 months)											
Dikici 2002	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/17 (82.4%)	10/15 (66.7%)	RR 1.24 (0.81 to 1.88)	160 more per 1000 (from 127 fewer to 587 more)	LOW
Clearance of HBeAg (24 months)											
Dikici 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/60 (53.3%)	21/60 (35%)	RR 1.52 (1 to 2.32)	182 more per 1000 (from 0 more to 462 more)	MODERATE
Seroconversion to anti-HBe (24 months)											
Dikici 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28/60 (46.7%)	21/60 (35%)	RR 1.33 (0.86 to	116 more per 1000 (from 49 fewer to 374 more)	LOW

									2.07)		
Undetectable HBV DNA (24 months)											
Dikici 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	51/60 (85%)	43/60 (71.7%)	OR 2.24 (0.91 to 5.53)	133 more per 1000 (from 20 fewer to 217 more)	LOW
ALT normalisation (24 months)											
Dikici 2004	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	47/60 (78.3%)	47/60 (78.3%)	RR 1 (0.83 to 1.21)	0 fewer per 1000 (from 133 fewer to 165 more)	MODERATE

[1] No details of randomisation or allocation concealment
[2] The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm
[3] The confidence interval is consistent with three clinical decisions; appreciable harm, no appreciable harm or benefit, appreciable benefit

Interferon alpha plus lamivudine (6 months) followed by Lamivudine alone (6 months) versus interferon alpha alone (6 months)

Table 187: Interferon alpha plus lamivudine (6 months) followed by Lamivudine alone (6 months) versus interferon alpha (6 months) - clinical study characteristics and clinical summary of findings

Quality assessment							**No of children**		**Effect**		**Quality**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interferon alpha+ lamivudine (Frequency %)**	**Interferon alpha (Frequency %)**	**Relative (95% CI)**	**Absolute**	
% of children with HBeAg loss (assessed at 6 months)											
Dikici 2004	1 RCT-unclear	Serious limitation	No serious inconsistency	No serious indirectness	Serious imprecision	none	31/60 (51.7%)	16/62 (25.8%)	RR 2.00 (1.23 to	258 more per 1000 (from 59 more to 583	LOW

Quality assessment							No of children		Effect		Quality
	blinding	s [a]			[b]				3.26)	more)	
% of children with HBeAg seroconversion (assessed at 6 months)											
Dikici 2004	1 RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	26/60 (43.3%)	14/62 (22.5%)	RR 1.92 (1.11 to 3.31)	208 more (25 more to 522 more)	LOW
% of children with undetectable DNA (assessed at 6 months)											
Dikici 2004	1 RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	none	53/60 (87.7%)	21/62 (33.8%)	RR 2.61 (1.82 to 3.74	545 more (278 more to 928 more)	MODERATE
% of children with HbsAg seroconversion (assessed at 6 months)											
Dikici 2004	1 RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	7/60	3/62 (4.8%)	RR 2.41 (0.65 to 8.89)	68 more per 1000 (from 17 fewer to 382 more)	VERY LOW
% of children with HBeAg loss (assessed at the end of 6 months follow-up)											
Dikici 2004	1 RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [c]	none	29/60 (48.3%)	22/62 (35%)	RR 1.36 (0.89 to 2.08)	128 more (39 fewer to 383 more)	LOW
% of children with HBeAg seroconversion (assessed at the end of 6 months follow-up)											
Dikici 2004	1 RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	29/60 (48.3%)	18/62 (28.3%)	RR 1.66 (1.04 to 2.66)	192 more (12 more to 482 more)	LOW
% of children with undetectable DNA (assessed at the end of 6 months follow-up)											
Dikici 2004	1 RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	none	53/60 (87.7%)	28/62 (45.7%)	RR 1.96 (1.46 to 2.61)	434 more (208 more to 727 more)	MODERATE
% of children with HBeAg loss (assessed at the end of 12 months follow-up)											
Dikici 2004	1 RCT-unclear	Serious limitation	No serious inconsistency	No serious indirectness	Serious imprecision	none	32/60 (53.3%)	29/62 (46.8%)	RR 1.14 (0.8 to	65 more per 1000 (from 94 fewer to 295	LOW

Quality assessment							No of children		Effect		Quality
	blinding	s [a]			[b]				1.63)	more)	
% of children with HBeAg seroconversion (assessed at the end of 12 months follow-up)											
Dikici 2004	1 RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	28/60 (46.7%)	20/62 (32.3%)	RR 1.45 (0.92 to 2.27)	145 more per 1000 (from 26 fewer to 410 more)	LOW
% of children with undetectable DNA (assessed at the end of 12 months follow-up)											
Dikici 2004	1 RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	51/60 (85.7%)	38/62 (61.5%)	RR 1.39 (1.11 to 1.74)	239 more (67 more to 454 more)	LOW
% of children with normalisation of ALT (assessed at the end of 12 months follow-up)											
Dikici 2004	1 RCT-unclear blinding	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [b]	none	47/60 (78.3%)	30/62 (48%)	RR 1.62 (1.21 to 2.16)	300 more (102 more to 561 more)	LOW

[a] *No details of randomisation and allocation concealment. Blinding not reported.*
[b] *The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm*
[c] *The confidence interval is consistent with three clinical decisions; appreciable harm, no appreciable harm or benefit, appreciable benefit.*

Table 188: Simultaneous LAM + IFN alpha 2a (6 months) vs sequential LAM alone 2 months then add IFN alpha 2a (6 months) for chronic hepatitis B in children

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Simultaneous LAM + IFN alpha 2a (6 months)**	**sequential LAM alone 2 months then add IFN alpha 2a (6 months)**	**Relative (95% CI)**	**Absolute**	
ALT normalization (12 months)											
Kansu	randomised	serious[1]	no serious inconsistenc	no serious indirectne	serious[2]	none	90/112 (80.4%)	47/65 (72.3%)	RR 1.11	80 more per 1000 (from 51 fewer to	LOW

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Simultaneous LAM + IFN alpha 2a (6 months)	sequential LAM alone 2 months then add IFN alpha 2a (6 months)	Relative (95% CI)	Absolute	Quality
2006	trials		y	ss					(0.93 to 1.33)	239 more)	
Anti HBe seroconversion (12 months)											
Kansu 2006	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	61/112 (54.5%)	15/65 (23.1%)	RR 2.36 (1.47 to 3.8)	314 more per 1000 (from 108 more to 646 more)	MODERATE
Undetectable HBV DNA (<5pg/mL) (12 months)											
Kansu 2006	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	100/112 (89.3%)	55/65 (84.6%)	RR 1.06 (0.93 to 1.19)	51 more per 1000 (from 59 fewer to 161 more)	MODERATE
Breakthrough HBV DNA (12 months)											
Kansu 2006	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious3	none	3/112 (2.7%)	2/65 (3.1%)	RR 0.87 (0.15 to 5.07)	4 fewer per 1000 (from 26 fewer to 125 more)	VERY LOW
ALT normalization (18 months)											
Kansu 2006	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	88/112 (78.6%)	49/65 (75.4%)	RR 1.04 (0.88 to	30 more per 1000 (from 90 fewer to 173 more)	MODERATE

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Simultaneous LAM + IFN alpha 2a (6 months)	sequential LAM alone 2 months then add IFN alpha 2a (6 months)	Relative (95% CI)	Absolute	Quality
									1.23)		
Anti HBe seroconversion (18 months)											
Kansu 2006	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	67/112 (59.8%)	26/65 (40%)	RR 1.5 (1.07 to 2.09)	200 more per 1000 (from 28 more to 436 more)	MODERATE
Undetectable HBV DNA (<5pg/mL) (18 months)											
Kansu 2006	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	90/112 (80.4%)	45/65 (69.2%)	RR 1.16 (0.96 to 1.4)	111 more per 1000 (from 28 fewer to 277 more)	LOW
Breakthrough HBV DNA (18 months)											
Kansu 2006	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/112 (8.9%)	9/65 (13.8%)	RR 0.64 (0.28 to 1.5)	50 fewer per 1000 (from 100 fewer to 69 more)	VERY LOW
ALT normalization (24 months)											
Kansu 2006	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	92/112 (82.1%)	44/65 (67.7%)	RR 1.21 (1 to 1.47)	142 more per 1000 (from 0 more to 318 more)	MODERATE
Anti HBe seroconversion (24 months)											
Kansu 2006	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64/112 (57.1%)	21/65 (32.3%)	RR 1.77 (1.2 to	249 more per 1000 (from 65 more to 517	MODERATE

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Simultaneous LAM + IFN alpha 2a (6 months)**	**sequential LAM alone 2 months then add IFN alpha 2a (6 months)**	**Relative (95% CI)**	**Absolute**	**Quality**
									2.6)	more)	
Undetectable HBV DNA (<5pg/mL) (24 months)											
Kansu 2006	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	84/112 (75%)	39/65 (60%)	RR 1.25 (1 to 1.57)	150 more per 1000 (from 0 more to 342 more)	MODERATE
Breakthrough HBV DNA (24 months)											
Kansu 2006	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/112 (5.4%)	5/65 (7.7%)	RR 0.7 (0.22 to 2.19)	23 fewer per 1000 (from 60 fewer to 92 more)	VERY LOW
Anti HBs seroconversion (24 months)											
Kansu 2006	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/112 (9.8%)	4/65 (6.2%)	RR 1.6 (0.53 to 4.81)	37 more per 1000 (from 29 fewer to 234 more)	VERY LOW

[1] No details of randomisation or allocation concealment
[2] The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm
[3] The confidence interval is consistent with three clinical decisions; appreciable harm, no appreciable harm or benefit, appreciable benefit

11.1.5.5 Economic evidence

Literature review

Three studies were included that included the relevant comparisons[21,43,78]. These are summarised in the economic evidence profiles below (Table 189 to Table 192). Comparisons relevant specifically to patients with lamivudine resistance are presented in Table 189 and Table 190. Comparisons relevant to sequential comparisons from first to third-line treatment are presented in Table 191 and Table 192.

No studies that specifically evaluated pharmacological sequences were excluded from the review.

Table 189: Single and combination therapies in LAM resistant CHB – Economic study characteristics

Study	Limitations	Applicability	Other comments
Dakin 2010 (UK)	Minor limitations [(a)]	Partially applicable [(b)]	Decision analytic model; comparators included sequences of lamivudine, adefovir, entecavir, tenofovir, best supportive care and combinations of adefovir and lamivudine and entecavir and adefovir; treatment effects estimated from a network meta-analysis of RCTs
Orlewska 2008 (Poland)	Potentially serious limitations [(c)]	Partially applicable [(d)]	Decision analytic model; comparators included entecavir and adefovir for lamivudine-resistant patients; treatment effects estimated from RCTs

(a) Unclear how closely effect estimates match the clinical evidence review; estimates of resource use associated with severe liver disease taken from costing study among hepatitis C patients; potential conflict of interest.

(b) Study population is appropriate and may be reflective of the case mix seen in clinical practice, but difficult to know if therapies are more, less or equally cost-effective in both HBeAg positive and negative, with and without compensated cirrhosis

(c) Unclear how closely treatment effect estimates match the NCGC clinical review; no resistance was assumed to develop for either entecavir or adefovir; unclear whether estimates of cost and resource use are from best available sources; potential conflict of interest (funded by Bristol Meyers Squibb, makers of entecavir)

(d) The study includes two comparators of interest, but not all comparators relevant to the review question (e.g. tenofovir is missing); costing perspective is health care payer in Poland, thus some uncertainty about applicability of Polish unit costs and estimates of resource use; costs and effects discounted at 5% per annum (3.5% preferred by NICE); changes in health-related quality of life estimated by general UK population, but estimates differ from other published CEAs that reference the same/similar study; no differentiation between HBeAg positive and negative CHB patients

Table 190: Single and combination therapies in LAM resistant CHB – Economic summary of findings

Study	Incremental cost	Incremental effects	ICER
Dakin 2010 (UK)			
LAM then BSC	base case	base case	
LAM then ETV	£14,038	0.31	Extendedly dominated by LAM then BSC and LAM then TDF
LAM then TDF	£15,737	1.12	£14,051
LAM then ADV	£515	-0.41	Dominated by LAM then TDF
LAM then TDF+LAM	£8,160	0.17	£48,000 compared to LAM then TDF (a)
LAM then	£4,850	-0.34	Dominated by LAM then TDF+LAM

Study	Incremental cost	Incremental effects	ICER
ADV+LAM			
Orlewska 2008 (Poland): Men			
LAM then ETV	least cost		
LAM then ADV	£1,442	-0.27	Dominated by ETV. Model results were insensitive to variations in health state utilities for compensated and decompensated cirrhosis and HCC, age at initiation of therapy, treatment duration, discounting rate and estimated treatment cost per health state.
Orlewska 2008 (Poland): Women			
LAM then ETV	least cost		
LAM then ADV	£1,458	-0.30	Dominated by ETV. Model results were insensitive to variations in health state utilities for compensated and decompensated cirrhosis and HCC, age at initiation of therapy, treatment duration, discounting rate and estimated treatment cost per health state.

(a) If a switch to monotherapy with tenofovir or adefovir is inappropriate following the development of resistance to LAM, then the ICER for LAM then TDF+LAM is £18,501 per QALY compared to LAM then BSC.

The evidence is quite heterogeneous and somewhat difficult to interpret. Dakin and colleagues provides the most complete analysis of comparators relevant to a LAM-resistant population. Their analysis indicates that a switch to tenofovir upon development of resistance is likely to be the most cost-effective strategy at a willingness to pay threshold of £20,000 per QALY gained. In this group of patients, tenofovir appears to dominate or extendedly dominate second-line use of ETV, ADV and combination ADV and LAM. However, based on previous discussions, it seems unlikely that a true 'switch' would take place upon development of resistance. Therefore, perhaps the more relevant comparison is that of adding in tenofovir to lamivudine. Compared to LAM then BSC (no treatment), this strategy has an ICER of £18,501, making it likely to be cost-effective given the NICE threshold of £20,000 per QALY gained.

Orlewska and colleagues found that entecavir was likely to dominate adefovir in the treatment of lamivudine resistant patients. Interestingly, Dakin and colleagues found that adefovir was more costly, more effective, and likely to be cost-effective compared to entecavir, producing 0.4 more QALYs at an additional lifetime cost of £2,214, for an ICER of £5,535.

It is likely that the differences between the studies can be attributed to the assumptions made about drug resistance. Orlewska and colleagues assumed that no resistance would develop on entecavir and adefovir therapy in the LAM-resistant group. Dakin and colleagues used higher rates of resistance for entecavir than adefovir in this same population.

Table 191: Single and combination therapies in nucleos(t)ide naive CHB – Economic study characteristics

Study	Limitations	Applicability	Other comments
Dakin 2010 (UK)	Minor limitations (a)	Partially applicable (b)	Decision analytic model; comparators included sequences of lamivudine, adefovir, entecavir, tenofovir, best supportive care and combinations of adefovir and lamivudine and entecavir and adefovir; treatment effects

Study	Limitations	Applicability	Other comments
			estimated from a network meta-analysis of RCTs
Jones 2009 (UK)	Minor limitations (c)	Partially applicable (d)	Decision analytic model; comparators included sequences of pegylated-α 2a, interferon 2a, lamivudine and adefovir; treatment effects estimated from RCTs

(a) Unclear how closely effect estimates match the clinical evidence review; estimates of resource use associated with severe liver disease taken from costing study among hepatitis C patients; potential conflict of interest.
(b) Study population is appropriate and may be reflective of the case mix seen in clinical practice, but difficult to know if therapies are more, less or equally cost-effective in both HBeAg positive and negative, with and without compensated cirrhosis
(c) normalisation of ALT used as key indicator of response for HBeAg negative patients (is this a limitation?); unclear how closely treatment effect estimates match the NCGC clinical review
(d) The study includes three comparators of interest, but not all comparators relevant to the review question (e.g. tenofovir, entecavir and combinations are missing as are strategies starting with any treatment other than interferon or pegylated interferon);

Table 192: Single and combination therapies in nucleos(t)ide naïve CHB – Economic summary of findings

Study	Incremental cost	Incremental effects	ICER(a)
Dakin 2010 (UK) (b)			
BSC	least cost	least effective	
LAM then BSC	£3,688	0.38	£9,705
LAM then TDF	£15,737	1.12	£14,051
TDF then LAM	£9,300	0.49	£18,980
TDF then TDF+LAM	£696	0.02	£34,800 (c)
TDF then TDF+LAM then ETV	£2	0.0	£38,474
Jones 2009 (UK)			
Peg-α 2a	least cost	least effective	
Peg-α 2a then LAM	£2,616	0.38	£6,884
Peg-α 2a then ADV	£13,222	0.45	extendedly dominated by Peg-α 2a then LAM and Peg-α 2a then LAM then ADV
Peg-α 2a then LAM then ADV	£844	0.07	£27,050 vs Peg-α 2a then LAM

(a) Note: These values may not match the values in Table X which were reported in the study; these ICERs have been recalculated using reported total costs and effects.
(b) All strategies starting with entecavir and adefovir or using these drugs as second-line therapy were dominated or extendedly dominated by the strategies presented in this table.
(c) If a switch to monotherapy is inappropriate following the development of resistance, then the ICER for TDF then TDF+LAM is £19,600 per QALY compared to LAM then TDF. Compared to LAM then LAM+TDF, the ICER is £5,400.

Dakin and colleagues found that in a population that was nucleos(t)ide naïve, a strategy of starting with tenofovir and then switching to lamivudine was likely to result in improved benefits at a reasonable cost compared to starting with lamivudine and then switching to tenofovir. However, based on previous discussions, it seems unlikely that a true 'switch' would take place upon development of resistance. Therefore, perhaps the more relevant comparison is that of adding in

lamivudine to tenofovir. Compared to lamivudine then tenofovir, this strategy has an ICER of £19,600, making it potentially cost-effective given the NICE threshold of £20,000 per QALY gained. Similarly, if the strategy of tenofovir followed by the combination tenofovir and lamivudine was compared to the strategy of lamivudine followed by combination lamivudine and tenofovir, then the ICER would be £5,400.

The study by Jones and colleagues represents an update to the original NICE health technology assessment undertaken in 2006. In this update, the authors use more recently published clinical evidence, more recent utility data derived from a UK population with CHB and NICE recommended discounting rates (3.5% for costs and benefits). In their original 2006 analysis[87], the authors found that pegylated INF-α 2a followed by lamivudine, with adefovir reserved as salvage for patients who develop lamivudine resistance was likely to be cost-effective (ICER=£11,498) compared to pegylated INF-α 2a followed by lamivudine without salvage therapy. This sequence was found to be more cost-effective than treating patients who have not responded to pegylated INF-α 2a with adefovir before lamivudine. These findings underpinned NICE guidance TA96: Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B.

Using the new evidence, utility data and discounting rates, results indicate that the most effective strategy with an ICER under the NICE willingness to pay threshold is pegylated INF-α 2a followed by lamivudine without salvage therapy. Whereas the addition of salvage therapy with adefovir in the previous analysis cost an extra £11,498 per QALY gained, using updated information the addition now costs an extra £27,050 per QALY gained. The authors note that the substantial difference between results of the original and the updated analyses can be attributed to a change in discounting rates (6% and 1.5% for costs and benefits, respectively in original to 3.5% for both in updated). When the same discounting rates are applied in the updated model (6% and 1.5%), the results change very little (ICER for pegylated INF-α 2a followed by lamivudine with adefovir salvage therapy is £12,171 compared to pegylated INF-α 2a followed by lamivudine alone). It is unclear as to whether the difference is driven more by the increase from 1.5% to 3.5% for benefits or by the decrease from 6% to 3.5% for costs.

Current NICE methods recommend using a 3.5% discounting rate for both costs and benefits, thus lending weight to the conclusion that pegylated INF-α 2a followed by lamivudine with adefovir salvage therapy is not cost-effective at a £20,000 per QALY willingness to pay threshold. However, NICE methods currently recommend performing a sensitivity analysis wherein the discounting rate for benefits is varied to 1.5% whilst holding the discounting rate for costs at 3.5%. It is possible that if such a sensitivity analysis was performed, then the ICER for pegylated INF-α 2a followed by lamivudine with adefovir salvage therapy would fall to somewhere between £12,171 and £27,050, perhaps to a value close to the NICE willingness to pay threshold.

Regardless of the problems associated with the discounting rate, Jones and colleagues did not include entecavir, tenofovir or combinations as comparators.

Another key difference between these two studies is that Jones and colleagues used the outcome of 'ALT normalisation' to define response in the population of patients with HBeAg negative CHB, whereas Dakin and colleagues used the outcome of achieving 'HBV DNA undetectable.'

Unit costs

In the addition to recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 193: Unit costs of drugs

Item	Cost	Notes

Item	Cost	Notes
Lamivudine (Zeffix)	Tablets, 100 mg net price 28-tab pack = £78.09	ca. £1,015 per year
Adefovir (Hepsera)	Tablets, 10 mg net price 30-tab pack = £296.73	ca. £3,610 per year
Entecavir (Baraclude)	Tablets, 500 micrograms net price 30-tab pack = £363.26; Tablets, 1 mg net price 30-tab pack = £363.26. Oral solution, 50 micrograms/mL net price 210-mL pack = £423.80.	ca. £4,420 per year
Tenofovir (Viread)	Tablets, 245 mg net price 30-tab pack = £240.46.	ca. £2,925 per year
Telbivudine (Sebivo)	Tablets, 600 mg net price 28-tab pack = £290.33	ca. £3,774 per year
Peg INF α 2a (Pegasys)	Injection, peginterferon alfa-2a, net price 135-microgram prefilled syringe = £107.76, 180-microgram prefilled syringe = £124.40.	£5971 per 48-week course
Adefovir + Lamivudine	10 mg + 100 mg	ca. £4,610
Adefovir + Entecavir	10 mg + 500 micrograms (NA naïve) 10 mg + 1 mg (resistant)	ca. £8,030
Emtricitabine plus tenofovir (Tenofovir + emtricitabine)	Tablets, 225 mg tenofovir+200 mg emtricitabine net price 30-tab pack = £418.50	ca. £5,092

Source: BNF September 2011

New cost-effectiveness analysis

This area was prioritised for new cost-effectiveness analysis. The results of this analysis can be found in section 11.1.8. There is also a full write-up of the methods and results in Appendix I.

11.1.6 Clinical Evidence statements

11.1.6.1 Sequential drug therapy (add-on or switching monotherapies) in achieving remission of the activity of CHB for HBeAg positive adults

One randomised trial of 60 treatment naïve patients suggested that sequential treatment of 4 weeks of lamivudine followed by pegylated interferon alpha-2b may be beneficial on reducing the proportion of patients with undetectable HBV DNA (<4.700 copies/ml) compared to 4 weeks of placebo followed by pegylated interferon alpha-2b when assessed at the end of 28 weeks of treatment and at 24 weeks follow up. (LOW QUALITY)

One randomised trial of 60 treatment naïve patients suggested that sequential treatment of 4 weeks of lamivudine followed by pegylated interferon alpha-2b may be beneficial on increasing the proportion of patients achieving HBeAg loss compared to 4 weeks of placebo followed by pegylated interferon alpha-2b when assessed at the end of 28 weeks of treatment. (VERY LOW QUALITY)

One randomised trial of 60 treatment naïve patients suggested that sequential treatment of 4 weeks of lamivudine followed by pegylated interferon alpha-2b may be beneficial on increasing the

proportion of patients achieving HBeAg loss compared to 4 weeks of placebo followed by pegylated interferon alpha-2b when assessed at 24 weeks follow up. (LOW QUALITY)

One randomised trial of 60 treatment naïve patients suggested that sequential treatment of 4 weeks of lamivudine followed by pegylated interferon alpha-2b may be neither beneficial nor harmful for the proportion of patients achieving ALT normalisation compared to 4 weeks of placebo followed by pegylated interferon alpha-2b when assessed at the end of 28 weeks of treatment. (VERY LOW QUALITY)

One randomised trial of 60 treatment naïve patients suggested that sequential treatment of 4 weeks of lamivudine followed by pegylated interferon alpha-2b may be beneficial on increasing the proportion of patients achieving ALT normalisation compared to 4 weeks of placebo followed by pegylated interferon alpha-2b when assessed at 24 weeks follow up. (VERY LOW QUALITY)

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One randomised trial of 69 treatment naïve patients suggested that switching from 8 weeks of lamivudine to 16 weeks of lamivudine plus interferon alpha followed by 28 weeks of lamivudine alone may be beneficial compared to continuing lamivudine for the following outcomes:

- reducing the proportion of patients with undetectable HBV DNA ($<1.4x10^5$ copies/mL) when assessed at the end of 52 weeks treatment and at 24 weeks follow up (LOW QUALITY)
- increasing the proportion of patients with ALT normalisation when assessed at the end of 52 weeks treatment (LOW QUALITY)

One randomised trial of 69 treatment naïve patients showed that switching from 8 weeks of lamivudine to 16 weeks of lamivudine plus interferon alpha followed by 28 weeks of lamivudine alone is beneficial on increasing the proportion of patients with ALT normalisation compared to continuing lamivudine when assessed at 24 weeks follow up. (MODERATE QUALITY)

One randomised trial of 69 treatment naïve patients suggested that there may be no difference between the therapy of switching from lamivudine to lamivudine plus interferon alpha and continuing lamivudine for the following outcomes:

- the proportion of patients with HBeAg loss when assessed at the end of 52 weeks treatment (VERY LOW QUALITY)
- the proportion of patients with histological improvement (≥2 points reduction in HAI score) as assessed at the end of 52 weeks treatment (VERY LOW QUALITY)
- the incidence of resistance as assessed at the end of 52 weeks treatment (VERY LOW QUALITY)

One randomised trial of 69 treatment naïve patients suggested that switching from lamivudine to lamivudine plus interferon alpha is beneficial on increasing the proportion of patients with HBeAg seroconversion compared to continuing lamivudine when assessed at the end of 52 weeks treatment. (VERY LOW QUALITY)

One randomised trial of 69 treatment naïve patients showed that switching from lamivudine to lamivudine plus interferon alpha is beneficial on increasing the proportion of patients with HBeAg seroconversion compared to continuing lamivudine when assessed at 24 weeks follow up. (MODERATE QUALITY)

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One randomised trial of 60 interferon treatment naïve patients suggested that sequential treatment of interferon alpha followed by interferon alpha plus lamivudine followed by lamivudine may be neither beneficial nor harmful when compared to treating with lamivudine alone for the following outcomes:

- the proportion of patients with undetectable HBV DNA (<2.5pg/mL) assessed at the end of 48 weeks of treatment and 52 weeks follow up (LOW QUALITY)
- the proportion of patients with ALT normalisation at the end of 48 weeks of treatment (LOW QUALITY)

One randomised trial of 60 interferon treatment naïve patients suggested that sequential treatment of interferon alpha followed by interferon alpha plus lamivudine followed by lamivudine may be neither beneficial nor harmful when compared to treating with lamivudine alone for the following outcomes:

- the proportion of patients with HBeAg seroconversion assessed at the end of 48 weeks of treatment and 52 weeks follow up (VERY LOW QUALITY)
- the proportion of patients with ALT normalisation at 52 weeks follow up (VERY LOW QUALITY)

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One randomised trial of 252 lamivudine refractory patients showed that switching from lamivudine to entecavir is beneficial on log reduction of HBV DNA compared to continuing lamivudine when assessed at the end of 52 weeks of treatment (HIGH QUALITY)

One randomised trial of 252 lamivudine refractory patients showed that switching from lamivudine to entecavir is beneficial on reducing the proportion of patients with undetectable HBV DNA (<300 copies/ml) compared to continuing lamivudine when assessed at the end of 52 weeks of treatment. (MODERATE QUALITY)

One randomised trial of 66 lamivudine refractory patients suggested that switching from lamivudine to entecavir may be beneficial on reducing the proportion of patients with undetectable HBV DNA (<400 copies/ml) compared to continuing lamivudine when assessed at the end of 52 weeks of treatment. (LOW QUALITY)

Two randomised trials of 313 lamivudine refractory patients showed that switching from lamivudine to entecavir is beneficial on increasing the proportion of patients achieving ALT normalisation compared to continuing lamivudine when assessed at the end of 52 weeks of treatment. (MODERATE QUALITY)

Two randomised trials of 311 lamivudine refractory patients suggested that switching from lamivudine to entecavir may be neither beneficial nor harmful when compared to continuing lamivudine for the following outcomes:

- the proportion of patients with HBeAg loss assessed at the end of 52 weeks of treatment (VERY LOW QUALITY)
- the proportion of patients with HBeAg seroconversion assessed at the end of 52 weeks of treatment (VERY LOW QUALITY)

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One randomised trial of 162 previously treated patients with lamivudine and persistent viraemia showed that switching treatment from lamivudine to telbivudine is beneficial when compared to continuing lamivudine for the following outcomes when assessed at the end of 52 weeks of treatment:

- log reduction HBV DNA (MODERATE QUALITY)
- the proportion of patients with undetectable HBV DNA (<300 copies)(MODERATE QUALITY)

One randomised trial of 162 previously treated patients with lamivudine and persistent viraemia suggested with considerable uncertainty that switching treatment from lamivudine to telbivudine may be neither beneficial nor harmful compared to continuing lamivudine for the following outcomes assessed at the end of 52 weeks of treatment:

- the proportion of patients with HBeAg loss (VERY LOW QUALITY)
- the proportion of patients with HBeAg seroconversion (VERY LOW QUALITY)

One randomised trial of 106 previously treated patients with lamivudine and persistent viraemia suggested with much uncertainty that switching treatment from lamivudine to telbivudine may be beneficial on increasing the proportion of patients with ALT normalisation compared to continuing lamivudine at the end of 52 weeks of treatment. (LOW QUALITY)

One randomised trial of 232 previously treated patients with lamivudine and persistent viraemia suggested that switching treatment from lamivudine to telbivudine may be neither beneficial nor harmful for the incidence of virological breakthrough (defined as a persistent [two consecutive determinations] on-treatment increase in HBV DNA of > 1 log10 above nadir) compared to continuing lamivudine when assessed at the end of 52 weeks of treatment. (VERY LOW QUALITY)

One randomised trial of 217 previously treated patients with lamivudine and persistent viraemia suggested that switching treatment from lamivudine to telbivudine may be neither beneficial nor harmful for the incidence of genotypic resistance compared to continuing lamivudine when assessed at the end of 52 weeks of treatment. (VERY LOW QUALITY)

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One randomised trial of 35 previously treated patients with lamivudine suggested that switching treatment from lamivudine to adefovir may be neither beneficial nor harmful for the incidence of genotypic resistance compared to continuing lamivudine when assessed at the end of 12 months of treatment. (VERY LOW QUALITY)

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One randomised trial of 92 lamivudine resistant patients suggested that switching from lamivudine treatment to lamivudine plus adefovir may be beneficial compared to switching from lamivudine to entecavir for the following outcomes assessed at the end of 12 months of treatment:

- log reduction HBV DNA (VERY LOW QUALITY)
- the proportion of patients with undetectable HBV DNA(<300 copies/mL) (VERY LOW QUALITY)

One randomised trial of 81 previously treated patients with lamivudine suggested that switching from lamivudine treatment to lamivudine plus adefovir may be neither beneficial nor harmful for the proportion of patients with ALT normalisation compared to switching from lamivudine to entecavir when assessed at the end of 12 months of treatment. (LOW QUALITY)

One randomised trial of 81 previously treated patients with lamivudine suggested that switching from lamivudine treatment to lamivudine plus adefovir may be neither beneficial nor harmful for the proportion of patients achieving HBeAg loss and seroconversion compared to switching from lamivudine to entecavir when assessed at the end of 12 months of treatment. (VERY LOW QUALITY)

One randomised trial of 92 previously treated patients with lamivudine suggested that switching from lamivudine treatment to lamivudine plus adefovir may be neither beneficial nor harmful for the incidence of resistance compared to switching from lamivudine to entecavir. (VERY LOW QUALITY)

11.1.6.2 Sequential drug therapy (add-on or switching monotherapies) in achieving remission of the activity of CHB for HBeAg negative adults

One randomised trial of 162 antiviral treatment naïve patients suggested that switching from lamivudine to lamivudine plus interferon alpha-2b may be harmful on the proportion of patients achieving ALT normalisation compared to continuing lamivudine therapy when assessed at the end of 24 weeks treatment. (LOW QUALITY)

One randomised trial of 162 antiviral treatment naïve patients suggested that switching from lamivudine to lamivudine plus interferon alpha-2b may be neither beneficial nor harmful compared to continuing lamivudine therapy for the following outcomes when assessed at the end of 24 weeks treatment:

- the proportion of patients with undetectable HBV DNA (<1000 copies/ml) (VERY LOW QUALITY)
- incidence of lamivudine resistance mutations (VERY LOW QUALITY)

……

One randomised trial of 162 antiviral treatment naïve patients suggested that sequential treatment of lamivudine alone followed by lamivudine plus interferon alpha-2b followed by interferon alpha-2b alone may be neither beneficial nor harmful on the proportion of patients with ALT normalisation compared to continuing lamivudine therapy when assessed at the end of 48 weeks of treatment (LOW QUALITY).

One randomised trial of 162 antiviral treatment naïve patients suggested that sequential treatment of lamivudine alone followed by lamivudine plus interferon alpha-2b followed by interferon alpha-2b alone may be beneficial on increasing the proportion of patients with ALT normalisation compared to continuing lamivudine therapy when assessed at 24 weeks follow up (LOW QUALITY).

One randomised trial of 162 antiviral treatment naïve patients suggested that sequential treatment of lamivudine alone followed by lamivudine plus interferon alpha-2b followed by interferon alpha-2b alone may be neither beneficial nor harmful on the proportion of patients with undetectable HBV DNA (<1000 copies/ml) compared to continuing lamivudine therapy when assessed at the end of 48 weeks of treatment and at 24 weeks follow up (VERY LOW QUALITY).

One randomised trial of 162 antiviral treatment naïve patients showed that sequential treatment of lamivudine alone followed by lamivudine plus interferon alpha-2b followed by interferon alpha-2b alone is beneficial on reducing the proportion of patients with resistance mutations compared to continuing lamivudine therapy when assessed at the end of 48 weeks treatment (MODERATE QUALITY).

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One randomised trial of 53 lamivudine resistant patients suggested that switching from lamivudine to adefovir may be neither beneficial nor harmful compared to combination treatment of lamivudine plus adefovir for the following outcomes:

- the proportion of patients with undetectable HBV DNA (<2000 copies/ml) assessed at the end of 3 months of treatment and at 9 months follow up (VERY LOW QUALITY)
- the proportion of patients with ALT normalisation assessed at the end of 3 months of treatment and at 9 months follow up (VERY LOW QUALITY)

One randomised trial of 53 lamivudine resistant patients suggested that switching from lamivudine to adefovir alone may be harmful on the proportion of patients with undetectable HBV DNA (<2000 copies/ml) compared to combination treatment of lamivudine plus adefovir at 3 months follow up. (VERY LOW QUALITY)

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One randomised trial of 25 lamivudine resistant adults suggested that switching from lamivudine plus adefovir combination therapy to adefovir monotherapy may be neither beneficial nor harmful on the proportion of patients with undetectable HBV DNA (<3.7 LGE/ml) compared to combination therapy of lamivudine plus adefovir when assessed at 12 months after randomization. (LOW QUALITY)

One randomised trial of 19 lamivudine resistant adults suggested that switching from lamivudine plus adefovir combination therapy to adefovir monotherapy may be neither beneficial nor harmful on the proportion of patients with undetectable HBV DNA (<3.7 LGE/ml) compared to combination therapy of lamivudine plus adefovir when assessed at 24 months after randomization. (LOW QUALITY)

One randomised trial of 13 lamivudine resistant adults suggested that switching from lamivudine plus adefovir combination therapy to adefovir monotherapy may be neither beneficial nor harmful on the proportion of patients with undetectable HBV DNA (<3.7 LGE/ml) compared to combination therapy of lamivudine plus adefovir when assessed at 30 months after randomization. (LOW QUALITY)

One randomised trial of 25 lamivudine resistant adults suggested that switching from lamivudine plus adefovir combination therapy to adefovir monotherapy may be beneficial on increasing the proportion of patients with ALT normalisation compared to combination therapy of lamivudine plus adefovir when assessed at 12 months after randomization. (VERY LOW QUALITY)

One randomised trial of 19 lamivudine resistant adults suggested that switching from lamivudine plus adefovir combination therapy to adefovir monotherapy may be beneficial on increasing the proportion of patients with ALT normalisation compared to combination therapy of lamivudine plus adefovir when assessed at 24 months after randomization. (VERY LOW QUALITY)

One randomised trial of 13 lamivudine resistant adults suggested that switching from lamivudine plus adefovir combination therapy to adefovir monotherapy may be neither beneficial nor harmful on the proportion of patients with ALT normalisation compared to combination therapy of lamivudine plus adefovir when assessed at 30 months after randomization. (VERY LOW QUALITY)

One randomised trial of 11 lamivudine resistant adults suggested that switching from lamivudine plus adefovir combination therapy to adefovir monotherapy may be beneficial on increasing the proportion of patients with HBeAg loss compared to combination therapy of lamivudine plus adefovir when assessed at 12, 24 and 30 months after randomization. (VERY LOW QUALITY)

One randomised trial of 11 lamivudine resistant adults suggested that switching from lamivudine plus adefovir combination therapy to adefovir monotherapy may be neither beneficial nor harmful on the proportion of patients with HBeAg seroconversion compared to combination therapy of lamivudine plus adefovir when assessed after 12 months of adefovir monotherapy. (VERY LOW QUALITY)

……

One randomised trial of 43 lamivudine resistant patients suggested that switching from lamivudine to adefovir plus lamivudine combination therapy may be neither beneficial nor harmful on the proportion of patients with undetectable HBV DNA (<1000 copies/ml) compared to switching from lamivudine to adefovir when assessed at the end of 12 months treatment. (VERY LOW QUALITY)

One randomised trial of 42 lamivudine resistant patients suggested that switching from lamivudine to adefovir plus lamivudine combination therapy may be neither beneficial nor harmful on the proportion of patients with ALT normalisation compared to switching from lamivudine to adefovir when assessed at the end of 12 months treatment. (VERY LOW QUALITY)

One randomised trial of 42 lamivudine resistant patients suggested that switching from lamivudine to adefovir plus lamivudine combination therapy may be beneficial on reducing the proportion of patients with undetectable HBV DNA (<1000 copies/ml) and increasing the proportion of patients with ALT normalisation compared to switching from lamivudine to adefovir when assessed at 12 months follow up. (VERY LOW QUALITY)

……

One randomised trial of 26 patients who responded to previous treatment for more than 3 years suggested that switching from lamivudine to entecavir may be neither beneficial nor harmful on the proportion of patients with undetectable HBV DNA (<2.6 log copies/ml) compared to continuing lamivudine when assessed at the end of mean 24 months treatment. (VERY LOW QUALITY)

One randomised trial of 26 patients who responded to previous treatment for more than 3 years suggested that switching from lamivudine to entecavir may be beneficial on reducing the proportion of patients with virological breakthrough and observed lamivudine-resistance mutations compared to continuing lamivudine when assessed at the end of mean 24 months treatment. (VERY LOW QUALITY)

……

One randomised trial of 45 patients previously treated with entecavir and with undetectable HBV DNA (<100 copies/mL) suggested that switching treatment from entecavir to lamivudine may be harmful to the proportion of patients with undetectable HBV DNA (<100 copies/ml) compared to continuing entecavir as assessed at the end of 96 weeks treatment. (LOW QUALITY)

One randomised trial of 45 patients previously treated with entecavir and with undetectable HBV DNA (<100 copies/mL) suggested that switching treatment from entecavir to lamivudine may be neither beneficial nor harmful to the proportion of patients with ALT normalisation compared to continuing entecavir as assessed at the end of 96 weeks treatment. (LOW QUALITY)

One randomised trial of 45 patients previously treated with entecavir and with undetectable HBV DNA suggested that switching treatment from entecavir to lamivudine may be harmful on the incidence of resistance compared to continuing entecavir as assessed at the end of 96 weeks treatment. (VERY LOW QUALITY)

11.1.6.3 Combination therapy in achieving remission of the activity of CHB for HBeAg negative adults

One randomised study of 360 people found a benefit of Pegylated interferon alpha-2a plus lamivudine versus pegylated interferon alpha-2a on the following outcomes:

% of people with HBV DNA <20,000 copies/ml (assessed at the end of 48 week treatment) (MODERATE QUALITY)

% of people with ALT normalisation (assessed at the end of 48 week treatment) (LOW QUALITY)

One randomised study of 360 people found no difference between Pegylated interferon alpha-2a plus lamivudine versus pegylated interferon alpha-2a on the following outcomes:

HBV DNA log reduction (copies/ml) (assessed at the end of 48 week treatment) (LOW QUALITY)

HBV DNA log reduction (copies/ml) (assessed at the end of 24 week follow up) (LOW QUALITY)

% of people with HBV DNA <20,000 copies/ml (assessed at the end of 24 week follow up) (LOW QUALITY)

% of people with HBsAg loss (assessed at the end of 24 week follow up) (VERY LOW QUALITY)

% of people with HBsAg seroconversion (assessed at the end of 24 week follow up) (VERY LOW QUALITY)

% of people with ALT normalisation (assessed at the end of 24 week follow up) (MODERATE QUALITY)

% of people with Histologic improvement (assessed at the end of 24 week follow up) (LOW QUALITY)

Resistance (genotypic mutation) (VERY LOW QUALITY)

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One randomised study of 360 people found a benefit of Pegylated interferon alpha-2a plus lamivudine versus lamivudine on the following outcomes:

HBV DNA log reduction (copies/ml) (assessed at the end of 48 week treatment) (LOW QUALITY)

% of people with HBV DNA < 20,000 copies/ml (assessed at the end of 48 week treatment) (MODERATE QUALITY)

% of people with ALT normalisation (assessed at the end of 48 week treatment) (MODERATE QUALITY)

HBV DNA log reduction (copies/ml) (assessed at the end of 24 week follow up) (LOW QUALITY)

% of people with HBV DNA < 20,000 copies/ml (assessed at the end of 24 week follow up) (LOW QUALITY)

% of people with HBsAg loss (assessed at the end of 24 week follow up) (VERY LOW QUALITY)

% of people with ALT normalisation (assessed at the end of 24 week follow up) (LOW QUALITY)

Resistance (genotypic mutation) (MODERATE QUALITY)

One randomised study of 360 people found no difference between Pegylated interferon alpha-2a plus lamivudine versus lamivudine on the following outcomes:

% of people with HBsAg seroconversion (assessed at the end of 24 week follow up) (VERY LOW QUALITY)

% of people with histologic improvement (assessed at the end of 24 week follow up) (LOW QUALITY)

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One randomised study of 48 people found no difference between Pegylated interferon alpha-2b plus lamivudine versus pegylated interferon alpha-2b on the following outcomes:

Normalisation of ALT end of 48 weeks treatment (LOW QUALITY)

HBsAg seroconversion after 24 weeks follow up (LOW QUALITY)

Two randomised studies of 171 people found no difference between Pegylated interferon alpha-2b plus lamivudine versus pegylated interferon alpha-2b on the following outcomes:

Normalisation of ALT after 24 weeks follow up (LOW QUALITY)

Undetectable HBV DNA at end of 48 weeks treatment (LOW QUALITY)

Undetectable HBV DNA after 24 weeks follow up (LOW QUALITY)

……

One randomised study of 60 people found a benefit of Pegylated interferon alpha plus adefovir versus pegylated interferon alpha on the following outcomes:

% of people with undetectable HBV DNA (assessed at the end of 48 weeks treatment) (LOW QUALITY)

One randomised study of 60 people found no difference between Pegylated interferon alpha plus adefovir versus pegylated interferon alpha on the following outcomes:

% of people with ALT normalisation (assessed at the end of 48 weeks treatment) (LOW QUALITY)

% of people with ALT normalisation (assessed at the end of 24 weeks follow up) (VERY LOW QUALITY)

% of people with undetectable HBV DNA (assessed at the end of 24 weeks follow up) (VERY LOW QUALITY)

% of people with HBsAg loss (assessed at the end of 24 weeks follow up) (VERY LOW QUALITY)

……

One randomised study of 80 people found a benefit of Interferon alpha plus lamivudine versus lamivudine on the following outcomes:

ALT normalisation - At 6 months of treatment (MODERATE QUALITY)

One randomised study of 50 people found a benefit of Interferon alpha plus lamivudine versus lamivudine on the following outcomes:

Undetectable HBV DNA - At 24 months of treatment (MODERATE QUALITY)

ALT normalisation - At 24 months of treatment (MODERATE QUALITY)

Virological breakthrough - At 24 months of treatment (MODERATE QUALITY)

Virological resistance - After 6 months of follow up (MODERATE QUALITY)

One randomised study of 80 people found no difference between Interferon alpha plus lamivudine versus lamivudine on the following outcomes:

Undetectable HBV DNA - At 6 months of treatment (LOW QUALITY)

One randomised study of 50 people found no difference between Interferon alpha plus lamivudine versus lamivudine on the following outcomes:

Discontinued due to adverse events - At 24 months of treatment (VERY LOW QUALITY)

One randomised study of 78 people found no difference between Interferon alpha plus lamivudine versus lamivudine on the following outcomes:

Undetectable HBV DNA - After 27 months of follow up (VERY LOW QUALITY)

ALT normalisation - After 27 months of follow up (VERY LOW QUALITY)

Virological breakthrough - At 12 months of treatment (VERY LOW QUALITY)

Histological improvement - At 12 months of treatment (VERY LOW QUALITY)

Two randomised studies of 128 people found a benefit of Interferon alpha plus lamivudine versus lamivudine on the following outcomes:

Undetectable HBV DNA - At 12 months of treatment (LOW QUALITY)

Virological resistance - At 12 months of treatment (MODERATE QUALITY)

Two randomised studies of 128 people found no difference between Interferon alpha plus lamivudine versus lamivudine on the following outcomes:

ALT normalisation - At 12 months of treatment (MODERATE QUALITY)

Two randomised studies of 128 people found a benefit of Interferon alpha plus lamivudine versus lamivudine on the following outcomes:

Virological breakthrough (MODERATE QUALITY)

Two randomised studies of 128 people found no difference between Interferon alpha plus lamivudine versus lamivudine on the following outcomes:

Undetectable HBV DNA - After 6 months of follow up (VERY LOW QUALITY)

ALT normalisation - After 6 months of follow up (LOW QUALITY)

Three randomised studies of 162 people found a benefit of Interferon alpha plus lamivudine versus lamivudine on the following outcomes:

Virological resistance (MODERATE QUALITY)

11.1.6.4 Combination therapy in achieving remission of the activity of CHB for lamivudine-resistant adults

Two randomised studies of 126 people found a benefit of Adefovir plus lamivudine versus lamivudine on the following outcomes:

Undetectable HBV DNA at end of treatment (MODERATE QUALITY)

ALT normalisation at end of treatment (MODERATE QUALITY)

HBeAg loss at end of treatment (MODERATE QUALITY)

Resistance at end of treatment (VERY LOW QUALITY)

Two randomised studies of 126 people found no difference between Adefovir plus lamivudine versus lamivudine on the following outcomes:

HBeAg seroconversion at end of treatment (VERY LOW QUALITY)

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One randomised study of 39 people found no difference between Adefovir plus lamivudine versus adefovir on the following outcomes:

Reduction in HBV DNA (assessed at the end of 48 weeks treatment) (LOW QUALITY)

% of people with undetectable HBV DNA (<1000 copies/ml) (assessed at the end of 48 weeks treatment) (VERY LOW QUALITY)

% of people with HBeAg loss (assessed at the end of 48 weeks treatment) (VERY LOW QUALITY)

% of people with HBeAg seroconversion (assessed at the end of 48 weeks treatment) (VERY LOW QUALITY)

% of people with ALT normalisation (assessed at the end of 48 weeks treatment) (VERY LOW QUALITY)

% of people withdrawn due to adverse events (MODERATE QUALITY)

One randomised study of 105 people found no difference between Emtricitabine plus tenofovir versus tenofovir on the following outcomes:

HBV DNA <400 copies/mL at 24 weeks of therapy (MODERATE QUALITY)

11.1.6.5 Combination therapy in achieving remission of the activity of CHB for coinfected adults

One randomised study of 61 people found a benefit of Pegylated interferon alpha-2a plus adefovir versus adefovir on the following outcomes:

Clearance of HDV RNA end of 48 weeks treatment (MODERATE QUALITY)

Clearance of HDV RNA after 24 weeks follow up (MODERATE QUALITY)

% of people with ALT normalisation (assessed at the end of 48 weeks treatment) (MODERATE QUALITY)

% of people with ALT normalisation (assessed at the end of 24 week follow up) (LOW QUALITY)

……

One randomised study of 60 people found no difference between Pegylated interferon alpha-2a plus adefovir versus Pegylated interferon alpha-2a on the following outcomes:

Clearance of HDV RNA end of 48 weeks treatment (MODERATE QUALITY)

Clearance of HDV RNA after 24 weeks follow up (MODERATE QUALITY)

% of people with ALT normalisation (assessed at the end of 48 weeks treatment) (MODERATE QUALITY)

% of people with ALT normalisation (assessed at the end of 24 week follow up) (VERY LOW QUALITY)

……..

One randomised study of 26 people found no difference between Interferon alfa-2b plus lamivudine versus interferon alfa-2b on the following outcomes:

% of people with detectable HDV DNA (assessed at the end of 48 weeks treatment) (VERY LOW QUALITY)

% of people with ALT normalization (assessed at the end of 48 weeks treatment) (VERY LOW QUALITY)

% of people with ALT normalization (assessed at the end of 96 weeks follow up) (LOW QUALITY)

Mortality (96 weeks follow up) (VERY LOW QUALITY)

% of people who underwent liver transplantation (assessed at the end of 96 weeks follow up) (VERY LOW QUALITY)

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One randomised study of 31 people found a benefit of interferon alfa-2b plus lamivudine versus lamivudine on the following outcomes:

% of people with undetectable HDV DNA (assessed at the end of 12 months treatment) (LOW QUALITY)

% of people with ALT normalization (assessed at the end of 12 months treatment) (LOW QUALITY)

One randomised study of 31 people found no difference between interferon alfa-2b plus lamivudine versus lamivudine on the following outcomes:

% of people with detectable HDV DNA (assessed at the end of 6 months follow up) (LOW QUALITY)

% of people with ALT normalization (assessed at the end of 6 months follow up) (VERY LOW QUALITY)

11.1.6.6 Sequential antiviral treatment for children with CHB

One randomised trial of 122 HBeAg positive children suggested that interferon alpha alone may be harmful on the proportion of children with HBeAg loss and HBeAg seroconversion when compared to sequential treatment of lamivudine alone followed by interferon alpha plus lamivudine followed by lamivudine alone as assessed at the end of 6 months of treatment (VERY LOW QUALITY).

One randomised trial of 122 HBeAg positive children suggested that interferon alpha alone may be harmful on reducing the proportion of children with undetectable HBV DNA (unclear threshold) when compared to sequential treatment of lamivudine alone followed by interferon alpha plus

lamivudine followed by lamivudine alone as assessed at the end of 6 months of treatment (LOW QUALITY).

One randomised trial of 122 HBeAg positive children suggested that interferon alpha alone may be neither beneficial nor harmful when compared to sequential treatment of lamivudine alone followed by interferon alpha plus lamivudine followed by lamivudine alone for the following outcomes:

- the proportion of children with HBsAg seroconversion as assessed at the end of 6 months of treatment (VERY LOW QUALITY)
- the proportion of children with HBeAg loss as assessed at 6 months follow up (VERY LOW QUALITY)
- the proportion of children with HBeAg seroconversion as assessed at 6 and 12 months follow up (VERY LOW QUALITY)

One randomised trial of 122 HBeAg positive children suggested that interferon alpha alone may be harmful on reducing the proportion of children with undetectable HBV DNA (unclear threshold) when compared to sequential treatment of lamivudine alone followed by interferon alpha plus lamivudine followed by lamivudine alone as assessed at 6 and 12 months follow up. (LOW QUALITY)

One randomised trial of 122 HBeAg positive children suggested that interferon alpha alone may be harmful on the proportion of children with HBeAg loss and ALT normalisation when compared to sequential treatment of lamivudine alone followed by interferon alpha plus lamivudine followed by lamivudine alone as assessed at 12 months follow up. (VERY LOW QUALITY)

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One randomised trial of 122 HBeAg positive children suggested that interferon alpha plus lamivudine followed by lamivudine alone may be better than interferon alpha alone for the following outcomes:

- the proportion of children with HBeAg loss (6 months) (LOW QUALITY)
- the proportion of children with HBeAg seroconversion (6 months) (LOW QUALITY)
- undetectable HBV DNA (unclear threshold) (6 months) (MODERATE QUALITY)
- the proportion of children with HBeAg seroconversion (6 months follow up) (LOW QUALITY)
- undetectable HBV DNA (unclear threshold) (6 months follow up) (MODERATE QUALITY)
- undetectable HBV DNA (unclear threshold) (12 months follow up) (LOW QUALITY)
- ALT normalisation (12 months follow up) (LOW QUALITY)

One randomised trial of 122 HBeAg positive children suggested that interferon alpha plus lamivudine followed by lamivudine alone may be neither beneficial nor harmful compared with interferon alpha alone for the following outcomes:

- the proportion of children with HBsAg seroconversion (6 months) (VERY LOW QUALITY)
- the proportion of children with HBeAg loss (6 months follow up) (LOW QUALITY)
- the proportion of children with HBeAg loss (12 months follow up) (LOW QUALITY)
- the proportion of children with HBeAg seroconversion (12 months) (LOW QUALITY)

Two randomised trials of 152 HBeAg positive children suggested that combination treatment of interferon alpha plus lamivudine followed by lamivudine alone may be neither beneficial nor harmful when compared to sequential treatment of lamivudine alone followed by interferon alpha plus lamivudine followed by lamivudine alone for the following outcomes:

- the proportion of children with HBeAg loss (12 months) (LOW QUALITY)
- the proportion of children with HBeAg seroconversion (12 months) (LOW QUALITY)
- the proportion of children with HBsAg clearance (12 months) (VERY LOW QUALITY)
- the proportion of children with HBsAg seroconversion as assessed at 12 months (VERY LOW QUALITY)
- the proportion of children with undetectable HBV DNA (unclear threshold) assessed at 12 months (VERY LOW QUALITY).
- Clearance of HBeAg (18 months) (LOW QUALITY)
- Seroconversion to anti-HBe (18 months) (LOW QUALITY)
- Undetectable HBV DNA (18 months) (VERY LOW QUALITY)

One randomised trial of 120 HBeAg positive children suggested that combination treatment of interferon alpha plus lamivudine be beneficial on the proportion of children with HBeAg loss when compared to sequential treatment of lamivudine alone followed by interferon alpha plus lamivudine followed by lamivudine alone as assessed at 24 months (follow up) (MODERATE QUALITY).

One randomised trial of 120 HBeAg positive children suggested that combination treatment of interferon alpha plus lamivudine be beneficial on the proportion of children with ALT normalisation when compared to sequential treatment of lamivudine alone followed by interferon alpha plus lamivudine followed by lamivudine alone at 24 months (follow up) (MODERATE QUALITY).

One randomised trial of 120 HBeAg positive children suggested that combination treatment of interferon alpha plus lamivudine may be neither beneficial nor harmful on the proportion of children with seroconversion to anti-HBe (24 months) (LOW QUALITY) or undetectable HBV DNA (24 months) (LOW QUALITY).

One randomised trial of 32 HBeAg positive children showed that combination treatment of interferon alpha plus lamivudine is neither beneficial nor harmful on the following outcomes:

- ALT normalisation (12 months) (LOW QUALITY)
- Clearance of HBsAg (18 months) (VERY LOW QUALITY)
- Seroconversion to anti-HBs (18 months) (VERY LOW QUALITY)
- ALT normalisation (18 months) (LOW QUALITY)

One randomised trial of 177 HBeAg positive children showed that simultaneous combination treatment of interferon alpha plus lamivudine is better than sequential LAM alone 2 months then adding IFN alpha 2a (6 months) on the following outcomes:

- Anti-HBe seroconversion (12 months) (MODERATE QUALITY)
- Anti-HBe seroconversion (18 months) (MODERATE QUALITY)
- ALT normalisation 24 months (MODERATE QUALITY)
- Anti-HBe seroconversion (24 months) (MODERATE QUALITY)
- Undetectable HBV DNA (24 months) (MODERATE QUALITY)

One randomised trial of 177 HBeAg positive children showed that combination treatment of interferon alpha plus lamivudine is neither beneficial nor harmful on the following outcomes:

- ALT normalisation (12 months) (LOW QUALITY)
- Undetectable HBV DNA (12 months) (MODERATE QUALITY)
- Breakthrough HBV DNA (12 months) (VERY LOW QUALITY)
- ALT normalisation (18 months) (MODERATE QUALITY)
- Undetectable HBV DNA (18 months) (MODERATE QUALITY)
- Breakthrough HBV DNA (18 months) (VERY LOW QUALITY)
- Breakthrough HBV DNA (24 months) (VERY LOW QUALITY)
- Anti-HBs seroconversion (24 months) (VERY LOW QUALITY)

11.1.7 Economic evidence statements

- No cost-utility analyses were identified comparing all interventions and possible sequences of interest in the treatment of patients with chronic hepatitis B
- One study found that in a population of patients with lamivudine-resistant CHB, a strategy of switching to or adding in tenofovir was likely to be cost-effective, with incremental cost-effectiveness ratios of £14,051 and £18,501 compared to no treatment, respectively. These strategies both represent better value for NHS resources than a switch to entecavir, adefovir and a combination of adefovir and lamivudine. This study was partially applicable and had minor limitations.
- One study found that in a population of patients with lamivudine-resistant CHB, a strategy of switching to entecavir was likely to be less costly and more effective than a strategy of switching to adefovir; however this study did not account for treatment resistance with either entacavir or adefovir. This study was partially applicable and had potentially serious limitations.
- One study found that a strategy of starting with tenofovir and then switching to or adding in lamivudine was likely to be cost-effective, with incremental cost-effectiveness ratios of £18,980 and £19,600 compared to a strategy of starting with lamivudine and switching to tenofovir, respectively. Compared to the strategy of lamivudine followed by combination lamivudine and tenofovir, the strategy of initial tenofovir followed by the combination tenofovir and lamivudine was also likely to be considered cost effective, with an ICER of £5,400. This study was partially applicable and had minor limitations.
- One study found that a strategy of starting with tenofovir and then adding in lamivudine and switching to entecavir was unlikely to be cost effective at willingness to pay thresholds of £20,000 and £30,000 per QALY, although there was uncertainty in this conclusion due to very small differences in additional cost and additional health gain compared a strategy of tenofovir followed by a combination of tenofovir and lamivudine. This study was partially applicable and had minor limitations.
- One study found that a strategy of starting with pegylated interferon-α 2a followed by lamivudine and then followed by adefovir as salvage therapy if lamivudine resistance developed was unlikely to be cost effective at a willingness to pay threshold of £20,000 per QALY gained; however, there was uncertainty in this result driven by the discounting rate applied to future costs and benefits. When future costs were discounted more and benefits discounted less, the strategy was likely to be highly cost-effective. This study was partially applicable and had potentially serious limitations.
- One study found that a strategy of starting with pegylated interferon- α 2a followed by a switch to adefovir was unlikely to be cost effective compared to a strategy of switching to lamivudine with or without adefovir salvage therapy if lamivudine resistance developed. This study was partially applicable and had potentially serious limitations.

- The results of the novel economic analysis show that Pegylated interferon alfa 2a is the most cost effective treatment as first line for the treatment of chronic hepatitis B infection. If patients do not respond to interferon treatment or undergo seroreversion or viral reactivation after treatment with pegIFN, then Tenofovir is the most cost effective treatment in HBeAg positive patients. An increased efficacy of entecavir in negative patients is also observed. There is a great deal of error in these estimates and it is hard to say with absolute certainty that tenofovir is more cost effective than entecavir; however, the reduced cost of tenofovir makes this more likely. If a patient does not respond to tenofovir in a very small number of patients, then adding in Lamivudine is likely to be cost effective. The cost of entecavir means that adding entecavir to tenofovir is unlikely to be cost effective.

11.1.8 Health economic modelling

11.1.8.1 Model overview

A summary of the novel economic evaluation that was conducted in order to answer this question can be found below. For the full methods and results please refer to Appendix I.

Population

The model was developed to consider a hypothetical population of HBeAg positive, nucleos(t)ide-naïve adults (aged ≥ 18 years) with detectible HBV DNA and evidence of active liver disease for whom antiviral treatment (interferon or nucleos(t)ide therapy) is considered appropriate, and a hypothetical population of HBeAg negative adults with detectable HBV DNA.

Comparators

The model was developed to evaluate the cost-effectiveness different monotherapies and combination nucleos(t)ide treatments after a prescribed course of peg-IFN α2a or following the development of drug resistance to the initial nucleos(t)ide analogues (NAs) therapy. In practice, there are several factors which influence the selection of sequential treatment options. Based on *in vitro* and *in vivo* studies, it is well recognised that resistance to LAM confers cross-resistance to other nucleosides that share the same site of action (L-Nucleosides) and reduces sensitivity to ETV (Table 194). Conversely, mutants that are resistant to ADV generally remain sensitive to L-nucleosides and ETV (Table 194). When patients are treated sequentially with drugs that have overlapping resistance profiles, the second therapy is not only less effective, but may also lead to multidrug resistance.[113] Another factor guiding the selection of appropriate treatment alternatives is that certain drugs may cause renal toxicity when used in combination (Adefovir and Tenofovir).

Four rules were laid down prior to selecting the treatments to go into the analysis:

1. ADV would not be part of any treatment sequence on the basis that TDF, the other drug that targets the same molecular site, is both cheaper and more effective.
2. No treatment sequence would be used that would confer a risk of toxicity when starting the second treatment.
3. No treatment sequence would be used that would confer cross resistance between the first and second treatment.
4. No treatment sequence that used LAM alone (i.e. not in combination) would be evaluated as the rate of resistance is too high (80% over five years) for it to be considered in regular practice. It may however be used in conjunction with other treatments as this prevents the increase of resistance.

If a patient infected with virus develops resistance to the second drug, it is assumed that they stop all antiviral treatment (receiving best supportive care from then onwards).

Combinations of NAs were not included as first line therapies within the model. Because peg-IFN α2a plus LAM as first line therapy was evaluated in trials included within the clinical review, the GDG decided to include this strategy within the model. Because there have been no trials of peg-IFN α2a plus newer NAs for treatment naïve patients, these combinations were not included in the model.

Peg-IFN α2b and emtricitabine + TDF (Emtricitabine plus tenofovir) were not included as comparators in the model because there are currently no published RCTs of Peg-IFN α2b or Emtricitabine plus tenofovir compared to any other therapy included in the clinical review. Therefore, these drugs could not be included in the network meta-analysis (see Appendix J). Telbivudine is not included as a comparator in the model as it is not currently recommended as part of the treatment pathway for patients with hepatitis B (TA 154).

Table 194: Antiviral cross resistance in CHB – From Zoulim 2012[113] and Zoulim & Locarnini 2009[112]

Pathway	Mutation variant	LMV	ETV	ADV	TFV
	Wild type	S	S	S	S
L-nucleoside (LMV)	M204I/V	R	I	S	S
Acyclic phosphate (ADV)	N236T	S	S	R	I
Shared (LMV, ADV)	A181T/V	R	S	R	I
Double (ADV, TFV)	A181T/V + N236T	R	S	R	R
D-Cyclopentane (ETV)	L180M + M204V/I ± I169 ± T184	R	R	S	S

I = intermediate sensitivity; R = resistant; S = sensitive. Telbivudine has been omitted from the original table as it is not a comparator in our model (as per TA 154).

Table 195: Comparators included in the model

#	Sequential drug therapy (add-on or monotherapy)
	No treatment (placebo)
2	Pegylated interferon alfa 2a → Tenofovir → Entecavir
3	Pegylated interferon alfa 2a → Entecavir → Tenofovir
4	Pegylated interferon alfa 2a → Tenofovir → Tenofovir + Lamivudine
5	Pegylated interferon alfa 2a → Tenofovir → Tenofovir + Entecavir
6	Pegylated interferon alfa 2a → Entecavir → Entecavir + Tenofovir
7	Pegylated interferon alfa 2a → Entecavir → Tenotofir + Lamivudine
8	Pegylated interferon alfa 2a+ Lamivudine → Tenofovir → Entecavir
9	Pegylated interferon alfa 2a + Lamivudine → Entecavir → Tenofovir
10	– Pegylated interferon alfa 2a + Lamivudine → Tenofovir → Tenofovir + Lamivudine
11	Pegylated interferon alfa 2a + Lamivudine → Tenofovir → Tenofovir + Entecavir
12	– Pegylated interferon alfa 2a + Lamivudine → Entecavir → Entecavir + Tenofovir
13	Pegylated interferon alfa 2a + Lamivudine → Entecavir → Tenofovir + Lamivudine
14	Tenofovir → Entecavir
15	Entecavir → Tenofovir
16	Tenofovir → Tenofovir + Lamivudine
17	Tenofovir → Tenofovir + Entecavir
18	Entecavir → Entecavir + Tenofovir

#	Sequential drug therapy (add-on or monotherapy)
19	Entecavir → Tenofovir + Lamivudine

For a full list of the excluded comparators please refer to Appendix I.

Time horizon, perspective, discount rates used

The analysis was undertaken from the perspective of the NHS and personal social services, in accordance with NICE guidelines methodology.[72] Relevant costs consisted of the cost of each antiviral drug, monitoring during therapy, and costs associated with progressive liver disease. All costs are reported in 2010/11 British pounds. The primary measure of outcome is the quality-adjusted life-year (QALY). The model was evaluated over a lifetime horizon with both costs and QALYs discounted at a rate of 3.5% per year. Alternative discount rates of 1.5% for QALYs and 3.5% for costs were explored in sensitivity analysis.

11.1.8.2 Approach to modelling

The natural history of chronic HBV infection can be divided into distinct phases of variable duration, characterised and diagnosed on the basis of HBeAg/anti-HBe serology, serum HBV DNA levels, and alanine aminotransferase (ALT) activity. In order to estimate the impact of short-term serological and virological changes on the long-term outcomes of people with CHB, a model illustrating the natural history of CHB was required. Disease progression was modelled as movements between 11 disease states of a Markov transition model (Figure 14).

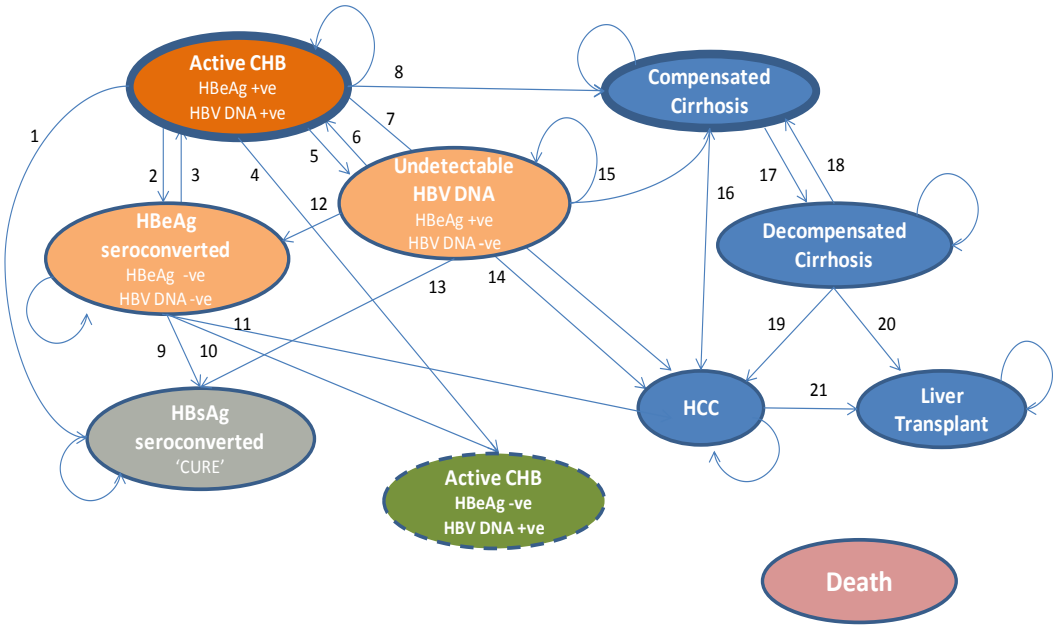
The effectiveness of each antiviral drug was estimated by applying treatment effects from the clinical review to the natural (baseline) rate of progression to HBeAg seroconversion and undetectable HBV DNA. Five-year rates of resistance to each drug were collected from the clinical literature. Upon developing resistance to a drug, patients were switched to another. HBeAg positive individuals were also eligible to 'serorevert' at rates dependant on type of antiviral drug they were treated with (Peg-IFN α2a, nucleotides, and nucleosides).

Therefore, differences between treatments are driven by the proportion of patients achieving HBeAg seroconversion, undetectable HBV DNA, rates of seroreversion, and development of drug resistance. By changing patients' serological, biochemical, histological or virological status, different antiviral drugs lead to differential rates of progression to health states in which they are more or less likely to develop progressive liver disease, HCC, liver transplantation, and death.

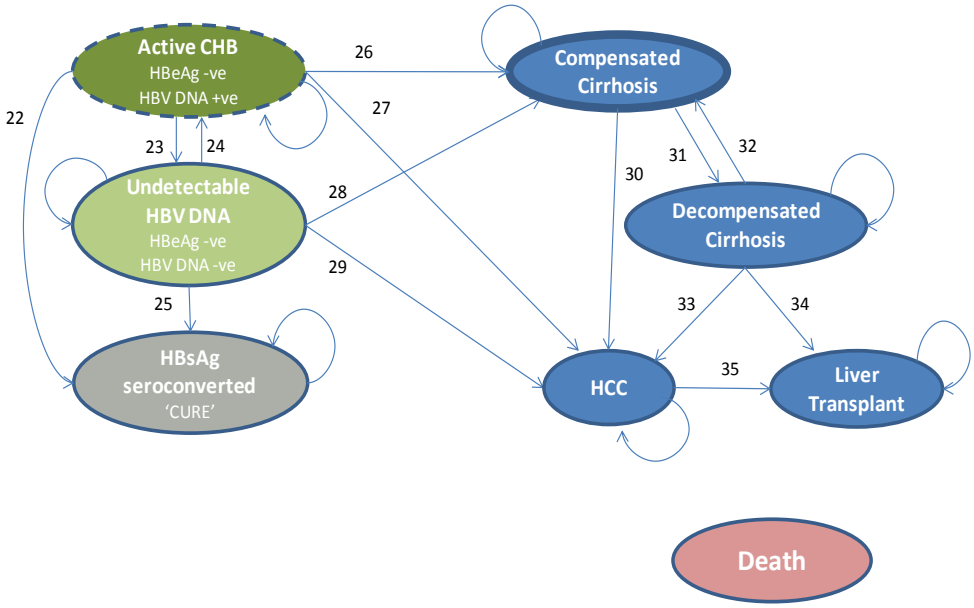
The model assumed that people may experience spontaneous improvements in their condition or reductions in viral load but the effect of treatment is to increase the probability of viral suppression and inactive carrier above the levels observed in untreated patients. The model also allows for any anti-viral treatment to have an impact on prognosis for patients in certain states, irrespective of viral load and type of treatment. Treatment has an impact on the risk of progression of disease. Patients will lose viral load at different rates depending on treatment.

Figure 14: Baseline transition probabilities

HBeAg positive CHB



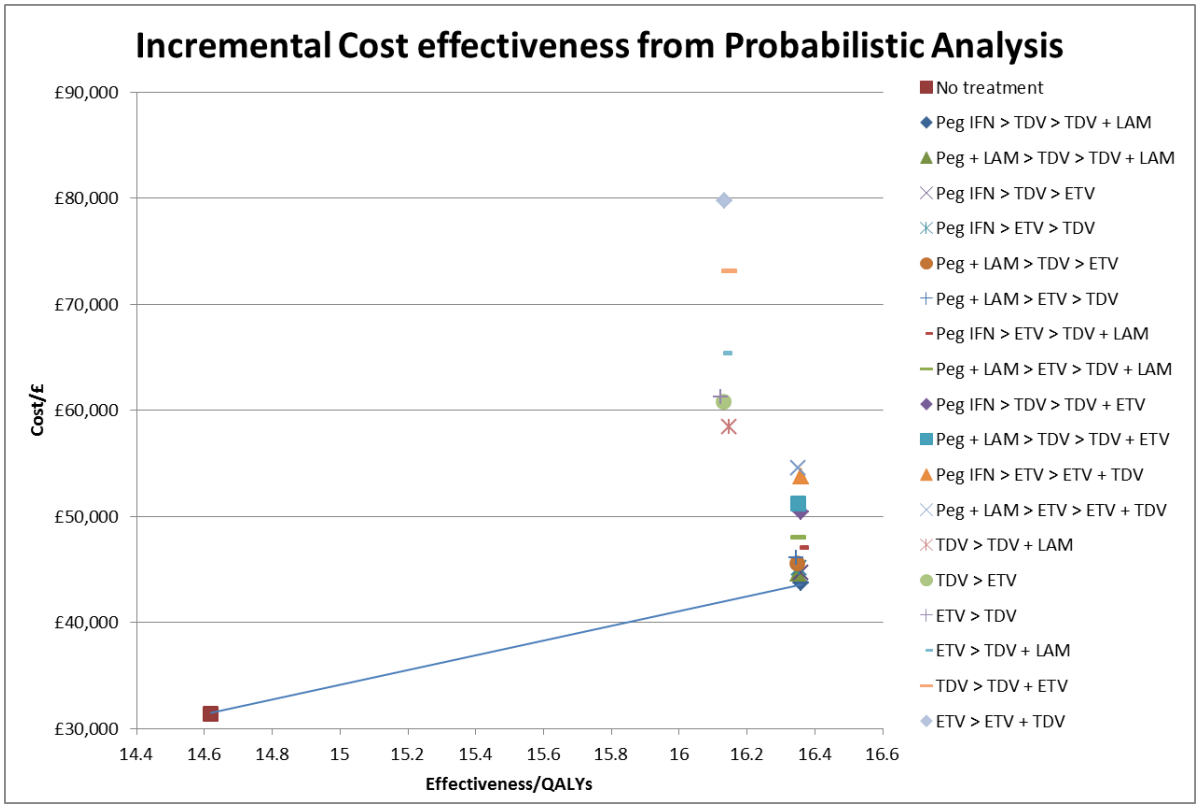
HBeAg negative CHB



11.1.8.3 Base case results

Figure 15 shows that when the costs and effects of each intervention are compared, all interventions are more effective than no treatment. However all sequences are higher cost than no treatment. The sequence that is considered most cost effective compared to the other sequences including no treatment is a sequence that includes Peg interferon, in non-responders they move onto Tenofovir as a second line treatment and then if this fails then adding Lamivudine to Tenofovir is cost effective. This result has a cost effectiveness probability of 70%. The option that has the next highest probability of being cost effective is the strategy but with peg interferon and Lamivudine to start with. This has a probability of around 24%. This means that adding Lamivudine to the Peg interferon could be effective but the two are fairly interchangeable.

Figure 15: Results of Probabilistic cost effectiveness analysis



The breakdown of results in Table 196 shows that the differences in both costs and effects between all interventions are small. The Incremental cost effectiveness ratio of the cost effective comparator Peg IFN > TDF > TDF + LAM is £7,488, which is well below the standard £20,000 per QALY threshold. Because many of the ICERs show that treatments are dominated, producing the net monetary benefit allows us to see what options would be best if a person was intolerant of Lamivudine or Tenofovir. This shows that the Peg IFN > TDF > ETV and Peg + LAM > TDF > ETV strategies are the next best options. However the probabilistic analysis also allows us to have a minimum and maximum rank, this shows that there is a large amount of uncertainty in the results.

Table 196: Results of Probabilistic Cost Effectiveness Analysis

Strategy	Cost	Effect	ICER	NMB	Rank (Max – Min)
No treatment	£32,754	14.618			
Peg IFN > TDF > TDF + LAM	£45,794	16.359	£7,488	£281,395	1 (6-1)
Peg + LAM > TDF > TDF + LAM	£46,495	16.351	£7,930	£280,523	2 (7-1)
Peg IFN > TDF > ETV	£46,856	16.358	£8,105	£280,303	3 (7-2)
Peg IFN > ETV > TDF	£47,547	16.355	£8,516	£279,554	4 (8-2)
Peg + LAM > TDF > ETV	£47,680	16.349	£8,625	£279,292	5 (10-2)
Peg + LAM > ETV > TDF	£48,416	16.347	£9,061	£278,516	6 (10-2)
Peg IFN > ETV > TDF + LAM	£49,657	16.358	£9,713	£277,508	7 (11-4)
Peg + LAM > ETV > TDF + LAM	£50,370	16.350	£10,172	£276,627	8 (11-4)

Strategy	Cost	Effect	ICER	NMB	Rank (Max – Min)
Peg IFN > TDF > TDF + ETV	£52,767	16.359	£11,492	£274,422	9 (13-5)
Peg + LAM > TDF > TDF + ETV	£53,389	16.351	£11,908	£273,629	10 (14-4)
Peg IFN > ETV > ETV + TDF	£56,615	16.358	£13,711	£270,550	11 (15-6)
Peg + LAM > ETV > ETV + TDF	£57,250	16.350	£14,145	£269,747	12 (16-8)
TDF > TDF + LAM	£59,150	16.146	£17,271	£263,778	13 (14-7)
TDF > ETV	£61,646	16.130	£19,107	£260,958	14 (16-10)
ETV > TDF	£62,222	16.123	£19,577	£260,243	15 (16-11)
ETV > TDF + LAM	£66,223	16.135	£22,068	£256,470	16 (17-15)
TDF > TDF + ETV	£73,643	16.146	£26,753	£249,285	17 (18-15)
ETV > ETV + TDF	£80,572	16.135	£31,530	£242,121	18 (18-17)

11.1.9 Network meta analysis summary

A hierarchical Bayesian network meta-analysis (NMA) was undertaken to estimate the relative efficacy of different antiviral treatments by using all the relevant RCT evidence (both indirect and direct treatment comparisons; mono-, combination and sequential therapy) included in the clinical evidence review (conventional pairwise meta-analysis). Full NMA chapter (including NMA protocol, methods, results and discussion and Winbug codes) can be found in the appendix J. Undetectable HBV DNA (<300 copies/mL) and HBeAg seroconversion at the end of one year treatment were considered as the two most important outcomes in assessing treatment response. WinBugs version 1.4 was used for the analysis. A total of six network meta-analyses were proposed:

HBeAg positive nucleos(t)ide naïve patients with CHB

1. Undetectable HBV DNA (<300copies/mL)

2. HBeAg seroconversion

HBeAg positive lamivudine resistant patients with CHB

3. Undetectable HBV DNA (<300copies/mL)

4. HBeAg seroconversion

HBeAg negative nucleos(t)ide naïve patients with CHB

5. Undetectable HBV DNA (<300copies/mL)

HBeAg negative lamivudine resistant patients with CHB

6. Undetectable HBV DNA (<300copies/mL)

In brief, many studies reported the proportion of patients with undetectable HBV DNA using different thresholds and/or unit measures (depending on the sensitivity of the HBV DNA assay) and in order to include all the data available, a validated statistical formula (ref) was applied to perform threshold transformation to standardise the threshold to <300copies/mL. Further details of the formula can be found in x. Many studies included mixed populations of nucleos(t)ide naïve and experienced patients. To be included in the nucleos(t)ide naïve networks, at least 2/3 of the total sample must be nucleos(t)ide naïve. Sensitivity analyses were performed by including studies i) with 100% nucleos(t)ide naïve patients and ii) that reported the outcome of undetectable HBV DNA at the predefined threshold of <300copies/mL. Potential sources of heterogeneity were explored by performing sensitivity analyses, especially if significant baseline differences between the treatment arms were observed, e.g. HBV DNA and ALT levels. Lamivudine was selected as the baseline comparator for reasons discussed in the full NMA chapter (appendix J)

Results

HBeAg positive nucleos(t)ide naïve patients with CHB

Twenty-one studies were included in the network of undetectable HBV DNA (<300copies/mL). All antiviral treatments were found to be superior to placebo. Entecavir, tenofovir and telbivudine were significantly more effective than lamivudine. Tenofovir was shown to have the highest probability of

being the best treatment in achieving undetectable HBV DNA (<300 copies/mL) at the end of one year treatment, followed by (2.4%). Median proportion of adults with undetectable HBV DNA for tenofovir was 94.1% (95% credible intervals 75.7 to 98.9%. In terms of median ranking, tenofovir was ranked first followed by pegylated interferon plus lamivudine combination therapy and entecavir.

Seventeen studies were included in the network of HBeAg seroconversion. There were no statistically significant differences between the antiviral treatments in achieving this outcome at the end of one year treatment. Interferon plus lamivudine combination therapy had highest probability (50.3%) of achieving HBeAg seroconversion, followed by switching from lamivudine to lamivudine plus interferon combination therapy (32.4%) and tenofovir (7.1%). The 95% credible intervals around the median rank for all the drugs were largely overlapped.

HBeAg positive lamivudine resistant patients with CHB (section J.3.1.5 in full NMA chapter)

In the absence of trial data on tenofovir in the lamivudine resistant population and given its clinical importance in this population, a trial based on nucleos(t)ide naïve population (ref) was indirectly used to inform both networks of undetectable HBV DNA (<300copies/mL) and HBeAg seroconversion, assuming the efficacy of tenofovir is comparable between the two populations as indicated by in vivo and in vitro studies. A systematic review of in vivo and in vitro studies was performed to support this assumption (appendix J) and it showed that lamivudine mutant strains (L180M + M204V/I) were sensitive to tenofovir, as compared to wild type (no mutation/ nucleos(t)ide naïve). Seven studies were included in the network of undetectable HBV DNA (<300copies/mL) and HBeAg seroconversion.

For the outcome undetectable HBV DNA (<300copies/mL), all antiviral treatments in the networks were shown to be significantly superior to lamivudine, except for adefovir. Tenofovir had the highest probability of achieving this outcome (66.2%) followed by entecavir plus adefovir combination therapy (33.8%). Median proportion of adults with undetectable HBV DNA for tenofovir and entecavir plus adefovir combination therapy were 89% (95% credible intervals 51.8 to 98.2%) and 82.4% (95% credible intervals 42.8 to 98%), respectively. For HBeAg seroconversion, there were no statistically significant differences between the antiviral treatments and there was a lack of precision on the median ranking of treatments.

HBeAg negative nucleos(t)ide naïve patients with CHB (section J.3.1.9 in full NMA chapter)

Sixteen studies were included in the network of undetectable HBV DNA (<300copies/mL). There were no statistically significant differences in the proportion of patients achieving undetectable HBV DNA (<300copies/mL) between the antiviral treatments. All antiviral treatments were found to be significantly superior to placebo, but the ORs were imprecise as suggested by the wide 95% confidence intervals. Tenofovir was shown to have the highest probability (76.6%) of being the best treatment in achieving this outcome, followed by entecavir (18%). A lack of precision was observed in terms of median ranks of treatment.

HBeAg negative lamivudine resistant patients with CHB (section J.3.1.12 in full NMA chapter)

No network meta-analysis could be conducted because only four studies met the inclusion criteria and they did not form a connected network.

Additional details of the data on model fit or convergence and results of sensitivity analyses for all the networks can be found in the full NMA chapter (appendix J).

Discussion and conclusion

Fitting of all the models were shown to be satisfactory, as demonstrated by residual deviance and deviance information criteria. No inconsistencies were found between the data from the conventional pairwise meta-analysis and the data generated from the NMA. All the sensitivity analyses did not significantly change the results. There were a number of limitations associated with this NMA, for instance, there were limited data for certain treatments in particular tenofovir. No NMA was performed for other outcomes such as histological improvement, resistance and adverse events, all of which would be important in decision making. It is important to note that the evaluation of clinical efficacy of antiviral treatments should take into account both results of the NMA, as well as results of the conventional pair wise meta-analysis (direct evidence). The NMA did not address the sequence of antiviral therapy. In addition, chronic hepatitis B is a lifelong condition which requires long term management and most included studies only reported outcomes at 1 year of treatment. Further limitations can be found in the full NMA chapter.

Based on the RCT evidence currently available, this NMA suggests that tenofovir is associated with the highest probability of achieving undetectable HBV DNA (<300copies/mL) in HBeAg positive and negative nucleos(t)ide naïve patients and HBeAg positive lamivudine resistant patients, at 1 year among all the antiviral drugs considered. Interferon plus lamivudine combination therapy is associated with the highest probability of achieving HBeAg seroconversion at 1 year of treatment; though there is uncertainty around the results therefore they should be interpreted with caution.

11.1.10 Recommendations and link to evidence

11.1.10.1 Adults - monotherapies, combinations and sequential

Recommendations	**31. Discuss treatment options, adverse effects and long-term prognosis with the patient before starting treatment.** **32. Re-assess the person's risk of exposure to HIV before starting treatment and offer repeat testing if needed.** **33. Peginterferon alfa-2a is recommended as an option for the initial treatment of adults with chronic hepatitis B (HBeAg-positive or HBeAg-negative), within its licensed indications. [This recommendation is from Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (NICE technology appraisal guidance 96).]** **34. Entecavir, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated. [This recommendation is from Entecavir for the treatment of chronic hepatitis B (NICE technology appraisal guidance 153).]** **35. Tenofovir disoproxil, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated. [This recommendation is from Tenofovir disoproxil fumarate for the treatment of hepatitis B (NICE technology appraisal guidance 173).]**

36. **Telbivudine is not recommended for the treatment of chronic hepatitis B. [This recommendation is from Telbivudine for the treatment of chronic hepatitis B (NICE technology appraisal guidance 154).]**
37. **People currently receiving telbivudine should have the option to continue therapy until they and their clinicians consider it appropriate to stop. [This recommendation is from Telbivudine for the treatment of chronic hepatitis B (NICE technology appraisal guidance 154).]**
38. **Do not offer adefovir dipivoxil for the treatment of chronic hepatitis B.**
39. **People currently receiving adefovir dipivoxil should be offered the option to switch to a different treatment. Offer tenofovir disoproxil or entecavir depending on previous antiviral exposure:**
    - **offer tenofovir disoproxil to people with a history of lamivudine resistance.**
40. **Antiviral treatment should be initiated only by an appropriately qualified healthcare professional with expertise in the management of viral hepatitis. Continuation of therapy under shared-care arrangements with a GP is appropriate.**

Treatment sequence in adults with HBeAg-positive chronic hepatitis B and compensated liver disease

41. **Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-positive chronic hepatitis B and compensated liver disease[ll].**
42. **Consider stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and/or if HBsAg is greater than 20,000 IU/ml, and offer second-line treatment in line with recommendations 43 and 44.**
43. **Offer tenofovir disoproxil as second-line treatment to people who do not undergo HBeAg seroconversion or who relapse (revert to being HBeAg positive following seroconversion) after first-line treatment with peginterferon alfa-2a.**
44. **Offer entecavir as an alternative second-line treatment to people who cannot tolerate tenofovir disoproxil or if it is contraindicated.**
45. **Review adherence in people taking tenofovir disoproxil who have detectable HBV DNA at 48 weeks of treatment and, if appropriate, provide support in line with Medicines adherence (NICE clinical guidance 76).**

ll Avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

	o If HBV DNA remains detectable at 96 weeks, and there is no history of lamivudine resistance, consider adding lamivudine to tenofovir disoproxil. o In people with a history of lamivudine resistance, consider adding entecavir to tenofovir disoproxil. **46. Do not stop nucleoside or nucleotide analogue treatment 12 months after HBeAg seroconversion in people with cirrhosis.** **Treatment sequence in adults with HBeAg-negative chronic hepatitis B and compensated liver disease** **47. Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-negative chronic hepatitis B and compensated liver disease[mm].** **48. Offer entecavir or tenofovir disoproxil as second-line treatment to people with detectable HBV DNA after first-line treatment with peginterferon alfa-2a.** **49. Consider switching from tenofovir disoproxil to entecavir, or from entecavir to tenofovir disoproxil, as third-line treatment in people who have detectable HBV DNA at 48 weeks of treatment.** **50. Do not stop nucleoside or nucleotide analogue treatment after achieving undetectable HBV DNA and HBsAg seroconversion in patients with cirrhosis.**
Relative values of different outcomes	The GDG stated that one of the main goals of therapy for chronic hepatitis B patients is to improve survival and quality of life by preventing progression of liver disease (decompensated cirrhosis and liver failure), hepatocellular carcinoma and death. This can be achieved by suppressing HBV DNA to undetectable levels. The GDG considered HBsAg loss and/or seroconversion to be the optimal goal of antiviral treatment and these are surrogate markers of sustained response for both HBeAg positive and negative patients. However this outcome is rarely achieved, given that the trial durations were short (1 year). In HBeAg positive patients, HBeAg seroconversion is considered to be the more desirable endpoint over HBV DNA suppression and is used to guide treatment cessation.
Trade off between clinical benefits and harms	There are advantages and disadvantages of pegylated interferon and nucleos(t)ide analogues. Main advantages for pegylated interferon include the drug being given for a finite duration and the absence of resistance; for nucleos(t)ides, their ability to suppress HBV DNA; with some nucleos(t)ides being more potent than others. Main disadvantages of nucleos(t)ide analogues are the long duration of treatment and the risk of developing resistance. The GDG was aware at the outset of the guideline that there was a vast range

mm Avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

of drugs and combinations of drugs that have been used to treat people with hepatitis B, and that, in order to make recommendations for practice, they needed to have an idea of the relative benefits and harms of the different drug strategies. It was therefore decided to investigate individual comparisons, but the ultimate aim was to bring the evidence together in a network meta-analysis across all relevant comparisons, and then to use results from this analysis to inform the health economic model.

The first stage in this process was to investigate the evidence for the head to head 'pair-wise' comparisons, considering the net benefits over harms in order to assess which was the most effective of the pair. Considering pair-wise comparisons first was also important in determining and investigating inconsistencies and risk of bias in a simpler way, so that this could inform execution and interpretation of the NMA. However, in practice there were insufficient trials in any one comparison to investigate heterogeneity amongst trials reporting the same comparison.

Evidence from pair wise treatment comparisons

Most of the evidence was in HBeAg positive treatment/nucleos(t)ide naïve patients. There were 34 trials comparing antiviral monotherapies or combination treatments and 8 comparing switching or sequential strategies. There was a total of 24 plus 7 comparisons, most of which involved single trials.

In people who were HBeAg negative, there were 16 trials and 11 comparisons of monotherapies or combination therapy, with most comparisons having one trial. There were 3 trials that investigated switching.

A number of studies investigated antiviral therapies in people who had resistance to lamivudine. There were 2 studies comparing adefovir plus lamivudine versus adefovir monotherapy and 2 studies considering switching.in people who are HBeAg positive with lamivudine resistance. There was one study of switching in people who were HBeAg negative with lamivudine resistance.

Full details of all these comparisons are included in the review, but here a summary is given of results related to the following drugs:

- Peg interferon alfa 2a, with or without lamivudine – this is the preferred first line treatment recommended by the NICE technology appraisal and because of its importance as a treatment of finite duration. The evidence on other pegylated interferons and non-pegylated interferons are not given here.
- Lamivudine in comparison with placebo, in order to investigate and report on its known resistance problems, alongside its efficacy and because lamivudine has a central role in the NMA as a common comparator
- A small set of potent nucleos(t)ide monotherapies, in order to determine possible first line alternatives for people unsuited to peg interferon and to determine the best second and third line treatments
- Some combinations of drugs versus monotherapy

In people with HBeAg positive disease:

Four studies compared *lamivudine versus placebo*: one was only for 12 weeks of treatment. The evidence showed a large clinically important benefit at the end of treatment for lamivudine in terms of: the number of patients with undetectable HBV DNA, ALT normalisation, HBeAg loss, HBeAg seroconversion and histological improvement. There was no important difference in the proportion with HBsAg seroconversion. One study showed a decrease in relative effectiveness (HBeAg seroconversion) for lamivudine after 16 weeks

follow up compared with the end of treatment. Lamivudine, in comparison with placebo showed a large increase in the risk of genotypic mutation. The evidence was generally of moderate quality and was consistent across studies.

Pegylated interferon alfa 2a with or without lamivudine versus lamivudine: one large study compared these drug combinations in a 3-arm trial.

At the end of 48 weeks treatment peg interferon plus lamivudine was clinically more effective than lamivudine in terms of the number of people with undetectable DNA, but there was no clinically important difference in the number with HBeAg seroconversion, HBeAg loss and withdrawal due to adverse events. The number with ALT normalisation was a clinically important benefit in favour of lamivudine.

At 24 weeks post treatment follow up, there was a larger clinically important benefit for undetectable HBV DNA: this was due to a large decline in the number of patients with the outcome in both groups, but more so in the lamivudine monotherapy group. However, for the HBeAg seroconversion outcome, there was an increase in the number of patients achieving seroconversion in the combination group, whilst the lamivudine number was similar. The direction of effect in the number of patients with ALT normalisation was reversed at follow up.

In terms of resistance (genotypic mutation), there was a clinically important harm in people on lamivudine alone compared to the combination

For *peginterferon monotherapy in comparison with lamivudine*, a more dramatic effect was observed: the number of people with undetectable HBV DNA and normal ALT at the end of treatment both showed a clinically important benefit in favour of lamivudine, although HBeAg seroconversion and HBeAg loss showed a clinically important benefit in favour of peg interferon.

At 24 weeks follow up, however, this behaviour was changed: the direction of effect for the number of patients with each of the outcomes HBV DNA undetectable and ALT normal was reversed; this was due to a large decrease in the number with normal ALT in the lamivudine group, whereas for the DNA outcome there was a decrease for both interventions, but more so for lamivudine. The absolute risk difference at 24weeks was approximately doubled for HBeAg seroconversion and this was mainly because of increases in the peginterferon group

The absolute difference in the proportion withdrawn due to adverse events was not clinically important. The evidence from this trial was mainly of moderate quality.

Tenofovir versus adefovir: the evidence from one RCT shows that tenofovir is much more effective in achieving undetectable HBV DNA (<400copies/ml) and ALT normalisation compared to adefovir at the end of 48 weeks treatment. No clinically important difference was observed for HBsAg loss, HBeAg seroconversion, or histological improvement between the two drugs.

Entecavir versus lamivudine, adefovir, tenofovir: Entecavir may be more effective in achieving undetectable HBV DNA (<300copies/mL) compared to lamivudine at the end of 48 weeks of treatment. No difference was found for HBeAg seroconversion, ALT normalisation and histological improvement between the two drugs. Entecavir has been shown to be more effective in achieving a greater log reduction of HBV DNA and less resistance compared to lamivudine. Compared to adefovir, entecavir was shown to be more effective in achieving undetectable HBV DNA (<300copies/mL) and may be more effective in achieving ALT normalisation at the end of 48 weeks treatment. No difference was observed for HBeAg loss/seroconversion between the two drugs.

Compared to entecavir, tenofovir may be more effective in achieving undetectable HBV DNA and HBeAg seroconversion and no difference was

observed for HBsAg loss and ALT normalisation between the two drugs at the end of 24 weeks treatment.

One large study compared the combination of entecavir plus tenofovir versus entecavir alone. The combination was more clinically effective than entecavir alone for the outcome of undetectable HBV DNA, but the monotherapy was clinically more effective for ALT normalisation. There was potentially a clinically important benefit in HBeAg loss, favouring monotherapy. There was no clinically important difference between the drugs for HBeAg seroconversion or HBsAg loss or discontinuation due to adverse events or virologic breakthrough, although this was worse for the combination. .

Sequential drugs: the GDG did not consider any of the strategies in the trials in the sequential review to be useful for informing practice, so these were not considered in discussions. For lamivudine refractory HBeAg positive patients, studies have suggested that switching from lamivudine to entecavir is effective in achieving undetectable HBV DNA (<300-<400copies/mL) and ALT normalisation compared to continuing lamivudine monotherapy at the end of 52 weeks treatment. Switching from lamivudine to lamivudine plus adefovir combination therapy maybe be more effective in achieving undetectable HBV DNA (<300copies/mL) compared to switching from lamivudine to entecavir at the end of 12 months treatment. No difference was observed in other outcomes.

HBeAg positive patients with lamivudine resistance

Data have suggested that entecavir is effective in achieving ALT normalisation compared to placebo at the end of 12 weeks treatment. Treatment duration was too short therefore results should be interpreted with caution. Emtricitabine plus tenofovir combination therapy was effective in achieving undetectable HBV DNA compared to tenofovir alone at the end of 24 weeks treatment but this finding disappeared at the end of 48 weeks treatment. The trial has a small sample size. Therefore, results should be interpreted with caution. No difference was observed between adefovir plus lamivudine combination therapy and adefovir alone for all the outcomes assessed at the end of 48 weeks treatment.

HBeAg negative treatment/nucleos(t)ide naïve patients

Evidence from one trial has showed that entecavir gave a clinically important benefit in achieving undetectable HBV DNA and (separately) ALT normalisation, compared to lamivudine at the end of 48 weeks treatment; there was a substantially larger incidence of resistance (both YMDD mutation and viral breakthrough) after 24 months treatment.

For pegylated interferon alfa 2a, one large trial showed that peg monotherapy in comparison with lamivudine gave a clinically important benefit in favour of lamivudine at the end of 48 weeks treatment for the HBV DNA undetectable outcome. This was reversed after 24 weeks follow up, mainly because of a greater reduction in the number of people with undetectable HBV DNA in the lamivudine group compared to the peginterferon group. ALT normalisation showed a similar behaviour, but this was partly because of an increase in the number of people ALT normal between the end of treatment and follow up.

In the comparison of the combination of peginterferon plus lamivudine versus lamivudine, ALT normalisation changed direction of effect between the end of therapy and 24 weeks follow up and the risk ratio for people with undetectable HBV DNA increased on follow up.

Comparing to adefovir, tenofovir is highly effective in achieving log reduction of HBV DNA and undetectable HBV DNA at the end of 48 weeks treatment.

There was no clinically important difference in the number of people with HBeAg seroconversion. No patients in the study had resistance at the end of 48 weeks.

For responders treated with lamivudine for more than 3 years, there was no difference in the proportion of undetectable HBV DNA between switching from lamivudine to entecavir and continuing lamivudine. However, the group that continued lamivudine was associated with a higher incidence of resistance. For HBeAg negative patients with previous treatment with entecavir with undetectable HBV DNA, switching from entecavir to lamivudine was ineffective in achieving undetectable HBV DNA, compared to those who continued entecavir at the end of 96 weeks treatment.

Network meta-analysis (NMA)

Six network meta-analyses were proposed, and five conducted, to obtain self consistent comparative effects between interventions and to provide rankings of the most effective treatments for two particular outcomes, HBV DNA and HBeAg seroconversion (only in HBeAg positive patients). Trial data for the comparisons of pegylated interferon, lamivudine and their combination were included in the NMA, using the results at 48 weeks. However, as discussed above, the optimum time of measurement for peginterferon regimens is 24 weeks following end of treatment. Therefore the NMAs underestimate the effectiveness of peginterferon and peginterferon plus lamivudine. To balance this, relative risks from the trials using values at 24 weeks were used in the economic model.

The NMA findings were as follows:

For people who are HBeAg positive , with the outcome undetectable HBV DNA at 12 months (21 trials), tenofovir had by far the greatest probability of being the most effective treatment (96%), followed by the combination of peg interferon 2a plus lamivudine (2.4%), then entecavir (0.6%).

For people who are HBeAg positive, with the outcome HBeAg seroconversion at 12 months (17 trials), interferon plus lamivudine had the greatest probability of being the most effective intervention (50%), followed by the sequence lamivudine to lamivudine plus interferon (32%), then the third highest probability was found for tenofovir (7%)

For people who are HBeAg positive with lamivudine resistance, with the outcome undetectable HBV DNA at 12 months (7 trials), tenofovir had the greatest probability of being the most effective intervention (66%), followed by entecavir plus adefovir (34%)

For people who are HBeAg positive with lamivudine resistance, with the outcome HBeAg seroconversion at 12 months (6 trials), tenofovir had the greatest probability of being the most effective intervention (40%), followed by entecavir plus adefovir (31%)

For people who are HBeAg negative for the outcome undetectable HBV DNA at 12 months (13 trials), tenofovir had the greatest probability of being the most effective outcome (77%), followed by entecavir (18%)

For people who are HBeAg negative with lamivudine resistance for the outcome undetectable HBV DNA at 12 months, there were only four trials and they did not form a linked network

On the basis of the clinical evidence, the GDG did not wish to recommend lamivudine in the UK because of its resistance problems and they noted that adefovir was clearly much less effective than tenofovir. They therefore decided not to model either adefovir or lamivudine monotherapy as antiviral therapy options: both of these decisions update the adefovir part of TA 96, which this guideline was charged to do.

Economic considerations	There was quite some uncertainty in the economic literature available on the initial therapy for patients with HBeAg positive or negative chronic hepatitis B. All the included studies had both potentially serious limitations and partial applicability, with none of them being a cost-utility analysis. For this reason, the GDG decided to give more weight to the results of the novel economic analysis which show that pegylated interferon alfa 2a is the most cost effective treatment as first line therapy for chronic hepatitis B infection. If patients do not respond to interferon treatment or undergo later seroreversion or viral reactivation, then tenofovir is the most cost effective treatment in HBeAg positive patients. An increased efficacy of entecavir in negative patients is also observed. There is a large amount of error in these estimates and it is hard to say with absolute certainty whether tenofovir is more cost effective than entecavir; however, the reduced cost of tenofovir makes this more likely. If a patient does not respond to tenofovir, then adding in lamivudine or switching to entecavir are both likely to be cost effective. The GDG felt that the model accurately represented the disease progression and that the sequences of treatments represented available care in the UK. The results of the model are therefore judged to be a useful indicator of cost effectiveness of different treatments. The review of published economic evidence found one study showing that entecavir was the most cost-effective initial treatment while a different study showed that tenofovir was the likely to be cost-effective. These conflicting results show the uncertainty on the cost-effectiveness of either treatment over the other. Adefovir was not included in the model as tenofovir is more effective and less costly. Some of the studies included in the economic review looked at strategies with adefovir (alone or in combination) and all concluded that other strategies not containing adefovir were cost-effective.
Quality of evidence	Monotherapy The majority of the evidence on HBeAg positive patients is of moderate to high quality . The only trial comparing tenofovir with adefovir (both HBeAg positive and negative) provides moderate to high quality evidence for all outcomes including undetectable HBV DNA, log reduction of HBV DNA and ALT normalisation. The evidence for entecavir versus lamivudine in HBeAg negative patients is of moderate to low quality Lamivudine resistant Many studies examining combination therapies gave rise to evidence of low to very low quality. The evidence on pegylated interferon and pegylated interferon plus lamivudine combination versus lamivudine is of moderate to very low quality Most of the evidence in the sequential therapy review was of low to very low quality, except for the trial of switching from lamivudine to entecavir versus lamivudine in HBeAg positive lamivudine refractory patients, which gives evidence of high to moderate quality. The GDG recognised the lack of evidence on some nucleos(t)ides such as tenofovir and noted there are only few follow up studies across all antiviral drugs. The GDG recognised the limitations of reporting different HBV DNA thresholds (the lowest limit of detection) by the trials and observed that this mainly reflects the improvement in sensitivity of HBV DNA assay over time. The GDG were aware that there is variability between studies with regards to study populations; a number of studies contained a mixed population of HBeAg positive and negative with different proportions of patients with cirrhosis across studies.

	Quality of the NMA Data for some treatment comparisons included in the NMA are limited, for example, there was only one trial evaluating tenofovir and the GDG recognised that problems with individual trials could bias the whole network. A number of studies on combination therapies and sequential therapies were not included as they did not meet the inclusion criteria defined in the NMA protocol (e.g. different treatment durations, majority of patients were nucleos(t)ide experienced and drug sequences were no longer used in clinical practice). Undetectable HBV DNA and HBeAg seroconversion were chosen as two of the most important clinical outcomes; NMA could not be performed for other outcomes such as resistance, side effects and ALT normalisation which also need to be taken into consideration. The GDG thought that side effects were rare for nucleos(t)ides and little or no resistance has been observed for more potent drugs like entecavir and tenofovir. Outcomes like histological improvement and HBsAg loss/seroconversion are not commonly reported by the trials. The NMA on the outcome of undetectable HBV DNA and the use of transformation to a threshold of 300 copies/ml could have led to errors and had the added complication of producing zero events in a number of studies, which was adjusted for in the analysis. It was noted however, that for the HBeAg positive patients more importance is placed on the HBeAg seroconversion outcome, and a lack of sensitivity to the HBV DNA results was demonstrated in the modelling.
Other considerations	The recommendations were based on both the evidence and the clinical opinion of the GDG. • The GDG acknowledged that the choice of antiviral treatment is influenced by a number of factors, including: 1) adverse events (e.g. discomfort or any kind of intolerance caused by pegylated interferon injections) and side effects such as renal toxicity with entecavir and tenofovir; 2) development of resistance (e.g. lamivudine resistance); 3) individual patient preference after discussion with clinicians about the benefits and harms of each antiviral drug; 4) cross-resistance of antiviral drugs. All of these factors should be taken into consideration when making a decision as to which drug to offer. The GDG was mindful that treatment recommendations should be considered in conjunction with the recommendations on thresholds for treatment, monitoring and stopping treatment and patient information on the different types of treatment for CHB - including awareness of the potential for short term (one-off) treatment with peg interferon versus potential for lifetime treatment with nucleo(t)sides, and side effects of drugs including resistance, and with reference to the patient's personalised care plan (Chapter 6). There is no evidence of drug resistance to tenofovir; however the GDG recognised that there are no trials with long term follow up (5-10 years follow up) and further research is required. The clinical evidence has not investigated all possible combinations of drugs and it may be that other combinations of drugs will provide a better combination of efficacy, whilst avoiding the development of resistance. The GDG noted two recent reports, one reviewing the evidence for cases of renal dysfunction in people with human immunodeficiency virus (HIV) infection receiving tenofovir[38]; and the other reporting proximal renal tubular

	dysfunction (RTD) in a small study in people with hepatitis B[33]. In the latter study RTD was observed in one of four patients who were treated with tenofovir after failing to meet the inclusion criteria of an adefovir RCT (i.e. the patients were probably not typical of people with hepatitis B). The GDG considered it important to investigate the long term safety of tenofovir, including the need for routine monitoring and therefore made a research recommendation.

11.1.10.2 Children and young people with chronic hepatitis B and compensated liver disease

Recommendations	**51. Discuss treatment options, adverse effects and long-term prognosis with the child or young person and with parents or carers (if appropriate) before starting treatment.** **52. Re-assess the child or young person's risk of exposure to HIV before starting treatment and offer repeat testing if necessary.** **53. Consider a 48-week course of peginterferon alfa-2a as first-line treatment in children and young people with chronic hepatitis B and compensated liver disease[nnoo].** **54. Consider a nucleoside or nucleotide analogue as second-line treatment in children and young people with detectable HBV DNA after first-line treatment with peginterferon alfa-2a[pp].**
Relative values of different outcomes	The GDG ideally considered HBsAg loss and/or seroconversion to be the optimal goal of antiviral treatment, but noted that this is rarely achieved. In HBeAg positive patients, HBeAg seroconversion was considered to be the more desirable endpoint over HBV DNA suppression. For children, particularly, the GDG regarded the absence of drug resistance to be a very important outcome important outcome, in view of the likely long duration of treatment over the child's lifetime.
Trade off between clinical benefits and harms	For an interferon naïve children population with CHB, 24 weeks treatment with interferon alpha 2b was found to be beneficial in terms of reducing the proportion of children with detectable HBV DNA and HBeAg loss compared to non treated children (Sokal 1998). Similarly, the combination of interferon alpha plus lamivudine was found to reduce the proportion of children with detectable HBV DNA and to improve the rates of HBeAg seroconversion when compared to interferon alone in a treatment naïve population (Dikici, 2004). Furthermore, the evidence on nucleos(t)ide use for previously treated children with CHB showed that both adefovir and lamivudine were beneficial in reducing the proportion of children with detectable HBV DNA, improving the rates of HBeAg loss and seroconversion and achieving ALT normalization when compared to placebo (Jonas 2002, Jonas 2008). However, as expected more children developed resistance after being treated with lamivudine (Jonas 2002) compared to those treated with placebo.

[nn] At the time of publication (June 2013), peginterferon alfa-2a did not have a UK marketing authorisation for use in children for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

oo Avoid use of peginterferon alfa-2a in pregnancy uless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy.

[pp] At the time of publication (June 2013), peginterferon alfa-2a, entecavir and tenofovir disoproxil did not have a UK marketing authorisation for use in children for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

	Because of the likely long duration of treatment, the prevention of development of resistance is paramount. Resistance to lamivudine confers cross-resistance to emtricitabine, telbivudine and entecavir. Circulating levels of resistant hepatitis B virus may also lead to increased resistant virus transmission. The GDG considered that safety issues, bearing in mind the likely long duration of nucleos(t)ide therapy must be given careful consideration. Focus on renal, bone and developmental problems in adult's raises the need for continued vigilance and the need for further evidence from longer term studies in children. The GDG noted that assessment of fibrosis is a sensitive area in children. Paediatricians are cautious in using drug treatments where long term safety is not determined. The expert co-optee informed the GDG that currently nucleoside agents were used infrequently and within a very small population of children. The GDG agreed that, in the absence of proven effective therapy, children and young people should ideally be treated with anti-viral therapy only in clinical trials, except for compassionate use or clinical need. The GDG, therefore, recommended that antiviral drugs could be considered in children, but included a footnote to the recommendation, that each of the antiviral drugs did not have UK marketing authorisation for use in children and that the prescriber should follow relevant professional guidance, taking full responsibility for the decision.
Economic considerations	No moderate- to high- quality published evidence of cost-effectiveness was available to inform recommendations for the treatment of children with CHB. One cost-benefit analysis was excluded due to poor applicability and very serious methodological limitations. Along with the clinical evidence, the GDG considered the unit cost of alternative treatments as well as the long term costs of progressive liver disease. The likely longer duration of nucleoside therapy in children favours the use of finite duration Interferons. The cost effectiveness evidence from the Novel economic evaluation may be extrapolated to this population as well suggesting the use of pegylated interferon as first line treatment.
Quality of evidence	Trials on children and young people are limited in this area. However, evidence from a RCT (moderate quality) with serious risk of bias (due to limited information on blinding, randomization procedure and allocation concealment) indicated increased rates of HBeAg loss supporting the use of a finite period of interferon therapy. The evidence on the benefit of using a combination therapy of a nucleoside (lamivudine) with interferon from a RCT with high risk of bias (moderate quality) for the outcome of reducing the proportion of children with detectable HBV DNA and of low quality for the outcomes of improved rates of HBeAg loss and seroconversion. Importantly, pre- and post-treatment viral resistance to lamivudine were not recorded. The GDG noted that this is not borne out in adult studies. Of some interest was the observation from a double blinded nucleotide study (albeit with small numbers) that there is evidence that treatment before the age of 7 is not beneficial for achieving ALT normalization and reducing the detectable HBV DNA levels. The GDG would encourage studies for interferon in children to be analysed according to age, genotype and durability of response determined. Because of the sparse database there is a need for cases to be referred to specialist centres and for consideration of inclusion into clinical trials of

	pegylated interferon and the newer drugs (ETV and TDF).
Other considerations	This recommendation on therapy of children with CHB was based on both the evidence reviewed and on the experience and opinion of the GDG. The GDG considered that treatment for CHB in childhood should be considered within the context of a clinical trial (or for compassionate use or clinical need) for the following main reasons: The lifetime risk of serious liver disease is higher in those infected as children so eradication of infection in childhood is desirable Quality of life issues, particularly in career and social opportunities, affect this group more than adults. The primary aims of treatment in children should be HBeAg and HBsAg loss or seroconversion. HBV DNA reduction is an important indicator but should not be at the expense of increased risk of drug resistance. Infected children are a continuing reservoir for ongoing transmission of infection within the population. The GDG did not recommend lamivudine and adefovir as monotherapies for children with CHB because of the incidence of increasing resistance and the concern it may affect future treatment options, and the unknown adverse effects. The decision not to recommend adefovir is based on the absence of any resistance data. The GDG considered that the benefit shown in reported outcomes for HBV DNA and ALT normalisation cannot be considered in the same way as for adults. Because of the duration of treatment in children resistance data is very important as this reflects a real clinical harm for this population. The GDG considered that interferon may interfere with child's growth and this should be considered in treatment planning and monitoring.

11.1.10.3 Adults who are co-infected with Hep C

Recommendations	**55. Offer peginterferon alfa and ribavirin in adults co-infected with chronic hepatitis B and C**
Relative values of different outcomes	HCV RNA at 6 months after treatment undetectable (sustained viral response) HBV DNA undetectable at the end of treatment HBeAg antibody status Normalisation of ALT
Trade off between clinical benefits and harms	There were no studies in this mixed population and the GDG drew on indirect evidence in patients with hepatitis C and a small amount of indirect evidence in patients with hepatitis B. The GDG agreed that sustained viral response rates (HCV RNA clearance 6 months after interferon and ribavirin therapy) is similar to HCV mono infected individuals and therefore co-infected individuals should be treated as in the relevant technology appraisals for hepatitis C. TAs 106 and 75 are based on evidence from RCTs, which show a better sustained virological response in patients receiving the combination of peg interferon alfa with ribavirin in comparison with other interventions. The GDG also noted indirect evidence from the monitoring review (section 12.1) of a sustained response in patients on peginterferon with or without

	ribavirin in patients who were HBeAg negative. Due to interference of HCV on HBV replication, a sustained viral response for Hep C may result in higher HBV replication.
Economic considerations	No published evidence of cost-effectiveness was available to inform recommendations for patients co-infected with CHB and HCV.
Quality of evidence	No RCTs available. Recommendations based on GDG experience and relevant Technology appraisals for hepatitis C.
Other considerations	The GDG agreed that in the treatment of co-infected patients, pegylated interferon is preferable to nucleos(t)ides because it may also benefit chronic hepatitis B as well as hepatitis C.

11.1.10.4 Adults who are co-infected with HDV

Recommendations	**56. Offer a 48-week course of peginterferon alfa-2a in people co-infected with chronic hepatitis B and hepatitis delta infection who have evidence of significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3)** **57. Consider stopping peginterferon alfa-2a if there is no decrease in HDV RNA after 6 months to 1 year of treatment. Otherwise continue treatment and re-evaluate treatment response annually** **58. Stop treatment after HBsAg seroconversion**
Relative values of different outcomes	The GDG considered the sustained clearance of HDV RNA, ALT normalisation and histological improvement as the most important outcomes.
Trade off between clinical benefits and harms	Evidence from RCTs demonstrated that treatment with 9 million units of interferon alpha 2a for 12 months improved patients' survival rate at 12 years follow up for patients co-infected with CHB and Delta compared to non treated group (farci, 1994, Farci 2004). In addition, for adults co-infected with CHB and Delta, treatment with interferon alpha (either 2a or 2b) for 12 months was beneficial for achieving ALT normalisation (at 6 months and 12 years), histological improvement (after 1 year of treatment) and reducing the proportion of patients who underwent liver transplantation compared to those who didn't receive any treatment (at 12 years) (Farci, 1994, Rosina, 1991). Although the proportion of patients with detectable HD RNA was reduced at 6 months in the patients treated with 9 million units of interferon alpha 2a, compared to 3 million units or no treatment; all patients had detectable levels of HDV RNA at 12 years follow up. Evidence from RCTs comparing combination therapies (interferon or pegylated interferon with either adefovir or lamivudine) found that there was no additional benefit of any outcome by adding adefovir or lamivudine to pegylated interferon (Wedemeyer, 2011, Canbakan 2006). The GDG were aware of other studies that reported a sustained rate of HDV RNA suppression of <30%. The GDG believed that interferon side effects impact significantly on patient compliance and acceptability.

Economic considerations	No published evidence of cost-effectiveness was available to inform recommendations for patients co-infected with CHB and CHDelta. The GDG considered the unit cost of alternative treatments as well as the long term costs of progressive liver disease. A high proportion of HDV and HBV co-infected individuals have cirrhosis at presentation. The clinical evidence shows that without treatment, patients in this group have poor survival outcomes, due to progressive liver disease. The goal of treatment would be to reduce progression to more severe states of liver fibrosis and cirrhosis, which are associated with significant costs and morbidity. The clinical evidence shows that interferon was more beneficial than no treatment, in terms of serological, biochemical, histological and survival outcomes. Although no formal analysis has been undertaken, the GDG considered it very likely that the costs of interferon or pegylated interferon would be offset by savings from progression to compensated and decompensated cirrhosis, HCC and liver transplantation. The clinical evidence shows that pegylated interferon was likely to be more effective than adefovir. The GDG was aware that treatment with pegylated interferon is more costly per year than treatment with adefovir, but they considered the additional costs would be outweighed by improved prognosis. The clinical evidence shows that combining interferon or pegylated interferon with nucleos(t)ide analogues such as lamivudine and adefovir confers no additional benefits and may actually cause harm. Therefore, the combination is likely to be dominated (more costly and less effective) by interferon or pegylated interferon used alone.
Quality of evidence	The evidence reviewed for the population of adults coinfected with CHB and Delta was limited and studies involved small numbers of patients because of the low prevalence of this disease and therefore the GDG interpreted the results with caution. However, the evidence on both the improved survival rate (at 12 years follow up) and ALT normalization (end of 1 year treatment) of patients treated with interferon alpha 2a was of moderate quality. The quality of evidence for the other outcomes (rate of undetectable HBV DNA, ALT normalization, histological improvement) supporting the use of interferon or pegylated interferon treatment for people coinfected with CHB and Delta ranged from low to very low mainly due to RCTs being at high risk of bias and serious or very serious imprecision. A good quality double blinded RCT comparing the clinical effectiveness of comparison of pegylated interferon plus adefovir versus either pegylated interferon or adefovir alone was downgraded as it used a mixed population of HBeAg positive and negative patients and therefore the results were interpreted with caution due to limited generalisability.
Other considerations	This recommendation was based on both the clinical evidence review and the experience and opinion of the GDG. The GDG noted that the numbers of co-infected patients in the UK was small and therefore it was important for them to be referred to a specialist. The GDG considered stopping interferon only in adults who become HBsAg negative, to avoid the risk of relapse.

11.2 Liver decompensation

11.2.1 Introduction

Cirrhosis is one of a number of possible end-stage results of untreated chronic hepatitis B. It is defined histologically as a diffuse hepatic process that is characterised by fibrosis and the replacement of the normal liver architecture with structurally abnormal nodules. The fibrosis is produced by the excessive deposition of extracellular matrix within the liver as a response to liver injury. Fibrosis is reversible upon removal of the injury but continuing cycles of nodular degeneration and regeneration caused by continuous insult to the liver will lead to cirrhosis. However, there is often a poor correlation between the histological findings and the clinical picture of the patient. Common signs and symptoms are those of fatigue, anorexia and weight loss, and reduced hepatic synthetic function including coagulopathy resulting from reduced production of clotting factors, decreased blood detoxification leading to hepatic encephalopathy and sensitivity to many drugs, and portal hypertension leading to variceal bleeding.

The main haematological manifestations are anaemia resulting from a combination of folate deficiency, haemolysis and hypersplenism. Coagulopathy may result from associated cholestasis leading to decreased vitamin K absorption and therefore underproduction of factors II, VII, IX and X. Platelets are reduced due to hypersplenism and the reduced production of thrombopoietin. These manifestations may all lead to fibrinolysis and, ultimately, disseminated intravascular coagulopathy.

Hepatic encephalopathy (HE) is characterised by a reduced level of consciousness, personality changes and a liver flap. It may result from the build-up of ammonia produced from the degradation of amino acids, which is usually detoxified in the liver into urea and glutamine. Ammonia is neurotoxic and affects transportation across the cell membranes of neurones. Commonly HE is precipitated suddenly by factors such as the use of diuretics, constipation or infection.

A number of pressure changes caused by the inability of the liver to compensate for variations in portal blood flow leads to a number of manifestations. These are exacerbated by the low protein levels in the blood caused by the reduced production of albumin by the liver. Effects of these dynamic changes include the development of portosystemic collaterals and anastomoses, especially around the gastro-oesophageal junction. These oesophageal varices are the main complication of high portal pressure and can lead to massive gastrointestinal haemorrhage. Multiple pulmonary and cardiac manifestations also occur with an increase in pleural effusions and arteriovenous shunting leading to the life-threatening complication of hepatopulmonary syndrome. Ascites is a common manifestation in patients with severe liver disease caused by a mixture of increased hepatic lymphatic flow and the absence of a transsinusoidal oncotic gradient.

A long duration of hepatitis B infection, high levels of DNA, the co-presence of alcohol consumption, and other concurrent hepatic viral infections such as hepatitis C or D all increase the risk of developing fibrosis and cirrhosis. A number of scoring systems for liver fibrosis have been developed. The two main ones used in this guideline are the Ishak score and the METAVIR score (see chapter 8 for details of the scoring systems). Even when significant fibrosis has occurred the liver can continue to compensate for the damage through regeneration. However certain factors can tip the balance in favour of decompensation. These include constipation, infection, increased alcohol intake, certain medications, bleeding (e.g. from oesophageal varices) and dehydration. This decompensation can result in any of the manifestations detailed above. Separate scoring systems are used for prognostication in cirrhosis. These include the Child-Turcotte-Pugh score[17,85] and the Model for End-stage Liver Disease (MELD) score [66](3).

Progression of HBV-related liver disease can also include the development of hepatocellular carcinoma (HCC), which is increased when heavy alcohol consumption and carcinogens such as

aflatoxins or smoking are present. HCC is also more likely to occur in males of an older age with a family history of HCC. The presence of cirrhosis is a strong predictor of subsequent HCC development, but between 30 and 50% of tumours are associated with hepatitis B in the absence of cirrhosis [5]. The presence of HBeAg and high levels of HBV DNA act as independent risk factors for the subsequent development of HCC[15,105,107].

The presence or absence of cirrhosis or hepatic decompensation are important factors when considering the urgency or indications for treatment, as well as the drug options available. Pegylated interferon may increase the risk of bacterial infections and hepatic decompensation in patients with advanced cirrhosis[82] and is contraindicated in patients who have already decompensated. However, it remains a good and safe option in patients that have well compensated cirrhosis. Nucleos(t)ide options need to take into account the overall complications and co-morbidities of the patient but should be targeted to ensure as fast an improvement in viral status as possible. Prolonged HBV DNA suppression can result from timely drug therapy, preventing further progression to decompensation [60,80] and even the reversal of cirrhosis [14].

11.2.2 Review question: In chronic hepatitis B infected people with cirrhosis, including those with liver decompensation, what is the clinical and cost effectiveness of antiviral treatment to prevent decompensation and/or liver transplantation?

Table 197: Protocol

Protocol	
Population	Adults with chronic hepatitis B virus infection and with compensated/decompensated cirrhosis
Intervention	Antiviral treatment (monotherapies or combinations) • Pegylated alpha-interferon • Tenofovir • Adefovir • Entecavir • Lamivudine • Telbivudine • Tenofovir plus emtricitabine combination therapy
Comparison	Placebo • Pegylated alpha-interferon • Tenofovir • Adefovir • Entecavir • Lamivudine • Telbivudine • Tenofovir plus emtricitabine combination therapy
Outcomes	Critical outcomes: • Liver transplantation • Mortality • Child-Pugh score • MELD score • Incidence of hepatocellular carcinoma • Incidence of resistance • Log reduction of HBV DNA (indication of drug potency)

Protocol	
	• Undetectable serum hepatitis B virus DNA (potential for add-on combination) • Quality of life measures • Incidence of hepatic decompensation • Complications such as ascites, variceal bleeding, spontaneous bacterial peritonitis, encephalopathy

11.2.2.1 Summary characteristics of included studies

Table 198: Compensated cirrhosis/ advanced fibrosis - HBeAg positive patients with chronic hepatitis B

Comparison	Included studies (N=)	Setting	Study population	Outcomes
Entecavir vs Lamivudine	Schiff 2008 (n=93)	3 multinational trials	Nucleos(t)ide-naïve patients with advanced fibrosis or cirrhosis (Ishak fibrosis score 4-6)	Assessed at end of 48 week treatment: • Mortality* • Resistance (virologic breakthrough due to genotypic resistance to ETV) • Undetectable HBV DNA (<300 copies/mL)
Lamivudine vs placebo	Liaw 2004 (n=651)	Multicentre international (41 sites)	Largely HBeAg (+) (58%) patients with histologically confirmed cirrhosis or advanced fibrosis (98% Asian) Ishak fibrosis score ≥4 Unclear whether the population was treatment naïve	Up to 24-30 months post treatment: • Incidence of hepatocellular carcinoma (HCC) • Mortality • ≥2 points increase in Child-Pugh score • Incidence of resistance (YMDD mutation or lamivudine resistance)

** Mortality was not reported for each individual group. An overall mortality was reported for HBeAg (+), (-) and lamivudine refractory patients combined.*

Table 199: Compensated cirrhosis/ advanced fibrosis - HBeAg negative patients with chronic hepatitis B

Comparison	Included studies (N=)	Setting	Study population	Outcomes
Entecavir vs. Lamivudine	Schiff 2008 (n=108)	3 multinational trials	Nucleos(t)ide-naïve with advanced fibrosis or cirrhosis (Ishak fibrosis score 4-6)	Assessed at end of 48 week treatment: • Mortality* • Resistance (virologic breakthrough due to genotypic resistance to ETV) • Undetectable HBV DNA (<300 copies/mL)

** Mortality was not reported for each individual group. An overall mortality was reported for HBeAg (+), (-) and lamivudine refractory patients combined.*

Table 200: Compensated cirrhosis/ advanced fibrosis - Lamivudine refractory patients

Comparison	Included studies	Setting	Study population	Outcomes
Entecavir vs. Lamivudine	Schiff 2008 (n=44)	3 multinational trials	Advanced fibrosis or cirrhosis (Ishak fibrosis score 4-6)	Assessed at end of 48 week treatment: • Mortality* • Resistance • (virologic breakthrough due to genotypic resistance to ETV) • Undetectable HBV DNA (<300 copies/mL)

** Mortality was not reported for each individual group. An overall mortality was reported for HBeAg (+), (-) and lamivudine refractory patients combined.*

Table 201: Decompensated cirrhosis – mixed HBeAg populations

Comparison	Included studies	Setting	Study population	Outcomes
Entecavir vs Adefovir	Liaw 2011 (n=191)	Multicentre international trials (52 sites)	Mixed CHB patients with hepatic decompensation (CTP score ≥7), ~50% HBeAg (+)	Assessed at 48 weeks: • Liver transplantation • Mortality • Incidence of

Comparison	Included studies	Setting	Study population	Outcomes
			and (-); experienced or naïve for treatment with nucleos(t)ide analogues 36% in ETV group and 33% in ADV group were lamivudine resistant.	hepatocellular carcinoma (HCC) • Resistance (genotypic mutation) • % of patients with undetectable HBV DNA (<300 copies/mL) • log reduction in HBV DNA • Child-Pugh score ≥ 2 points decrease • Mean change in Model for end stage liver disease score (MELD)
Tenofovir (TDF) vs. tenofovir plus emtricitabine (FTC) combination therapy	Liaw 2011A (n=90)	International multicentre trial (39 sites including Europe, Canada, Singapore, Taiwan, the US)	Mixed population (>60% HBeAg negative) 62.2 % in TDF group and 60 % in Tenofovir plus emtrictabine group received previous lamivudine/ adefovir treatment.	Assessed at 48 week treatment: • Liver transplantation • Mortality • Hepatocellular carcinoma • Resistance (virologic breakthough due to genotypic resistance) • % of patients with undetectable HBV DNA (<400 copies/mL) • log reduction in HBV DNA • Model for end stage liver disease score (MELD) • ≥2 points decrease in Child-Pugh score • Complications – ascites and encephalopathy
Tenofovir vs. Entecavir	Liaw 2011A (n=67)	International multicentre trial (39 sites incl. Europe, Canada, Singapore, Taiwan,	Mixed population (>60% HBeAg negative) 62.2 % in TDF	Assessed at 48 week treatment: • Liver transplantation • Mortality

Comparison	Included studies	Setting	Study population	Outcomes
		the US)	group and 59.1 % in ETV group received previous lamivudine/ adefovir treatment.	• Hepatocellular carcinoma • Resistance (virologic breakthough due to genotypic resistance) • % of patients with undetectable HBV DNA (<400 copies/mL) • log reduction in HBV DNA • Model for end stage liver disease score (MELD) • ≥2 points decrease in Child-Pugh score • Complications – ascites and encephalopathy
Entecavir vs. tenofovir plus emtricitabine (FTC) combination therapy	Liaw 2011A (n=90)	International multicentre trial (39 sites incl. Europe, Canada, Singapore, Taiwan, the US)	Mixed population (>60% HBeAg negative) 59.1 % in ETV and 60% in tenofovir plus emtricitabine group received previous lamivudine/ adefovir treatment.	Assessed at 48 week treatment: • Liver transplantation • Mortality • Hepatocellular carcinoma • Resistance (virologic breakthough due to genotypic resistance) • % of patients with undetectable HBV DNA (<400 copies/mL) • log reduction in HBV DNA • Model for end stage liver disease score (MELD) • ≥2 points decrease in Child-Pugh score • Complications – ascites and encephalopathy

11.2.3 Clinical evidence

We searched for randomised studies comparing the clinical effectiveness of different antiviral treatments in chronic hepatitis B infected patients with compensated (advanced fibrosis) and decompensated cirrhosis. A total of four randomised trials have been identified and included in this review. Two studies included patients with an Ishak fibrosis score of at least 4 (advanced fibrosis or cirrhosis), and the remaining two studies included decompensated cirrhotic patients. Forest plots can be found in appendix G.

11.2.3.1 Pharmacological antiviral therapies for CHB infected HBeAg positive adults with compensated cirrhosis (or advanced fibrosis)

Comparison of entecavir versus lamivudine in CHB patients with compensated cirrhosis (or advanced fibrosis)

Table 202: Entecavir versus lamivudine (Treatment naïve CHB patients with compensated cirrhosis or advanced fibrosis) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Entecavir; Frequency (%)	Lamivudine Frequency (%)	Relative; Risk Ratio (RR) (95% CI)	Absolute	
% of patients with undetectable HBV DNA (assessed at end of 48 weeks treatment)											
1 Schiff 2008	RCT- double blinded	Serious limitations [a,b]	No serious inconsistency	No serious indirectness	Serious imprecision [c]	none	42/46 (91.3%)	27/47 (57.4%)	RR 1.59 (1.22 to 2.06)	339 more per 1000 (from 126 more to 609 more)	LOW
Mortality (assessed at end of 48 weeks treatment) (Overall result for HBeAg positive, negative and lamivudine refractory patients combined)											
1 Schiff 2008	RCT- double blinded	Serious limitations [a,b]	No serious inconsistency	Serious indirectness [d]	Very serious imprecision [e]	none	3/120 (2.5%)	4/125 (3.2%)	RR 0.78 (0.18 to 3.42)	7 fewer per 1000 (from 26 fewer to 77 more)	VERY LOW

(a) No details on randomisation and unclear allocation concealment.
(b) Post-hoc descriptive subgroup analysis.
(c) The confidence interval is consistent with two clinical decisions – appreciable benefit and no appreciable benefit or harm.
(d) Mixed population - HBeAg (+) and (-) and lamivudine refractory patients
(e) The confidence interval is consistent with three clinical decisions - appreciable benefit, no appreciable benefit or harm and appreciable harm.

Comparison of lamivudine versus placebo in CHB patients with compensated cirrhosis or advanced fibrosis

Table 203: Lamivudine versus placebo (CHB patients with compensated cirrhosis or advanced fibrosis) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lamivudine; Frequency (%)	Placebo; Frequency (%)	Relative; Risk Ratio (RR) or Peto OR (95% CI)	Absolute	
% of patients with incidence of hepatocellular carcinoma (up to 30 months follow up)											
1 Liaw 2004	RCT- double blinded	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Serious imprecision [c]	none	17/436 (3.9%)	16/215 (7.4%)	RR 0.52 (0.27 to 1.02)	36 fewer per 1000 (from 54 fewer to 1 more)	VERY LOW
Mortality (up to 30 months follow up)											
1 Liaw 2004	RCT- double blinded	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Very serious imprecision [d]	none	2/436 (0.46%)	0/215 (0%)	PETO OR 4.46 (0.23 to 85.16)	0 more per 1000 (from 0 fewer to 10 more)	VERY LOW
% of patients with incidence of resistance (up to 30 months follow up)											
1 Liaw 2004	RCT- double blinded	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	No serious imprecision	none	209/433 (48.3%)	11/214 (5.1%)	RR 9.39 (5.24 to 16.83)	431 more per 1000 (from 218 more to 814 more)	LOW
% of patients with ≥2 points increase in Child-Pugh score (up to 30 months follow up) (Better indicated by lower values)											
1 Liaw 2004	RCT- double blinded	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	No serious imprecision	none	15/436 (3.4%)	19/215 (8.8%)	RR 0.39 (0.2 to 0.75)	54 fewer per 1000 (from 22 fewer to 71 fewer)	LOW

(a) No details on randomisation procedure. Partially double-blind. % loss to follow up not reported.
(b) Mixed population of HBeAg (+) and (-). 58% patients were HBeAg (+) in each arm. 98% Asians.
(c) The confidence interval is consistent with two clinical decisions - appreciable benefit and no appreciable benefit or harm.
(d) The confidence interval is consistent with three clinical decisions - appreciable benefit, no appreciable benefit or harm and appreciable harm.

11.2.3.2 Pharmacological antiviral therapies for CHB infected HBeAg negative adults with compensated cirrhosis (or advanced fibrosis)

Comparison of entecavir versus lamivudine in CHB patients with compensated cirrhosis (or advanced fibrosis)

Table 204: Entecavir versus lamivudine (Treatment naïve CHB patients with compensated cirrhosis or advanced fibrosis) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Entecavir; Frequency (%)	Lamivudine Frequency (%)	Relative; Risk Ratio (RR) (95% CI)	Absolute	
% of patient with undetectable HBV DNA (assessed at end of 48 weeks treatment)											
1 Schiff 2008	RCT- double blinded	Serious limitations [a,b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	49/51 (96.1%)	35/57 (61.4%)	RR 1.56 (1.26 to 1.94)	344 more per 1000 (from 160 more to 577 more)	MODERATE
Mortality (assessed at end of 48 weeks treatment) (Overall result for HBeAg positive, negative and lamivudine refractory patients combined)											
1 Schiff 2008	RCT- double blinded	Serious limitations [a,b]	no serious inconsistency	Serious indirectness [c]	Very serious imprecision [d]	none	3/120 (2.5%)	4/125 (3.2%)	RR 0.78 (0.18 to 3.42)	7 fewer per 1000 (from 26 fewer to 77 more)	VERY LOW

(a) No details on randomisation and unclear allocation concealment.
(b) Post-hoc descriptive subgroup analysis.
(c) Mixed population - HBeAg (+) and (-) and lamivudine refractory patients
(d) The confidence interval is consistent with three clinical decisions - appreciable benefit, no appreciable benefit or harm and appreciable harm.

11.2.3.3 Pharmacological antiviral therapies for lamivudine refractory CHB patients with compensated cirrhosis (or advanced fibrosis)

Comparison of entecavir versus lamivudine in CHB patients with compensated cirrhosis or advanced fibrosis

Table 205: Entecavir versus lamivudine (CHB patients with compensated cirrhosis or advanced fibrosis) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Entecavir; Frequency (%)	Lamivudine Frequency (%)	Relative; Risk Ratio (RR)/ Peto OR (95% CI)	Absolute	
% of patient with undetectable HBV DNA (assessed at end of 48 weeks treatment)											
1 Schiff 2008	RCT- double blinded	Serious limitations [a,b]	No serious inconsistency	No serious indirectness	Very serious imprecision[c]	none	3/23 (13%)	0/21 (0%)	Peto OR 7.44 (0.73 to 75.68)	13 more per 1000 (from 2 fewer to 28 more)	VERY LOW
Mortality (assessed at end of 48 weeks treatment) (Overall result for HBeAg positive, negative and lamivudine refractory patients combined)											
1 Schiff 2008	RCT- double blinded	Serious limitations [a,b]	no serious inconsistency	Serious indirectness [d]	Very serious imprecision [c]	none	3/120 (2.5%)	4/125 (3.2%)	RR 0.78 (0.18 to 3.42)	7 fewer per 1000 (from 26 fewer to 77 more)	VERY LOW

(a) No details on randomisation and unclear allocation concealment.
(b) Post-hoc descriptive subgroup analysis.
(c) The confidence interval is consistent with three clinical decisions - appreciable benefit, no appreciable benefit or harm and appreciable harm.
(d) Mixed population - HBeAg (+) and (-) and lamivudine refractory patients.

11.2.3.4 Pharmacological antiviral therapies for CHB patients with decompensated cirrhosis

Comparison of entecavir versus adefovir in CHB patients with decompensated cirrhosis

Table 206: Entecavir versus adefovir (CHB patients with decompensated cirrhosis) - clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Entecavir; Frequency (%) or mean (SD)	Adefovir; Frequency (%)or mean (SD)	Relative; Risk Ratio (RR) (95% CI)	Absolute	
% of patients with undetectable HBV DNA (<300copies/mL) (assessed at end of 48 weeks treatment) - Overall (ACC analysis)											
1 Liaw 2011	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	no serious imprecision	none	57/71 (80.3%)	18/62 (29%)	RR 2.77 (1.84 to 4.15)	514 more per 1000 (from 244 more to 915 more)	LOW
% of patients with undetectable HBV DNA (<300 copies/mL) (assessed at end of 48 weeks treatment) - HBeAg (+) (ITT analysis)											
1 Liaw 2011	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	no serious indirectness	Serious imprecision [c]	none	25/54 (46.3%)	9/51 (17.6%)	RR 2.62 (1.36 to 5.07)	286 more per 1000 (from 64 more to 718 more)	LOW
% of patients with undetectable HBV DNA (<300 copies/mL) (assessed at end of 48 weeks treatment) - HBeAg (-) (ITT analysis)											
1 Liaw 2011	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	no serious indirectness	no serious imprecision	none	32/46 (30.4%)	9/40 (77.5%)	RR 3.09 (1.69 to 5.67)	470 more per 1000 (from 155 more to 1000 more)	MODERATE
% of patients with Child-Turcotte-Pugh score ≥2 points decrease (assessed at end of 48 weeks treatment) (Better indicated by lower values)											
1 Liaw 2011	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Serious imprecision [c]	none	35/71 (49.3%)	25/62 (40.3%)	RR 1.22 (0.83 to 1.79)	89 more per 1000 (from 69 fewer to 319 more)	VERY LOW
Log reduction of HBV DNA (assessed at end of 48 weeks treatment) (HBeAg (+) subgroup)											

Quality assessment							No of patients		Effect		Quality
1 Liaw 2011	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	no serious indirectness [b]	no serious imprecision [d]	none	5.07 (0.93)	4.21 (1.47)	-	MD 0.86 higher (0.26 to 1.46 higher)	MODERATE
Log reduction of HBV DNA (assessed at end of 48 weeks treatment) (HBeAg (-) subgroup)											
1 Liaw 2011	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	no serious indirectness	no serious imprecision [d]	none	4.27 (0.71)	3.58 (1.28)	-	MD 0.69 higher (0.18 to 1.2 higher)	MODERATE
Resistance (assessed at end of 48 weeks treatment)											
1 Liaw 2011	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	no serious imprecision	none	0/71 (0%)	0/62 (0%)	not pooled	not pooled	LOW
% of patients with incidence of hepatocellular carcinoma (assessed at end of 48 weeks treatment)											
1 Liaw 2011	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Serious imprecision [c]	none	12/71 (16.9%)	18/62 (29%)	RR 0.58 (0.31 to 1.11)	122 fewer per 1000 (from 200 fewer to 32 more)	VERY LOW
Mortality (assessed at end of 48 weeks treatment)											
1 Liaw 2011	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Serious imprecision [c]	none	23/71 (32.4%)	29/62 (46.8%)	RR 0.69 (0.45 to 1.06)	145 fewer per 1000 (from 257 fewer to 28 more)	VERY LOW
Liver transplantation (assessed at end of 48 weeks treatment)											
1 Liaw 2011	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Serious imprecision [e]	none	11/71 (15.5%)	3/62 (4.8%)	RR 3.2 (0.94 to 10.96)	106 more per 1000 (from 3 fewer to 482 more)	VERY LOW
Model for end-stage liver disease score (MELD score) (change from baseline) (assessed at end of 48 weeks treatment) (Better indicated by lower values)											
1 Liaw 2011	RCT- unclear blinding	Serious limitations [a]	No serious inconsistency	Serious indirectness [b]	Serious imprecision [f]	none	2.6 (2.6)	1.7 (1.97)	-	MD 0.9 higher (0.12 to 1.68 higher)	VERY LOW

(a) No details on randomisation, unclear allocation concealment and no blinding.
(b) Mixed HBeAg population - ~50% were HBeAg positive.
(c) The confidence interval is consistent with two clinical decisions - appreciable benefit and no appreciable benefit or harm.
(d) The mean difference reached the default MID.

(e) The confidence interval is consistent with two clinical decisions - no appreciable benefit or harm and appreciable harm.
(f) The mean difference did not reach default MID.

Comparison of tenofovir plus emtricitabine combination therapy versus tenofovir in CHB patients with decompensated cirrhosis

Table 207: Tenofovir plus emtricitabine combination therapy versus tenofovir (CHB patients with decompensated cirrhosis) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TDF + FTC Mean (SD), median (range), frequency (%)	Tenofovir Mean (SD), median (range), frequency (%)	Relative Mean difference (MD), Risk Ratio (RR) (95% CI)	Absolute	
Liver transplantation (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Very serious imprecision [d]	none	4/40 (10%)	2/32 (6.3%)	RR 1.60 (0.31 to 8.19)	38 more per 1000 (from 43 fewer to 449 more)	VERY LOW
Log reduction of HBV DNA (assessed at end of 48 weeks treatment) (Better indicated by lower values)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Serious imprecision [b]	none	3.72 (1.77)	3.3 (1.51)	-	MD 0.42 higher (0.34 lower to 1.18 higher)	LOW
% of patients with undetectable HBV DNA (<400copies/mL) (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Serious imprecision [c]	none	35/40 (87.5%)	23/32 (71.9%)	RR 1.22 (0.95 to 1.56)	158 more per 1000 (from 36 fewer to 402 more)	LOW
% of patients with Child Turcotte Pugh score≥2 point decrease (assessed at end of 48 weeks treatment) (Better indicated by lower values)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness	Serious imprecision [c]	none	12/25 (48%)	7/27 (25.9%)	RR 1.85 (0.87 to	220 more per 1000 (from 34	LOW

Quality assessment							Summary of findings				
				[a]					3.95)	fewer to 765 more)	
Change in Model for endstage liver disease score (MELD) from baseline (assessed at end of 48 weeks treatment) (Better indicated by lower values)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	[e]	none	-2 (-18, 4)	-2 (-12, 3)	-	-	MODERATE [e]
% of patients with incidence of resistance (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	no serious imprecision	none	0/40 (0%)	0/32 (0%)	not pooled	not pooled	MODERATE
Ascites (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Very serious imprecision [d]	none	2/40 (5%)	4/32 (12.5%)	RR 0.4 (0.08 to 2.05)	75 fewer per 1000 (from 115 fewer to 131more)	VERY LOW
Encephalopathy (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Very serious imprecision [d]	none	1/40 (2.5%)	3/32 (9.4%)	RR 0.27 (0.03 to 2.44)	68 fewer per 1000 (from 91 fewer to 135 more)	VERY LOW
Hepatocellular carcinoma (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Very serious imprecision [d]	none	1/40 (2.5%)	3/32 (9.4%)	RR 0.27 (0.03 to 2.44)	68 fewer per 1000 (from 91 fewer to 135 more)	VERY LOW
Mortality (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Very serious imprecision [d]	none	2/40 (5%)	2/32 (6.3%)	RR 0.8 (0.12 to 5.37)	12 fewer per 1000 (from 55 fewer to 273 more)	VERY LOW

(a) Mixed population; 60% and 68.9% in the Emtricitabine + tenofovir and Tenofovir groups were HBeAg negative respectively.

(b) The mean difference did not reach the default MID.
(c) The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm.
(d) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.
(e) Imprecision could not be estimated as no relative/absolute effect could be calculated.

Comparison of entecavir versus tenofovir in CHB patients with decompensated cirrhosis

Table 208: Entecavir versus tenofovir (CHB patients with decompensated cirrhosis) - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Entecavir Mean (SD), median (range), frequency (%)	Tenofovir Mean (SD), median (range), frequency (%)	Relative (95% CI)	Absolute	
Liver transplantation (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness[a]	Very serious imprecision [d]	none	0/16 (0%)	2/32 (6.3%)	Peto OR 0.22 (0.01 to 4.22)	60 fewer per 1000 (from 180 fewer to 60 more)	VERY LOW
Log reduction of HBV DNA (assessed at end of 48 weeks treatment) (Better indicated by lower values)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness[a]	Serious imprecision [b]	none	3.24 (1.91)	3.24 (1.91)	-	MD 0.06 lower (1.13 lower to 1.01 higher)	LOW
% of patients with undetectable HBV DNA (<400copies/mL) (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness[a]	Serious imprecision [c]	none	12/16 (75%)	23/32 (71.9%)	RR 1.04 (0.73 to 1.49)	29 more per 1000 (from 194	LOW

Quality assessment							Summary of findings				
										fewer to 352 more)	
% of patients with Child-Pugh score≥2 point decrease (assessed at end of 48 weeks treatment) (Better indicated by lower values)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness[a]	Very serious imprecision [d]	none	5/12 (41.7%)	7/27 (25.9%)	RR 1.61 (0.64 to 4.05)	158 more per 1000 (from 93 fewer to 791 more)	VERY LOW
Change in Model for end-stage liver disease score (MELD) from baseline (assessed at end of 48 weeks treatment) (Better indicated by lower values)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness[a]	[e]	none	-2 (-10, 1)	-2 (-12, 3)	-	-	MODERATE [e]
% of patients with incidence of resistance (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness[a]	no serious imprecision	none	0/16 (0%)	0/32 (0%)	not pooled	not pooled	MODERATE
Ascites (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Serious imprecision [d]	none	4/16 (25%)	4/32 (12.5%)	RR 2.0 (0.57 to 6.98)	125 more per 1000 (from 54 fewer to 748 more)	VERY LOW
Encephalopathy (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Very serious imprecision [d]	none	4/16 (25%)	4/32 (12.5%)	RR 2.0 (0.57 to 6.98)	125 more per 1000 (from 54 fewer to 748 more)	VERY LOW
Hepatocellular carcinoma (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Very serious imprecision [d]	none	1/16 (6.3%)	3/32 (9.4%)	RR 0.67 (0.08 to 5.91)	31 fewer per 1000 (from 86 fewer to 460 more)	VERY LOW

Quality assessment							Summary of findings				
Mortality (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness[(a)]	Very serious imprecision [(d]	none	2/16 (12.5%)	2/32 (6.3%)	RR 2 (0.31 to 12.92)	62 more per 1000 (from 43 fewer to 745 more)	VERY LOW

(a) Mixed population; 68.2% and 68.9% in the Entecavir and Tenofovir groups were HBeAg negative respectively.
(b) The mean difference did not reach the default MID.
(c) The confidence interval is consistent with two clinical decisions; appreciable benefit, no appreciable benefit or harm.
(d) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.
(e) Imprecision could not be estimated as no relative/absolute effect could be calculated.

Comparison of tenofovir plus emtricitabine combination therapy versus entecavir in CHB patients with decompensated cirrhosis

Table 209: Tenofovir plus emtricitabine combination therapy versus entecavir (CHB patients with decompensated cirrhosis - clinical study characteristics and clinical summary of findings

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TDF + FTC Mean (SD), median (range), frequency (%)**	**Entecavir Mean (SD), median (range), frequency (%)**	**Relative Mean difference (MD), Risk Ratio (RR),Peto Odds ratio (OR) (95% CI)**	**Absolute**	
Liver transplantation (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness[(a)]	Very serious imprecision [(d)]	none	4/40 (10%)	0/16 (0%)	Peto OR 4.40 (0.47 to 40.93)	100 more per 1000 (from 20	VERY LOW

Quality assessment							Summary of findings				
										fewer to 220 more)	
Log reduction of HBV DNA (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness[a]	Serious imprecision [b]	none	3.72 (1.77)	3.24 (1.91)	-	MD 0.48 higher (0.6 lower to 1.56 higher)	LOW
% of patients with undetectable HBV DNA (<400copies/mL) (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness[a]	Serious imprecision [c]	none	35/40 (87.5%)	12/16 (75%)	RR 1.17 (0.86 to 1.58)	127 more per 1000 (from 105 fewer to 435 more)	LOW
% of patients with Child-Pugh score ≥2 point decrease (assessed at end of 48 weeks treatment) (Better indicated by lower values)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness[a]	Very serious imprecision [d]	none	12/25 (48%)	5/12 (41.7%)	RR 1.15 (0.53 to 2.52)	62 more per 1000 (from 196 fewer to 633 more)	VERY LOW
Change in Model for end-stage liver disease (MELD) from baseline (assessed at end of 48 weeks treatment) (Better indicated by lower values)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness[a]	[e]	none	-2 (-18, 4)	-2 (-10, 1)	not pooled	not pooled	MODERATE [d]
% of patients with incidence of resistance (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness[a]	no serious imprecision	none	0/40 (0%)	0/16 (0%)	not pooled	not pooled	MODERATE
Ascites (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness [a]	Serious imprecision [c]	none	2/40 (5%)	4/16 (25%)	RR 0.2 (0.04 to 0.99)	200 fewer per 1000 (from 2 fewer to 240 fewer)	LOW

Quality assessment							Summary of findings				
Encephalopathy (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness [(a)]	Very serious imprecision [(d)]	none	1/40 (2.5%)	1/16 (6.3%)	RR 0.4 (0.03 to 6.01)	38 fewer per 1000 (from 61 fewer to 313 more)	VERY LOW
HCC (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness [(a)]	Very serious imprecision [(d)]	none	1/40 (2.5%)	1/16 (6.3%)	RR 0.4 (0.03 to 6.01)	38 fewer per 1000 (from 61 fewer to 313 more)	VERY LOW
Mortality (assessed at end of 48 weeks treatment)											
1 Liaw 2011A	RCT-double blinded	No serious limitations	No serious inconsistency	Serious indirectness[(a)]	Very serious imprecision [(d)]	none	2/40 (5%)	2/16 (12.5%)	RR 0.4 (0.06 to 2.6)	75 fewer per 1000 (from 117 fewer to 200 more)	VERY LOW

(a) Mixed population; 60% and 68.2% in the Emtricitabine+ tenofovir and Entecavir groups were HBeAg negative respectively.
(b) The mean difference did not reach the default MID.
(c) The confidence interval is consistent with two clinical decisions; appreciable benefit and no appreciable benefit or harm.
(d) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm, appreciable harm.
(e) Imprecision could not be estimated as no relative/absolute effect could be calculated.

Comparison of telbivudine versus lamivudine for patients with decompensated cirrhosis

Table 210: Telbivudine versus lamivudine for people with chronic hepatitis B and decompensated cirrhosis- clinical study characteristics and clinical summary of findings

Quality assessment	No of patients	Effect	Quality	

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Telbivudine versus lamivudine	Control	Relative (95% CI)	Absolute		
HBV DNA <10,000 copies/mL - 52 weeks of treatment												
1: Chan 2012	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	85/114 (74.6%)	71.9%	RR 1.04 (0.89 to 1.21)	29 more per 1000 (from 79 fewer to 151 more)	⨁⨁⨁⨁ HIGH	
HBV DNA <10,000 copies/mL - 104 weeks of treatment												
1: Chan 2012	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision	none	65/114 (57%)	48.3%	RR 1.18 (0.92 to 1.51)	87 more per 1000 (from 39 fewer to 246 more)	⨁⨁⨁◯ MODERATE	
Undetectable HBV DNA <300 copies/mL - 52 weeks of treatment												
1: Chan 2012	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision	none	74/114 (64.9%)	61.4%	RR 1.06 (0.87 to 1.29)	37 more per 1000 (from 80 fewer to 178 more)	⨁⨁⨁◯ MODERATE	
Undetectable HBV DNA <300 copies/mL - 104 weeks of treatment												
1: Chan 2012	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision	none	56/114 (49.1%)	39.5%	RR 1.24 (0.93 to 1.67)	95 more per 1000 (from 28 fewer to 264 more)	⨁⨁⨁◯ MODERATE	
ALT normalisation - 52 weeks of treatment												
1: Chan 2012	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	54/114 (47.4%)	50%	RR 0.95 (0.73 to 1.24)	25 fewer per 1000 (from 135 fewer to 120 more)	⨁⨁⨁⨁ HIGH	
ALT normalisation - 104 weeks of treatment												

Quality assessment							No of patients		Effect		Quality	
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Telbivudine versus lamivudine**	**Control**	**Relative (95% CI)**	**Absolute**		
1: Chan 2012	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	nserious imprecision	none	51/114 (44.7%)	38.6%	RR 1.16 (0.85 to 1.58)	62 more per 1000 (from 58 fewer to 224 more)	⨁⨁⨁◯ MODERATE	
Histological improvement - 52 weeks of treatment												
1: Chan 2012	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/114 (31.6%)	38.6%	RR 0.82 (0.57 to 1.17)	69 fewer per 1000 (from 166 fewer to 66 more)	⨁⨁⨁◯ MODERATE	
Histological improvement - 104 weeks of treatment												
1: Chan 2012	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision	none		40.4%	RR 0.96 (0.69 to 1.32)	16 fewer per 1000 (from 125 fewer to 129 more)	⨁⨁⨁◯ MODERATE	

11.2.4 Economic evidence

Note that this area was prioritised for novel economic analysis

11.2.4.1 Literature review

One cost-effectiveness study was included [44] which compared the cost-effectiveness of, adefovir and entacavir alone and as salvage strategies after the development of viral resistance on lamivudine for people with active viral replication and chronic HBV cirrhosis. Half of the hypothetical population entering the model had compensated cirrhosis and the other half decompensated cirrhosis. The analysis was undertaken from a 'third party payer perspective' in the USA. This study is summarised in the economic evidence profile below (Table 211 and Table 212) and the full evidence table is in Appendix F.

Table 211: No treatment vs. Adefovir monotherapy vs. Adefovir salvage strategy vs. Entecavir monotherapy vs. Entecavir salvage strategy in people with active viral replication and HBV cirrhosis – Economic study characteristics

Study	Limitations	Applicability	Other comments
Kanwal 2006 (USA)[44]	Potentially serious limitations (a)	Partially applicable (b)	Decision analytic model Population: People with Hepatitis B cirrhosis and active viral replication Horizon: Lifetime Perspective: USA healthcare system Outcomes: QALYs Costs: Drugs, follow-up care, and cirrhosis care costs.

(a) Quality of life estimates were adopted from people with Hepatitis C, not HBV; triangular distribution assumed for all inputs; results of probabilistic analysis not fully reported.

(b) Baseline population was 50% compensated cirrhosis and 50% decompensated cirrhosis – results were not reported separately and results of sensitivity analysis varying these proportions was not reported; comparative effectiveness of entecavir based on histological improvement with no long term resistance data (1% per year was assumed).

Table 212: No treatment vs. Adefovir monotherapy vs. Adefovir salvage strategy vs. Entecavir monotherapy vs. Entecavir salvage strategy in people with active viral replication and HBV cirrhosis – Economic summary of findings

Study	Incremental cost (£)	Incremental effects (QALY)	ICER (£/QALY)	Uncertainty
Kanwal 2006 (USA)	Adefovir monotherapy vs No treatment £15,113 Entecavir monotherapy vs adefovir monotherapy £3,287	Adefovir monotherapy vs No treatment 1.2 Entecavir monotherapy vs adefovir monotherapy 0.2	Adefovir monotherapy vs No treatment £12,595 Entecavir monotherapy vs adefovir monotherapy £16,436	A cost effectiveness acceptability curve comparing entecavir monotherapy to adefovir monotherapy reported that at a threshold of approximately £20k per QALY, entecavir monotherapy was cost effective in approximately 55% of simulations.

Note: these values have been estimated based on a graph. Strategies using adefovir and entecavir as salvage therapies were excluded from the analysis by extended dominance.
Costs converted from 2008 US dollars using purchasing power parities.[77]

11.2.4.2 Health Economic model

A model was constructed that enabled the GDG to make conclusions on the most cost effective treatment for decompensated cirrhosis. The results of the model can be found below. For a more complete write-up of the methods and results, please see appendix H.

A.1.1.1 Population

The model evaluated a hypothetical cohort of people with decompensated cirrhosis due to CHB. In accordance with the studies used to inform evidence of effectiveness, the cohort had an average age of 52, 78% male, and 47% were HBeAg positive. Approximately 38% of the population had been previously exposed to lamivudine and 21% had previous adefovir exposure, this was important due to the presence of resistance.

A.1.1.2 Comparators

Patients entering the model received one of ten interventional strategies (Table 214). Interferon was not included as a comparator as it is contraindicated in people with cirrhosis. Lamivudine was not included because no randomised evidence of its effectiveness in this population was identified by the systematic review. There are several factors which influence the selection of appropriate second line treatment options. Based on *in vitro* and *in vivo* studies, it is well recognised that resistance to lamivudine confers cross-resistance to other L-nucleosides and reduces sensitivity to entecavir (Table 213). Conversely, mutants that are resistant to adefovir generally remain sensitive to L-nucleosides and entecavir (Table 213). When patients are treated sequentially with drugs that have overlapping resistance profiles, the second therapy is not only less effective, but may also lead to the selection of multidrug resistance. Another factor guiding the selection of appropriate treatment alternatives is that certain drugs may cause renal toxicity when used in combination. Therefore, all sequences and combinations of treatments other than those in which patients would be resistant to the second-line agent before starting treatment or would be at risk of toxicity were included in the analysis. A list all included treatment sequences is presented in Table 214. Tenofovir + Emtricitibine is included as a comparator as there was evidence found for it and it allowed indirect comparisons to be made between interventions. The GDG also suggested that it is used widely in hepatitis B decomopensated cirrhosis, even though it is not on licence for this indication.

Table 213: Antiviral cross resistance in CHB – From Zoulim 2012[113] and Zoulim & Locarnini 2009[112]

Pathway	Amino acid substitution	LMV	ETV	ADV	TFV
	Wild type	S	S	S	S
L-nucleoside (LMV)	M204I/V	R	I	S	S
Acyclic phosphate (ADV)	N236T	S	S	R	I
Shared (LMV, ADV)	A181T/V	R	S	R	I
Double (ADV, TFV)	A181T/V + N236T	R	S	R	R
D-Cyclopentane (ETV)	L180M + M204V/I ± I169 ± T184	R	R	S	S

I = intermediate sensitivity; R = resistant; S = sensitive. Telbivudine has been omitted from the original table as it is not a comparator in our model (as per TA 154).

Table 214: Comparators included in the model

1	No treatment
2	Adefovir → Tenofovir
3	Adefovir → Entecavir

4	Adefovir → Tenofovir + Emtricitabine
5	Entecavir → Adefovir
6	Entecavir → Tenofovir
7	Entecavir → Entecavir + Tenofovir
8	Entecavir → Tenofovir + Emtricitabine
9	Tenofovir → Entecavir
10	Tenofovir + Emtricitabine → Entecavir

11.2.4.3 Unit costs

Current UK unit costs are provided below to aid interpretation of cost effectiveness evidence.

Table 215: Current drug costs

Item	Cost	Annual cost
Lamivudine (Zeffix)	Tablets, 100 mg net price 28-tab pack = £78.09	ca. £1,015
Adefovir (Hepsera)	Tablets, 10 mg net price 30-tab pack = £296.73	ca. £3,610
Entecavir (Baraclude)	Tablets, 500 micrograms net price 30-tab pack = £363.26; Tablets, 1 mg net price 30-tab pack = £363.26. Oral solution, 50 micrograms/mL net price 210-mL pack = £423.80.	ca. £4,420
Tenofovir (Viread)	Tablets, 245 mg net price 30-tab pack = £240.46.	ca. £2,925
Telbivudine (Sebivo)	Tablets, 600 mg net price 28-tab pack = £290.33	ca. £3,774
Emtricitabine (Emtriva)	Capsules, 200mg net price 30-cap pack = £163.50	ca. £1, 989
Peg INF α 2a (Pegasys)	Injection, peginterferon alfa-2a, net price 135-microgram prefilled syringe = £107.76, 180-microgram prefilled syringe = £124.40.	£5971 (48-week course)

Source: BNF September 2011

A.1.2 Base case results

The results of the base case analysis show that tenofovir + emtricitabine followed by entecavir is the most effective strategy for the treatment of people with decompensated cirrhosis due to CHB. This strategy results in an additional 0.19 QALYs and is £23, 050 more costly than the next most effective treatment, at a cost of £121, 147 per QALY gained. Because this strategy far exceeds the £20, 000 to £30,000 threshold, it is not considered to represent a cost effective use of NHS resources.

After excluding strategies that are dominated or extendedly, the base case analysis shows that tenofovir followed by entecavir is the next most effective strategy with an ICER of £13, 858 per QALY gained. Taking into account uncertainty surrounding each model input, there is an 87.1% probability that tenofovir followed by entecavir is the most cost-effective treatment strategy for people with

decompensated cirrhosis due to CHB. The cost and QALYs associated with each strategy are reported in Table 216.

Figure 16: Strategies for the treatment of decompensated cirrhosis due to chronic CHB

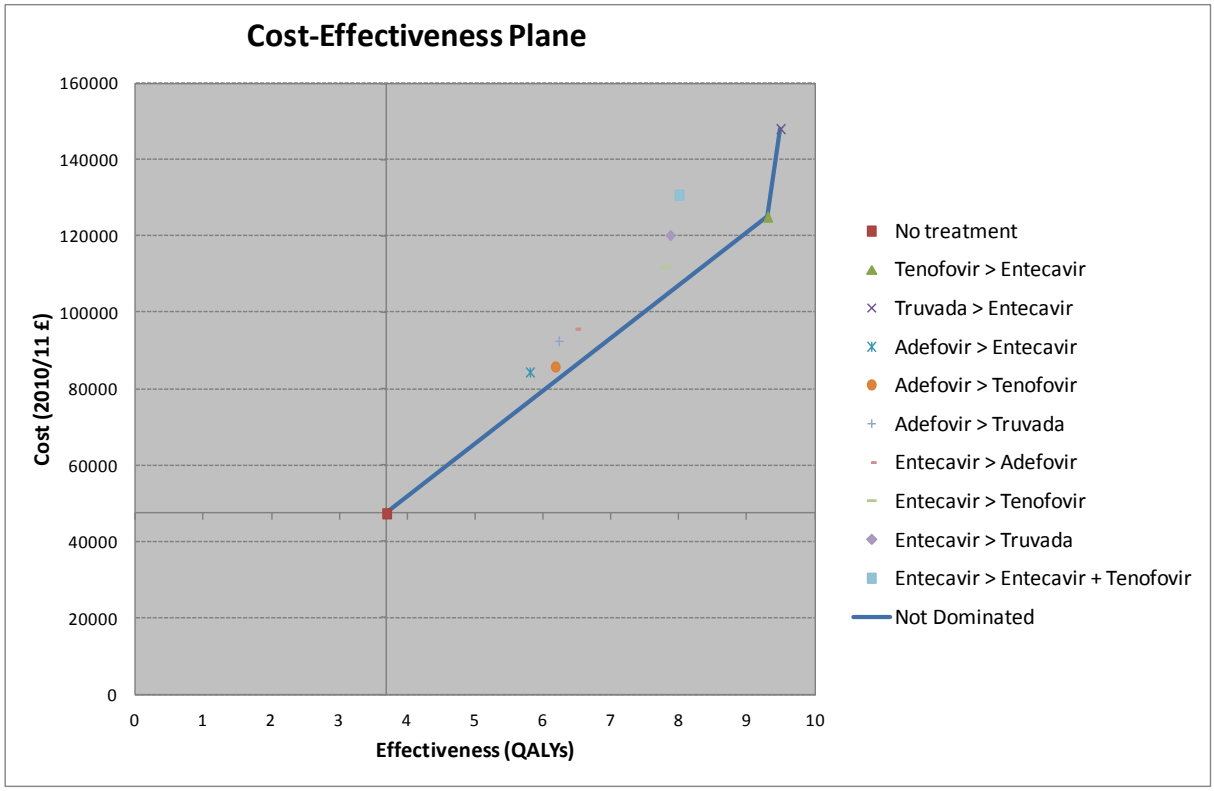


Table 216: Results of the base case analysis (probabilistic)

Strategy	Total Cost	Inc. Cost	Total Eff	Inc. Eff	Cost per QALY gained (ICER)	At £20,000 threshold		
						NMB	Probability Cost effective	Rank by NMB
No treatment	£47, 382	Baseline	3.689	Baseline	Baseline	£26, 389	1.17%	10
Adefovir > Entecavir	£84, 415		5.796		Extendedly Dominated	£31, 509	0.29%	8
Adefovir > Tenofovir	£85, 836		6.170		Extendedly Dominated	£37, 563	2.41%	4
Entecavir > Adefovir	£92, 552		6.223		Extendedly Dominated	£33, 670	2.03%	6
Adefovir > Tenofovir + emtricitabine	£95, 735		6.470		Extendedly Dominated	£31, 904	0.00%	7
Entecavir > Tenofovir	£112, 036		7.794		Extendedly Dominated	£43, 853	0.97%	2
Entecavir > Tenofovir + emtricitabine	£120, 244		7.862		Extendedly Dominated	£37, 001	0.61%	5
Tenofovir > Entecavir	£125, 106	£77, 724	9.297	5.609	£13, 858	£60, 841	87.11%	1

Strategy	Total Cost	Inc. Cost	Total	Inc.	Cost per	At £20,000 threshold		
Entecavir > Entecavir + Tenofovir	£130, 833		7.993		Dominated	£29, 024	0.01%	9
Tenofovir + emtricitabine > Entecavir	£148, 156	£23, 050	9.488	0.190	£121, 174	£41, 595	5.39%	3

Sensitivity analyses were also conducted that allowed the GDG to see what the impact of various assumptions were on the overall result, however, these showed very little difference to the base case result.

11.2.5 Evidence statements

11.2.5.1 Clinical evidence statements

Compensated cirrhosis (or advanced fibrosis) – HBeAg positive adults

Entecavir versus lamivudine

- One randomised study with 93 nucleos(t)ide-naïve HBeAg positive patients suggested that entecavir may be beneficial on increasing the proportion of patients achieving undetectable HBV DNA levels (<300copies/mL) compared to lamivudine when assessed at the end of 48 weeks treatment (LOW QUALITY).

Lamivudine versus placebo

- One randomised study with 651 patients with mixed HBeAg status (majority HBeAg positive) suggested that there may be no difference between lamivudine and placebo for the following outcomes assessed at up to 30 months follow up:
  - The proportion of patients with incidence of hepatocellular carcinoma (VERY LOW QUALITY);
  - Mortality (VERY LOW QUALITY).
- One randomised study with 651 patients with mixed HBeAg status (majority positive) suggested that lamivudine may be beneficial on having fewer patients with ≥2 points increase in Child-Pugh score compared to placebo at up to 30 months follow up (LOW QUALITY).
- One randomised study with 647 patients with mixed HBeAg status (majority positive) suggested that lamivudine may be harmful with respect to the proportion of patients with incidence of lamivudine resistance compared to placebo at up to 30 months follow up (LOW QUALITY).

Compensated cirrhosis (or advanced fibrosis) – HBeAg negative adults

Entecavir versus lamivudine

- One randomised study with 108 nucleos(t)ide-naïve HBeAg negative patients showed that entecavir is beneficial on increasing the proportion of patients achieving undetectable HBV DNA levels (<300 copies/mL) compared to lamivudine when assessed at the end of 48 weeks treatment (MODERATE QUALITY).

Compensated cirrhosis (or advanced fibrosis) – lamivudine refractory patients

Entecavir versus lamivudine

- One randomised study with 44 nucleos(t)ide-naïve HBeAg negative patients suggested that there may be no difference in the proportion of patients achieving undetectable HBV DNA levels (<300copies/mL) between entecavir and lamivudine when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).
- One randomised study with 245 HBeAg positive, negative and lamivudine refractory patients (mixed population) suggested that there may be no difference in all-cause mortality incidence between entecavir and lamivudine, assessed at the end of 48 weeks treatment (VERY LOW QUALITY).

Decompensated cirrhosis – mixed HBeAg populations

Entecavir versus adefovir

- One randomised study with a mixed population of 133 patients (50% HBeAg positive and 50% HBeAg negative) with decompensated liver disease suggested that entecavir may be beneficial on increasing the proportion of patients with undetectable HBV DNA compared to adefovir in the overall HBeAg positive and negative analysis assessed at the end of 48 weeks treatment (LOW QUALITY).
- One randomised study with 105 HBeAg positive patients (subgroup analysis) with decompensated liver disease suggested that entecavir may be beneficial on increasing the proportion of patients with undetectable HBV DNA compared to adefovir assessed at the end of 48 weeks treatment (LOW QUALITY).
- One randomised study with 86 HBeAg negative patients (subgroup analysis) with decompensated liver disease showed that entecavir is beneficial on increasing the proportion of patients with undetectable HBV DNA compared to adefovir assessed at the end of 48 weeks treatment (MODERATE QUALITY).
- One randomised study with 65 HBeAg positive patients with decompensated liver disease showed that entecavir is beneficial on log reduction of HBV DNA compared to adefovir when assessed at the end of 48 weeks treatment (MODERATE QUALITY).
- One randomised study with 65 HBeAg negative patients with decompensated liver disease showed that entecavir is beneficial on log reduction of HBV DNA compared to adefovir when assessed at the end of 48 weeks treatment (MODERATE QUALITY).
- One randomised study with a mixed population of 133 patients (50% HBeAg positive and 50% HBeAg negative) with decompensated liver disease suggested that entecavir may be beneficial on increasing the proportion of patients with the proportion of patients with Child-Pugh score ≥2 points decrease compared to adefovir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).
- One randomised study with a mixed population of 133 patients (50% HBeAg positive and 50% HBeAg negative) with decompensated liver disease suggested that there may be no difference between entecavir and adefovir on the following outcomes when assessed at the end of 48 weeks treatment:
    - Change in Model for end-stage liver disease score (MELD) from baseline (VERY LOW QUALITY).
- One randomised study with a mixed population of 133 patients (50% HBeAg positive and 50% HBeAg negative) with decompensated liver disease suggested that entecavir may be beneficial on increasing the proportion of patients with incidence of hepatocellular carcinoma and reducing

mortality compared to adefovir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).

- One randomised study with a mixed population of 133 patients (50% HBeAg positive and 50% HBeAg negative) with decompensated liver disease suggested that entecavir may be harmful in increasing the proportion of patients underwent liver transplantation compared to adefovir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).

Tenofovir plus emtricitabine versus tenofovir

- One randomised study with a mixed population of 72 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that tenofovir plus emtricitabine may neither be beneficial or harmful on reducing liver transplantation rates compared to tenofovir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).
- One randomised study with a mixed population of 72 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that there may be no difference in mortality incidence between tenofovir plus emtricitabine and tenofovir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).
- One randomised study with a mixed population of 72 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that tenofovir plus emtricitabine may be beneficial on reducing the proportion of patients with hepatocellular carcinoma compared to tenofovir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).
- One randomised study with a mixed population of 72 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that tenofovir plus emtricitabine may be beneficial on log reduction of HBV DNA compared to tenofovir when assessed at the end of 48 weeks treatment (LOW QUALITY).
- One randomised study with a mixed population of 72 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that tenofovir plus emtricitabine may be beneficial on increasing the proportion of patients with undetectable HBV DNA (<400copies/mL) compared to tenofovir when assessed at the end of 48 weeks treatment (LOW QUALITY).
- One randomised study with a mixed population of 52 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that tenofovir plus emtricitabine may be beneficial on increasing the proportion of patients with Child-Pugh score ≥2 points decrease compared to tenofovir when assessed at the end of 48 weeks treatment (LOW QUALITY).
- One randomised study with a mixed population of 72 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that tenofovir plus emtricitabine may be beneficial on having fewer patients with ascites (complications) compared to tenofovir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).
- One randomised study with a mixed population of 72 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that tenofovir plus emtricitabine may be beneficial on having fewer patients with encephalopathy (complications) compared to tenofovir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).

Entecavir versus tenofovir

- One randomised study with a mixed population of 48 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that entecavir may be beneficial on reducing liver transplantation rates compared to tenofovir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).
- One randomised study with a mixed population of 48 patients (>65% HBeAg negative in both arms) with decompensated cirrhosis suggested that there may be no difference in mortality

incidence between entecavir and tenofovir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).

- One randomised study with a mixed population of 48 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that there may be no difference between entecavir and tenofovir, in the proportion of patients with hepatocellular carcinoma when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).
- One randomised study with a mixed population of 48 patients (>65% HBeAg negative in both arms) with decompensated cirrhosis suggested that there may be no difference in log reduction of HBV DNA between entecavir and tenofovir when assessed at the end of 48 weeks treatment (LOW QUALITY).
- One randomised study with a mixed population of 48 patients (>65% HBeAg negative in both arms) with decompensated cirrhosis suggested that there may be no difference in the proportion of patients with undetectable HBV DNA (<400copies/mL) between entecavir and tenofovir when assessed at the end of 48 weeks treatment (LOW QUALITY).
- One randomised study with a mixed population of 39 patients (>65% HBeAg negative in both arms) with decompensated cirrhosis suggested that entecavir may be beneficial on increasing the proportion of patients with Child-Pugh score ≥2 points decrease compared to tenofovir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).
- One randomised study with a mixed population of 48 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that entecavir may be harmful on having more patients with ascites (complications) compared to tenofovir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).
- One randomised study with a mixed population of 48 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that entecavir may be harmful on having more patients with encephalopathy (complications) compared to tenofovir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).

Tenofovir plus emtricitabine versus entecavir

- One randomised study with a mixed population of 56 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that tenofovir plus emtricitabine may be harmful in terms of having greater liver transplantation rates compared to entecavir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).
- One randomised study with a mixed population of 56 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that there may be no difference in mortality incidence between tenofovir plus emtricitabine and tenofovir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).
- One randomised study with a mixed population of 56 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that there may be no difference between tenofovir plus emtricitabine and entecavir, in the proportion of patients with hepatocellular carcinoma when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).
- One randomised study with a mixed population of 56 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that there may be no difference in log reduction of HBV DNA between tenofovir plus emtricitabine and entecavir when assessed at the end of 48 weeks treatment (LOW QUALITY).
- One randomised study with a mixed population of 56 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that tenofovir plus emtricitabine may be beneficial on increasing the proportion of patients with undetectable HBV DNA (<400copies/mL) compared to entecavir when assessed at the end of 48 weeks treatment (LOW QUALITY).

- One randomised study with a mixed population of 37 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that there may be no difference in the proportion of patients with Child-Pugh score ≥2 points decrease between tenofovir plus emtricitabine and entecavir when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).
- One randomised study with a mixed population of 56 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that tenofovir plus emtricitabine may be beneficial on having fewer patients with ascites (complications) compared to tenofovir when assessed at the end of 48 weeks treatment (LOW QUALITY).
- One randomised study with a mixed population of 56 patients (>60% HBeAg negative in both arms) with decompensated cirrhosis suggested that there may be no difference between tenofovir plus emtriciabine and entecavir in the proportion of patients with encephalopathy (complications) when assessed at the end of 48 weeks treatment (VERY LOW QUALITY).

11.2.5.2 Economic evidence statements

- For people with active viral replication and chronic HBV cirrhosis, treatment with tenofovir is the optimal first line treatment. If tenofovir is not tolerated, then moving on to Entecavir treatment would be the appropriate second line therapy.

11.2.6 Recommendations and link to evidence

Recommendations	**59. Manage decompensated liver disease in adults in conjunction with a liver transplant centre.** **60. Do not offer peginterferon alfa-2a to people with chronic hepatitis B and decompensated liver disease.** **61. Offer entecavir as first-line treatment in people with decompensated liver disease if there is no history of lamivudine resistance** o Offer tenofovir disoproxil to people with a history of lamivudine resistance. o Reduce the dose of tenofovir disoproxil in people with renal impairment, in line with guidance in the summary of product characteristics.
Relative values of different outcomes	The following outcomes were considered significant by the GDG: • Progression to transplantation • Mortality • Reduction in MELD/CP scores • Incidence of hepatocellular carcinoma • Antiviral resistance Complications such as: • Ascites • Variceal bleeding • Encephalopathy • Spontaneous bacteria peritonitis (decompensated group only) Other outcomes: • Undetectable HBV DNA • Log reduction of HBV DNA • Quality of life
Trade off between clinical benefits and harms	Evidence from RCTs demonstrated that treatment of nucleos(t)ide naïve people with compensated cirrhosis with entecavir for 48 weeks improved the proportion of patients with undetectable HBV DNA (<300 copies/mL) compared to lamivudine (Schiff 2008). There was no impact on overall mortality. However, no difference was seen in lamivudine refractory patients. No amino acid substitutions associated with ETV resistance were seen. Evidence from RCTs demonstrated that treatment of people with decompensated liver disease with entecavir for 48 weeks improved the proportion of patients with undetectable HBV DNA (<300 copies/mL), reduced the incidence of hepatocellular carcinoma, and led to a reduction in mortality compared with adefovir treatment (Liaw 2011). Both drugs resulted in an improvement in Child-Pugh and Model for End-stage Liver Disease (MELD)

	scores but there was no difference between the two drugs. More patients required liver transplantation in the entecavir group than adefovir group, which the GDG felt was a reflection of the lower mortality and higher fitness for surgery in the entecavir-treated people. Evidence from a RCT demonstrated that treatment of people with decompensated liver disease with entecavir for 48 weeks led to an increased proportion achieving a ≥2 point decrease in their Child-Pugh score compared with tenofovir treatment (Liaw 2011A). However, this did not result in a mortality benefit. No resistance mutations causing virologic breakthrough were seen in either group. The same RCT demonstrated that the treatment of people with decompensated liver disease with tenofovir plus emtricitabine for 48 weeks improved the proportion with undetectable HBV DNA (<400 copies/mL) compared with entecavir but no difference in ≥2 point reduction in Child-Pugh score or mortality (Liaw 2011A). This RCT also demonstrated that treatment of people with decompensated liver disease with tenofovir plus emtricitabine for 48 weeks improved the proportion with undetectable HBV DNA, ≥2 point decrease in Child-Pugh score but did not improve mortality compared to tenofovir alone. For compensated cirrhosis there is evidence for a reduction in HBV DNA in people treated with entecavir. No RCTs could currently be identified comparing tenofovir plus emtricitabine with entecavir. The GDG felt that tenofovir plus emtricitabine is likely to be at least as effective (as found in people with decompensated cirrhosis), with a much reduced risk of developing drug resistance. For people with decompensated cirrhosis the evidence suggests that there is benefit of treatment with entecavir compared to adefovir and tenofovir. However, tenofovir plus emtricitabine did lead to a further decrease in HBV DNA compared with entecavir. The GDG therefore felt that tenofovir plus emtricitabine is likely to suppress viral DNA and is less prone to resistance mutations and therefore may be the favoured drug in the long-term. The GDG noted that the combination drug does not currently have a licence for hepatitis B in the UK.
Economic considerations	One economic paper was included in the review which found that in people with active viral replication and chronic HBV cirrhosis, beginning treatment with adefovir is more likely to result in improved health at a reasonable cost compared to no treatment. Entecavir appears to be more effective but is also more expensive than adefovir. At a threshold of £20k per QALY gained, there is approximately a 55% probability that entecavir will be cost-effective compared to adefovir. There is therefore a high degree of uncertainty surrounding this result. Although initiating treatment with adefovir or entecavir salvage on emergence of viral resistance was not found to be cost-effective, when faced with a patient who has already developed resistance to lamivudine, this study found that switching to adefovir appears to be more cost effective than switching to entecavir on the basis of current viral resistance data. At baseline, half the population included in this analysis were assumed to have compensated cirrhosis and the remainder decompensated cirrhosis. People with compensated cirrhosis could develop decompensated cirrhosis, and people with decompensated cirrhosis could regress back to compensated cirrhosis. Following re-compensation, people were eligible to decompensate a second time. People could develop hepatocellular carcinoma at any stage and only people with decompensated cirrhosis or carcinoma were eligible for a liver transplant. The authors report that they varied this prevalence between 0% and 100% in sensitivity analysis; however, the results of this analysis are

	not reported in the paper. The paper however had potentially serious limitations and partial applicability; also it did not include other strategies such as teneofovir, therefore the GDG decided to give more weight to the conclusions of the original economic model. This shows that the most cost effective treatment for decompensated cirrhosis is likely to be the use of tenofovir followed by entecavir if tenofovir is not tolerated or fails. These treatments both have very low or non-existent resistance rates. The regime of tenofovir > entecavir is more expensive than other treatments but also considerably more effective than all but one sequence of treatments. The Incremental cost effectiveness ratio associated with the sequence tenofovir > entecavir is £13,858 compared to no treatment, which is within the NICE cost effectiveness threshold of £20,000 per QALY gained. The only treatment sequence that is more effective is tenofovir + emtricitabine > entecavir however, this has an ICER of over £120,000 per QALY gained compared to the tenofovir > entecavir strategy.
Quality of evidence	Two trials were found on decompensated cirrhotic patients (baseline CP score ≥7). Entecavir was shown to be beneficial in terms of increasing the proportion of people achieving undetectable HBV DNA and log reduction in HBV DNA, reported by one trial which was of moderate quality (no details of randomisation procedure, unclear allocation concealment and no blinding). Lower incidence of hepatocellular carcinoma and lower mortality were found in those who received entecavir (both very low quality). Evidence from a trial on emtricitabine plus tenofovir (TDF + FTC combination therapy) vs. tenofovir vs. entecavir showed tenofovir plus emtricitabine (TDF + FTC) was beneficial for the proportion of people achieving undetectable HBV DNA compared to tenofovir and entecavir (both low quality due to mixed HBeAg population and imprecision). A greater proportion of people with ≥2 point's decrease in Child-Pugh score was also found in the tenofovir plus emtricitabine group, compared to tenofovir (low quality). When compared to tenofovir, entecavir was shown to be beneficial by having a larger proportion of patients with ≥2 points decrease in Child-Pugh score (very low quality). The GDG considered clinical events such as ascites, variceal bleeding as a marker of liver disease progression and they often require hospitalisation. However, the number of people experienced these events was often small (very serious imprecision) and they were not commonly reported as individual outcomes by the trials. Overall there was limited evidence for CHB infected people with compensated cirrhosis. Evidence from a RCT suggested no difference between lamivudine and placebo (low to very low quality, due to no details on randomisation procedure given, loss to follow up not reported, mixed population of HBeAg positive and negative, imprecision). Another RCT indicated more people achieving undetectable HBV DNA in people who received entecavir, compared to lamivudine (moderate to low quality, due to no details of randomisation procedure, unclear allocation concealment, post-hoc descriptive subgroup analyses, imprecision).
Other considerations	Interferon-alpha is not used in decompensated cirrhosis because its immuno-stimulant properties exacerbate the liver failure. No evidence was found for interferon-alpha. This recommendation is based on the GDG expert opinion. For people with decompensated cirrhosis, the GDG also took into consideration a recent safety issue with tenofovir, highlighted by the FDA in their review of safety data from the clinical trial GS-US-174-0108. A higher

	proportion of tenofovir exposed patients with decompensated disease experienced an increase in serum creatinine ≥ 0.5 mg/dL over baseline, and a creatinine clearance < 50 mL/min. However, trial GS-US-174-0108 was too small to allow adequate evaluation of these events. Therefore, based on appropriate scientific data, the FDA has determined that the manufacturer is required to conduct a prospective 5-year pre-OLT (orthotopic liver transplant) registry study to collect and analyse data regarding renal function in patients with chronic hepatitis B and decompensated liver disease treated with tenofovir disoproxil fumarate and a comparator group taking another nucleoside analogue, such as entecavir. Pending the results of this trial, the GDG did not feel it appropriate to recommend tenofovir, despite the superior cost-effectiveness of the strategy tenofovir followed by entecavir. Therefore, they recommended entecavir for patients with decompensated cirrhosis. In making this recommendation, the GDG noted the similar clinical effectiveness of entecavir and tenofovir, and the cost effectiveness evidence that the next best strategy was entecavir followed by tenofovir. The GDG consider tenofovir to be appropriate treatment for compensated cirrhosis but there is no RCT data available. Many RCTs examined CHB HBeAg positive/negative patients with a proportion of them had compensated cirrhosis. The GDG felt that the data on use of tenofovir plus emtricitabine and tenofovir in decompensated cirrhosis allowed extrapolation towards justifying its use in compensated cirrhosis (indirect evidence). The GDG acknowledge that very few children with CHB infection (except those with fulminant hepatitis) develop decompensated disease. The GDG confirmed that current practice for the treatment of decompensated cirrhosis varies by region. In areas that are able to supply tenofovir plus emtricitabine at a cheaper price due to HIV tariffs then this option is used. However, in those areas where it can only be obtained at list price, then tenofovir with lamivudine is used.

11.3 Pregnancy

11.3.1 Introduction

Mother to baby transmission of hepatitis B at or around the time of birth (perinatal infection) is one of the major routes of transmission of hepatitis B and is responsible for the maintenance of the numbers of persistently infected people within some areas of high endemicity. In other areas of high endemicity, infections may occur in childhood from children who have been perinatally infected, known as horizontal infection [55]. The earlier the time of infection, the higher the risk of the infection becoming persistent [65] and the longer the period of infection, the higher the chance of morbidity and mortality later in life[28] . Interruption of perinatal infection is therefore important in reducing the adverse clinical outcomes of chronic hepatitis B infections. Studies on perinatal transmission identified HBeAg as a significant risk factor with between 70-90% of babies born to HBsAg and HBeAg positive mothers most at risk of acquiring a persistent infection [3]. The relationship between HBeAg and the risk of transmission has now been more clearly related to the levels of circulating HBV DNA as a more direct measurement of infectivity [99]. Babies born to women who were HBeAg negative were at a much lower risk of infection, but very rarely developed a neonatal

acute hepatitis B, which can lead to fulminant hepatitis. Such infections are associated with HBeAg negative variants, which express high levels of HBV DNA in the absence of HBeAg, the most common of these variants have a mutation in the precore region of the HBV genome [10] , but a variety of other HBeAg negative viraemic variants exist and are related to the particular virus genotype[2] .

The current protocol for the prevention of perinatal transmission of hepatitis B relies on post exposure prophylaxis started immediately after birth with vaccine alone or vaccine with the addition of HBIG. The schedules used have been shown in studies to be 90% effective in preventing perinatal transmission [56]. Those babies most likely to become infected are those born to mothers with very high viraemias defined as $>10^7$IU/ml[100,110]. The addition of an antiviral agent for the woman in the last trimester of her pregnancy to reduce viraemia and consequently lower the risk of infection to the infant might be considered. Such treatment would be for a limited period for the purpose of reducing the risk of infection to the baby. If the woman requires treatment based on her own clinical condition then that treatment would be continued through the pregnancy.

The use of antiviral drugs in pregnancy may carry risks to the baby and there is also the possibility of risk to the woman of heightened immune response on withdrawal of drug resulting in 'acute hepatitis' all of which require careful management.

The World Health Organisation has previously advised that breastfeeding is safe for women with chronic hepatitis B virus infection when their infants have received HBV vaccinations[101]. HBsAg has been detected in small quantities in breast milk but no evidence of mother to infant transmission of HBV via breast-milk has been found. A meta-analysis and systematic review of ten studies found no increase in HBsAg or HBV DNA levels at 6 to 12 months of age in 751 breast-fed infants versus 873 nonbreast-fed infants[88]. Infants in the study had all been vaccinated against hepatitis B virus. Therefore there is unlikely to be any risk of transmission in breastfed fully vaccinated infants.

11.3.2 Review question: In pregnant/lactating women with chronic hepatitis B what is the clinical and cost-effectiveness of anti-viral therapy in order to reduce risk of vertical transmission from mother to infant?

Table 217: PICO characteristics of review question

Protocol	
Population	Pregnant and lactating women with chronic hepatitis B virus infection
Intervention	• Tenofovir • Lamivudine • Telbivudine • Emtricitabine plus tenofovirtenofovir plusemtricitabine • Entecavir • Adefovir
Comparison	• No therapy/ control • Tenofovir • Lamivudine • Telbivudine • Emtricitabine plus tenofovirtenofovir plusemtricitabine • Entecavir • Adefovir
Outcomes	Critical outcomes: • newborn (0-9 months) and infant (9-15 first months) HBV DNA positivity

Protocol	
	• newborn (0-9 months) and infant (9-15 first months) HBeAg seropositivity • newborn (0-9 months) and infant (9-15 first months) HBsAg seropositivity Secondary outcomes: • Maternal HBV DNA reduction • Congenital abnormalities • Adverse events • Incidence of resistance

11.3.3 Clinical evidence

We searched for randomised and observational studies comparing the clinical efficacy of different antiviral treatments in pregnant or lactating women with chronic hepatitis B. A total of five studies have been identified and included in this review, of which two are randomised controlled trials and three are prospective open-label studies. Three studies compared lamivudine versus no therapy (with or without hepatitis B immunoglobulin (HBIG) and/or vaccine) during the third trimester. Two studies compared telbivudine versus no therapy (with or without HBIG and/or vaccine) during the second or third trimester. All studies included HBeAg positive pregnant women and were conducted in the Asia Pacific regions (China and Philippines). Forest plots can be found in appendix G.

11.3.3.1 Summary characteristics of included studies

Table 218: Summary characteristics of included studies

Comparison Study design	Included studies (N=)	Setting	Study population	Outcomes
Lamivudine [vaccine + hep B immunoglobulin (HBIG)*] versus placebo [vaccine + HBIG*] during the 3rd trimester (from week 32 gestation to week 4 postpartum). Double blinded RCT	Xu 2009 (N=155)	China and Philippines	HBeAg positive pregnant women aged 16 and over with an estimated gestational age of 26-30 wks at screening who had detectable serum HBsAg and serum HBV DNA >1000 MEq/mL Infants All received 3 doses of vaccine (within 24h of birth, week 4 and 24), with or without a single 200IU dose of HBIG, given within 24h of birth.	Critical outcomes: Newborns and infants (12, 28 and 52 weeks) HBsAg positivity Newborns and infants (12, 28 and 52 weeks) HBV DNA positivity Secondary outcomes: Maternal HBV DNA reduction Adverse events (mothers and infants) Congenital abnormalities
Lamivudine [no vaccine] versus HBIG [no vaccine] versus no therapy [no	Li 2003 (N=150)	China	HBsAg positive pregnant women normal liver and kidney function.	Critical outcomes: Newborns HBsAg positivity Newborns HBeAg positivity Newborns HBV DNA positivity

Comparison Study design	Included studies (N=)	Setting	Study population	Outcomes
vaccine] from 28 week of gestation until a month after delivery RCT			Infants All received positive and/or active immune prophylaxis at 24 hours after delivery	Secondary outcomes: Maternal HBV DNA reduction (after administration of agents) Adverse events (mothers and infants)
Lamivudine [vaccine + HBIG*] versus no therapy [vaccine + HBIG*] during the 3rd trimester (gestation weeks 24-32) Prospective open label study	Yu 2012 (N=200)	China	HBeAg positive pregnant women with HBV DNA>=107 copies/ml in gestation period between 24 and 32 weeks. Infants *All received 200IU of HBIG injections after birth and at day 15, and 20 µg hepatitis B vaccine (3 doses: after birth, at week 4 and 24)	Critical outcomes: 1) Newborns and infants HBV DNA positivity 2) Newborns and infants HBsAg positivity Secondary outcomes: Maternal undetectable HBV DNA (<5x102 copies/ml to 1x 109 copies/ml) prior to delivery Adverse events (infants) Congenital abnormalities
Telbivudine [vaccine + HBIG*] versus no therapy [vaccine + HBIG*] during the 2nd or 3rd trimester (gestation weeks 20-32) Prospective open label study	Han 2011 (N=229)	China	HBeAg positive pregnant aged 20-40 years, gestational age between 20-32 weeks, women with CHB, levels of HBV DNA>107 copies/mL. Infants *All received 3 doses of vaccine 20µg (within 12h of birth, at week 4 and 24) and 200IU doses of HBIG within 2h after birth and at day 15.	Critical outcomes: Newborn and infant (28 weeks) HBV DNA positivity Newborn and infant (28 weeks) HBsAg seropositivity Secondary outcomes: Maternal undetectable HBV DNA (<500 copies/ml) Congenital anomalies Serious adverse events
Telbivudine [vaccine + HBIG*] versus no therapy [vaccine + HBIG*] during the 2nd or 3rd trimester (gestation weeks 12-30) Prospective open label study	Pan 2012 (N=88)	China	HBeAg positive pregnant aged 20-40 years, gestational age between 12-30 weeks, women with CHB, levels of HBV DNA>6 log10 copies/mL and increased levels of ALT (>1x times the upper limit of normal (ULN=40 IU/mL) and <10 times ULN). Infants *All received 3 doses of vaccine 20µg (within 12h of birth, at week 4 and	Critical outcomes: Newborn and infant (28 weeks) HBV DNA positivity Newborn and infant (28 weeks) HBeAg seropositivity Newborn and infant (28 weeks) HBsAg seropositivity Secondary outcomes: Maternal undetectable HBV DNA (<500 copies/ml) Congenital anomalies Serious adverse events

Comparison Study design	Included studies (N=)	Setting	Study population	Outcomes
			24) and 200IU doses of HBIG within 2h after birth and at day 15.	

**Infants received HBIG and/or vaccine*

11.3.3.2 Comparison of lamivudine (vaccine+HBIG) during the 3rd trimester of pregnancy versus placebo (vaccine+HBIG)

Table 219: Lamivudine versus no therapy- clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamivudine (vaccine+ HBIG)**	**Placebo (vaccine+ HBIG)**	**Relative ratio or Peto OR (95% CI)**	**Absolute**	
HBsAg seropositivty at birth (newborns)											
1 Xu 2009	RCT-double blinded	Serious [(a)]	no serious inconsistency	no serious indirectness	very serious imprecision [(b)]	none	17/56 (30.4%)	14/59 (23.7%)	RR 1.28 (0.7 to 2.34)	66 more per 1000 (from 71 fewer to 318 more)	VERY LOW
HBsAg seropositivty at birth (newborns)											
1 Yu 2012	Observational study	Serious [(c)]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association reduced effect for RR >> 1 or RR << 1	9/94 (9.6%)	29/91 (31.9%)	RR 0.3 (0.15 to 0.6)	223 fewer per 1000 (from 127 fewer to 271 fewer)	MODERATE
HBsAg seropositivity at 1 month (newborns)											
1 Yu 2012	Observational study	Serious [(c)]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association reduced effect for RR >> 1 or RR << 1	0/94 (0%)	10/91 (11%)	Peto OR 0.12 (0.03 to 0.42)	110 fewer per 1000 (from 40 fewer to 180 fewer)	MODERATE
HBsAg seropositivity at week 12 (infants)											
1 Xu 2009	RCT-double blinded	Serious [(a)]	no serious inconsistency	no serious indirectness	very serious imprecision [(b)]	none	5/56 (8.9%)	6/59 (10.2%)	RR 0.88 (0.28 to 2.72)	12 fewer per 1000 (from 73 fewer to 175 more)	VERY LOW

Quality assessment							No of patients		Effect		Quality
HBsAg seropositivity at week 28 (infants)											
1 Xu 2009	RCT-double blinded	Serious [a]	no serious inconsistency	no serious indirectness	very serious imprecision [b]	none	3/56 (5.4%)	6/59 (10.2%)	RR 0.53 (0.14 to 2.01)	48 fewer per 1000 (from 87 fewer to 103 more)	VERY LOW
HBsAg seropositivity at week 52 (infants)											
1 Xu 2009	RCT-double blinded	Serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/49 (20.4%)	23/41 (56.1%)	RR 0.36 (0.2 to 0.67)	359 fewer per 1000 (from 185 fewer to 449 fewer)	MODERATE
HBsAg seropositivity at week 52 (infants)											
1 Yu 2012	Observational study	Serious [c]	no serious inconsistency	no serious indirectness	Serious [d]	none	0/94 (0%)	7/91 (7.7%)	RR 0.06 (0 to 1.11)	72 fewer per 1000 (from 77 fewer to 8 more)	VERY LOW
HBV DNA positivity at birth (newborns)											
1 Xu 2009	RCT-double blinded	Serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/56 (12.5%)	24/59 (40.7%)	RR 0.31 (0.14 to 0.66)	281 fewer per 1000 (from 138 fewer to 350 fewer)	MODERATE
HBV DNA positivity at 1 month (newborns)											
1 Yu 2012	Observational study	Serious [c]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association reduced effect for RR >> 1 or RR << 1	0/94 (0%)	10/91 (11%)	Peto OR 0.12 (0.03 to 0.42)	110 fewer per 1000 (from 40 fewer to 180 fewer)	MODERATE
HBV DNA positivity at week 12 (infants)											
1 Xu 2009	RCT-double blinded	Serious [a]	no serious inconsistency	no serious indirectness	very serious imprecision [b]	none	11/56 (19.6%)	14/59 (23.7%)	RR 0.83 (0.41 to 1.67)	40 fewer per 1000 (from 140 fewer to 159	VERY LOW

Quality assessment							No of patients		Effect		Quality
										more)	
HBV DNA positivity at week 28 (infants)											
1 Xu 2009	RCT-double blinded	Serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	6/56 (10.7%)	9/59 (15.3%)	RR 0.7 (0.27 to 1.85)	46 fewer per 1000 (from 111 fewer to 130 more)	VERY LOW
HBV DNA positivity at week 52 (infants)											
1 Xu 2009	RCT-double blinded	Serious [a]	no serious inconsistency	no serious indirectness	Serious [d]	none	4/49 (8.2%)	9/41 (22%)	RR 0.37 (0.12 to 1.12)	138 fewer per 1000 (from 193 fewer to 26 more)	LOW
HBV DNA positivity at week 52 (infants)											
1 Yu 2012	Observational study	Serious [c]	no serious inconsistency	no serious indirectness	no serious imprecision [d]	strong association reduced effect for RR >> 1 or RR << 1	0/94 (0%)	7/91 (7.7%)	Peto OR 0.12 (0.03 to 0.55)	80 fewer per 1000 (from 20 fewer to 130 fewer)	MODERATE
Maternal undetectable HBV DNA (before delivery)											
1 Yu 2012	Observational study	Serious [c]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association reduced effect for RR >> 1 or RR << 1	29/94 (30.9%)	0/91 (0%)	Peto OR 10.19 (4.62 to 22.47)	310 more (from 210 to 400 more)	MODERATE
Maternal log HBV DNA (before delivery) (Better indicated by lower values)											
1 Yu 2012	Observational study	Serious [c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3.18 (1.52)	7.81 (0.86)	MD -4.63 (-4.97 to -4.29)	MD 4.63 lower (4.97 to 4.29 lower)	LOW
Infants adverse events											
1 Xu 2009	RCT-double	Serious [a]	no serious inconsiste	no serious indirectness	very serious imprecision	none	10/56	12/59	RR 0.88 (0.41 to	not pooled	VERY LOW

Quality assessment							No of patients		Effect		Quality
	blinded		ncy		[b]				1.87)		
Infants serious adverse events											
1 Xu 2009	RCT-double blinded	Serious [a]	no serious inconsistency	no serious indirectness	very serious imprecision [b]	none	5/56 (8.9%)	3/59 (5.1%)	RR 1.76 (0.44 to 7.01)	39 more per 1000 (from 28 fewer to 306 more)	VERY LOW
Maternal serious adverse events											
1 Xu 2009	RCT-double blinded	Serious [a]	no serious inconsistency	no serious indirectness	very serious imprecision [b]	none	1/89 (1.1%)	1/61 (1.6%)	RR 0.69 (0.04 to 10.75)	5 fewer per 1000 (from 16 fewer to 160 more)	VERY LOW
Maternal adverse events											
1 Xu 2009	RCT-double blinded	Serious [a]	no serious inconsistency	no serious indirectness	very serious imprecision [b]	none	7/89 (7.9%)	6/61 (9.8%)	RR 0.8 (0.28 to 2.26)	20 fewer per 1000 (from 71 fewer to 124 more)	VERY LOW
Postpartum haemorrhage											
1 Yu 2012	Observational study	Serious [c]	no serious inconsistency	no serious indirectness	Serious imprecision [d]	none	33/94 (35.1%)	36/91 (39.6%)	RR 0.89 (0.61 to 1.29)	44 fewer per 1000 (from 154 fewer to 115 more)	VERY LOW
Caesarean section											
1 Yu 2012	Observational study	Serious [c]	no serious inconsistency	no serious indirectness	Serious [d]	none	48/94 (51.1%)	45/91 (49.5%)	RR 1.03 (0.78 to 1.38)	15 more per 1000 (from 109 fewer to 188 more)	VERY LOW
Preterm birth											
1 Yu 2012	Observational study	Serious [c]	no serious inconsistency	no serious indirectness	very serious imprecision [b]	none	7/94 (7.4%)	8/91 (8.8%)	RR 0.85 (0.32 to 2.24)	13 fewer per 1000 (from 60 fewer to 109	VERY LOW

Quality assessment							No of patients		Effect		Quality
										more)	
Neonatal asphyxia											
1 Yu 2012	Observational study	Serious [c]	no serious inconsistency	no serious indirectness	very serious imprecision [b]	none	4/94 (4.3%)	6/91 (6.6%)	RR 0.65 (0.19 to 2.21)	23 fewer per 1000 (from 53 fewer to 80 more)	VERY LOW
Malformation											
1 Yu 2012	Observational study	Serious [c]	no serious inconsistency	no serious indirectness	very serious imprecision [b]	none	0/94 (0%)	1/91 (1.1%)	Peto OR 0.13 (0.00 to 6.60)	10 fewer per 1000 (from 40 fewer to 20 more)	VERY LOW

(a) No information on randomisation procedure or allocation concealment.
(b) Confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm and appreciable harm
(c) Patients participated in the intervention or control groups based on their preferences.
(d) Confidence interval is consistent with two clinical decisions; appreciable benefit and no appreciable benefit or harm

11.3.3.3 Comparison of lamivudine during the 3rd trimester of pregnancy (no vaccine) versus HBIG (no vaccine)

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamivudine (no vaccine)**	**HBIG (no vaccine)**	**Relative (95% CI)**	**Absolute**	
HBsAg seropositivity at birth (newborns)											
1 Li 2003	RCT-unclear blinding	Very serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	1/43 (2.3%)	3/56 (5.4%)	RR 0.43 (0.05 to 4.03)	31 fewer per 1000 (from 51 fewer to 162 more)	VERY LOW
HBeAg seropositivity at birth (newborns)											

Quality assessment							No of patients		Effect		Quality
1 Li 2003	RCT-unclear blinding	Very serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	7/43 (16.3%)	7/56 (12.5%)	RR 1.3 (0.49 to 3.43)	37 more per 1000 (from 64 fewer to 304 more)	VERY LOW
HBV DNA positivity at birth (newborns)											
1 Li 2003	RCT-unclear blinding	Very serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	7/43 (16.3%)	9/56 (16.1%)	RR 1.01 (0.41 to 2.5)	2 more per 1000 (from 95 fewer to 241 more)	VERY LOW
Maternal HBV DNA reduction (after administration of agents) (Better indicated by lower values)											
1 Li 2003	RCT-unclear blinding	Very serious [a]	no serious inconsistency	no serious indirectness	Serious [c]	none	2.16 (1.27)	2.09 (2.28)	MD 0.07 (-0.64 l to 0.78)	MD 0.07 higher (0.64 lower to 0.78 higher)	VERY LOW

(a) No information on blinding, randomization or allocation concealment.
(b) Confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm and appreciable harm
(c) Confidence interval is consistent with two clinical decisions; appreciable benefit and no appreciable benefit or harm

11.3.3.4 Comparison of lamivudine (no vaccine) during the 3rd trimester of pregnancy versus no therapy (no vaccine)

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lamivudine (no vaccine)**	**No therapy (no vaccine)**	**Relative (95% CI)**	**Absolute**	
HBsAg seropositivity at birth (newborns)											
1 Li 2003	RCT-unclear	Very serious [a]	no serious inconsistency	no serious indirectness	Serious [b]	none	1/43 (2.3%)	8/52 (15.4%)	RR 0.15 (0.02 to	131 fewer per 1000 (from	VERY LOW

Quality assessment							No of patients		Effect		Quality
	blinding								1.16)	151 fewer to 25 more)	
HBeAg seropositivity at birth (newborns)											
1 Li 2003	RCT- unclear blinding	Very serious [a]	no serious inconsistency	no serious indirectness	very serious [c]	none	7/43 (16.3%)	11/52 (21.2%)	RR 0.77 (0.33 to 1.81)	49 fewer per 1000 (from 142 fewer to 171 more)	VERY LOW
HBV DNA positivity at birth (newborns)											
1 Li 2003	RCT- unclear blinding	Very serious [a]	no serious inconsistency	no serious indirectness	Serious [b]	none	7/43 (16.3%)	17/52 (32.7%)	RR 0.5 (0.23 to 1.09)	163 fewer per 1000 (from 252 fewer to 29 more)	VERY LOW
Maternal HBV DNA reduction (after administration of agents) (Better indicated by lower values)											
1 Li 2003	RCT- unclear blinding	Very serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2.16 (1.27)	0.82 (2.73)	MD 1.34 (0.51 to 2.17)	MD 1.34 higher (0.51 to 2.17 higher)	LOW

(a) No information on blinding, randomization or allocation concealment.
(b) Confidence interval is consistent with two clinical decisions; appreciable benefit and no appreciable benefit or harm
(c) Confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm and appreciable harm

11.3.3.5 Comparison of telbivudine (vaccine+ HBIG) during the 2nd or 3rd trimester versus no therapy (vaccine+ HBIG)

Table 220: Telbivudine versus no therapy- clinical study characteristics and clinical summary of findings

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Telbivudine**	**No therapy**	**Relative Risk or Peto OR**	**Absolute**	

Quality assessment							No of patients		Effect		Quality
									(95% CI)		
HBsAg positivity at birth (newborns)											
1 Han 2011	Observational study	Very serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	reduced effect for RR >> 1 or RR << 1	13/136 (9.6%)	28/94 (29.8%)	RR 0.32 (0.18 to 0.59)	203 fewer per 1000 (from 122 fewer to 244 fewer)	VERY LOW
HBeAg positivity at birth (newborns)											
1 Pan 2012	Observational study	Very serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	54/54 (100%)	35/35 (100%)	RR 1 (0.95 to 1.05)	0 fewer per 1000 (from 50 fewer to 50 more)	VERY LOW
HBV DNA positivity at birth (newborns)											
1 Han 2011	Observational study	Very serious [a]	no serious inconsistency	no serious indirectness	serious[b]	none	123/136 (90.4%)	75/94 (79.8%)	RR 1.13 (1.01 to 1.27)	104 more per 1000 (from 8 more to 215 more)	VERY LOW
Congenital anomalies											
1 Han 2011	Observational study	Very serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/136 (0%)	0/94 (0%)	-	0 more per 1000 (from 0 more to 0 more)	LOW
HBsAg positivity at week 28 (infants)											
1 Han 2011	Observational study	Very serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association3 reduced effect for RR >> 1 or RR << 13	0/132 (0%)	7/88 (8%)	Peto OR 0.08 (0.02 to 0.35)	80 fewer per 1000 (from 140 fewer to 200 fewer)	LOW
HBeAg positivity at week 28 (infants)											
1 Pan 2012	Observational	Very serious [a]	no serious inconsistency	no serious indirectness	serious[b]	strong association	0/54 (0%)	3/35 (8.6%)	Peto OR 0.07	90 fewer per 1000 (from	VERY LOW

Quality assessment							No of patients		Effect		Quality
	study					reduced effect for RR >> 1 or RR << 1			(0.01 to 0.77)	190 fewer to 10 more)	
HBV DNA positivity at week 28 (infants)											
1 Han 2011	Observational study	Very serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association reduced effect for RR >> 1 or RR << 1	0/132 (0%)	7/88 (8%)	Peto OR 0.08 (0.02 to 0.35)	80 fewer per 1000 (from 140 fewer to 200 fewer)	LOW
Serious adverse events (infants)											
1 Han 2011	Observational study	Very serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/132 (0%)	0/88 (0%)	-	0 fewer per 1000 (from 0 fewer to 0 fewer)	LOW
pneumonia (infants)											
1 Han 2011	Observational study	Very serious [a]	no serious inconsistency	no serious indirectness	very serious[c]	none	6/136 (4.4%)	5/94 (5.3%)	RR 0.83 (0.26 to 2.64)	9 fewer per 1000 (from 39 fewer to 87 more)	VERY LOW
low birth weight											
1 Han 2011	Observational study	Very serious [a]	no serious inconsistency	no serious indirectness	very serious[c]	strong association reduced effect for RR >> 1 or RR << 1	1/36 (2.8%)	1/94 (1.1%)	RR 2.61 (0.17 to 40.64)	17 more per 1000 (from 9 fewer to 422 more)	VERY LOW
Maternal undetectable HBV DNA (<500 copies/ml) (prior to delivery)											
1 Han 2011	Observational study	Very serious [a]	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association reduced effect for RR >> 1 or	44/135 (32.6%)	0/94 (0%)	Peto OR 8.09 (4.15 to 15.76)	330 more (from 250 to 410 more)	MODERATE

Quality assessment							No of patients		Effect		Quality
						RR << 1					
adverse events (mothers)											
1 Han 2011	Observational study	Very serious [a]	no serious inconsistency	no serious indirectness	very serious [c]	strong association reduced effect for RR >> 1 or RR << 1	12/135 (8.9%)	5/94 (5.3%)	RR 1.67 (0.61 to 4.59)	36 more per 1000 (from 21 fewer to 191 more)	VERY LOW
Caesarean section											
1 Han 2011	Observational study	Very serious [a]	no serious inconsistency	no serious indirectness	Serious[b]	none	75/135 (55.6%)	44/94 (46.8%)	RR 1.19 (0.91 to 1.54)	89 more per 1000 (from 42 fewer to 253 more)	VERY LOW

(a) Case control study. Patients received one treatment or another based on their preference.
(b) Confidence interval is consistent with two clinical decisions; appreciable harm and no appreciable benefit or harm
(c) Confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm and appreciable harm

11.3.4 Economic evidence

Published literature

One study was identified that evaluated the cost-effectiveness of lamivudine compared to routine care for the prevention of vertical transmission of hepatitis B.[39] This study is summarised in the economic evidence profile below (Table 221) and evidence table in Appendix F.

The authors of this study claim to have conducted it from a Taiwanese societal perspective. As per protocol, this study would normally be excluded from the economic evidence review. However, the costs used to inform this model were obtained from American, Israeli and Italian publications. Therefore, from a costing perspective this study is more applicable than it first appears. Although the model transition probabilities were taken from studies with 'an emphasis on high endemic areas in Asia', the figures quoted appear applicable to a UK perspective. A major limitation of the analysis was that it included the cost of lost productivity due to early death. This was calculated using Taiwan's per capita income multiplied by the number of years between the age of death and average age of retirement (65 years). Although these costs have been excluded in sensitivity analysis, the authors have not reported the results of this analysis numerically.

Two of the three studies used to inform the evidence of effectiveness in this study were included in the current clinical review (Li 2003[58] and Xu 2009[104]). However, the estimate of the effectiveness of lamivudine in preventing infant HBsAg seropositivity [0.52 (95% CI 0.24, 0.94)] is much greater than that identified in the current clinical review [0.89 (95% CI 0.51, 1.55)], presumably due to the inclusion of van Zonneveld 2003[94] in the former. Therefore, lamivudine prophylaxis is likely to be less cost-effective than reported by this analysis.

No relevant economic evaluations comparing any of the other antiviral therapies were identified. Please refer to Appendix M for a list of studies excluded from this review.

Table 221: Economic evidence profile: Lamivudine use in late pregnancy in addition to vaccination versus vaccination only

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Hung 2011[39] Taiwan	Partially applicable (a)	Potentially serious limitations (b)	• Markov decision model • Perspective: Taiwanese societal • Costs: Vaccine, antiviral and healthcare costs over a lifetime of HBV infection, lost productivity due to early death. • Outcomes: QALYs and infections averted.	£23 (c)	0.0024 QALYs	Prophylactic lamivudine dominant	Probabilistic analysis showed that prophylactic lamivudine therapy was cost-effective in 94% of simulations at a threshold of $20,000 (£12,790). The authors reported that when productivity loss costs were excluded in sensitivity analysis, prophylactic lamivudine remained cost-effective. However, the results of this analysis were not reported numerically.

(a) Conducted from the perspective of the Taiwanese healthcare system, however resource use and unit costs are applicable to OECD setting; resource use and unit costs obtained from American; Israeli and Italian sources and reported as 2008 US dollars; indirect costs (productivity loss due to early death) have been included; costs discounted at 3% per year; QALYs do not appear to have been discounted.

(b) The authors selected transition probabilities from sources where HBV is highly endemic; however these probabilities appear relevant to the UK. The results of sensitivity analysis are not fully reported.

(c) Converted from 2008 US dollars using purchasing power parities[77]

New cost-effectiveness analysis

This question was not prioritised for original health economic modelling.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 222: Cost of prophylactic antiviral therapy

Non-proprietary (proprietary)	Dose (per day)	Net price per pack
Routine care (HBV vaccine)	4 x 10 µg	£9.67 [0.5ml pre-filled syringe (20 µg per mL)]
Lamivudine (Zeffix)	100 mg (tablets)	£78.09 (28 tablets/pack)
Adefovir (Hepsera)	10 mg (tablets)	£296.73 (30 tablets/pack)
Telbivudine (Sebivo)	600 mg (tablets)	£290.33 (28 tablets/pack)
Tenofovir (Viread)	245 mg (tablets)	£240.46 (30 tablets/pack)
Tenofovir + Emtricitabine (Emtricitabine plus tenofovir)	245mg tenofovir + 200mg emtricitabine (tablets)	£418.50 (30 tablets/pack)

11.3.5 Evidence statements

11.3.5.1 Clinical evidence statements

One randomized trial of 115 pairs of HBeAg positive mothers and their newborns suggested that lamivudine during the third trimester (in addition to newborn's vaccination and receipt of HBIG) may be neither beneficial nor harmful on reducing the proportion of newborns/infants with the following outcomes:

- HBsAg seropositivity at birth, at 12 and 28 weeks after birth (VERY LOW QUALITY)
- HBV DNA positivity at 12 and 28 weeks after birth (VERY LOW QUALITY)

One randomized trial of 115 pairs of HBeAg positive mothers and their newborns showed that lamivudine treatment (in addition to newborn's vaccination and receipt of HBIG) during the third trimester of pregnancy is beneficial on reducing the proportion of newborns with HBV DNA positivity at birth compared to placebo (MODERATE QUALITY).

One randomized trial of 90 pairs of HBeAg positive mothers and their newborns showed that lamivudine treatment (in addition to newborn's vaccination and receipt of HBIG) during the third trimester of pregnancy is beneficial on reducing the proportion of infants with HBsAg seropositivity at 52 weeks compared to placebo (MODERATE QUALITY).

One randomized trial of 90 pairs of HBeAg positive mothers and their newborns suggested that lamivudine treatment (in addition to newborn's vaccination and receipt of HBIG) during the third trimester of pregnancy may be beneficial on reducing the proportion of infants with HBV DNA positivity at 52 weeks compared to placebo (LOW QUALITY).

One observational study of 185 pairs of HBeAg positive mothers and their newborns suggested that lamivudine treatment (in addition to newborn's vaccination and receipt of HBIG) during the third trimester of pregnancy may be beneficial on reducing the proportion of newborns with HBsAg seropositivity at birth and at 1 month after birth compared to no therapy during pregnancy (VERY LOW QUALITY).

One observational study of 185 pairs of HBeAg positive mothers and their newborns showed that lamivudine treatment (in addition to newborn's vaccination and receipt of HBIG) during the third trimester of pregnancy is beneficial on reducing the proportion of newborns with HBV DNA positivity at 1 month after birth compared to no therapy during pregnancy (MODERATE QUALITY).

One observational study of 185 HBeAg positive mothers showed that lamivudine treatment during the third trimester of pregnancy is beneficial on reducing the maternal log HBV DNA levels before delivery compared to no therapy during pregnancy (MODERATE QUALITY).

One observational study of 185 pairs of HBeAg positive mothers and their newborns suggested that lamivudine treatment (in addition to newborn's vaccination and receipt of HBIG) during the third trimester of pregnancy may be neither beneficial nor harmful on reducing the proportion of newborns/infants with the following outcomes compared to no therapy during pregnancy:

- HBV DNA positivity at 12 months after birth (LOW QUALITY)
- HBsAg seropositivity at 12 months after birth (LOW QUALITY).

One randomized trial of 150 HBeAg positive mothers suggested that lamivudine treatment during the third trimester of pregnancy may be neither beneficial nor harmful on the incidence of serious and non serious maternal adverse events compared to placebo (VERY LOW QUALITY).

One observational study of 185 pairs of HBeAg positive mothers and their newborns suggested that lamivudine treatment (in addition to newborn's vaccination and receipt of HBIG) during the third trimester of pregnancy may be neither beneficial nor harmful on the incidence of the following adverse events compared to no therapy during pregnancy:

- Postpartum haemorrhage (VERY LOW QUALITY)
- Caesarean section (VERY LOW QUALITY)
- Preterm birth (VERY LOW QUALITY)
- Neonatal asphyxia (VERY LOW QUALITY)
- Malformation (VERY LOW QUALITY)

…….

One randomised trial of 99 pairs of a mixed group of HBeAg positive and negative mothers and their newborns suggested that lamivudine treatment (without newborn's vaccination and receipt of HBIG) during the third trimester of pregnancy may be neither beneficial nor harmful on reducing the following outcomes compared to only receipt of HBIG during pregnancy:

- the proportion of newborns with HBsAg, HBeAg and HBV DNA positivity at birth (VERY LOW QUALITY)
- the maternal HBV DNA levels (after administration of treatment) (VERY LOW QUALITY).

…….

One randomised trial of 95 pairs of a mixed group of HBeAg positive and negative mothers and their newborns suggested that lamivudine treatment (without newborn's vaccination and receipt of HBIG) during the third trimester of pregnancy may be beneficial on reducing the following outcomes:

- the proportion of newborns with HBsAg and HBV DNA positivity at birth compared to no therapy during pregnancy (VERY LOW QUALITY)
- The maternal HBV DNA levels (after administration of treatment) (VERY LOW QUALITY).

One randomised trial of 95 pairs of a mixed group of HBeAg positive and negative mothers and their newborns suggested that lamivudine treatment (without newborn's vaccination and receipt of HBIG) during the third trimester of pregnancy may be neither beneficial nor harmful on reducing the proportion of newborns with HBeAg seropositivity at birth compared to no therapy during pregnancy (VERY LOW QUALITY)

…….

One observational study of 230 pairs of HBeAg positive mothers and their newborns suggested that telbivudine treatment during the second or third trimester of pregnancy (in addition to newborn's vaccination and receipt of HBIG) may be beneficial on reducing the proportion of newborns with HBsAg and HBV DNA positivity at birth compared to no therapy during pregnancy (VERY LOW QUALITY).

One observational study of 230 pairs of HBeAg positive mothers and their newborns suggested that telbivudine treatment during the second or third trimester of pregnancy may be neither beneficial nor harmful on the following outcomes compared to no therapy during pregnancy:

- reducing the proportion of newborns with HBeAg positivity at birth and at 28 weeks after birth (VERY LOW QUALITY)
- reducing the proportion of newborns with HBsAg and HBV DNA positivity at 28 weeks after birth (LOW QUALITY)

- congenital anomalies (LOW QUALITY)
- serious adverse events for infants (LOW QUALITY)
- pneumonia for infants (VERY LOW QUALITY)
- low birth weight (VERY LOW QUALITY)
- adverse events for mothers (VERY LOW QUALITY)
- caesarean section (VERY LOW QUALITY)

11.3.5.2 Economic evidence statements

One study found that the use of prophylactic lamivudine plus neonatal vaccination in the third trimester of pregnancy was more effective and less expensive than neonatal vaccination alone (Partial applicability and potentially serious limitations).

11.3.6 Recommendations and Links to evidence

Recommendations	**62. Discuss with pregnant women the benefits and risks of antiviral treatment for them and their baby.** **63. Offer tenofovir disoproxil to women with HBV DNA greater than 10^7 IU/ml in the third trimester to reduce the risk of transmission of HBV to the baby[qq].** **64. Monitor quantitative HBV DNA 2 months after starting tenofovir disoproxil and ALT monthly after the birth to detect postnatal HBV flares in the woman.** **65. Stop tenofovir disoproxil 4 to 12 weeks after the birth unless the mother meets criteria for long-term treatment (see recommendations 22, 23 and 27 to 29).** **66. Offer active and passive hepatitis B immunisation in infants and follow up in line with the guidance below:** o Hepatitis B antenatal screening and newborn immunisation programme: best practice guidance o Immunisation against infectious disease (the Green book) o Hepatitis B and C: ways to promote and offer testing. NICE public health guidance 43 (2012). o Reducing differences in the uptake of immunisations. NICE public health guidance 21 (2009). **67. Advise women that there is no risk of transmitting HBV to their babies through breastfeeding if guidance on hepatitis B immunisation has been followed, and that they may continue antiviral treatment while they are breastfeeding.**
Relative values of different outcomes	The GDG considered newborns/infants HBsAg, HBeAg and HBV DNA seropositivity as the most critical outcomes. Outcome data for serological HBsAg reported at 52 or 28 weeks was thought to be the most useful.

[qq] At the time of publication (June 2013), tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Trade off between clinical benefits and harms	Lamivudine in the third trimester of pregnancy (in addition to HBV vaccine and HBIg) was found to be beneficial in reducing the proportion of newborns with HBV DNA seropositivity, infants HBV DNA and HBsAg seropositivity at 52 weeks compared to placebo (in addition to HBV vaccine and HBIg). However, this must be balanced against the potentially toxic side effects of the drug on mothers and infants. Telbivudine (in addition to HBV vaccine and HBIg) in the second or third trimester of pregnancy was also found that it may be beneficial in reducing the proportion of newborns with HBsAg and HBV DNA seropositivity at birth without the risk of malformations and other serious adverse events for mothers and infants. The GDG noted the earlier the time of infection in an individual's life the greater the risk of that infection becoming persistent and for a longer period of time, and this may increase the risk of morbidity and mortality later in life. Therefore the prevention of perinatal infection is extremely important. The current protocol in the UK of post exposure prophylaxis given immediately after birth with vaccination of the baby is recognised as being effective in preventing perinatal transmission. The GDG highlighted the importance of the protection of the mother and the concerns held by clinicians about the teterogenic risk posed. The GDG agreed that the choice of treatment was between entecavir and tenofovir and noted the FDA pregnancy risk categories for both drugs, with Tenofovir in category B which means that there is no evidence of risk in humans, whereas there was not the same level of evidence available for entecavir and this is recognised by the different category allocated. The GDG considered that the use of tenofovir was appropriate due to its increased potency and because it carries a lower teterogenic risk to mother and baby. The GDG acknowledged that there is evidence that tenofovir is safe from its extensive use in the HIV population, and that as entecavir isn't used to treat HIV there is a lack evidence of its safety for this drug. The group were in strong agreement that the indirect evidence was applicable, and tenofovir would be the preferred option for the short term treatment of pregnant women with hepatitis B.
Economic considerations	The GDG discussed the risk of contracting CHB and the risk of toxicity associated with antiviral drugs. They noted that tenofovir carries a lower teratogenic risk, has a higher barrier to resistance, and is known to be more effective than lamivudine in individuals who are not pregnant. The group agreed that preventing cases of CHB transmission and at the lowest risk to mother and child, the increased cost of tenofovir would likely be outweighed by the increase in quality of life associated with its use.
Quality of evidence	Two randomized trials (Xu 2009, Li 2003) and one observational study (Yu 2012) were included that examined the efficacy of lamivudine on reducing the risk of vertical transmission from mother to child. The most important trial on lamivudine was a double blinded randomized trial on HBeAg positive mothers and their infants (Xu 2009) and the evidence on beneficial outcomes of HBsAg and HBV DNA seropositivity was rated of moderate quality due to lack of information on randomization procedure and allocation concealment. The other trial (Li 2003) used a mixed group of HBeAg positive and negative mothers with CHB that did not provide information on blinding, randomisation procedure and allocation concealment. The evidence on telbivudine (in addition to HBV vaccine and HBIg) was rated from low to very low as it came from two prospective open-label studies (Han 2011, Pan 2012) and pregnant women were divided into telbivudine and no therapy groups according to their individual preferences. Three studies (Yu 2012, Han 2011 and Pan 2012) reported the use of double dose of HBIg (within 24 hours of birth and day 15 post-partum) and four

	studies (Xu 2009, Yu 2012, Han 2011 and Pan 2012) reported the use of 3 doses of HBV vaccines (within 24 hours of birth, weeks 4 and 24 post-partum) and they are not consistent with the UK vaccination schedules (Green book). Therefore, evidence should be interpreted with caution. One Economic study was found that was partially applicable and had potentially serious limitations, therefore any conclusions drawn in the economic considerations, should be interpreted with caution as well.
Other considerations	The recommendations are based on clinical expert opinion. No controlled studies have been identified for other nucleos(t)ide analogues, including tenofovir. Lamivudine and telbivudine are not currently used in clinical practice. The GDG recognised that short-term antiviral therapy works effectively in the HIV population and agreed the same should apply to the hepatitis B population. The GDG considered that tenofovir is a drug that is highly potent, and would be permissible for use in pregnancy as used in the HIV field, and has a high barrier to resistance and therefore should be recommended. The GDG agreed that entecavir is not currently used. The GDG were aware of data on post partum flares in hepatitis B which indicated a possible benefit in treating beyond 4 weeks to provide additional protection for the mother. No evidence was identified for lactating mothers. The GDG considered that the amount of antiviral drugs and/or their metabolites present in the breast milk is very low and there is no evidence suggesting harms associated with breastfeeding during treatment in the mothers, given that the new born or infants are immunised by following the vaccination schedules (Green book) and Best Practice Guide[23] and their status are monitored accordingly. The GDG agreed that as well as discussing treatment options with pregnant women, the importance of vaccination of their baby should be stressed. It was noted that published audits have shown that adherence to vaccination schedules is poor, and not all babies are followed up and tested at 12 months to ensure that the intervention has been effective. It was agreed that signposts to information on vaccination in the NICE guidance Reducing the differences in the uptake of immunisations and the Department of Health's Immunisation against infectious disease (the Green Book) should be made. The GDG agreed that studies on the long term effects of tenofovir in pregnant women were needed.

11.4 Prophylactic treatment

11.4.1 Introduction

Studies have shown that reactivation of HBV replication occurs at a rate of 20% to 50% in HBsAg positive patients receiving immunosuppressive therapy. Most cases of HBV reactivation are asymptomatic but severe hepatitis and death due to hepatic failure can occur. Reactivation of HBV has also been reported in HBsAg negative, hepatitis B core antibody (anti-HBc) positive patients but the incidence is lower and occurs mainly in the setting of potent immunosuppression such as regimens that include rituximab. Other guidelines [25,59,63] recommend that patients be tested for HBsAg and anti-HBc prior to starting immunosuppressive therapy or cancer chemotherapy

In many situations the use of these treatments cannot be avoided. Instead an approach needs to be taken to recognise patients at risk of hepatitis B reactivation and then monitoring put in place to identify reactivation at as early a stage as possible. There are three options for intervening with anti-hepatitis B drug therapies. Prophylaxis covers the initiation of antiviral therapy upon or just before starting an immunosuppressive intervention. The duration of antiviral therapy will then be for as long as the patient is at risk. Pre-emptive therapy involves monitoring the HBV DNA viral load at regular intervals and only starting therapy when a virologic reactivation (increase in viral load) is observed, but before any corresponding hepatological reactivation (increase in ALT). Waiting until the virological reactivation leads to a rise in ALT before treating is referred to as therapeutic treatment. The consequent timing of therapy will therefore have an impact on the risk of clinical disease and also the duration of antiviral therapy required.

11.4.2 Review question: In people who are immunocompromised, what is the clinical and cost effectiveness of prophylactic treatment in reducing risk of hepatitis B virus reactivation and severity of flares?

For full details see review protocol in Appendix C.

Table 223: PICO characteristics of review question

Protocol	
Population	Children, young people and adults with CHB infection who receive immunosuppressive (including all) or cytotoxic chemotherapy.
Intervention	• Prophylactic treatment • Lamivudine • Adefovir • Tenofovir • Entecavir • Tenofovir plus emtricitabineEmtricitabine plus tenofovirTelbivudine
Comparison	• No treatment or placebo • Lamivudine • Adefovir • Tenofovir • Entecavir • Tenofovir plus emtricitabineEmtricitabine plus tenofovir • Telbivudine

Protocol	
Outcomes	**Primary outcomes:** • Viral reactivation (serum HBV DNA) • Clinical reactivation (ALT) • Mortality **Secondary outcomes:** • Hepatic failure • Cirrhosis • Hepatocellular carcinoma • Resistance

11.4.3 Clinical evidence

We searched for studies comparing the clinical efficacy of different prophylactic treatments in reducing risk of HBV reactivation and severity of flares in people who are immunocompromised. A total of 12 studies were identified and included in this review, of which 4 were RCTs and 8 were non-RCTs with historical controls.

Causes of immunosuppression vary across trials and there are mainly three categories:

1. HBsAg positive cancer patients undergoing chemotherapy, or other forms of cytotoxic therapy (including transarterial chemolipiodolisation):

    - Breast cancer
    - Non-hodgkin's lymphoma and/or hodgkin's lymphoma
    - Hepatocellular carcinoma
    - Nasopharyngeal cancer
    - All cancers, including gastrointestinal cancers, lung cancers, gynaecologic malignancies and all of the above.

2. HBsAg positive patients undergoing hematopoietic cell (bone marrow) and solid organ transplantation, or patients receiving HBsAg positive bone marrow.

3. Patients with non-malignant diseases (including autoimmune disease and hypersensitive disease).

Analysis was performed according to the cause of immunosuppression (as listed above). However, no studies were identified for non-malignant diseases.

In this review, prophylactic, pre-emptive and therapeutic treatments are defined as follows:

- Prophylactic treatment is defined as initiating anti-HBV treatment prior to initiating immunosuppressive treatment.
- Pre-emptive treatment is defined as initiation of anti-HBV treatment only when there is evidence of virological reactivation (monitored by serum HBV DNA levels), after initiation of immunosuppressive treatment.
- Therapeutic treatment is defined as initiating anti-HBV treatment only when there is an elevation of ALT levels, after initiation of immunosuppressive treatment.

Timing of treatment varied between studies; seven studies started prophylactic treatment 7 days prior to immunosuppressive and two studies started prophylactic treatment from day one of immunosuppressive therapy. In terms of duration of prophylactic treatment, most studies continued

prophylactic treatment until 6, 8, 24 weeks after completion of chemotherapy, or until 24 or 52 weeks after completion of transarterial chemo-lipiodolisation or hematopoietic stem cell transplantation.

Forest plots can be found in appendix G.

11.4.3.1 Summary characteristics of included studies

Immunocompromised adults with CHB infection who are HBsAg positive

Table 224: Included studies in CHB infected patients who are HBsAg positive

Included studies Study design	N	Patient characteristics	Drug comparisons (based on the pre-specified definitions, as given above)	Timing/ duration of prophylactic or pre-emptive or therapeutic treatment	Length of F/U	Outcomes (authors' definitions)
Long 2011 RCT Single centre	42	HBsAg positive breast cancer patients undergoing chemotherapy	1.Prophylactic lamivudine (100mg/day) (n=21) 2.No prophylactic lamivudine (n=21) • Steroid use: unclear	7 days prior to chemotherapy and continued until 8 weeks after chemotherapy	8 weeks after completion of chemotherapy	**1. HBV reactivation** -increase in HBV DNA >10 fold, compared with baseline or an absolute increase of >1x10^9 copies/mL in the absence of any other systemic infection **2. Hepatitis** -3xULN (58U/L) or an absolute increase of ALT >100U/L compared with baseline. **3. All-cause mortality** **4. Hepatitis due to HBV reactivation** **5. Mortality due to HBV reactivation**
Hsu 2008 RCT Multi-centre	51	HBsAg positive non-Hodgkin's lymphoma undergoing chemotherapy	1.Prophylactic lamivudine (100mg/day) (n=26) 2.Therapeutic lamivudine (n=25) Chemotherapy regimen was: Cyclophosphamide (750mg/m2), doxorubicin	1.Start from day 1 of chemotherapy and continued until 8 weeks after completion of chemotherapy. 2. Patients received chemotherapy alone and started LAM only if ALT elevated to >1.5 fold ULN during F/U and continued LAM treatment until	52 weeks of ending chemotherapy	**1. HBV reactivation** during the 12 months after starting chemotherapy **2. Hepatitis** ->3 fold increase of ALT (>100U/L) **3.Resistance**

Included studies Study design	N	Patient characteristics	Drug comparisons (based on the pre-specified definitions, as given above)	Timing/ duration of prophylactic or pre-emptive or therapeutic treatment	Length of F/U	Outcomes (authors' definitions)
			(50mg/m2), vincristine (1.4mg/m2/d) and prednisolone (60mg/m2/d) on days 1-7.	hepatitis was resolved.		
Lau 2003 RCT	30	HBsAg positive lymphoma patients undergoing chemotherapy	1.Prophylactic lamivudine (100mg/day) (n=15) 2.Pre-emptive lamivudine (n=14) • Steroid use: yes, but % unclear	1.started 7 days before chemotherapy and then continued for at least 6 weeks after completion of chemotherapy 2. started if there was serological evidence of HBV reactivation (via serial 2 week interval HBV DNA monitoring)	At least 6 weeks after completion of chemotherapy	**1. Hepatitis** ->3 fold increase of ALT on 2 consecutive occasions at least 5 days apart **2. Hepatitis due to HBV reactivation** -preceded or accompanied by an increase of HBV DNA >10 times compared with baseline and HBV DNA turned from negative to positive
Jang 2006 RCT Single centre	76	Patients with HBV related hepatocellular carcinoma (HCC) undergoing transarterial chemo-lipiodolisation (TACL)	1.Prophylactic lamivudine (100mg/day) (n=38) 2.Preemptive lamivudine (n=38) • No steroid use	1.Day 1 of TACL and continued for 52 weeks after the completion of TACL. 2.start LAM immediately when there is HBV reactivation	52 weeks after completion of immunosuppressive therapy	**1. HBV reactivation** ->10 fold increase in HBV DNA compared with baseline **2. Hepatitis** -≥3 fold increase in ALT that exceeded 100U/L (reference range 33U/L) **3. All-cause mortality** **4. Hepatitis due to HBV reactivation** -≥3 fold increase in ALT that exceeded 100U/L (reference range 33U/L) in patients with HBV reactivation in the absence of systemic infection. **5. Hepatic decompensation** **6. Hepatic decompensation due to HBV reactivation**

– Li 2011 Retrospective non-RCT Multicentre	123	HBsAg positive lymphoma patients undergoing chemotherapy	1.Prophylactic entecavir (0.5mg/day) (n=34) 2.Prophylactic lamivudine (100mg/day) (n=89) • 100% received steroids	Both drugs administered 7 days before chemotherapy and ending 24 weeks after completion of chemotherapy.	24 weeks after completion of chemotherapy	**1. HBV reactivation** -an increase in HBV DNA ≥10 fold or an absolute increase ≥10^5 copies/mL compared with baseline. **2. Hepatitis** -≥3 fold increase in ALT >58U/L or an absolute increase in ALT to >100U/L compared with baseline. **3. Hepatitis due to HBV reactivation** -HBV reactivation preceding or accompanying hepatitis during and after 6 months of chemotherapy, in the absence of systemic infection. **4. Severe hepatic failure** **5. Mortality due to hepatic failure** **6. Resistance**
Included studies **Study design**	**N**	**Patient characteristics**	**Drug comparisons (based on the pre-specified definitions, as given above)**	**Timing/ duration of prophylactic or pre-emptive or therapeutic treatment**	**Length of F/U**	**Outcomes (authors' definitions)**
						7. Mortality due to be HBV reactivation
Li 2006 Non-randomised trial	156	HBsAg positive lymphoma undergoing chemotherapy	1.Prophylactic lamivudine (100mg/day) (n=40) 2.No prophylactic lamivudine (historical controls) (n=116) • 92% received steroid	7 days prior to chemotherapy and continued until 8 weeks after chemotherapy	At least 12 weeks after completion of chemotherapy	**1. Hepatitis** -an increase of ≥3 fold in ALT (>1.25xULN of 50U/L) or an absolute increase of ALT>100U/L, compared with baseline. **2. All-cause mortality** **3. Hepatitis due to HBV reactivation** -an increase in HBV DNA >10fold compared with baseline, or an absolute increase >10^5 copies/mL in the absence of systemic infection **4.Resistance**

Yeo 2004A Non-randomised trial	258	HBsAg positive cancer patients undergoing cytotoxic chemotherapy	1.Prophylactic lamivudine (100mg/day) (n=65) 57% received steroids 2.No prophylactic lamivudine (historical controls) (n=193) • 47% received steroids	Started within 7 days before start of chemotherapy and continued until 8 weeks after stopping chemotherapy.	8 weeks after completion of chemotherapy	**1. Hepatitis** -≥3 fold increase in ALT that exceeded the ULN of <58U/L or an absolute increase of >100U/L, compared with baseline **2. All-cause mortality** **3. Hepatitis due to HBV reactivation** -an increase of HBV DNA of 10 fold compared with baseline or an absolute increase of >1000x10^5 ge/mL, in the absence of other systemic infection. **4. Mortality due to HBV reactivation**
Yeo 2005 Non-randomised trial	37	HBsAg positive nasopharyngeal cancer patients undergoing chemotherapy	1.Prophylactic lamivudine (100mg/day) (n=16) 33% received steroids 2.No prophylactic lamivudine (historical controls) (n=21) • 44% received steroids	Started before chemotherapy and until 8 weeks after stopping chemotherapy	8 weeks after completion of chemotherapy	**1. Hepatitis** -≥3 fold increase in ALT that exceeded the ULN of <58U/L or an absolute increase of >100U/L, compared with baseline **2. Hepatitis due to HBV reactivation** -an increase of HBV DNA of 10 fold compared with baseline or an absolute increase of >1000x10^5 ge/mL, in the absence of other systemic infection. **3. Mortality due to HBV reactivation**
Huang 2009 Non-RCT	32	HBsAg positive non-Hodgkin's lymphoma patients undergoing high dose chemotherapy and autologous hematopoietic stem cell transplantation	1.Prophylactic lamivudine (100mg/day) (n=20) 2.No prophylactic lamivudine (historical controls) (n=12)	Started 7 days before and until at least 24 weeks after transplantation	At least 24 weeks after completion of HSCT	**1. Hepatitis due to HBV reactivation** -≥10 fold increase in HBV DNA compared with baseline or an absolute increase of >10^5 copies/mL **2. All-cause mortality** **3. Mortality due to hepatic failure** **4. Resistance**

Hui 2005A Non-randomised trial	33*	Patients who underwent hematopoietic stem cell transplantation (HSCT) using HBsAg positive bone marrow	1.Prophylactic lamivudine (prospectively treated) (n=19) 2.No prophylactic lamivudine (historical controls) (n=14)	Started before marrow harvest and HSCT, and continued for 52 weeks after HSCT	Median of 12-13 months	**1. HBV-related hepatitis** ->3 fold ALT elevation on 2 consecutive determinations, 5 days apart in the absence of systemic infections; and this was preceded by HBV DNA elevation to >10 times, compared to baseline value.
Lau 2002 Non-randomised trial	40	HBsAg positive patients undergoing allogeneic hematopoietic cell transplantation	1.Prophylactic lamivudine (n=20) 2.No prophylactic before and after transplantation (n=20)	Started 7 days before transplantation until 52 weeks after transplantation	52 weeks after transplantation	**1. Hepatitis** ->3 fold ALT elevation on 2 consecutive determinations, 5 days apart, compared to baseline value, in the absence of systemic infections **2. Hepatitis due to HBV reactivation** -HBV DNA elevation to >10 times, compared to baseline value, plus the above. **3. All-cause mortality**
Chan 2002	67	HbsAg positive patients who underwent renal allograft transplantation. Immunosuppressive treatment after kidney transplantation: 1) Methylprednisolone 0.5g intravenously followed by prednisolone 30mg/d 2) Cyclosporine 0.8mg/kg/d (azathioprine was used before cyclosporine	1. Preemptive lamivudine (100mg/day) was started if patients satisfied either criteria:a) HBV DNA>$2.83x10^8$ copies/ml in patients with normal ALT or b) HBV DNA>$2.83x10^7$ copies/ml in patients with increased ALT and/or a liver biopsy showing significant hepatitis	The median duration of lamivudine treatment was 190 days (range 85-385) for the prophylactic group and 139 days (range 17-276) for the therapeutic group.	82 +/- 58 months after transplantation (range 13-212 months)	**1. All-cause mortality** **2.Mortality due to liver complications**

		availability). Steroid resistant rejection was treated with anti-thymocyte globulin or anti-CD3 antibody.	(n=15) 2. No preemptive treatment (n=52)			

**The number of people came from the subgroup analysis of HBsAg positive patients. The study also included HBsAg negative patients as another subgroup; however, HBV vaccine was given to these people instead of antiviral prophylactic treatment; therefore this has been excluded from this review.*

Immunocompromised adults with CHB infection who are HBsAg negative, anti-HBc positive and anti-HBs negative

No relevant studies have been identified.

Immunocompromised adults with CHB infection who are HBsAg negative, anti-HBc positive and anti-HBs positive

No relevant studies have been identified.

Immunocompromised children with CHB infection who are HBsAg positive or negative

No relevant studies have been identified.

11.4.3.2 Prophylactic therapies in reducing HBV reactivation and severity of flares among immunocompromised CHB infected adults who are HBsAg positive

Comparison of prophylactic entecavir versus prophylactic lamivudine, according to causes of immunosuppression

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Entecavir Frequency (%)	Lamivudine Frequency (%)	Relative Risk/ PETO OR (95% CI)	Absolute	
% lymphoma patients undergoing chemotherapy with HBV reactivation (24 weeks after completion of chemotherapy)										
Li 2011	1 observational study	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [b]	4/34 (11.8%)	18/89 (20.2%)	RR 0.58 (0.21 to 1.6)	85 fewer per 1000 (from 160 fewer to 121 more)	VERY LOW
% lymphoma patients undergoing chemotherapy with hepatitis (24 weeks after completion of chemotherapy)										
Li 2011	1 observational study	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [c]	2/34 (5.9%)	24/89 (27%)	RR 0.22 (0.05-0.87)	210 fewer per 1000 (from 35 fewer to 256 fewer)	LOW
% lymphoma patients undergoing chemotherapy with hepatitis due to HBV reactivation (24 weeks after completion of chemotherapy)										
Li 2011	1 observational study	Serious limitations [a]	No serious inconsistency	No serious indirectness	Serious imprecision [c]	0/34 (0%)	11/89 (12.4%)	PETO OR 0.22 (0.06 to 0.88)	94 fewer per 1000 (from 13 fewer to 115 fewer)	LOW
% lymphoma patients undergoing chemotherapy with severe hepatic failure (24 weeks after completion of chemotherapy)										

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Entecavir Frequency (%)	Lamivudine Frequency (%)	Relative Risk/ PETO OR (95% CI)	Absolute	
Li 2011	1 observational study	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	0/34 (0%)	1/89 (1.1%)	PETO OR 0.25 (0 to 20.09)	8 fewer per 1000 (from 11 fewer to 175 more)	VERY LOW
All-cause mortality in lymphoma patients undergoing chemotherapy (24 weeks after completion of chemotherapy)										
Li 2011	1 observational study	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	0/34 (0%)	1/89 (1.1%)	PETO OR 0.25 (0 to 20.09)	8 fewer per 1000 (from 11 fewer to 175 more)	VERY LOW
Resistance in lymphoma patients undergoing chemotherapy (24 weeks after completion of chemotherapy)										
Li 2011	1 observational study	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	0/34 (0%)	1/89 (1.1%)	PETO OR 0.25 (0 to 20.09)	8 fewer per 1000 (from 11 fewer to 175 more)	VERY LOW

(a) Non-randomised design with historical controls was used.
(b) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm and appreciable harm.
(c) The confidence interval is consistent with two clinical decisions; appreciable benefit and no appreciable benefit or harm.

Comparison of prophylactic lamivudine versus no prophylactic treatment, according to causes of immunosuppression

Quality assessment	Summary of findings		
		Effect	Quality

Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Prophylactic lamivudine Frequency (%)	No prophylactic treatment Frequency (%)	Relative Risk/ PETO OR (95% CI)	Absolute	
% breast cancer patients undergoing chemotherapy with HBV reactivation (RCT) (8 weeks after completion of chemotherapy)										
Long 2011	1 randomised controlled trial	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision	0/21 (0%)	6/21 (28.6%)	PETO OR 0.1 (0.02 to 0.57)	247 fewer per 1000 (from 100 fewer to 278 fewer)	MODERATE
% breast cancer patients undergoing chemotherapy with hepatitis (RCT) (8 weeks after completion of chemotherapy)										
Long 2011	1 randomised controlled trial	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	5/21 (23.8%)	3/21 (14.3%)	RR 1.67 (0.46 to 6.1)	96 more per 1000 (from 77 fewer to 729 more)	VERY LOW
% of cancer patients undergoing chemotherapy with hepatitis (non-RCTs) (8 weeks after completion of immunosuppressive therapy)										
Li 2006 Yeo 2004A Yeo 2005	3 observational studies	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	19/121 (15.7%)	153/330 (46.4%)	RR 0.35 (0.23 to 0.53)	301 fewer per 1000 (from 218 fewer to 357 fewer)	LOW
% of patients undergoing stem cell (bone marrow) transplantation with hepatitis (non-RCTs) (52 weeks after completion of transplantation)										
Lau 2002	1 observational study	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)	8/20 (40%)	16/20 (80%)	RR 0.5 (0.28 to 0.89)	400 fewer per 100 (from 88 fewer to 576 fewer)	VERY LOW
All-cause mortality in breast cancer patients undergoing chemotherapy (RCT) (8 weeks after completion of chemotherapy)										
Long 2011	1 randomised controlled trial	Serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision	0/21	1/21	PETO OR	41 fewer per	VERY LOW

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Prophylactic lamivudine Frequency (%)	No prophylactic treatment Frequency (%)	Relative Risk/ PETO OR (95% CI)	Absolute	
		(a)			(b)	(0%)	(4.8%)	0.14 (0 to 6.82)	1000 (from 48 fewer to 207 more)	
All-cause mortality, in cancer patients undergoing chemotherapy (non-RCTs) (8 weeks after completion of immunosuppressive therapy)										
Li 2006 Yeo 2004A	2 observational studies	No serious limitations	No serious inconsistency	No serious indirectness	Very Serious imprecision (b)	5/105 (4.8%)	29/309 (9.4%)	RR 0.55 (0.23 to 1.32)	42 fewer per 1000 (from 72 fewer to 30 more)	VERY LOW
All-cause mortality, in patients undergoing stem cell (bone marrow) transplantation (non-RCTs) (24 and 52 weeks after transplantation)										
Huang 2009 Lau 2002	2 observational studies	No serious limitations	No serious inconsistency	Serious indirectness (d)	No serious imprecision	7/40 (17.5%)	16/32 (50%)	RR 0.34 (0.16 to 0.72)	330 fewer per 1000 (from 140 fewer to 420 fewer)	VERY LOW
% breast cancer patients undergoing chemotherapy with hepatitis due to HBV reactivation (RCT) (8 weeks after completion of chemotherapy)										
Long 2011	1 randomised controlled trial	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision	0/21 (0%)	0/21 (0%)	Not pooled	Not pooled	MODERATE
% of cancer patients undergoing chemotherapy with hepatitis due to HBV reactivation (non-RCTs) (8 weeks after completion of immunosuppressive therapy)										
Yeo 2004A Yeo 2005	2 observational studies	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	3/81 (3.7%)	53/214 (24.8%)	RR 0.17 (0.06 to 0.49)	206 fewer per 1000 (from 126 fewer to 233	LOW

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Prophylactic lamivudine Frequency (%)	No prophylactic treatment Frequency (%)	Relative Risk/ PETO OR (95% CI)	Absolute	
									fewer)	
% patients undergoing stem cell (bone marrow) transplantation with hepatitis due to HBV reactivation (non-RCTs) (24 and 52 weeks after completion of transplantation)										
Huang 2009 Hui 2005 Lau 2002	3 observational studies	No serious limitations	No serious inconsistency	Serious indirectness (d)	No serious imprecision	5/59 (8.5%)	22/46 (47.8%)	RR 0.17 (0.07 to 0.42)	397 fewer per 1000 (from 277 fewer to 445 fewer)	VERY LOW
Mortality due to HBV reactivation, in breast cancer patients undergoing chemotherapy (RCT) (8 weeks after completion of chemotherapy)										
Long 2011	1 randomised controlled trial	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision	0/21 (0%)	0/21 (0%)	Not pooled	Not pooled	MODERATE
Mortality due to HBV reactivation, in patient undergoing chemotherapy (non-RCTs) (8 weeks after completion of immunosuppressive therapy)										
Yeo 2004A Yeo 2005	2 non-randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	0/81 (0%)	6/214 (2.8%)	PETO OR 0.24 (0.04 to 1.44)	21 fewer per 1000 (from 27 fewer to 12 more)	VERY LOW
Mortality due to HBV reactivation, in patients undergoing stem cell (bone marrow) transplantation (non-RCTs) (24 and 52 weeks after completion of immunosuppressive therapy)										
Huang 2009 Lau 2002	2 non-randomised trials	No serious limitations	No serious inconsistency	Serious indirectness (d)	No serious imprecision	0/40 (0%)	5/32 (15.6%)	PETO OR 0.08 (0.01 to 0.51)	142 fewer per 1000 (from 70	VERY LOW

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Prophylactic lamivudine Frequency (%)	No prophylactic treatment Frequency (%)	Relative Risk/ PETO OR (95% CI)	Absolute	
									fewer to 154 fewer)	
Resistance in cancer patients undergoing chemotherapy (non-RCTs) (monitored at least 12 weeks after completion of immunosuppressive therapy)										
Huang 2009	1 non-randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	1/40 (2.5%)	0/116 (0%)	PETO OR 49.4 (0.56 to 4393.79)	-	VERY LOW
Resistance in patients undergoing stem cell (bone marrow) transplantation (non-RCTs) (24 weeks after completion of transplantation)										
Li 2006	1 non-randomised trial	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision (b)	1/20 (5%)	0/12 (0%)	PETO OR 4.95 (0.09 to 283.86)	-	VERY LOW

(a) No details on randomisation procedure and allocation concealment; not blinded.
(b) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm and appreciable harm.
(c) The confidence interval is consistent with two clinical decisions; appreciable benefit and no appreciable benefit or harm.
(d) Cessation of prophylactic treatment was different across trials.

Comparison of prophylactic lamivudine versus pre-emptive lamivudine (start Lamivudine only when there was HBV reactivation after starting immunosuppressive therapy), according to causes of immunosuppression

Quality assessment	Summary of findings		
		Effect	Quality

Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Prophylactic lamivudine Frequency (%)	Pre-emptive lamivudine Frequency (%)	Relative Risk/ PETO OR (95% CI)	Absolute	
% cancer patients undergoing chemotherapy with HBV reactivation (minimum 6 weeks to 52 weeks after completion of chemotherapy/immunosuppressive therapy)										
Jang 2006 Lau 2003	2 randomised controlled trial	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision	1/51 (2%)	23/51 (45.1%)	RR 0.06 (0.01 to 0.32)	424 fewer per 1000 (from 307 fewer to 446 fewer)	MODERATE
% HBV related hepatocellular carcinoma patient undergoing transarterial lipiolisation with hepatitis (52 weeks after completion of immunosuppressive therapy)										
Jang 2006	1 randomised controlled trial	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)	6/36 (16.7%)	16/37 (43.2%)	RR 0.39 (0.17 to 0.87)	264 fewer per 1000 (from 56 fewer to 359 fewer)	LOW
All-cause mortality, in cancer patients undergoing chemotherapy (minimum 6 weeks to 52 weeks after completion of chemotherapy/immunosuppressive therapy)										
Jang 2006 Lau 2003	2 randomised controlled trial	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (d)	4/51 (7.8%)	4/51 (7.8%)	RR 1.02 (0.29 to 3.56)	2 more per 1000 (from 55 fewer to 201 more)	VERY LOW
% lymphoma patients undergoing chemotherapy with hepatic failure (minimum 6 weeks after completion of chemotherapy)										
Lau 2003	1 randomised controlled trial	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (d)	0/15 (0%)	1/14 (7.1%)	PETO OR 0.14 (0 to 6.82)	61 fewer per 1000 (from 71 fewer to 273 more)	VERY LOW
% cancer patients undergoing chemotherapy with hepatitis due to HBV reactivation (minimum 6 weeks to 52 weeks after completion of chemotherapy/immunosuppressive therapy)										

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Prophylactic lamivudine Frequency (%)	Pre-emptive lamivudine Frequency (%)	Relative Risk/ PETO OR (95% CI)	Absolute	
Jang 2006 Lau 2003	2 randomised controlled trial	Serious limitations [a]	No serious inconsistency	No serious indirectness	No serious imprecision	1/51 (2%)	18/51 (35.3%)	RR 0.08 (0.02 to 0.42)	325 fewer per 1000 (from 205 fewer to 346 fewer)	MODERATE
Mortality due to HBV reactivation, in cancer patients undergoing chemotherapy (minimum 6 weeks to 52 weeks after completion of chemotherapy/immunosuppressive therapy)										
Jang 2006 Lau 2003	2 randomised controlled trial	Serious limitations [a]	No serious inconsistency	No serious indirectness	Very serious imprecision [d]	0/51 (0%)	1/51 (2.0%)	PETO OR 0.14 (0 to 7.01)	17 fewer per 1000 (from 20 fewer to 103 more)	VERY LOW
% HBV related hepatocellular carcinoma patient undergoing transarterial lipiolisation with hepatic decompensation (52 weeks after completion of immunosuppressive therapy)										
Jang 2006	1 randomised controlled trial	Serious limitations [b]	No serious inconsistency	No serious indirectness	Very serious imprecision [d]	1/36 (2.8%)	5/37 (13.5%)	RR 0.21 (0.03 to 1.67)	107 fewer per 1000 (from 131 fewer to 91 more)	VERY LOW
% HBV related hepatocellular carcinoma patient undergoing transarterial lipiolisation with hepatic decompensation due to HBV reactivation (52 weeks after completion of immunosuppressive therapy)										
Jang 2006	1 randomised controlled trial	Serious limitations [b]	No serious inconsistency	No serious indirectness	Very serious imprecision [d]	0/36 (0%)	3/37 (8.1%)	PETO OR 0.13 (0.01 to 1.3)	70 fewer per 1000 (from 80 fewer to 22	VERY LOW

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Prophylactic lamivudine Frequency (%)	Pre-emptive lamivudine Frequency (%)	Relative Risk/ PETO OR (95% CI)	Absolute	
									more)	

(a) No details on randomisation procedure in one study; all trials are not blinded.
(b)Not blinded.
(c)The confidence interval is consistent with two clinical decisions; appreciable benefit and no appreciable benefit or harm.
(d)The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm and appreciable harm

Comparison of prophylactic lamivudine versus therapeutic lamivudine (start Lamivudine only when there was hepatitis/ALT elevation after starting immunosuppressive therapy), according to causes of immunosuppression

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Prophylactic lamivudine Frequency (%)	Therapeutic lamivudine Frequency (%)	Relative Risk/ PETO OR (95% CI)	Absolute	
% of non-Hodgkin's lymphoma patients undergoing chemotherapy with HBV reactivation (during lamivudine treatment)										
Hsu 2008	1 randomised controlled trial	Serious limitations (a)	No serious consistency	Serious indirectness (b)	Very serious imprecision (b)	3/21 (14.3%)	13/13 (100%)	RR 0.16 (0.06 to 0.43)	840 fewer per 1000 (from 570 fewer to 940 fewer)	LOW
% of non-Hodgkin's lymphoma patients undergoing chemotherapy with hepatitis (during lamivudine treatment)										

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Prophylactic lamivudine Frequency (%)	Therapeutic lamivudine Frequency (%)	Relative Risk/ PETO OR (95% CI)	Absolute	
Hsu 2008	1 randomised controlled trial	Serious limitations (a)	No serious consistency	Serious indirectness (b)	Very serious imprecision (b)	4/21 (19%)	13/13 (100%)	RR 0.21 (0.09 to 0.49)	790 fewer per 1000 (from 510 fewer to 910 fewer)	LOW
% of non-Hodgkin's lymphoma patients undergoing chemotherapy with hepatitis due to HBV reactivation (during lamivudine treatment)										
Hsu 2008	1 randomised controlled trial	Serious limitations (a)	No serious consistency	Serious indirectness (b)	Very serious imprecision (b)	4/21 (19%)	1/13 (7.7%)	RR 2.48 (0.31 to 19.81)	114 more per 1000 (from 53 fewer to 1000 more)	LOW
% of non-Hodgkin's lymphoma patients undergoing chemotherapy with HBV reactivation (52 weeks of ending chemotherapy)										
Hsu 2008	1 randomised controlled trial	Serious limitations (a)	No serious consistency	Serious indirectness (b)	Very serious imprecision (c)	5/21 (23.8%)	3/13 (23.1%)	RR 1.03 (0.29 to 3.61)	7 more per 1000 (from 164 fewer to 602 more)	VERY LOW
% of non-Hodgkin's lymphoma patients undergoing chemotherapy with hepatitis (52 weeks of ending chemotherapy)										
Hsu 2008	1 randomised controlled trial	Serious limitations (a)	No serious consistency	Serious indirectness (b)	Very serious imprecision (c)	7/21 (33.3%)	3/13 (23.1%)	RR 1.44 (0.45 to 4.62)	102 more per 1000 (from 127 fewer to 836 more)	VERY LOW
% of non-Hodgkin's lymphoma patients undergoing chemotherapy with hepatitis due to HBV reactivation (52 weeks of ending chemotherapy)										

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Prophylactic lamivudine Frequency (%)	Therapeutic lamivudine Frequency (%)	Relative Risk/ PETO OR (95% CI)	Absolute	
Hsu 2008	1 randomised controlled trial	Serious limitations (a)	No serious consistency	Serious indirectness (b)	Very serious imprecision (c)	4/21 (19%)	1/13 (7.7%)	RR 2.48 (0.31 to 19.81)	114 more per 1000 (from 53 fewer to 1000 more)	VERY LOW
Mortality due to hepatitis, in non-Hodgkin's lymphoma patients undergoing chemotherapy (52 weeks of ending chemotherapy)										
Hsu 2008	1 randomised controlled trial	Serious limitations (a)	No serious consistency	Serious indirectness (b)	Very serious imprecision (c)	2/21 (9.5%)	0/13 (0%)	PETO OR 5.31 (0.29 to 96.13)	-	VERY LOW
Resistance, in non-Hodgkin's lymphoma patients undergoing chemotherapy (52 weeks of ending chemotherapy)										
Hsu 2008	1 randomised controlled trial	Serious limitations (a)	No serious consistency	Serious indirectness (b)	Very serious imprecision (c)	2/21 (9.5%)	0/13 (0%)	PETO OR 5.31 (0.29 to 96.13)	-	VERY LOW

(a) This is not a blinded trial.
(b) The two groups are heterogeneous with the therapeutic group containing more patients with HBeAg positive disease and more patients with a very high DNA quantity.
(c) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm and appreciable harm.

Comparison of pre-emptive lamivudine therapy (starting lamivudine only when there was HBV DNA and/or ALT elevation and/or significant hepatitis after starting immunosuppressive therapy) versus no therapy, according to causes of immunosuppression

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preemptive LAM	No therapy	Relative (95% CI)	Absolute	

Quality assessment							No of patients		Effect		Quality
Overall mortality , in kidney allograft recipients undergoing chemotherapy (end of follow up- mean 82 (SD 58) months after transplantation)											
1	observational study	Serious [(a)]	No serious inconsistency	No serious indirectness	Very serious imprecision [(b)]	strong association reduced effect for RR >> 1 or RR << 1	0/12 (0%)	14/52 (26.9%)	RR 0.14 (0.01 to 2.21)	232 fewer per 1000 (from 267 fewer to 326 more)	VERY LOW
Mortality due to liver complications, in kidney allograft recipients undergoing chemotherapy (end of follow up- mean 82 (SD 58) months after transplantation)											
1	observational study	Serious [(a)]	No serious inconsistency	No serious indirectness	Very serious imprecision [(b)]	strong association reduced effect for RR >> 1 or RR << 1	0/12 (0%)	8/52 (15.4%)	RR 0.24 (0.01 to 3.89)	117 fewer per 1000 (from 152 fewer to 445 more)	VERY LOW

(a) Non-randomised design with historical controls was used.
(b) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm and appreciable harm.

11.4.4 Economic evidence

Economic considerations

Reactivation of HBV replication with an increase in HBV DNA and ALT levels have been reported in 20% to 50% of hepatitis B carriers undergoing immunosuppressive or cancer chemotherapy.[61] Reactivation of HBV replication is more common when chemotherapeutic regimens that include corticosteroids are used. [61]

Prophylactic antiviral treatment is usually administered to hepatitis B carriers at the onset of cancer chemotherapy or a finite course of immunosuppressive therapy, and maintained for six months afterward. Lamivudine and entecavir are the preferred antiviral drugs due to their lack of nephrotoxicity.

According to the studies included in the clinical review, prophylactic lamivudine therapy is more effective than no treatment, pre-emptive lamivudine, and therapeutic lamivudine at preventing HBV reactivation, hepatic failure, and mortality. Prophylactic entecavir is more effective than prophylactic lamivudine. However, it is also more expensive (Table 222). The cost of prophylactic entecavir must be weighed against the costs and consequences of reactivation of HBV.

Is the extra cost of entecavir prophylaxis justified/outweighed by the infections averted with its use?

Published literature

No relevant economic evaluations of comparing different prophylactic treatments for immuno-compromised people with hepatitis B were identified.

New cost-effectiveness analysis

This question was not prioritised for original health economic modelling.

Unit costs

In the absence of recent UK cost-effectiveness analysis, average cost of each course of therapy was presented to aid consideration of cost effectiveness (Table 225). The costs included in this table represent the average cost per person for each treatment alternative and were calculated by multiplying the duration of treatment reported by the trials included in the clinical review (Table 226) by the unit cost for each drug reported by the BNF. For patients undergoing pre-emptive or prophylactic therapy, the cost was multiplied by the proportion of patients experiencing HBV reactivation.

Table 225: Cost of prophylactic antiviral therapy

Non-proprietary (proprietary)	Dose (per day)	Net price per pack	Estimated cost of treatment course per patient (range)
Pre-emptive LAM (Zeffix)	100 mg (tablets)	£78.09 (28 tablets/pack)	£132 (£114 to £282)[a]
Therapeutic LAM (Zeffix)	100 mg (tablets)	£78.09 (28 tablets/pack)	£175 (£21 to £347)b
Prophylactic LAM (Zeffix)	100 mg (tablets)	£78.09 (28 tablets/pack)	£582 (260 to £1088)
Prophylactic ETV (Baraclude)	500 µg (tablets)	£363.26 (30 tablets/ pack)	£2707 (£1210 to £5060)

(a) Cost per pack multiplied by the duration of therapy reported by Lau 2003 and the proportion of patients who received pre-emptive lamivudine after experiencing HBV reactivation (45.1%) in the trials by Lau 2003 and Jang 2006.

(b) Cost per pack multiplied by the duration of therapy reported by Hsu 2008 and the proportion of patients who received therapeutic lamivudine after experiencing HBV reactivation (23.1%) in the trail by Hsu 2008.

Table 226: Duration of treatment in included studies

	Median (range) duration of treatment in days			
	Prophylactic	**Pre-emptive**	**Therapeutic**	**No therapy**
Long 2011	189 (147 to 231)			Not relevant
Hsu 2008	190 (85 to 385)		139 (17 to 276)	
Lau 2003	224 (56 to 399)	105 (91 to 224)		
Jang 2006	Not reported	Not reported		
Li 2006	210 (140 to 721)*			Not relevant
Li 2011¥	366 (range NR)*			
Yeo 2004A	161 (56 to 367)			Not relevant
Yeo 2005	146 (78 to 323)			Not relevant
Huang 2009	183 (91 to 304)			Not relevant
Hui 2005	Not reported			Not relevant
Lau 2002	Not reported			Not relevant
Mean	**209 (93 to 390)**	**105 (91 to 224)**	**139 (17 to 276)**	**Not relevant**

** Based on the median and range reported for both CHOP therapy and duration of treatment following chemotherapy, assuming each cycle of CHOP is 3 weeks. ¥ This trial compared prophylactic lamivudine to entecavir; the treatment duration was reported to be equal.*

11.4.5 Clinical evidence statements

One observational study of 123 lymphoma patients undergoing chemotherapy found a benefit of prophylactic entecavir versus prophylactic lamivudine on the following outcomes:

Hepatitis (24 weeks after completion of chemotherapy) (LOW QUALITY)

Hepatitis due to HBV reactivation (24 weeks after completion of chemotherapy) (LOW QUALITY)

One observational study of 123 lymphoma patients undergoing chemotherapy found no difference between prophylactic entecavir versus prophylactic lamivudine on the following outcomes:

HBV reactivation (24 weeks after completion of chemotherapy) (VERY LOW QUALITY)

Severe hepatic failure (24 weeks after completion of chemotherapy) (VERY LOW QUALITY)

All-cause mortality (VERY LOW QUALITY)

Resistance (VERY LOW QUALITY)

……

One randomised trial of 42 breast cancer patients undergoing chemotherapy found a benefit of prophylactic lamivudine versus no prophylactic treatment on the following outcomes:

HBV reactivation (8 weeks after completion of chemotherapy) (MODERATE QUALITY)

One randomised trial of 42 breast cancer patients undergoing chemotherapy found no difference between prophylactic lamivudine versus no prophylactic treatment on the following outcomes:

Hepatitis (8 weeks after completion of chemotherapy) (VERY LOW QUALITY)

All-cause mortality (8 weeks after completion of chemotherapy) (VERY LOW QUALITY)

Three observational studies of 551 cancer patients undergoing chemotherapy found a benefit of prophylactic lamivudine versus no prophylactic treatment on hepatitis (8 weeks after completion of immunosuppressive therapy) (LOW QUALITY)

One observational study of 40 patients undergoing stem cell (bone marrow) transplantation found a benefit of prophylactic lamivudine versus no prophylactic treatment on hepatitis (52 weeks after completion of transplantation) (VERY LOW QUALITY)

Two observational studies of 414 cancer patients undergoing chemotherapy found no difference between prophylactic lamivudine versus no prophylactic treatment on all-cause mortality (8 weeks after completion of immunosuppressive therapy) (VERY LOW QUALITY)

Two observational studies of 72 patients undergoing stem cell (bone marrow) transplantation found a benefit of prophylactic lamivudine versus no prophylactic treatment on the following outcomes:

All-cause mortality (24 and 52 weeks after transplantation) (VERY LOW QUALITY)

Mortality due to HBV reactivation (24 and 52 weeks after completion of immunosuppressive therapy) (VERY LOW QUALITY)

Two observational studies of 295 patients undergoing chemotherapy found a benefit of prophylactic lamivudine versus no prophylactic treatment on hepatitis due to HBV reactivation (8 weeks after completion of immunosuppressive therapy) (LOW QUALITY)

Two observational studies of 295 patients undergoing chemotherapy found no difference between prophylactic lamivudine versus no prophylactic treatment on mortality due to HBV reactivation (8 weeks after completion of immunosuppressive therapy) (VERY LOW QUALITY)

Three observational studies of 105 patients undergoing stem cell (bone marrow) transplantation found a benefit of prophylactic lamivudine versus no prophylactic treatment on hepatitis due to HBV reactivation (24 and 52 weeks after completion of transplantation) (VERY LOW QUALITY)

One observational study of 156 cancer patients undergoing chemotherapy found no difference between prophylactic lamivudine versus no prophylactic treatment on resistance (monitored at least 12 weeks after completion of immunosuppressive therapy) (VERY LOW QUALITY)

One observational study of 32 patients undergoing stem cell (bone marrow) transplantation found no difference between prophylactic lamivudine versus no prophylactic treatment on resistance (24 weeks after completion of transplantation) (VERY LOW QUALITY)

……

Two randomised trials of 102 cancer patients undergoing chemotherapy found a benefit of prophylactic lamivudine versus pre-emptive lamivudine (start Lamivudine only when there was HBV reactivation after starting immunosuppressive therapy) on the following outcomes:

HBV reactivation (minimum 6 weeks to 52 weeks after completion of chemotherapy/ immunosuppressive therapy) (MODERATE QUALITY)

Hepatitis due to HBV reactivation (minimum 6 weeks to 52 weeks after completion of chemotherapy/immunosuppressive therapy) (MODERATE QUALITY)

Two randomised trials of 102 cancer patients undergoing chemotherapy found no difference between prophylactic lamivudine versus pre-emptive lamivudine (start Lamivudine only when there was HBV reactivation after starting immunosuppressive therapy) on the following outcomes:

All-cause mortality (minimum 6 weeks to 52 weeks after completion of chemotherapy/ immunosuppressive therapy) (VERY LOW QUALITY)

Mortality due to HBV reactivation (minimum 6 weeks to 52 weeks after completion of chemotherapy/immunosuppressive therapy) (VERY LOW QUALITY)

One randomised trial of 73 cancer patients undergoing chemotherapy found a benefit of prophylactic lamivudine versus pre-emptive lamivudine (start Lamivudine only when there was HBV reactivation after starting immunosuppressive therapy) on the following outcomes:

Hepatitis (52 weeks after completion of immunosuppressive therapy) (LOW QUALITY)

One randomised trial of 73 cancer patients undergoing chemotherapy found no difference between prophylactic lamivudine versus pre-emptive lamivudine (start Lamivudine only when there was HBV reactivation after starting immunosuppressive therapy) on the following outcomes:

Hepatic decompensation (52 weeks after completion of immunosuppressive therapy) (VERY LOW QUALITY)

Hepatic decompensation due to HBV reactivation (52 weeks after completion of immunosuppressive therapy) (VERY LOW QUALITY)

One randomised trial of 29 cancer patients undergoing chemotherapy found no difference between prophylactic lamivudine versus pre-emptive lamivudine (start Lamivudine only when there was HBV reactivation after starting immunosuppressive therapy) on the following outcomes:

Hepatic failure (minimum 6 weeks after completion of chemotherapy) (VERY LOW QUALITY)

……

One randomised controlled trial of 34 non-Hodgkin's lymphoma patients undergoing chemotherapy found a benefit of prophylactic lamivudine versus therapeutic lamivudine (start Lamivudine only when there was hepatitis/ALT elevation after starting immunosuppressive therapy) on the following outcomes:

HBV reactivation (during lamivudine treatment) (LOW QUALITY)

Hepatitis (during lamivudine treatment) (LOW QUALITY)

One randomised controlled trial of 34 non-Hodgkin's lymphoma patients undergoing chemotherapy found no difference between prophylactic lamivudine versus therapeutic lamivudine (start Lamivudine only when there was hepatitis/ALT elevation after starting immunosuppressive therapy) on the following outcomes:

Hepatitis due to HBV reactivation (during lamivudine treatment) (LOW QUALITY)

HBV reactivation (52 weeks of ending chemotherapy) (VERY LOW QUALITY)

Hepatitis (52 weeks of ending chemotherapy) (VERY LOW QUALITY)

Hepatitis due to HBV reactivation (52 weeks of ending chemotherapy) (VERY LOW QUALITY)

Mortality due to hepatitis (52 weeks of ending chemotherapy) (VERY LOW QUALITY)

Resistance (52 weeks of ending chemotherapy) (VERY LOW QUALITY)

……

One observational study of 64 kidney allograft recipients undergoing chemotherapy found no difference between pre-emptive lamivudine therapy (starting lamivudine only when there was HBV DNA and/or ALT elevation and/or significant hepatitis after starting immunosuppressive therapy) versus no therapy on the following outcomes:

Overall mortality (end of follow up: mean 82 (SD 58) months after transplantation) (VERY LOW QUALITY)

Mortality due to liver complications (end of follow up: mean 82 (SD 58) months after transplantation) (VERY LOW QUALITY

11.4.6 Recommendations and link to evidence

Recommendations	**68. Perform the following tests in people who are HBsAg and/or anti-HBc positive before starting immunosuppressive therapy for autoimmune or atopic diseases, chemotherapy, bone marrow or solid organ transplantation:** o antibody to hepatitis B surface antigen (anti-HBs) o plasma or serum HBV DNA level o ALT. **69. In people who are HBsAg positive and have HBV DNA greater than 2000 IU/ml, offer prophylaxis with entecavir or tenofovir disoproxil[rr].** o Start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after HBeAg seroconversion and HBV DNA is undetectable. **70. In people who are HBsAg positive and have HBV DNA less than 2000 IU/ml, offer prophylaxis:** o Consider lamivudine[ss] if immunosuppressive therapy is expected to last less than 6 months. – Monitor HBV DNA monthly in people treated with lamivudine and change to tenofovir disoproxil if HBV DNA remains detectable after 3 months.

[rr] At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[ss] At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

	o Consider entecavir or tenofovir disoproxil[tt] if immunosuppressive therapy is expected to last longer than 6 months o Start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after stopping immunosuppressive therapy. **71. In people who are HBsAg negative and anti-HBc positive (regardless of anti-HBs status) and are starting rituximab or other B cell-depleting therapies:** o offer prophylaxis with lamivudine[uu] o start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after stopping immunosuppressive therapy. **72. In people who are HBsAg negative, anti-HBc positive and anti-HBs negative and are not taking rituximab or other B cell-depleting therapies:** o monitor HBV DNA monthly and offer prophylaxis to people whose HBV DNA becomes detectable – consider lamivudine[vv] in people with HBV DNA less than 2000 IU/ml and for whom immunosuppressive therapy is expected to last less than 6 months; change to tenofovir disoproxil if HBV DNA remains detectable after 6 months – consider entecavir or tenofovir disoproxil[ww] in people with HBV DNA greater than 2000 IU/ml and for whom immunosuppressive therapy is expected to last longer than 6 months – continue antiviral therapy for a minimum of 6 months after stopping immunosuppressive therapy. **73. Do not offer prophylaxis to people who are HBsAg negative and anti-HBc and anti-HBs positive who are not taking rituximab or other B cell-depleting therapies.**
Relative values of different outcomes	Viral reactivation (serum HBV DNA) Clinical reactivation (ALT elevation) All-cause mortality The GDG regarded these outcomes to be equally important for decision making.

tt At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

uu At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

vv At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

ww At the time of publication (June 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Trade off between clinical benefits and harms	The risk of reactivation, both virological (HBV DNA) and clinical (ALT), is high in hepatitis B positive patients receiving chemotherapy or immunosuppressive therapy, especially when these regimens include corticosteroids or rituximab. Therefore, HBsAg, anti- HBc and anti-HBs testing should be performed in people who are at high risk of HBV infection to enable for identification, prophylaxis and monitoring. Evidence suggested prophylactic treatment (initiation prior to starting immunosuppressive therapy) is generally more effective, compared to pre-emptive (initiation only when there is virological reactivation) and therapeutic treatment (initiation only when there is hepatitis) in patients undergoing chemotherapy, haematopoietic stem cell / bone marrow or solid organ transplantation The GDG agreed that resistance to lamivudine is less likely to occur during prophylaxis versus treatment because the duration of prophylactic therapy is relatively short (less than 12 months). This was supported by the evidence. More efficacious drugs with a higher barrier to resistance such as entecavir and tenofovir should be given to patients if duration of immunosuppressive therapy is anticipated to be more than 12 months.
Economic considerations	The GDG considered the average cost of prophylaxis and pre-emptive/therapeutic treatment, as well as the probability and consequences of HBV reactivation. The group agreed that the increased cost of prophylactic therapy was likely to be justified by the long term costs and QALYs gained by avoiding viral reactivation in immunocompromised individuals. The GDG thought that if the immunosuppressive therapy duration is less than 6 months, lamivudine was likely to represent the most cost-effective prophylactic strategy in people who are HBsAg positive and HBV DNA is <2,000 IU/ml and those HBsAg negative and anti-HBc positive as resistance was unlikely to be a significant concern over this time period. If the immunosuppressive therapy duration is more than 12 months), the GDG thought that the risk of resistance to lamivudine is a concern and the increased cost and effectiveness of entecavir and tenofovir is likely to represent the most cost-effective use of NHS resources. In people who are HBsAg positive and have an HBV DNA level >2,000IU/mL, the GDG considered the most effective treatment to be also the most cost-effective strategy in this group.
Quality of evidence	One retrospective study of HBsAg positive patients (Li 2011N=123) undergoing chemotherapy suggested benefits in terms of having fewer patients with all-cause hepatitis [low quality] and hepatitis due to HBV reactivation [low quality] in the prophylactic entecavir group at 24 weeks after completion of chemotherapy, compared to the prophylactic lamivudine group. One randomised controlled trial of HBsAg positive patients found that prophylactic lamivudine showed benefits for reducing the proportion of HBV reactivation [moderate quality], compared to no prophylactic treatment at 8 weeks after completion of chemotherapy. This trial did not show benefit or harm in terms of hepatitis occurrence [very low quality]. However, three observational studies (prophylactic lamivudine arm was followed prospectively with historical controls) (N=451) suggested benefit for reducing the proportion of hepatitis in the prophylactic lamivudine arm at 8 weeks after completion of chemotherapy, comparing to no prophylactic treatment [low quality]. Two randomised trials (N=102) showed benefit in reducing the proportion of HBV reactivation in the prophylactic lamivudine group relative to those who received pre-emptive lamivudine, at 6-52 weeks after completion of chemotherapy [moderate quality]. One of the trials (N=73) also showed benefit in having a relatively smaller proportion of hepatitis and hepatic decompensation in the prophylactic lamivudine group at 52 weeks after

	completion of chemotherapy [low and very low quality, respectively]. One randomised trial compared prophylactic lamivudine with therapeutic lamivudine and suggested that during chemotherapy treatment, prophylactic lamivudine showed benefit in having fewer patients with HBV reactivation and hepatitis, compared to those received therapeutic lamivudine [low quality]. However, at 52 weeks after chemotherapy treatment, prophylactic lamivudine did not demonstrate benefit in both outcomes [very low quality]. Therapeutic lamivudine showed benefit in all-cause mortality and mortality due to liver complications at the end of follow up (mean 82 months after transplantation) comparing to no treatment in patients undergoing immunosuppressive treatment after kidney transplantation in one observational study [very low quality]. No evidence was identified for HBsAg negative patients
Other considerations	The recommendations were based on the evidence and GDG expert opinion. No evidence was identified for children and young people. The GDG considered the recommendations for adults could be extrapolated to children. No evidence was identified for tenofovir; however the GDG considered tenofovir to be an efficacious drug and should be given as an option. The GDG took into consideration the different risks of reactivation in people who were HBsAg positive and negative; the risk was generally small in HBsAg negative patients and so a pre-emptive approach that includes monthly monitoring of HBV DNA alongside chemotherapy was considered to be the most cost-effective option. The choice of anti-viral pre-emptive treatment was determined by HBV DNA levels using the more efficacious drugs when there was a rapid rise to levels greater than 2000 IU/ ml The exception to this pre-emptive approach was people receiving more aggressive chemotherapy regimens, such as the monoclonal antibody rituximab. Depletion of B lymphocytes by rituximab is thought to contribute to loss of HBV control in people who are HBsAg negative,[79] thereby increasing their risk of reactivation and death.[26] The GDG therefore recommended a prophylactic approach for patients receiving rituximab or similar treatments.

12 Monitoring and surveillance

12.1 Monitoring

12.1.1 Introduction

Patients with HBsAg positive hepatitis B need follow-up and monitoring prior to treatment, during treatment and after HBeAg or HBsAg seroconversion. The tests that need to be used and the frequency of testing will be dependent upon the patient's serological profile, HBV DNA viral load and the medications that they are currently receiving. For medications the summary of product characteristics tends to give guidance on the frequency of monitoring to assess safety and effectiveness. However, these testing regimens were usually adopted during the phase III trials and may not reflect current or ideal clinical practice.

Monitoring will start shortly after a patient is diagnosed with CHB. For those patients who are deemed not to require treatment at that time, continuous follow up is needed to assess when they are at risk of developing fibrosis and disease progression. The group of patients that are most likely to fall into this category are those in the immune-tolerant phase of disease, who are HBeAg positive, have high serum HBV DNA levels but normal ALT. The absence of an elevation in ALT means it is likely that no liver damage is occurring and that treatment will be less effective without immune system augmentation. Monitoring will need to be frequent enough to identify any transient flares in ALT. The other group likely to require monitoring prior to treatment are those who are HBeAg negative, anti-HBe positive with normal ALT levels and low HBV DNA viral loads (previously called inactive HBsAg carriers). These people need monitoring to begin with to ensure that they are truly inactive carriers but then the frequency of monitoring after the first year in this phase needs to be determined to again ensure that ALT flares are recognised.

Monitoring during treatment is carried out to evaluate effectiveness, identify potential stopping points and to be alerted to adverse effects of the medications. The particular tests that need to be carried out will depend on the drug used. For pegylated interferon (PEG-IFN), treatment is usually finite, with 12 months of planned treatment but early stopping points if it is evident that the treatment is ineffective. PEG-IFN has a number of adverse effects that need to be monitored for. It can lead to reductions in neutrophil and platelet counts, and can also lead to anaemia. Pre-existing abnormalities in thyroid function may be exacerbated and the development of new abnormalities of thyroid stimulating hormone (TSH) has been seen on treatment. Fluctuations in liver function tests are a normal result of therapy and may reflect immune clearance of the virus augmented by the interferon.

For nucleos(t)ide analogues (NAs) the length of treatment is usually long-term unless HBeAg seroconversion or HBsAg clearance occurs. Therefore much of the monitoring is to identify relapses, whether virologic or biochemical that may indicate that drug resistance has developed or there is not complete adherence to therapy. In addition continuous monitoring to ensure early identification of adverse effects also needs to occur.

Both adefovir and tenofovir have side effect profiles that require monitoring during treatment. Monitoring of phosphate levels is usually carried out during treatment along with urea and electrolytes for both drugs.

Following HBeAg seroconversion or HBsAg loss, treatment may be stopped with both PEG-IFN and NAs. A proportion of patients who discontinue treatment due to HBeAg seroconversion may serorevert and require retreatment [86,93]. Therefore some monitoring will need to continue to identify disease relapse.

12.1.2 Review question: How frequently should monitoring tests be done to ascertain virological, serological, biochemical response and resolution of fibrosis (HBeAg and antibody, HBsAg and antibody, ALT and transient elastography) and resistance (HBV DNA increase or virological breakthrough) in people with chronic hepatitis b?

Table 227: Protocol

Protocol	Heading
Population	Children, young people and adults with chronic hepatitis B virus infection (CHB).
Predictive factors (monitoring tests)	• HBV DNA levels at different points in treatment • HBeAg loss, seroconversion at different points in treatment • ALT normalization at different points in treatment • HBsAg seroconversion at different points in treatment • Incidence of resistance (HBV DNA increase or virological breakthrough)
Outcomes	• virological response (undetectable HBV DNA, viral breakthrough) • serological response (HBeAg loss/seroconversion, HBsAg loss/seroconversion) • biochemical response (ALT normalization, ALT flare) • resolution of fibrosis (histological improvement) • side effects • resistance We will also consider composite outcomes coming from two or more of the above types of responses.
Analysis	Stratified analysis by disease state: • HBeAg positive HBV DNA positive, ALT normal • inactive carriers (HBeAg negative and ALT normal) • patients on IFN treatment/ stopping rules • patients on NUC treatment/ stopping rules (patients on different NUCs will be presented separately) • patients off treatment • children with CHB

12.1.3 Clinical evidence

The evidence review is concerned with the prognosis of people who have a change in virological, serological and histological parameters, and specifically, we are concerned with how quickly that change occurs. Therefore the predictive factor is the change from baseline at particular time points or the absolute value of the quantity at two or more time points, and whether these predictive factors are predictive of progression of disease. The review necessarily investigates the magnitude of the change in predicting the outcome, but is not necessarily concerned with which are the best parameters to monitor. Consequently, where different measures of response are reported, we have plotted the numbers on the same forest plot by outcome.

12.1.3.1 Summary characteristics of included studies

Table 228: HBeAg positive patients with HBV DNA positive and ALT normal

Included studies	Patient characteristics	Predictive factors	Outcomes
Feld 2007	HBeAg positive patients with HBsAg positive for ≥6 months (N=32)	HBV DNA levels	ALT elevation: (a change from normal ALT to elevated ALT) (40IU/ml) from one visit to the next
Chu 2007	HBeAg positive patients with normal ALT level (0-36 U/L), no evidence of cirrhosis , no concomitant infection with hepatitis C or delta at the baseline and no antiviral therapy before entry or during follow up who had documented seroconversion from HBeAg to anti-HBe (N=48)	Maximal ALT during HBeAg positive phase (immune clearance phase)	Reactivation of hepatitis B: raise to more than twice the ULN of ALT levels, accompanied by positive serum HBV DNA (>1.4 X 10^5 copies/ml)

Table 229: Inactive carriers (HBeAg negative and ALT normal) with CHB

Included studies	Patient characteristics	Predictive factors	Outcomes
Kumar 2009	Asymptomatic HBeAg negative, normal ALT (<40IU/L); HBsAg positive for ≥6 months (N=217; 43 events)	ALT levels Serum HBV DNA	Spontaneous ALT flare: ALT rise to > ULN x2 , accompanied by HBV DNA levels of ≥10^5 copies/ml or 100-fold rise in HBV DNA from the previous levels
Feld 2007	Asymptomatic HBeAg negative, anti-HBe positive, normal ALT (<40IU/L); HBsAg positive for ≥6 months (N=74)	HBV DNA levels	ALT elevation: (a change from normal ALT to elevated ALT) (40IU/ml) from one visit to the next

Table 230: HBsAg positive carriers (mixed population of HBeAg positive and negative)

Included studies	Patient characteristics	Predictive factors	Outcomes
Arai 2012	HBsAg positive carriers (persistent HBV infection) (treatment naïve) (N=423) 183 HBeAg positive and 240 HBeAg negative patients	Quantitative HBsAg levels Serum HBV DNA levels	HBsAg seroclearance (cut off <0.03IU/ml)

Table 231: Patients with CHB on interferon treatment

Included studies	Patient characteristics	Predictive factors	Outcomes
Heijink 2000	Patients with positivity in serum for at least 6 months and presence of HBeAg and HBV DNA in serum (N=162)	HBeAg levels HBV DNA	Composite response: simultaneous negative result for HBeAg and HBV DNA (<=1.6 pg/ml)
Janssen 1994	Patients HBeAg and HBV DNA (+)(N=12)	HBeAg HBV DNA	HBsAg levels
Baltayiannis 2006	HBeAg (-) CHB patients who were HBsAg and HBV DNA (+) at least two occasions 6 months apart (N=63) .	HBV DNA	Relapse: increase of ALT levels above the normal range and detectable HBV DNA levels at the end of treatment of when responses were not maintained for 6-12 months follow up with the presence of HBsAg (non sustained relapse).
Rijckborst 2010	HBeAg negative patients(N=133)	HBsAg HBV DNA	Sustained response (SR): the combined presence of serum HBV DNA levels below 10,000 copies/ml (1714 IU/ml) and normalization of ALT at the end of follow up (week 72)
Perillo 1993	patients positive for HBeAg and HBV DNA before interferon alpha treatment	HBV DNA HBeAg loss	Composite response: HBV DNA loss by the end of treatment and HBeAg loss during a 6-to 9- month post treatment
Fried 2008	HBV infected HBeAg positive patients who have previously received peginterferon alfa-2a plus oral placebo for 48 weeks (N=271)	HBeAg HBV DNA	Response: achievement of HBeAg seroconversion at the end of 72 weeks (48 weeks of treatment and 24 weeks follow up). Late response: not having achieved HBeAg seroconversion by the end of therapy, but achieved seroconversion by the end of the 24 week follow up.
Moucari 2009	HBeAg negative patients with presence of HBsAg in serum for more than 6 months who were treated with pegylated interferon for 48 weeks (n=48).	HBV DNA levels HBsAg levels	End of treatment response (EOT): undetectable serum HBV DNA at the end of treatment. Sustained virological response (SVR): undetectable serum HBV DNA at 24 weeks after end of treatment
ter Borg 2006	HBeAg positive patients who received peginterferon alfa 2b +/- lamivudine for 52 weeks and were followed for 26 weeks (n=266) from Janssen 2005 trial	Decline in HBV DNA levels	HBeAg loss at the end of follow up

Included studies	Patient characteristics	Predictive factors	Outcomes
Rijckborst et al, 2012.	HbeAg negative patients who were treated in three trials (PARC (pegylated IFN a-2a +/- ribavirin for 48 weeks), phase III trial (pegylated IFN a-2a for 48 weeks), PegBeliver study (pegylated IFN a-2a for 96 weeks))	HBsAg decline and/or >=2log HBV DNA decline at 12 weeks	Sustained response: combined presence of serum HBV DNA<2000 IU/ml and normal ALT after 24 weeks of post-treatment
Piratvisuth et al, 2011.	HbeAg positive patients treated with peginterferon alfa-2a alone (n=204) or in combination with lamivudine (n=195) and with HBsAg values available at all time points (baseline, weeks 12, 24, 48 and 72). The majority of patients were infected with HBV genotype B (32.6%) or genotype C (58.4%).	HBsAg levels at baseline, at 12 and 24 weeks during treatment	HbeAg seroconversion 6 months after treatment HBV DNA<=2,000 IU/ml 6 months post treatment 3) HBsAg clearance 6 months post treatment
Marcellin et al, 2012.	HBeAg negative patients received peginterferon alfa-2a (180µg/week)+/- lamivudine (100mg/day) for 48 weeks as part of the large, multicentre, randomized Phase 3 study (Marcellin, 2009).	HBsAg levels at 12 and 24 weeks	HBV DNA<=2,000 IU/ml (=10,000 copies/ml) HBsAg clearance at 1 and 5 years post treatment

Table 232: Patients with CHB on NUC treatment

Included studies	Patient characteristics	Predictive factors	Outcomes
Jaroszewicz 2011	Mixed HBeAg (+) and (-); patients underwent NUC treatment who achieved HBV DNA suppression (N=126)	Quantitative HBsAg decrease	HBsAg loss/clearance

Table 233: Patients with CHB on lamivudine treatment

Included studies	Patient characteristics	Predictive factors	Outcomes
Franca 2007	Patients presenting with	Resistance	ALT flare: increase in ALT > 3 x

Included studies	Patient characteristics	Predictive factors	Outcomes
	clinical or biochemical signs of acute active hepatitis (N=28)		ULN from normal levels in the preceding samples.
Llop 2009	Retrospective study CHB patients treated with Lamivudine or Adefovir between 2001 and 2006 (N=66)	HBV DNA	Virologic response: undetectable HBV DNA (<200 copies)
Kim 2007A	HBeAg (+) and (-) patients that underwent lamivudine therapy for more than 6 months (N=221)	HBV DNA HBeAg Anti HBe ALT	Viral breakthrough (undetectable group: reversion of HBV DNA to detectable levels during therapy; persistently detectable HBV DNA group: a rebound of HBV DNA to a level >1log10 of the lowest level recorded during therapy) HBeAg loss ALT normalisation
Wang 2010A	HBeAg (+) patients; ALT ≥2x upper limit of normal (ULN), HBV DNA ≥10^5copies/ml; met the American Association for the Study of Liver Diseases (AASLD) cessation criterion (N=125)	HBeAg loss/seroconversion	Virologic relapse: reappearance of serum HBV DNA ≥10^4 copies/ml with/without reappearance of HBeAg
Gramenzi 2011	HBeAg (-) and NA naïve (N=42)	HBsAg levels HBV DNA	Virological breakthrough: an increase in viral load >1 log10 IU/ml when compared to the nadir achieved under antiviral treatment
Park 2005	HBeAg (+) naïve CHB patients (N=340)	Quantitative HBeAg	Viral breakthrough: reappearance of HBV DNA in serum on two or more occasions after its initial disappearance Viral response: simultaneous HBeAg seroconversion and HBV DNA negativity on two occasions at least 1 month apart
Thompson 2007	Mixed HBeAg (+) and (-) with HBsAg in serum for ≥6 months and elevated ALT	Detectable HBV DNA	HBeAg seroconversion Lamivudine resistance: patients who were suspected of LAM resistance due to increase in viral load, or reappearance of HBV DNA in a patient with previously undetectable HBV DNA

Included studies	Patient characteristics	Predictive factors	Outcomes
Hsieh 2009	Mixed HBeAg (+) and (-); positive for HBsAg for ≥6 months who developed resistance after LAM therapy	HBV genotype	Lamivudine resistance: detectable mutation strain within 12 months of treatment
Chan 2011	HBeAg negative patients who had continuous lamivudine treatment for at least 12 months and had post-treatment follow up for at least 12 months.	Quantitative HBsAg HBV DNA	Sustained off treatment response, defined as HBV DNA ≤200IU/ml at 12 months post-treatment

Table 234: Patients with CHB on adefovir treatment

Included studies	Patient characteristics	Predictive factors	Outcomes
Llop 2009	CHB patients treated with Lamivudine or Adefovir between 2001 and 2006 (N=66) Setting: Spain	Serum HBV DNA	Virologic response (defined as undetectable HBV DNA (<200 copies))

Table 235: Patients with CHB on entecavir treatment

Included studies	Patient characteristics	Predictive factors	Outcomes
Jung 2010A	HBeAg (+) treatment naïve CHB patients receiving entecavir for more than 1 year(N=51)	ALT normalisation Undetectable HBV DNA HBeAg loss HBeAg seroconversion	HBsAg response: decrease in the HBsAg level>1log10 IU/ml from baseline at 12 months after treatment
Chon 2011	Patients older than 16 years old with persistent serum HBsAg for more than 6 months and BBV genotype C. (N=420)	HBV DNA levels HBV DNA reduction from baseline	Undetectable HBV DNA (<12 IU/ml)
Lee 2011A	HBeAg (+) and (-) patients with CHB (N=101)	HBV DNA HBsAg	For HBeAg (+): treatment response defined as serum HBV DNA undetectable or HBeAg loss/seroconversion. For HBeAg (-): treatment response defined as serum HBV DNA undetectable.

Table 236: Patients with CHB off treatment

Included studies	Patient characteristics	Predictive factors	Outcomes
Wong 2004	Patients aged 16-70 years with detectable HBsAg and HBeAg, serum HBV DNA levels of at least 5 pg/ml and ALT levels less than 10 times the upper limit of the normal range before randomized to 5 years of treatment with lamivudine. At the end of 5 years of treatment all patients had harboured YMDD mutants for at least 2 years (N=58)	ALT levels HBV DNA levels	ALT flare: ALT>= 5 x ULN together with detectable HBV DNA in the follow up after stopping lamivudine
Lee 2002A	CHB patients treated with lamivudine and being positive for serum HBsAg, HBeAg and HBV DNA over 6 months after LAM therapy (N=124).	HBV DNA levels	Relapse: reappearance of serum HBV DNA and an increase in ALT at least 3 x ULN
Lee 2003	Patients who exhibited HBeAg loss/seroconversion during lamivudine therapy and agreed to receive extended lamivudine therapy (N=49)	HBV DNA levels	Virological relapse was defined as post treatment reappearance of serum HBV DNA as measured by the DHCII assay, and/or HBeAg in two consecutive tests.

Table 237: Children with CHB

Included studies	Patient characteristics	Predictive factors	Outcomes
Nagata 1999	Children with chronic HBV infection that were HBV DNA and HBeAg (+) for at least 6 months before treatment (N=22)	HBeAg levels HBeAg seroconversion HBsAg levels HBsAg seroconversion HBV DNA levels	Virological response: HBV DNA negativity and HBeAg seroconversion within 18 months of treatment completion.

12.1.3.2 HBeAg positive patients with detectable HBV DNA and normal ALT levels

Predictive factor: HBV DNA

One small prospective cohort study (Feld 2007) examined the time course of development of ALT elevation in patients who were HBeAg positive with different HBV DNA levels. The population consisted of 32 patients who were followed every 3 months for up to 5 years. The study reported a

multivariable Cox regression analysis for the time to ALT elevation and found no significant predictors. The study also reported a series of Kaplan Meier plots showing the development of ALT elevations over time, comparing various HBV DNA cut-offs. Time zero corresponded to times at which the patients were ALT normal (≤40 IU/ml). The study found that HBV DNA was not predictive of future ALT at any threshold.

The Kaplan Meier plots showed the following proportions of patients with an increase in ALT levels: at 3 months about 8%; at 6 months 10-20%; at 12 months 33%.

Predictive factor: ALT

One prospective cohort study (Chu et al 2007) was conducted in 133 HBeAg positive patients with normal ALT (≤36IU/L) (in the immune-tolerant phase). Cox proportional hazards multivariable analysis was carried out based on variables that had p-values ≤ 0.1 on univariate analysis; there were 5 covariates and 26 events, giving a ratio of events to covariates of 5.2.

The study found that people with an ALT level above 5 x ULN during the immune-tolerance phase, in comparison with people below 2 x ULN, were significantly associated with hepatitis reactivation (defined as ALT >2xULN and HBV DNA >1.4x10^5 copies/ml) at a minimum of one year following HBeAg seroconversion (mean follow up 5.8 years (SD 4.2)) . The evidence was considered to be only of partial relevance to this review, because it did not address times of monitoring, but indicated that monitoring ALT levels should occur.

Table 238: Thresholds of ALT levels for hepatitis reactivation during immune tolerance phase at a minimum of 1 year follow up

	Multivariable analysis*▪	
Threshold of ALT during HBeAg positive (immune clearance) phase	Hazard ratio (95% CI)	P value
<2 x ULN 2-5 x ULN >5 x ULN	– 1 (referent) 2.75 (95%CI 0.89 to 8.47) 3.57 (95%CI 1.22 to 10.46)	 0.08 **0.02**

**Cox proportional hazards regression models.*

▪ *Multivariable model included gender, genotype, two ALT categories and age at HBeAg seroconversion, factors significant (p<0.1) on univariate analysis.*

12.1.3.3 Inactive carriers with CHB (defined as HBeAg negative patients and normal ALT levels)

Two studies (Kumar 2009 in 217 patients; Feld 2007 in 74 patients) investigated the value of ALT and HBV DNA monitoring tests in predicting future ALT flares or elevation among inactive carriers with CHB at different time intervals.

Biochemical response

Predictive factor: ALT levels

In one prospective cohort study (Kumar 2009), 217 asymptomatic CHB patients/inactive carriers were followed for a median of 69 months and the study investigated ALT fluctuations in these patients by examining the time to spontaneous ALT flare after study entry (defined as ALT increased to ULN x 2, accompanied by HBV DNA levels of ≥10^5 copies/ml; or a 100-fold rise in HBV DNA from the previous levels), to determine the optimal ALT monitoring frequency. During a median of 69

months follow up (range 12 to 144 months), 43/217 (20%) developed spontaneous ALT flares (with an annual rate of 4.3%).

Table 239 shows the various percentiles of the time to spontaneous ALT flare after study entry for the 43 people (20%) who had flares; the median time to spontaneous ALT flare was 25 months (range 1 to 128). The authors reported that the 10th percentile was 3.4 months, and they suggested that ALT monitoring every 3 months can detect approximately 90% of ALT flares and would help identify patients who require antiviral therapy. The conclusions are based on the people who had flares and did not take into account those who had not had a flare during the course of the study.

Table 239: Time to spontaneous ALT flare after enrolment into the study from baseline, in asymptomatic HBeAg negative CHB infected patients with normal ALT at presentation (Kumar 2009)

Percentiles	Time (months)
5	2.2
10	**3.4**
15	5.0
20	5.0
25	6.0
30	9.6
35	14.0
40	19.0
45	23.2
50	25.0
55	34.4
60	39.2
65	54.0
70	62.0
75	67.0
80	70.0
85	77.0
90	97.2
95	116.4
100	128.0

Predictive factor: HBV DNA

Another small prospective cohort study (Feld 2007) examined the time course of development of ALT elevation in patients with different HBV DNA levels. The population consisted of 74 asymptomatic HBeAg negative patients who were followed every 3 months for up to 5 years. The study reported a multivariable Cox regression analysis for the time to ALT elevation and found the significant predictors were HBV DNA level (10,000 copies/ml and 100,000 copies/ml cutoffs) and the number of previous ALT elevations. This analysis, however, did not allow us to draw conclusions on monitoring frequency and for this purpose we used the authors' series of Kaplan Meier plots showing the development of ALT elevations over time, comparing various HBV DNA cut-offs; these were univariate comparisons. Time zero corresponded to times at which the patients were ALT normal (≤40 IU/ml). In order to consider the frequency of monitoring, data were extracted on the proportion of patients who had ALT elevation at different time points using the Kaplan Meier plots or the text if reported.

Table 240: Value of HBV DNA threshold of 10,000copies/ml for the prediction of future ALT elevation in inactive carriers in the subsequent 6, 12 and 36 months of follow up (Feld 2007)

	% patients had ALT elevation (>40IU/ml)	Unadjusted odds ratio (95%CI)
At 6 months		
HBV DNA >10,000 copies/ml + normal ALT (n= 43)	21%*	7.94 (95%CI 0.95 to 66.39)
HBV DNA <10,000 copies/ml + normal ALT (n=31)	2.9%	
At 12 months		
HBV DNA >10,000 copies/ml + normal ALT	43	21.60 (95C%CI 2.69 to 173.32)
HBV DNA <10,000 copies/ml + normal ALT	2.9%	
At 36 months		
HBV DNA >10,000 copies/ml + normal ALT	77.6%	5.22 (95%CI 1.90 to 14.37)
HBV DNA <10,000 copies/ml + normal ALT	37.6%	

** Figures are taken from graphical presentation so are an approximation*

The unadjusted odds ratio for the predictive factor 10,000 copies/ml HBV DNA was not significant at 6 months, showed a large significant effect at 12 months and decreased in magnitude at 36 months (although remaining significant). For people with DNA levels of between 10,000 and 100,000 copies/ml, the study reported that 10.6% patients had an elevated ALT level by six months, and 20% by 12 months.

Different HBV DNA thresholds were also tested: 30,000copies/ml (Table 241), 50,000copies/ml (Table 242) and 100,000copies/ml (Table 243).

The unadjusted odds ratios for thresholds of 30,000 and 50,000 copies/ml were smaller than for the 10,000 threshold (i.e. less discriminating), but the 50,000 threshold was significant at 6 months; however, this would be at the expense of having more patients untreated (9% raised ALT for people with a HBV DNA threshold below 50,000 copies/ml).

Table 241: Value of HBV DNA threshold of 30,000 copies/ml for the prediction of future ALT elevation in HBeAg negative patients with normal ALT, at 6, 12 and 36 months follow up (Feld 2007)*

	% patients had ALT elevation (>40IU/ml)	Unadjusted odds ratio (95%CI)
At 6 months		
HBV DNA >30,000 copies/ml + normal ALT (n=27)	23%	3.07 [95% CI 0.78 to 12.07)
HBV DNA <30,000 copies/ml + normal ALT (n=47)	8%	
At 12 months		
HBV DNA >30,000 copies/ml + normal ALT	40%	2.90 (95%CI 1.01 to 8.35)
HBV DNA <30,000 copies/ml + normal ALT	19%	
At 36 months		
HBV DNA >30,000 copies/ml + normal ALT	70%	– 1.61 (95%CI 0.59 to 4.43)
HBV DNA <30,000 copies/ml + normal ALT	60%	

** Figures are taken from graphical presentation so are an approximation.*

Table 242: Value of HBV DNA threshold of 50,000 copies/ml for the prediction of future ALT elevation in HBeAg negative patients with normal ALT, at 6, 12 and 36 months follow up (Feld 2007)*

	% patients had ALT elevation (>40IU/ml)	Unadjusted odds ratio (95%CI)
At 6 months		–
HBV DNA >50,000 copies/ml + normal ALT (n=25)	26%	
HBV DNA <50,000 copies/ml + normal ALT (n=49)	9%	4.38 [95% CI 1.14 to 16.79)
At 12 months		
HBV DNA >50,000 copies/ml + normal ALT	44%	
HBV DNA <50,000 copies/ml + normal ALT	18%	3.52 (95%CI 1.20 to 10.36)
At 36 months		
HBV DNA >50,000 copies/ml + normal ALT	68%	
HBV DNA <50,000 copies/ml + normal ALT	61%	1.08 (95%CI 0.41 to 2.84)

** Figures are taken from graphical presentation so are an approximation.*

HBV DNA thresholds of 100,000 and 200,000 copies/ml (not reported here) showed the ability to discriminate at six months between those who will and will not develop an elevated ALT, with large odds ratios being obtained; however, the number of patients who had HBV DNA above those levels were small; results should be interpreted with caution.

Table 243: Value of HBV DNA threshold of 100,000 copies/ml for the prediction of future ALT elevation in HBeAg negative patients with normal ALT, at 6, 12 and 36 months follow up (Feld 2007)*

	% patients had ALT elevation over time (>40IU/ml)	
At 6 months		
HBV DNA >100,000 copies/ml + normal ALT (n=16)	41%	14.26 (95% CI 3.10 to 65.53)
HBV DNA <100,000 copies/ml + normal ALT (n=58)	6%	
At 12 months		
HBV DNA >100,000 copies/ml + normal ALT	67%	10.56 (95%CI 3.00 to 37.14)
HBV DNA <100,000 copies/ml + normal ALT	17%	
At 36 months		
HBV DNA >100,000 copies/ml + normal ALT	67%	1.34 (95%CI 0.41 to 4.39)
HBV DNA <100,000 copies/ml + normal ALT	62%	

** Figures are taken from graphical presentation so are an approximation, except 67% reported in the text.*

The authors concluded that:

- HBV DNA values less than 10,000 copies/ml can predict persistently normal ALT for at least one year.
- Those with HBV DNA values 10,000-100,000 copies/ml can safely be monitored at 6 monthly intervals.
- HBV DNA>100,000 copies/ml are highly predictive of future ALT elevation and this group of patients require frequent follow up.

12.1.3.4 HBsAg positive carriers (mixed population of HBeAg positive and HBeAg negative)

HBsAg serological response

Predictive factors: quantitative HBsAg and ALT levels

A retrospective study (Arai 2012) of 423 HBsAg carriers (not requiring treatment) (240 HBeAg negative and 183 HBeAg positive) investigated serial measurements of quantitative HBsAg every 6-12 months in predicting future HBsAg seroclearance, defined as HBsAg level <0.03IU/ml. The study conducted multivariable analyses for baseline predictors, but the change with time was not included. Only 25 patients had seroconversion.

The study showed graphically the serial changes in HBsAg levels for each of the 25 patients who had subsequent seroconversion, but did not compare this with people who did not achieve seroconversion.

The study also showed graphically fluctuations in ALT levels before seroconversion and not afterwards in these patients.

12.1.3.5 Patients with CHB on pegylated interferon treatment

We included eleven studies (Baltayiannis 2006, Fried 2008, Heijink 2000, Janssen 1994, Marcellin 2012 (and its substudy, Lampertico 2012), Moucari 2009, Perillo 1993, Piratvisuth 2011, Rijckborst 2010, Rijckborst 2012, ter Borg 2006) investigating the frequency of monitoring tests in predicting different types of responses among patients with CHB on interferon or pegylated interferon treatment. The majority of studies have identified potential stopping rules for interferon or pegylated interferon treatment in patients who may have high probability of no response.

Results are presented below by HBeAg positivity and response type. Then monitoring frequency data is summarised across the different response measures, for each of HBeAg positive and negative disease, including representation on forest plots. This enabled the GDG to look at trends for monitoring frequencies. Emphasis is placed on multivariable analyses where possible. Results are given for both pegylated and non-pegylated interferons, and it was expected that these interventions would behave similarly with respect to monitoring.

HBeAg positive patients: serological response

Three studies (Fried 2008, Janssen 1994, ter Borg 2006) compared the correlation of HBeAg and HBV DNA levels during treatment with interferon alpha or pegylated interferon alfa-2a with the patients' serological response at the end of treatment. One study (Piratvisuth 2011) investigated the predictive ability of HBsAg levels at 12 and 24 weeks during treatment.

The study by Fried (2008) was a retrospective analysis of a group of 274 HBeAg positive patients who had previously received pegylated interferon alfa-2a monotherapy for 48 weeks in a randomized trial (Lau 2005). This study looked at serological response which was defined as achievement of HBeAg seroconversion at the end of 48 weeks of treatment and 24 weeks follow up and late response as not having achieved HBeAg seroconversion by the end of therapy but achieved by the end of 24 weeks follow up. There were 87 responders to treatment.

The authors reported only the proportions of responders at 72 weeks by different thresholds of HBeAg and HBV DNA at 12 weeks during treatment and no indication of the risk of the outcome by HBeAg level or any p-values is given at that time point; it was stated only that the NPV for a threshold of 100 was lower than 96% (the 24 week value) for 4, 8 and 12 weeks (Table 251).

Table 244: Value of serum HBeAg levels and HBV DNA at 12 weeks of pegylated interferon treatment for the prediction of serological response at the end of 24 weeks follow up after the end of treatment in 271 HBeAg positive patients

	N, % of responders (HBeAg seroconversion at week 72) (N=87)	N, % of non responders (N=184)
HBeAg (PEIU/ml) at 12 weeks during treatment*		
<10	53%	47%
10-100	23%	77%
>100	14%	86%
HBV DNA (log10 copies/ml) at 12 weeks during treatment*		
<3	64%	36%
3-5	49%	51%
5-7	29%	71%
>=7	21%	79%

** The study has provided only proportions and no frequencies could be calculated (no information was given on the different groups of HBeAg and HBV DNA levels at 12 weeks of treatment)*

Table 245 gives the predictive value of different thresholds of HBeAg and HBV DNA at 24 weeks during pegylated interferon treatment for response at 24 weeks follow up post treatment. The results demonstrated that HBeAg levels above 100 PEIU/ml at 24 weeks versus below that threshold gave a significant odds ratio for serological response at 24 weeks follow up and the proportion responding below the threshold was only 4% The authors also reported results from the receiver operating characteristic curves for both predictive factors of HBeAg and HBV DNA at 24 weeks during treatment that showed that HBeAg levels had greater power to predict HBeAg seroconversion at 24 weeks follow up than HBV DNA levels (P=0.014).

Table 245: Value of serum HBeAg levels and HBV DNA at 24 weeks of pegylated interferon treatment for the prediction of serological response at the end of 24 weeks follow up after the end of treatment in 271 HBeAg positive patients

	N, % of responders (n=85)	N, % of non responders (n=178)	Unadjusted OR (95%CI)
HBeAg (PEIU/ml) at 24 weeks during peg interferon treatment			
<10 (n=137, 52%)	71/137 (52%)	66/137	<10 vs ≥10 OR 8.61 (95%CI 4.50 to 16.47); for the ≥10 group response rate of 11%
10-100 (n=54, 21%)	11/54 (20%)	43/54	<100 vs ≥100 OR 17.30 (95%CI 5.26 to 56.93); for the ≥100 group response of 4%
>100 (n=72, 27%)*	3/72 (4%)	69/72	
HBV DNA (log10 copies/ml) at 24 weeks during treatment			
<5 log copies/ml (n=118, 45%)	53% (62/118)	56/118	<5 vs ≥5 OR 5.87 (95% CI 3.31 to 10.42); for the ≥5 group response of 16%
5-9 copies/ml (n=89, 34%)	17% (15/89)	74/89	<9 vs ≥9 OR 3.55 (95%CI 1.60 to 7.91); for the ≥9 group response of

	N, % of responders (n=85)	N, % of non responders (n=178)	Unadjusted OR (95%CI)
			14%
>9 copies/ml (n=56, 21%)**	14% (8/56)	(46/56)	

** The accuracy of HBeAg and HBV DNA at 24 weeks to predict serological response was assessed using the receiver operating characteristic curve.*

In relation to late serological response (achievement of HBeAg seroconversion at 24 weeks follow up but previously seroconverted at the end of 48 weeks of treatment), the authors gave only a narrative presentation of results and concluded that there was a divergence between HBeAg and HBV DNA dynamics among late responders, with a persistent decrease in HBeAg levels, whereas HBV DNA levels remained relatively flat. The authors believed that this reinforces the view that quantitative HBeAg measurements are more predictive of HBeAg seroconversion than HBV DNA levels.

The second study by Janssen (1994) was a prospective small sample size study (N=12) for people receiving interferon treatment for 4 months. No numerical results were presented.

The study by ter Borg (2006) was a further investigation of HBeAg positive patients in an RCT (Janssen 2005) comparing peginterferon alfa 2b plus lamivudine versus peginterferon plus placebo in 266 patients; 33% of the patients had been previously treated with interferon (21%) or lamivudine (12%). Patients received treatment for 52 weeks and then were followed for a further 26 weeks, after which time HBeAg loss was determined; this occurred in 95 patients. The study took serum samples for HBV DNA measurement at the start of therapy and monthly thereafter to the end of treatment.

The study examined patterns of HBV DNA decline and reported that patients in the combination group had significantly lower mean HBV DNA levels than the monotherapy group at all times during therapy, but after stopping therapy the combination group relapsed, whereas the monotherapy group did not, leaving the DNA levels similar at 26 weeks post-treatment.

In the combination group, the study reported that there was a small significant difference in HBV DNA levels between responders and non-responders (calculated to be 0.62 log (95%CI 0.17 to 1.07), whereas the difference for the monotherapy group was much larger (calculated to be 1.37 log (95%CI 0.74 to 2.00). The test for subgroup differences was 72% (see the forest plot in Appendix G). The study then further analysed patterns of response in the monotherapy group and identified five patterns of behaviour (Table 246):

Table 246: Patterns of HBV DNA decline in patients receiving peginterferon alfa 2b monotherapy and their effect on HBeAg loss and HBsAg loss

	HBeAg loss n(%)	HBsAg loss n(%)
Decline patterns		
Early decline: >1 log reduction in HBV DNA during week 0-4 of therapy (n=23)	12 (52%)	1 (4%)
Delayed decline: ≥2 log reduction from baseline in HBV DNA during weeks 4-32 without early decline (n=32)	20 (63%)	7 (22%)
Late decline: ≥2 log reduction from baseline in HBV DNA between weeks 32 and 52, without previous decline patterns (n=13)	4 (31%)	0 (0%)
Post-treatment decline: ≥2 log reduction from baseline in HBV DNA after week 52, without previous decline	3 (27%)	0 (0%)

	HBeAg loss n(%)	HBsAg loss n(%)
patterns (n=11)		
No substantial decline at any time point (n=44)	5 (11%)	0 (0%)
Unadjusted odds ratios for HBeAg loss and HBsAg loss		
Early decline versus all other patterns	OR 2.32 (95%CI 0.92 to 5.82)	Peto OR 0.65 (95%CI 0.10 to 4.05)
Early plus delayed decline versus all other patterns	OR 6.49 (95%CI 2.85 to 14.77)	Peto OR 10.72 (95%CI 2.55 to 45.06)
Any decline during treatment versus no decline during treatment	OR 6.61 (95%CI 2.72 to 16.06)	Peto OR 6.81 (95%CI 1.62 to 28.63)

The Piratvisuth 2011 study conducted a retrospective analysis of 399 HBeAg positive patients, who had been treated with Peg interferon alfa 2a with or without lamivudine in an RCT (Lau 2005 trial). The analysis was restricted to those with HBsAg measurements at baseline, 12, 24, 48 and 72 weeks and also to those who had 24 weeks follow up outcome data (i.e. there was a possibility of selection bias). The majority of patients were genotype B and C.

The study used ROC analysis to determine the optimum threshold (<1,500 IU/ml) based on an NPV of 95% or more; a second additional threshold was also introduced (>20,000 IU/ml). The study then examined the predictive ability of these (absolute) HBsAg thresholds at 12 and 24 weeks during pegylated interferon treatment for three response outcomes: HBV DNA response ≤ 2000 IU/ml, HBeAg seroconversion and HBsAg clearance, each at six months post treatment.

The study also reported that, similar to ter Borg 2006, there was a significant difference between responders and non-responders in HBV DNA decline at 12, 24, 48 and 72 weeks for monotherapy (p value 0.0019 at 12 weeks), but no significant difference for the combination therapy at any time except 72 weeks. Differences in predictive ability of HBsAg decline between mono- and combination therapies were not investigated.

In addition, it was reported that the decline in HBsAg over time was similar in pegylated interferon with and without Lamivudine, so results were combined for the monotherapy and combination therapy. However, the decline in HBV DNA levels was substantially greater in the combination therapy with lamivudine versus the monotherapy at 12, 24, 48 weeks, but not at 72 weeks (24 weeks post treatment).

There was no multivariable analysis, but sufficient data to allow calculation of unadjusted odds ratios and these are shown in the forest plots in Appendix G and in the summary table (Table 260). Results were also given for the different genotypes.

Table 247: Value of HBsAg levels at 12 and 24 weeks of pegylated interferon treatment for the prediction of serological response at the end of 24 weeks follow up after the end of treatment in 399 HBeAg positive patients

HBeAg seroconversion at 24 weeks post treatment; monitoring at 12 weeks

	SR	No SR	Unadjusted OR
HBsAg < 1500 at 12 weeks	51	39	OR (<1500 versus >1500 IU/ml: 3.29 (95%CI 2.09 to 5.51)); for >1500 risk of 32% OR (< 20,000 versus >20,000): 3.33 (95%CI 1.80 to 6.16); for >20,000 risk of 16%
HBsAg 1500-20,000	72	151	
HBsAg >20,000 IU/ml	14	72	

HBeAg seroconversion at 24 weeks post-treatment; monitoring at 24 weeks

	SR	No SR	Unadjusted OR
HBsAg < 1500 at 24 weeks	74	62	OR (<1500 versus >1500 IU/ml: 3.79 (95%CI 2.44 to 5.89)); for >1500 risk of 24% OR (< 20,000 versus >20,000): 3.25 (95%CI 1.49 to 7.13); for >20,000 risk of 15%
HBsAg 1500-20,000	55	156	
HBsAg >20,000 IU/ml	8	44	

HBsAg clearance at 24 weeks post treatment; monitoring at 12 weeks

	SR	No SR	Unadjusted OR
HBsAg < 1500 at 12 weeks	10	80	Peto OR (<1500 versus >1500 IU/ml: 8.70 (95%CI 2.72 to 27.77)); for >1500 risk of 2% Peto OR (< 20,000 versus >20,000): 1.83 (95%CI 0.56 to 5.95); for >20,000 risk of 2%
HBsAg 1500-20,000	5	218	
HBsAg >20,000 IU/ml	2	84	

HBsAg clearance at 24 weeks post-treatment; monitoring at 24 weeks

	SR	No SR	Unadjusted OR
HBsAg < 1500 at 24 weeks	16	120	Peto OR (<1500 versus >1500 IU/ml: 16.18 (95%CI 5.81 to 45.04); for >1500 risk of 0.4% Peto OR (< 20,000 versus >20,000): 3.31 (95%CI 0.78 to 1400); for >20,000 risk of 0%
HBsAg 1500-20,000	1	210	
HBsAg >20,000 IU/ml	0	52	

Genotype B:

HBeag seroconversion at 24 weeks post treatment; monitoring at 12 weeks

	SR	No SR	Unadjusted OR
HBsAg < 1500 at 12 weeks	17	17	OR (<1500 versus >1500 IU/ml: 2.56 (95%CI 1.14 to 5.72); for >1500 risk of 28%
HBsAg 1500-20,000	24	43	
HBsAg >20,000 IU/ml	3	26	

HBeAg seroconversion at 24 weeks post treatment; monitoring at 24 weeks

	SR	No SR	Unadjusted OR
HBsAg < 1500 at 24 weeks	24	24	OR (<1500 versus >1500 IU/ml: 3.10 (95%CI 1.45 to 6.61); for >1500 risk of 24%
HBsAg 1500-20,000	18	48	
HBsAg >20,000 IU/ml	2	14	

Genotype C:

HBeAg seroconversion at 24 weeks post treatment; monitoring at 12 weeks

	SR	No SR	Unadjusted OR
HBsAg < 1500 at 12 weeks	32	22	OR (<1500 versus >1500 IU/ml: 3.97 (95%CI 2.10 to 7.50); for >1500 risk of 27%
HBsAg 1500-20,000	42	97	
HBsAg >20,000 IU/ml	6	34	

HBeAg seroconversion at 24 weeks post treatment; monitoring at 24 weeks

	SR	No SR	Unadjusted OR
HBsAg < 1500 at 24 weeks	44	35	OR (<1500 versus >1500 IU/ml: 4.12 (95%CI 2.31 to 7.36); for >1500 risk of 23%
HBsAg 1500-20,000	34	97	
HBsAg >20,000 IU/ml	2	21	

HBeAg positive patients: composite responses

Undetectable HBV DNA and HBeAg loss

One prospective study by Heijink 2000 followed 139 (85.8%) HBeAg positive patients during 16 weeks of interferon alpha treatment. Those patients who didn't respond to the "standard 16 week treatment" were randomized to receive a further 16 weeks of interferon treatment ("prolonged therapy") or no treatment ("controls"). The study investigated the association between the measurements of HBeAg levels (PEI Uml^{-1}) and HBV DNA levels (pg ml^{-1}) at 4^{th} and 8^{th} weeks during treatment and the response to standard (end of 16 weeks) or prolonged interferon treatment (end of 32 weeks). Response was defined as a simultaneous negative result for HBeAg and HBV DNA (≤1.6 pg ml^{-1}).

Multivariable analysis was based on the following (continuous) parameters: pretreatment HBeAg level, change in HBeAg from baseline to week 4 and from baseline to week 8, HBV DNA level at baseline, and change in HBV DNA level from baseline to week 4 and from baseline to week 8. There were 25 events at 16 weeks. The study reported that only the baseline level of HBeAg and the change to 8 weeks in HBeAg were the only significant predictors. The authors concluded that the study may have identified cessation criteria that allow stopping of interferon therapy in patients who have a high probability of non response (Table 248, Table 249).

Table 248: Geometric mean titres (GMT) of HBeAg and HBV DNA at 4^{th} and 8^{th} week of treatment by responder status in the "standard 16-week interferon treatment" in a sample of 139 HBeAg positive patients on interferon treatment and p values

	"Standard therapy group" (16 weeks of INFa therapy)		P values	
Predictive factors	**Responders (n=25)**	**Non responders (N=114)**	**Univariate analysis**	**Multivariable analysis**
HBeAg (PEI Uml-1) geometric mean titres (GMT)				Not reported**
• 4th week after starting of INFa treatment	10*	700*	**P=0.001**	
• 8th week after starting of INFa treatment	6.5*	400*	**P=0.001**	
HBV DNA (pg ml-1) geometric mean titres (GMT)				
• 4th week after starting of INFa treatment	7.6*	40*	NS	Not reported***
• 8th week after starting of INFa treatment	5.0*	20*	NS	

** Figures are taken from graphical presentation so maybe an approximation of the actual values.*
***The authors mentioned that HBeAg decrease from the start of therapy to week 8 were the most important factors determining response with no mention on statistical significance*
**** The authors mentioned that this factor did not add any predictive value to response at week 16.*
P values in bold denotes statistically significant result (P<0.05)

Table 249: Geometric mean titres (GMT) of HBeAg and HBV DNA at 4th, 8th and 16th week of treatment by responder status in the "prolonged 32-week interferon treatment" in a sample of 139 HBeAg positive patients on interferon treatment and p values

	"Prolonged 32-week therapy group" (previously non responders at 16-week of treatment)		
Predictive factors	**Responders at 52 weeks (n=16)**	**Non responders at 52 weeks (n=42)**	**P values (univariate analysis)**
HBeAg (PEI Uml-1) geometric mean titres (GMT)			
• 4th week after starting of INFa treatment	100*	888*	P<0.01
• 8th week after starting of INFa treatment	61*	600*	P<0.01
• 16th week after starting of INFa treatment	9*	420*	NS

** Figures are taken from graphical presentation so maybe an approximation of the actual values.*

Another study (Perillo 1993) of 29 HBeAg positive patients investigated the predictive role of HBV DNA and HBeAg loss at the 8th and 12th week during interferon treatment with the composite response as defined by HBV DNA loss at end of treatment and HBeAg loss during a 6- to 9-month post treatment observation period. The only information provided in relation to the predictive value of HBV DNA during treatment on the response was that HBV DNA became undetectable at an earlier interval during treatment (but no information was given on actual time interval) in 13 out of 16 responders (81%).

In the same study, results were presented for the predictive value of HBeAg decrease at 8 and 12 weeks during interferon treatment for the achievement of composite response (Table 250). All (100%) and 92.3% of patients who achieved a 90% decrease or less in HBeAg levels at 8 and 12 weeks of treatment respectively were non responders at the end of 6-9 months follow up period after the end of treatment (Table 250).

Table 250: Value of decrease in HBeAg activity at 8 and 12 weeks of interferon treatment for the prediction of composite response in 29 HBeAg positive patients

Predictor	Responders (n=16)	Non responders (n=13)	Unadjusted Peto odds ratio (95%CI)
At 8 weeks during interferon treatment			
>90% decrease in HBeAg	11	0	16.77 (95%CI 3.81 to 73.81)
≤90% decrease in HBeAg	5	13	
At 12 weeks during interferon treatment			
>90% decrease in HBeAg	14	1	21.89 (95%CI 5.19 to 92.29)
≤90% decrease in HBeAg	2	12	

HBeAg negative patients: virological response

One prospective study (Moucari, 2009) in HBeAg negative patients with CHB investigated the predictive value of monitoring HBV DNA and HBsAg levels in the first 12 and 24 weeks of pegylated interferon treatment on response at the end of treatment (defined as undetectable HBV DNA <70 copies/ml) and sustained virological response at 24 weeks follow up after the end of treatment.

The authors reported the results of non parametric tests, which were that the only statistically significant factor to predict virological response at the end of pegylated interferon treatment was the mean decrease in HBV DNA in the first 12 and 24 weeks of treatment. HBV DNA decrease at 12 and 24 weeks was not associated with sustained virological response (Table 251, Table 252).

Table 251: Value of mean decrease of HBV DNA in the first 12 and 24 weeks of pegylated interferon treatment for the prediction of virological response at the end of treatment in 48 HBeAg negative patients

	Responders (end of 48 weeks of peg IFN treatment) (n=30)	Non responders (end of 48 weeks of peg IFN treatment) (n=18)	P value*
Mean decrease in HBV DNA in the first 12 weeks of treatment (SD) in log10 copies/ml	4.1 (1.9)	2.2 (1.7)	**0.01**
Mean decrease in HBV DNA in the first 24 weeks of treatment (SD) in log10 copies/ml	5.1 (1.9)	2.2 (2.3)	**0.002**

**P value is derived from non parametric tests (Mann-Whitney test);* p values in bold denotes statistically significant result

Table 252: Value of mean decrease of HBV DNA in the first 12 and 24 weeks of pegylated interferon treatment for the prediction of sustained virological response at the end of 24 weeks follow up after the end of treatment in 48 HBeAg negative patients

	Patients with SVR (end of 24 weeks after the end of treatment) (n=12)	Patients with no SVR (end of 24 weeks after the end of treatment) (n=36)	P value
Decrease in HBV DNA in the first 12 weeks of treatment (mean, SD) in log10 copies/ml	4.1 (1.9)	3.0 (1.7)	0.1
Decrease in HBV DNA in the first 24weeks of treatment (mean, SD) in log10 copies/ml	5.1 (1.9)	4.2 (1.4)	0.2

**P value is derived from non parametric tests (Mann-Whitney test);* p values in bold denotes statistically significant result *(P<0.05)*

The study also reported the predictive value of HBsAg levels (using the thresholds of 0.5 and 1 $\log_{10}$ copies/ml for 12 and 24 weeks during treatment respectively), which allowed calculation of unadjusted odds ratios to predict sustained virological response at 24 weeks follow up after the end of treatment (Table 253).

Table 253: Value of serum HBsAg levels in the first 12 and 24 weeks of pegylated interferon treatment for the prediction of sustained virological response at the end of 24 weeks follow up after the end of treatment in 48 HBeAg negative patients

	Patients with SVR (end of 24 weeks after the end of treatment) (n=12)	Patients with no SVR (end of 24 weeks after the end of treatment) (n=36)	Unadjusted odds ratio (95%CI)
At 12 weeks during peg interferon treatment			
HBsAg ≥0.5 $\log_{10}$ IU/ml	8 (88.9%)	1	OR = 70.00 (95%CI 6.87 to 713.74) for low risk group rate of 10.2%
HBsAg <0.5 $\log_{10}$ IU/ml	4 (10.2%)	35	

	Patients with SVR (end of 24 weeks after the end of treatment) (n=12)	Patients with no SVR (end of 24 weeks after the end of treatment) (n=36)	Unadjusted odds ratio (95%CI)
At 24 weeks during peg interferon treatment			
HBsAg ≥1 log_{10} IU/ml	11 (91.7%)	1	OR = 385 (95%CI 22.19 to 6678) for a low risk group rate of 2.8% AUC= 0.944 (for all thresholds)
HBsAg <1 log_{10} IU/ml	1 (2.8%)	35	

** The HBsAg threshold was chosen to maximise sensitivity and specificity based on receiver operating characteristic curve.*

The study by Marcellin (2012) was was a retrospective analysis of 120 HBeAg negative patients receiving peg interferon alfa 2a with or without lamivudine. The data were taken from a follow up study of the Marcellin 2004 randomised trial (n= 230), but the Marcellin 2012 analysis was necessarily restricted to patients who had HBsAg values measured at all time points (baseline, 12, 24, 48 weeks and 24 weeks post treatment). The study investigated the effect of HBsAg decline on virological response, defined as HBV DNA ≤ 2000 IU/ml at 1 year and 5 years; the study also investigated HBsAg clearance at 1 and 5 years post-treatment. The stated that response at 6 months follow up post treatment was not investigated because of the high rate of relapse between 6 and 12 months.

Receiver Operating Characteristics (ROC) curve analysis at 12 and 24 weeks was used to identify the optimum HBsAg decline, based on maximising the negative predictive value (NPV). The analysis identified a change from baseline of ≥ 10% log10.This study reported differing kinetic behaviour for peg interferon monotherapy and the combination therapy with lamivudine: for the monotherapy, there was a significant difference between responders and non-responders in HBV DNA decline at 12, 24, and 48 weeks (i.e. during treatment) and also at 24 weeks post treatment (p value 0.05 at 12 weeks), but no significant difference for the combination therapy at any time point. Differences in predictive ability of HBsAg decline between mono- and combination therapies were not investigated.

Table 254 gives the predictive value of a decline of 10% or more decline in log HBsAg at 12 and 24 weeks during pegylated interferon treatment for HBV DNA response at one and five years post treatment. This allowed calculation of unadjusted odds ratios and these are shown in the forest plots in Appendix G and in the summary table (Table 261).

Table 254: Value of HBsAg decline ≥ 10% log at 12 and 24 weeks of pegylated interferon treatment for the prediction of virological response at the end of 1 year and 5 years follow up after the end of treatment in 120 HBeAg negative patients

At 1 year post-treatment for HBV DNA outcome

12 weeks	SR	No SR			24 weeks	SR	No SR	
HBsAg decline ≥ 10% log	25	28	53		HBsAg decline ≥ 10% log	29	38	67
< 10%	11	56	67		No decline	7	46	53
	36	84	120			36	84	120

At 5 years for DNA outcome

12 weeks	SR	No SR			24 weeks	SR	No SR	

12 weeks	SR	No SR			24 weeks	SR	No SR	
HBsAg decline ≥ 10% log	22	31	53		HBsAg decline ≥ 10% log	24	43	67
< 10%	9	58	67		No decline	7	46	53
	31	89	120			31	89	120

At one year for HBsAg clearance outcome, there were only six events, and only p-values and PPVs and NPVs were reported.

HBeAg negative patients: composite responses

Undetectable HBV DNA and ALT normalization

A follow up study (Rijckborst 2010) of 107 patients from an RCT assessed the value of monitoring HBsAg and HBV DNA and a combination of these two markers during treatment with peg interferon to predict sustained response (SR) in HBeAg negative patients, the majority of whom were genotype D (79%). Sustained response (SR) was defined as the combined presence of serum HBV DNA levels below 10,000 copies/ml (1714 IU/ml) and normalization of ALT at the end of 24 weeks follow up (week 72). The two randomized groups received pegylated interferon-alpha plus ribavirin or pegylated interferon alfa-2b plus placebo. No significant difference was found in the number of sustained responders between the two groups (14/53 in the monotherapy group and 10/54 in the combination) so results were presented in the study for the whole sample.

The authors reported in a multivariable logistic regression analysis with 24 events (with no details of covariates) that the decline of HBV DNA during treatment performed better with respect to the prediction of SR than HBsAg declines at week 4, 8 and 12. For HBsAg, the declines at 4 weeks and 8 weeks were not predictive of sustained response in logistic regression analysis, but the decline at 12 weeks was significant; HBV DNA was a significant predictor even at 4 weeks. No odds ratios or even p values were given.

The authors plotted ROC curves at different thresholds and calculated areas under the curve: AUC for HBsAg alone was 0.69 at week 12; this compares with the HBV DNA alone of about 0.70 and the combination of HBsAg with HBV DNA of 0.74. The best model for fit (which was based on the area under the ROC curve (AUC) and Akaike's information criterion (AIC)), was achieved through a combination of any HBsAg decline and /or an HBV DNA decline of ≥ 2 log copies/ml. The performance of the model at week 24 did not improve significantly in comparison with the performance at week 12 (P=0.37). Whether patients were in monotherapy or in combination groups was not associated with SR at any time point (P≥0.35 for all time points).

Based on these results, that the decline of combination markers HBsAg and HBV DNA at week 12 better predicted the SR than individual predictors, the authors identified a stopping rule (cut off point) for HBV DNA to discontinue interferon therapy in patients who have a very low chance of SR, while maintaining more than 95% of sustained responders on treatment. This rule targeted patients who had no decline in HBsAg and less than 2 log copies/ml decline in HBV DNA level at 12 weeks. Data are shown in Table 256, and these allowed calculation of unadjusted Peto odds ratios (which are shown on forest plots in Appendix G and are recorded in Table 261.

Table 255: Value of HBV DNA decline, HBsAg decline and the combination at 12 weeks of peg interferon treatment for the prediction of sustained response

	SR	No SR	Total			SR	No SR	Total
DNA≥2log	19	43	62		HBsAg decline	16	32	48

	SR	No SR	Total			SR	No SR	Total
DNA < 2log	5	35	40		No decline	8	46	54
Total	24	78	102		Total	24	78	102

	SR	No SR	Total
DNA≥2log & decline HBsAg	11	17	28
DNA ≥2log & no decline HBsAg	8	26	34
DNA<2log & decline HBsAg	5	15	20
DNA <2log & no decline HBsAg	0	20	20
Total	24	78	102

For the stopping rule of a decline of less than 2 log DNA and no decline in HBsAg, the Peto odds ratio for one or both of these declines predicting a composite response is 5.01(95%CI 1.59 to 15.76) for a risk of 0% in the stopping rule patients.

The authors emphasise the 100% negative predictive value (NPV) for their stopping rule. However, it is noted that the rule was validated in the same population as it was derived, and secondly, it was a small study, so 100% could be achieved by chance. The confidence interval around the NPV is fairly wide: 100% (95%CI 83 to 100), which gives uncertainty.

Thus, in this small study, with no adjustment for confounders, and with wide confidence intervals, and validation in the derivation study, we would not be confident of recommending this stopping rule.

The authors concluded that:

- All patients who didn't achieve a decline in HBsAg levels and whose HBV DNA levels decreased less than 2 log copies/ml (20% of the study population) were non responders.
- Patients in whom both the HBsAg and HBV DNA declines were achieved (and HBV DNA levels decline at least 2 log copies/ml) had the highest probability of SR (39%) which was almost double the overall response rate of sustained response in the sample (22%).
- There was no difference in the thresholds used for HBsAg and HBV DNA declines at week 12 between the treatment groups (monotherapy and combination) in the study.

A further study from the same author, Rijckborst 2012, conducted a validation study in HBeAg negative patients to investigate the stopping rule derived in Rijckborst 2010. Patients in the validation cohort were from two RCTs:

- 85 patients from solely the peg interferon alfa 2a monotherapy arm of the Marcellin 2004 trial monotherapy for 48 weeks; genotype B/C/D was 21/40/25%
- 75 patients from the Lampertico 2010 ("PegBeLiver")trial, which compared 48 versus 96 weeks of monotherapy; the genotype was 93% D.

The study had some limitations: it was a retrospective analysis restricted to those with HBsAg measurements at baseline and at 12 weeks, and patients also had to have 24 weeks follow up post treatment (thus, there was a possibility of selection bias). Patients receiving peg IFN plus lamivudine were excluded from the analysis because of the suppression of HBV DNA during the treatment period, which changes after ceasing treatment. The outcome was sustained response, defined as HBV DNA < 2000 IU/ml and normal ALT 24 weeks post treatment; 32/85 and 25/75 achieved a sustained response. Data are shown in Table 256, and these allowed calculation of unadjusted odds ratios (which are shown on forest plots in Appendix G and are recorded Table 261.

Table 256: Value of HBV DNA decline, HBsAg decline and the combination at 12 weeks of peg interferon treatment for the prediction of sustained response: all validation cohorts

	SR	No SR	Total			SR	No SR	Total
DNA≥2log	46	70	116		HBsAg decline	33	43	76
DNA < 2log	11	33	44		No decline	24	60	84
Total	57	103	160		Total	57	103	160

	SR	No SR	Total			SR	No SR	Total
HBsAg decline & DNA ≥2log	23	31	54		DNA≥2log and/or decline HBsAg	56	82	138
One or neither	34	72	106		DNA<2log + no decline HBsAg	1	21	22
Total	57	103	160		Total	57	103	160

The authors also looked at the effect of genotype in the validation trials (between-trials comparison in unadjusted analysis). This is shown in Table 257

Table 257: Value of HBV DNA decline, HBsAg decline and the combination at 12 weeks of peg interferon treatment for the prediction of sustained response: all validation cohorts, by genotype

D Genotype	SR	No SR	Total		non D Genotype	SR	No SR	Total
HBsAg decline	13	18	31		HBsAg decline	20	25	45
No decline	12	48	60		No decline	12	12	24
Total	25	66	91		Total	32	37	69

D Genotype	SR	No SR	Total		non D Genotype	SR	No SR	Total
DNA decline ≥2log	19	41	60		DNA decline ≥2log	27	29	56
< 2 log	6	25	31		< 2 log	5	8	13
Total	25	66	91		Total	32	37	69

D Genotype	SR	No SR	Total		non D Genotype	SR	No SR	Total
HBsAg decline & DNA ≥2log	7	10	17		HBsAg decline & DNA ≥2log	16	21	37
No decline or 1 decline	18	56	74		No decline or 1 decline	16	16	32
Total	25	66	91		Total	32	37	69

D Genotype	SR	No SR	Total		non D Genotype	SR	No SR	Total
Decline in either measure	25	49	74		Decline in either measure	31	33	64
No HBsAg decline & DNA < 2log	0	17	17		No HBsAg decline & DNA < 2log	1	4	5

D Genotype	SR	No SR	Total		non D Genotype	SR	No SR	Total
Total	25	66	91		Total	32	37	69

One of the studies included in the Rijckborst 2012 validation study also reported a multivariable analysis for the end point of HBV DNA < 3400 IU/ml at 24 and 48 weeks post treatment (Lampertico 2010). Logistic regression analysis was conducted and the covariates were: age, height, weight, gender, genotype, treatment regimen, baseline ALT level, baseline HBV DNA level, cirrhosis, HBV DNA level (continuous) at week 12, HBV DNA level (continuous) at week 24, HBsAg level (continuous) at week 12 and HBsAg level (continuous) at week 24, and decline in HBsAg level at 24 weeks.

There were 28 patients with a virological response at 24 weeks follow up and 22 at 48 weeks, so the ratio of events to covariates was small (around 2 for 24 weeks follow up), which reduces the study quality.

The study reported that the only significant predictors in the multivariable analysis at 48 weeks post treatment were: HBsAg level at week 24 on-treatment and a 96 week course of peginterferon (versus 48 weeks). The decline in HBsAg at 24 weeks and the HBsAg level at 12 weeks were assumed not to be independent predictors.

Table 258: Value of HBsAg level (continuous) at 24 weeks of peginterferon treatment for the prediction of virological response in HBeAg negative patients

	Odds ratio (95% CI) per log IU/ml	P value
HBsAg level (continuous) at 24 weeks	0.222 (95%CI 0.092 to 0.536)	0.0008

** P value is derived from logistic regression analysis; other covariates included age, height, weight, gender, genotype, treatment regimen, baseline ALT level, baseline HBV DNA level, cirrhosis, HBV DNA level (continuous) at week 12, HBV DNA level (continuous) at week 24, HBsAg level (continuous) at week 12 and decline in HBsAg level at 24 weeks.*

HBeAg negative patients: composite relapse - detectable HBV DNA and ALT elevation

A prospective follow up study (Baltayiannis, 2006) of 63 HBeAg negative patients showed that patients with HBV DNA levels above 10,000 copies/ml measured at 6 months during interferon-a treatment were more likely to relapse earlier than patients with HBV DNA levels less than or equal to the threshold of 10,000 copies/ml (Table 259). Relapse during the 6 year follow up was defined in the study as an increase of ALT levels above the normal range and detectable HBV DNA levels at the end of treatment. There were 12 patients in biochemical and virological remission after 6 years and 36 responders after 12 months (end of treatment); this gives a low ratio of events to covariates in the multivariable analysis.

Table 259: Value of HBV DNA levels at 6 months of interferon treatment for the prediction of relapse in 63 HBeAg negative patients

	Multivariable analysis*		Univariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
HBV DNA>10,000 copies/ml at 6 months	5.73 (1.16-28.25)	0.032	7.53 (1.73-32.85)	0.007

** P value is derived from Cox's proportional hazards regression analysis; other covariates included age (>45 years), gender, alcohol, ALT at baseline, histological grade and stage.*

Summary of findings across response outcomes

The findings from the interferon based studies are shown for all response outcomes at different times in the summary forest plots in the Appendix and in Table 260 and Table 261 below:

Table 260: summary results for HBeAg positive patients

Study	Predictor and time	Outcome and number with outcome	OR Unadjusted (95%CI)	NPV (95%CI)
HBsAg level as predictor				
Piratusuth* 2011	HBsAg level ≤1500 IU/ml; 12 weeks	≤2000 IU/ml HBV DNA at 6 months post treatment 112/399	OR = 4.67 (95%CI 2.83 to 7.68) for low risk group rate of 20.4%	80% (75 to 84)
Piratusuth 2011	HBsAg level ≤1500 IU/ml; 24 weeks	≤2000 IU/ml HBV DNA at 6 months post treatment 112/399	OR = 5.91 (95%CI 3.68 to 9.50) for low risk group rate of 15.6%	84% (79 to 89)
Piratusuth 2011	HBsAg level ≤20,000 IU/ml; 12 weeks	≤2000 IU/ml HBV DNA at 6 months post treatment 112/399	OR = 6.83 (95%CI 2.88 to 16.17) for low risk group rate of 7.0%	93% (85 to 97)
Piratusuth 2011	HBsAg level ≤20,000 IU/ml; 24 weeks	≤2000 IU/ml HBV DNA at 6 months post treatment 112/399	OR =11.60 (95%CI 2.77 to 48.55) for a low risk group rate of 3.8%	96% (87 to 100)
Piratusuth 2011	HBsAg level ≤1500 IU/ml; 12 weeks	HBsAg clearance at 6 months post treatment 17/399	Peto OR = 8.70 (95%CI 2.72 to 27.77) for low risk group rate of 2.3%	98% (95 to 99)
Piratusuth 2011	HBsAg level ≤1500 IU/ml; 24 weeks	HBsAg clearance at 6 months post treatment 17/399	Peto OR = 16.18 (95%CI 5.81 to 45.04) for low risk group rate of 0.4%	100% (98 to 100)
Piratusuth 2011	HBsAg level ≤20,000 IU/ml; 12 weeks	HBsAg clearance at 6 months post treatment 17/399	Peto OR = 1.83 (95%CI 0.56 to 5.95) for low risk group rate of 2.3% i.e. not statistically significant	98% (92 to 100)
Piratusuth 2011	HBsAg level ≤20,000 IU/ml; 24 weeks	HBsAg clearance at 6 months post treatment 17/399	Peto OR = 3.31 (95%CI 0.78 to 14.00) for low risk group rate of 0% i.e. not statistically significant	100% (93 to 100)
Piratusuth 2011	HBsAg level ≤1500 IU/ml; 12 weeks	HBeAg seroconversion at 6 months post treatment 137/399	OR = 3.39 (95%CI 2.09 to 5.51) for low risk group rate of 27.8%	72% (67 to 77)
Piratusuth 2011	HBsAg level ≤1500 IU/ml; 24 weeks	HBeAg seroconversion at 6 months post treatment 137/399	OR = 3.79 (95%CI 2.44 to 5.89) for low risk group rate of 24.0%	76% (70 to 81)
Piratusuth 2011	HBsAg level ≤20,000 IU/ml; 12	HBeAg seroconversion at 6 months post	OR = 3.33 (95%CI 1.80 to 6.16) for low risk group	84% (74 to 91)

Study	Predictor and time	Outcome and number with outcome	OR Unadjusted (95%CI)	NPV (95%CI)
	weeks	treatment 137/399	rate of 16.3%	
Piratusuth 2011	HBsAg level ≤20,000 IU/ml; 24 weeks	HBeAg seroconversion at 6 months post treatment 137/399	OR = 3.25 (95%CI 1.49 to 7.13) for low risk group rate of 15.4%	85% (72 to 93)
Effect of Genotype				
Piratusuth 2011 Genotype B	HBsAg level ≤1500 IU/ml; 12 weeks	HBeAg seroconversion at 6 months post treatment 44/130	OR = 2.56 (95%CI 1.14 to 5.72) for low risk group rate of 28.1%	72% (62 to 91)
Piratusuth 2011 Genotype C	HBsAg level ≤1500 IU/ml; 12 weeks	HBeAg seroconversion at 6 months post treatment 80/233	OR = 3.97 (95%CI 2.10 to 7.50) for low risk group rate of 26.8%	73% (66 to 80)
Change in HBV DNA levels as predictor				
ter Borg 2006	Early decline: HBV DNA > 1 log decline during weeks 0-4	HBeAg loss/seroconversion, 24 weeks post treatment 44/123	OR = 2.32 (95%CI 0.92 to 5.82) for other patterns rate of 32% i.e. not statistically significant	68% (58 to 77)
ter Borg 2006	Early + delayed decline: HBV DNA ≥2 log decline during weeks 0-32	HBeAg loss/seroconversion, 24 weeks post treatment 44/123	OR = 6.49 (95%CI 2.85 to 14.77) for other patterns rate of 18%	82% (71 to 91)
ter Borg 2006	Any decline during treatment: HBV DNA ≥2 log decline	HBeAg loss/seroconversion, 24 weeks post treatment 44/123	OR = 6.61 (95%CI 2.72 to 16.06) for no decline during treatment rate of 15%	85% (73 to 94)
ter Borg 2006	Early decline: HBV DNA > 1 log decline during weeks 0-4	HBsAg loss, 24 weeks post treatment 8/123	Peto OR = 0.65 (95%CI 0.10 to 4.05) for other patterns rate of 7% i.e. not statistically significant	93% (86 to 97)
ter Borg 2006	Early + delayed decline: HBV DNA ≥2 log decline during weeks 0-32	HBsAg loss, 24 weeks post treatment 8/123	Peto OR = 10.72 (95%CI 2.55 to 45.06) for other patterns rate of 0%	100% (95 to 100)
ter Borg 2006	Any decline during treatment: HBV DNA ≥2 log decline	HBsAg loss, 24 weeks post treatment 8/123	Peto OR = 6.81 (95%CI 1.62 to 28.63) for no decline during treatment rate of 0%	100% (94 to 100)
HBV DNA level as predictor				
Fried 2006	< 5 log HBV DNA ; 24 weeks	HBeAg seroconversion at 24 weeks post treatment 85/265	OR = 5.87 (95% CI 3.31 to 10.42); for the ≥5 group response of 16%	84% (77 to 90)
Fried 2006	< 9 log HBV DNA ; 24 weeks	HBeAg seroconversion at 24 weeks post treatment	OR = 3.55 (95%CI 1.60 to 7.91); for the ≥9 group response of 14%	86% (74 to 90)

Study	Predictor and time	Outcome and number with outcome	OR Unadjusted (95%CI)	NPV (95%CI)
		85/265		

Table 261: Summary of results for HBeAg negative patients

Study	Predictor and time	Outcome and number with outcome	OR Unadjusted (95%CI)	NPV (95%CI)
Change in HBsAg as predictor				
Moucari 2009	Change in HBsAg ≥0.5 log 12 weeks	HBV DNA at 6 months post treatment 12/48	OR = 70.00 (95%CI 6.87 to 713.74) for low risk group rate of 10.2%	90% (76 to 97)
Moucari 2009	Change in HBsAg ≥1.0 log 24 weeks	HBV DNA at 6 months post treatment 12/48	OR = 385 (95%CI 22.19 to 6678) for a low risk group rate of 2.8%	97% (85 to 100)
Marcellin 2012	Change in HBsAg ≥10% log; 12 weeks	≤2000 IU/ml HBV DNA at 1 year post treatment 36/120	OR = 4.55 (95%CI 1.96 to 12.72) for a low risk group rate of 16.4%	84% (73 to 92)
Marcellin 2012	Change in HBsAg ≥10% log; 24 weeks	≤2000 IU/ml HBV DNA at 1 year post treatment 36/120	OR = 5.02 (95%CI 1.98 to 10.55) for a low risk group rate of 13.2%	87% (75 to 95)
Rijckborst 2010	HBsAg any decline from baseline; 12 weeks	HBV DNA ≤2000 & normal ALT at 6 months post treatment ; 24/102	OR = 2.88 (95%CI 1.10 to 7.52) for a low risk group rate of 14.8%	85% (73 to 93)
Rijckborst 2012 Validation	HBsAg any decline from baseline 12 weeks	HBV DNA ≤2000 & normal ALT at 6 months post treatment ; 57/160	OR = 1.92 (95%CI 1.00 to 3.70) for a low risk group rate of 28.6% i.e. not statistically significant	71% (61 to 81)
Marcellin 2012	Change in HBsAg ≥10% log; 12 weeks	≤2000 IU/ml HBV DNA at 5 years post treatment 31/120	OR = 4.57 (95%CI 1.88 to 11.13) for a low risk group rate of 13.4%	87% (76 to 94)
Marcellin 2012	Change in HBsAg ≥10% log; 24 weeks	≤2000 IU/ml HBV DNA at 5 years post treatment 31/120	OR = 3.67 (95%CI 1.43 to 9.38) for a low risk group rate of 13%	87% (75 to 95)
HBsAg as predictor in multivariable analysis (substudy of Marcellin 2012)				
Lampertico 2012	HBsAg level (continuous) at 24 weeks	HBV DNA < 3400 IU/ml at 48 weeks post treatment 22/103	OR = 0.222 (95%CI 0.092 to 0.536) per log IU/ml	
Lampertico 2012	(1) HBsAg level at 12 weeks (2) Decline in	HBV DNA < 3400 IU/ml at 48 weeks post treatment	Not statistically significant	

Study	Predictor and time	Outcome and number with outcome	OR Unadjusted (95%CI)	NPV (95%CI)
	HBsAg at 24 weeks	22/103		
Change in HBV DNA as predictor				
Rijckborst 2010	Decline in HBV DNA ≥2 log; 12 weeks	HBV DNA ≤2000 & normal ALT at 6 months post treatment ; 24/102	OR = 3.09 (95%CI 1.05 to 9.12) for a low risk group rate of 12.5%	88% (73 to 96)
Rijckborst 2012 Validation	Decline in HBV DNA ≥2 log; 12 weeks	HBV DNA ≤2000 & normal ALT at 6 months post treatment ; 57/160	OR = 1.97 (95%CI 0.91 to 4.29) for a low risk group rate of 25.0% i.e. not statistically significant	75% (63 to 87)
Stopping rule: HBV DNA decline and/or HBsAg decline				
Rijckborst 2010	Decline in HBV DNA ≥2 log and/or any decline in HBsAg 12 weeks	HBV DNA ≤2000 & normal ALT at 6 months post treatment ; 24/102	Peto OR = 5.01(95%CI 1.59 to 15.76) for a low risk group rate of 0%	100% (83 to 100)
Rijckborst 2012 Validation	Decline in HBV DNA ≥2 log and/or any decline in HBsAg 12 weeks	HBV DNA ≤2000 & normal ALT at 6 months post treatment ; 57/160	Peto OR = 4.77 (95%CI 1.87 to 12.16) for a low risk group rate of 4.5%	95% (75 to 100)
Effect of genotype				
Rijckborst 2012 Validation Genotype D	Decline in HBV DNA ≥2 log and/or any decline in HBsAg 12 weeks	HBV DNA ≤2000 & normal ALT at 6 months post treatment ; 25/91	Peto OR = 5.35(95%CI 1.65 to 17.31) for a low risk group rate of 0%	100% (80 to 100)
Rijckborst 2012 Validation Genotype non D	Decline in HBV DNA ≥2 log and/or any decline in HBsAg 12 weeks	HBV DNA ≤2000 & normal ALT at 6 months post treatment ; 36/69	Peto OR = 3.09 (95%CI 0.50 to 18.89) for a low risk group rate of 20%; i.e. not statistically significant	80% (28 to 99)

12.1.3.6 Patients with CHB on nucleos(t)ides (NUC) treatment

One study (Jaroszewicz, 2011) in CHB patients who received nucleos(t)ide treatment (including lamivudine, entecavir, adefovir, tenofovir and other treatments) was found.

HBsAg loss

Predictive factor: quantitative HBsAg

One retrospective study (Jaroszewicz, 2011) assessed the predictive ability of HBsAg levels during treatment to determine HBsAg clearance at 3 years after virological response (VR). The 95 patients

had mixed HBeAg positive and negative status, and received various NUC treatments (LAM, n=29; ETV, n=24; ADV, n=12; TDF, n=9; other treatments, n=21). The study investigated the predictive ability of a decrease in quantitative HBsAg levels at three time points - 6 months of NUC treatment, at the point of virologic response (VR; continuous HBV DNA suppression <100 IU/ml) and 2 years after VR. The decline of HBsAg levels was divided into 3 groups: strong decrease (more than 0.5 log10 IU/ml), moderate decrease (10% from baseline to 0.5log 10 IU/ml) and no decrease (<10% change from baseline).

The authors reported that:

- HBsAg decrease during NUC treatment is generally small (Table 262)
- Early HBsAg decrease during the first 6 months of NUC therapy was not predictive for HBsAg loss (the difference between more than 0.5 log10 IU/ml and less than this threshold was not statistically significant; p=0.34, although only 6 patients achieved HBsAg loss) .
- HBsAg suppression is a rare event during NUC therapy (Table 262Table 263).
- 42% (5/12) patients with a strong HBsAg decrease 2 years after virologic response cleared HBsAg, but no patients with a decrease above 0.5 log10 IU/ml achieved HBsAg loss. Therefore, monitoring quantitative HBsAg after HBV DNA suppression might be useful to identify patients who clear HBsAg.

Table 262: Early HBsAg decrease during first 6 months on treatment (n=95) (Jaroszewicz, 2011)

	%*	Median HBsAg decrease
>0.5 log 10 IU/ml strong decrease	25	1.00 log10
10% - 0.5 log 10 IU/ml moderate decrease	44	0.21 log10
<10% no decrease	31	-0.10 log10

**the study only provided proportions and frequencies (n) could not be estimated.*

Table 263: Late HBsAg decrease 2 years after virologic response during NUC treatment (n=64) (Jaroszewicz, 2011)

Level of HBsAg decrease during 2 years	n(%)	Median HBsAg decrease
>0.5 log 10 IU/ml decrease	12 (19%)	0.84 log10
10% - 0.5 log 10 IU/ml decrease	34 (53%)	0.21 log10
<10% decrease from baseline	18 (28%)	-0.05 log10

12.1.3.7 Patients with CHB on lamivudine treatment

Nine studies examined the frequency of using different monitoring tests for predicting various responses (virological, serological, biochemical responses) and lamivudine resistance (Franca 2007; Gramenzi, 2011; Hsieh 2009; Llop, 2009; Kim 2007; Park 2005; Thompson 2007). Two studies investigated the stopping rules of lamivudine treatment (Kim 2007A; Wang 2010). This section explores the use of monitoring to predict a positive treatment response, to predict the adverse development of virological breakthrough or resistance (which may lead to stopping or changing therapy), and to predict seroconversion/loss with a view to stopping treatment because of success (effectiveness). The data for response to treatment and virological breakthrough / resistance are plotted for all outcomes and predictors on two forest plots shown in Appendix G.

Combined serological and virological response

Predictive factor: quantitative serum HBeAg

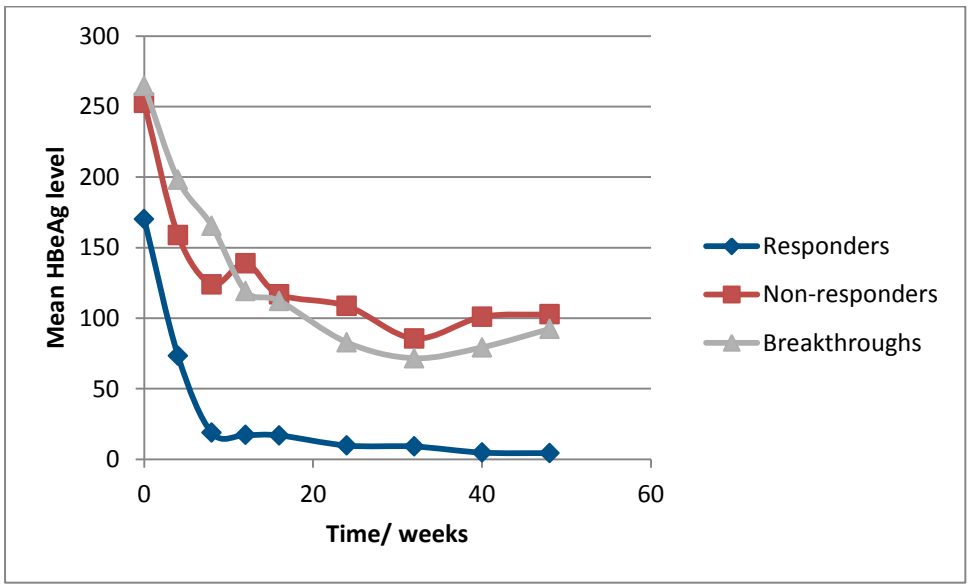
One retrospective study (Park 2005) in HBeAg positive treatment naïve CHB patients (N=340) examined the decrease of HBeAg levels at monthly intervals to predict response (HBeAg seroconversion and HBV DNA negativity on two occasions at least one month apart). It used the serial monthly measurements to identify patterns of response and analysed the usefulness of these patterns to predict long term response, using Cox multivariable regression (see below).

Patients had one of three responses to treatment: response, non-response and virological breakthrough. The mean HBeAg levels during therapy in the responder group were significantly lower than in the nonresponder and breakthrough groups (Table 264)

Table 264: Mean HBeAg levels (sample rate/cut off rate at monthly intervals during lamivudine therapy according to the types of response (responders, nonresponders, breakthrough) (Park 2005)*

Week	0	4	8	12	16	24	32	40	48
Responders (n=109)	170.2	73.3	18.8	17.2	16.9	9.7	9	4.7	4.3
Non-responders (n=149)	252.5	158.8	124	138.9	116.8	108.6	85.6	100.9	102.7
Breakthroughs (n=82)	264.6	198.2	165.5	119.2	112.2	82.8	71.6	79.3	92.3

*mean HBeAg levels were significantly lower in the responders than in nonresponder and breakthrough groups ($p<0.001$)



Responders were associated with the largest maximal decrease of HBeAg over time, compared to non-responders and breakthroughs (Table 268).

Table 265: Distribution of the decrease of HBeAg level since the start of therapy, according to different groups of response (Park 2005)

	Virological response up to 48 weeks

Maximal decrease of HBeAg since start of lamivudine therapy until at the point of response	Responders (n, frequency) (n=109)	Nonresponders (n, frequency) (n=149)	Breakthroughs (n, frequency) (n=82)
<50%	1	37	13
50-74%	3	36	29
75-89%	2	29	13
90-98%	31	38	20
>99%	72	9	7

Three groups were created according to reduction rates in HBeAg, in order to describe the changing patterns of HBeAg, compared with pre-treatment HBeAg levels, by serial monitoring (measured every 2 months until HBeAg seroconversion) during LAM therapy:

1. 'Decrescendo' pattern: continuously decreasing HBeAg levels to more than 90% of the pretreatment values over time (n=195)
2. 'Decrescendo-crescendo' pattern: a continuous decrease to more than 90% of the pre-treatment values, and then progressively increase of HBeAg levels(n=65)
3. No change or fluctuating pattern (n=80)

Table 266: Changing patterns of quantitative HBeAg levels during treatment in responders, non-responders and breakthroughs (Park 2005)

	Virological outcomes		
Predictive factors	**Responders (n=109)**	**Nonresponders (n=149)**	**Breakthroughs (n=82)**
Continuous decrease to >90% of pre-treatment HBeAg values (n=195)	53.8%	42.1%	4.1%
No change/fluctuation (n=80)	2.5%	71.2 %	26.3%
Continuous decrease of >90% of pre-treatment HBeAg values, then progressively increasing HBeAg levels (n=65)	3.1%	15.4%	81.5%

The different patterns of HBeAg were examined as a predictor of response (HBeAg seroconversion) in multivariable Cox regression analyses (Table 273). The authors did not report explicitly which factors were entered into the multivariable analysis, although it is implied that those factors significant on univariate analysis were included. For HBeAg seroconversion, these were: total duration of lamivudine therapy, pre-treatment HBeAg levels, the changing patterns of HBeAg levels, pre-treatment ALT levels and the decrease in HBeAg levels from the start of therapy to week 8, for 109 events.

Table 267: Odds ratios of predictive factors of HBeAg seroconversion using multivariable* stepwise Cox's regression model (Park 2005)

	HBeAg seroconversion; OR (95% CI)
Continuously decreasing HBeAg levels to >90% of pretreatment values over time	14.64 (95%CI 3.49 to 61.5)
*Continuous decrease of >90% of pre-treatment HBeAg values, then progressively increasing HBeAg levels plus no change or fluctation	1.0 (referent)

**assumed to be compared to referent group comprising the patients in the other two groups, i.e. those who had a continuous decrease of >90% of pre-treatment HBeAg values, then progressively increasing HBeAg levels and those who had no change or fluctuation (OR=1.00).*

For HBeAg conversion, other significant predictors were: duration of lamivudine therapy, pre-treatment HBeAg levels and pre-treatment ALT levels, all as continuous variables.

Virological response

Predictive factor: serum HBV DNA

One retrospective study (Llop 2009) in a mixed population (majority HBeAg negative) examined monitoring the change in serum HBV DNA levels (measured as mean decrease in log viral load or mean viral load decrease from baseline) at different time points (week 12 and 24) during lamivudine (N=31) treatment in predicting virological response (undetectable HBV DNA <200 copies/ml) at week 48 (Table 268Table 269). The authors concluded that a decrease in HBV DNA at week 12 can predict virologic response at 1 year in CHB patients treated with lamivudine; however, there are insufficient data given to investigate this further and the results are regarded with caution.

Table 268: Differences in pattern of decrease in HBV DNA in responders versus nonresponders to lamivudine (Llop 2009)

Predictive factors	Weeks	Virologic response at 1 year		
		Responders (n=16)	Non responders (n=15)	p
Mean viral load decrease (in log)	4	1.2 (±1.8)	2.7 (±1.3)	0.2
	12	2.7 (±0.99)	2.7 (±1.5)	0.9
	24	2.8 (±1.2)	3.5 (±1.3)	0.2
Mean viral load decrease from baseline (%)	4	19.5 (±26.3)	33.5 (±13.6)	0.3
	12	49.2 (±13.2)	38.3 (±20.4)	*0.03*
	24	52.1 (±14.5)	50.8 (±15.4)	0.8

**p values statistically significant (p<0.05). Categorical data were compared with Student's t- test (univariate analysis).*

Table 269: Area under the ROC curve at week 12 from treatment onset with lamivudine (Llop 2009)

	AUC
Viral load decrease at week 12 from baseline (%)	0.675

Another retrospective study (Chan 2011) in 53 HBeAg negative patients who had continuous lamivudine treatment for a minimum of 12 months investigated HBV DNA levels at baseline, month 6 and at end of lamivudine treatment (mean duration, 27 months) in predicting sustained response, defined as HBV DNA ≤200 IU/ml at 12 months post treatment follow up. HBV DNA levels at month 6 or at the end of lamivudine were not significantly different, but there were very few events; the study did not compare the predictive ability of levels above and below a threshold.

Table 270: HBV DNA levels in the prediction of sustained response at month 12 post-treatment

	Responders	**Non-responders**	**P value**
HBV DNA (log IU/ml)			
Month 6	2.2 (0.9)	2.4 (1.1)	0.68
End of treatment	2.0 (0.7)	2.5 (1.6)	0.56

*mean duration of treatment=27 months

Table 271: ROC curves for HBV DNA at month 6 and 12

	Area under ROC curve (95% CI)	P value
Month 6		
Absolute HBV DNA	0.46 (0.26-0.66)	0.69
Reduction in HBV DNA	0.52 (0.31-0.73)	0.83
End of treatment		
Absolute HBV DNA	0.44 (0.24-0.63)	0.55
Reduction in HBV DNA	0.51 (0.27-0.72)	0.96

*mean duration of treatment=27 months

One prospective study (Kim 2007) (N=221) in a mixed group of HBeAg positive and negative patients examined if monitoring HBV DNA for 6 months after the start of lamivudine therapy predicted HBeAg loss at 12 or 24 months after the start of therapy. The population was divided into 2 groups: 1) patients with undetectable HBV DNA (n=204) and 2) patients with persistently detectable HBV DNA (n=17); 78 people had HBeAg loss at 12 months and 124 at 24 months; all were in the undetectable group. The authors suggested that early cessation of treatment in this group may be advised. However, the number of patients with persistently detectable HBV DNA was small (N=17).

Table 272: Cumulative rates of HBeAg loss at 12 and 24 months after start of lamivudine treatment in patients with undetectable and persistently detectable HBV DNA levels (Kim 2007A)

	Cumulative rate of HBeAg loss**	
HBV DNA levels during the initial 6 months of treatment	**12 months after LAM initiation**	**24 months after LAM initiation**
Group 1 (undetectable HBV DNA < 2.83 x 10^5 copies/ml) (n=204)	78 (38%)	124 (61%)
Group 2 (persistently detectable HBV DNA) (n=17)	0 (0)	0(0)
Unadjusted odds ratio for undetectable versus detectable	21.72 (95%CI 1.29 to 366.31) for detectable group rate of 0%	21.31 (95%CI 1.27 to 357.49) for detectable group rate of 0%
P value	P<0.001*	P<0.001*

**p values analysed using the Mann-Whitney U-test and Fisher exact test to test for differences between the two group.*
***Cumulative rate was calculated by the Kaplan-Meier method and log-rank test.*

Predictive factor: HBsAg levels

One retrospective study (Chan 2011) in 53 HBeAg negative patients who had continuous lamivudine treatment for a minimum of 12 months investigated quantitative HBsAg levels at baseline, month 6 and at the end of lamivudine treatment (mean 27 months) in predicting sustained response, defined as HBV DNA ≤200 IU/ml at 12 months post treatment follow up. Patients had received lamivudine for 34 months (SD±23; range 12-76). Only nine patients (17%) achieved sustained response. Results suggested that HBsAg levels were significantly lower in the responders at month 6 and end of treatment, compared to the non-responders. In addition, there was a significantly greater reduction of HBsAg from baseline in the responders at month 6 and 12 (end of treatment). The area under the ROC curves were generally greater at the end of treatment than that at month 6, suggesting that HBsAg measurement at the end of treatment (mean 27 months) was more accurate

than at month 6 to predict sustained response 12 months post treatment. However, there were only 9 events so these conclusions should be regarded with caution.

Table 273: Quantitative HBsAg levels and reduction of HBsAg from baseline in the prediction of sustained response at month 12 post-treatment

	Responders	Non-responders	P value
HBsAg (log IU/ml)			
Baseline	2.9 (1.4)	3.3 (0.6)	0.38
Month 6	2.1 (1.1)	3.2 (0.5)	0.001
End of treatment*	0.8 (1.7)	3.1 (0.6)	<0.001
Reduction of HBsAg from baseline			
Month 6	0.8 (1.0)	0.03 (0.40)	<0.001
End of treatment	2.1 (1.7)	0.2 (0.5)	<0.001

*mean duration of treatment=27 months

Table 274: ROC curves for HBsAg at baseline, month 6 and 12

	Area under ROC curve (95% CI)	P value
Month 6		
Absolute HBsAg level	0.84 (0.69-0.99)	0.001
Reduction in HBsAg level	0.75 (0.55-0.94)	0.011
End of treatment		
Absolute HBsAg level	0.91 (0.78-1.00)	<0.001
Reduction in HBsAg level	0.96 (0.89-1.00)	<0.001

*mean duration of treatment=27 months

The study reported the proportions of patients who had a sustained response at 12 months post treatment according to the cut-off of 3 log10 IU/ml:

Table 275: % of patients with a drop of HBsAg < or ≥0.7 log10 IU/ml at 6 months of lamivudine treatment on sustained response (Chan 2011)

	Sustained response at 12months		Unadjusted odds ratio (95%CI)
Predictive factor	Sustained response (n=9)	No SR (n=44)	
HBsAg >3 log10 IU/ml	6	9	7.78 (95%CI 1.62 to 37.3) for below threshold risk of 8%
HBsAg ≤3 log10 IU/ml	3	35	

The study also reported Kaplan Maier plots investigating the predictive value of different cut off values of HBsAg at the end of lamivudine treatment for sustained response at 12 months post treatment and for HBsAg seroclearance. The log rank p value was significant for the two thresholds examined: above 2 log10 IU/ml for HBsAg at the end of treatment and an HBsAg reduction of more than 1 log10 IU/ml.

Biochemical response

Predictive factor: HBV DNA

One prospective study (Kim 2007) (N=221) of a mixed group of HBeAg positive and negative patients examined if monitoring HBV DNA during the 6 months after the start of lamivudine therapy predicted ALT normalisation at 6 and 12 months after start of therapy. The population was divided into 2 groups: 1) patients with undetectable HBV DNA (n=204) and 2) patients with persistently detectable HBV DNA (n=17). Results are given in Table 276 in which the adjusted odds ratio is also calculated. The authors suggested that early cessation of treatment in the persistently detectable DNA group may be advised. However, the number of patients with persistently detectable HBV DNA was low and results should be interpreted with caution.

Table 276: Rates of ALT normalisation at 6 and 12 months after start of lamivudine treatment in patients with undetectable and persistently detectable HBV DNA levels (Kim 2007A)

	Rate of ALT normalisation	
Predictive factors during the initial 6 months of treatment	6 months after LAM initiation *	**12 months after LAM initiation***
Group 1 (undetectable HBV DNA) (n=204)	161 (79%)	145 (71%)
Group 2 (persistently detectable HBV DNA) (n=17)	8 (47%)	5 (28%)
Unadjusted odds ratio P value*	4.21 (95%CI 1.53 to 11.56) P <0.003	5.90 (95%CI 1.99 to 17.48) P<0.001

**p values analysed using the Mann-Whitney U-test and Fisher exact test to test for differences between the two groups.*

Virological breakthrough

Virological breakthrough is an increase in the HBV DNA levels in patients who have already achieved a response to treatment. It can be considered to be one of the first manifestations of drug resistance.

Predictive factor: quantitative serum HBsAg (HBsAg decrease)

One retrospective analysis of a prospective cohort study in 42 patients, 9 (21%) with cirrhosis, (Gramenzi 2011) investigated whether quantitative serum HBsAg (assessed every 6 months) was predictive of future virological breakthrough (VB) in HBeAg negative patients that were on long term lamivudine therapy (N=42); overall, 35/41 patients developed VB. The study found that HBsAg (a decrease of below versus above 0.7 log 10/ml) predicts virologic breakthrough, whereas HBV DNA (detectable versus undetectable HBV DNA) at 6 months of lamivudine treatment was not a significant predictor (Table 277, Table 278, Table 279, Table 280).

Table 277: Cumulative incidence of viral breakthrough (median time of 27 months)

(N=42)	**Cumulative incidence of viral breakthrough over time***
12 months	3 (7%)
24 months	11 (27%)
36 months	26 (63%)
60 months	31 (73%)

*Cumulative incidence of virologic breakthrough was assessed by the Kaplan-Meier method.

Table 278: % of patients with a drop of < or ≥0.7 log10 IU/ml at 6 months of lamivudine treatment on virologic breakthrough (N=41)(Gramenzi 2011)

Predictive factor between pre-treatment and month 6	Virologic breakthrough up to 60 months		Unadjusted odds ratio (95%CI)
	Virologic breakthrough	No Virologic breakthrough	
Decline of HBsAg <0.7 log10IU/ml	35/38 (92%)	3/38 (8%)	71.00 (95%CI 3.01 to 1673.63) for large decline risk of 0%
Deline HBsAg ≥0.7 log10IU/ml	0/3 (0%)	3/3 (100%)	

Table 279: % of patients with undetectable or detectable HBV DNA at 6 months of lamivudine treatment on virologic breakthrough (N=41) (Gramenzi 2011)

Predictive factor between pre-treatment and month 6	Virologic breakthrough up to 60 months		Unadjusted odds ratio (95%CI)
	Virologic breakthrough	No Virologic breakthrough	
Detectable HBV DNA (≥6 IU/ml)	12/13 (93%)	1/13 (7%)	2.61 (95%CI 0.27 to 24.94) for undetectable DNA risk of 82%
Undetectable HBV DNA (<6IU/ml)	23/28 (82%)	5/28 (18%)	

Table 280: % of HBV DNA negative patients with a drop of < or ≥0.7 log10 IU/ml at 6 months of lamivudine treatment on virologic breakthrough (N=28) (Gramenzi 2011)

Predictive factor between pre-treatment and month 6	Virologic breakthrough up to 60 months		Unadjusted odds ratio (95%CI)
	Virologic breakthrough	No Virologic breakthrough	
HBsAg <0.7 log10 IU/ml	23/25 (92%)	2/25 (8%)	65.80 (95%CI 2.58 to 1675.70) for larger decline risk of 0%
HBsAg ≥0.7 log10 IU/ml	0/3 (0%)	3/3 (100%)	

Predictive factor: quantitative serum HBeAg

One retrospective study (Park 2005) of HBeAg positive naïve CHB patients (N=340) examined the decrease of HBeAg levels at monthly intervals to predict virological breakthrough (reappearance of HBV DNA on two occasions at least 1 month apart). It used the serial monthly measurements to identify patterns of response and analysed the effectiveness of these patterns to predict long term response, using Cox multivariable regression (see below). For further details see same study above.

The different patterns of HBeAg were examined as a predictor of viral breakthrough in multivariable Cox regression analyses (Table 281) the authors did not report explicitly which factors were entered into the multivariable analysis, although it is implied that those factors significant on univariate analysis were included. For viral breakthrough, these were: the changing patterns of HBeAg levels, the total duration of lamivudine therapy and pre-treatment HBV DNA levels, for 80 events. It was noted that, in the breakthrough group, the change in HBeAg levels started to occur around 32 weeks of therapy.

Table 281: Odds ratios of predictive factors of HBeAg seroconversion and viral breakthrough using multivariable* stepwise Cox's regression model (Park 2005)

	Viral breakthrough; OR (95% CI)
Continuous decrease of >90% of pre-treatment HBeAg values, then progressively increasing HBeAg levels	19.7 (95%CI 7.74 to 49.97)**
No change or fluctuation	10.17 (95%CI 3.83 to 27.0)**

***compared to the referent group of patient who had a continuously decreasing HBeAg levels of >90% of pretreatment values over time (OR=1.00).*

There were no other predictors that were significant on multivariable analysis for viral breakthrough.

The authors concluded that the changing patterns of quantitative HBeAg levels by serial monitoring during lamivudine therapy may not only allow the prediction of treatment responses, but also an early recognition of a viral breakthrough.

Predictive factor: HBV DNA

One study (Kim 2007A) in a mixed population of HBeAg (+) and (-) patients (N=221) distinguished two groups of patients: those who had persistently detectable HBV DNA (2.83×10^5 copies/ml) during the initial 6 months after the start of lamivudine treatment and those whose serum HBV DNA converted to undetectable levels during the first 6 months after initiation of lamivudine; viral breakthrough in the latter group was defined as a reversal to detectable levels, and breakthrough in the former group was defined as a rebound of serum DNA to detectable levels during therapy. The rate of breakthrough was significantly higher in the persistently detectable group (Table 282). The study suggested that early cessation of lamivudine therapy is required in this group of patients.

Table 282: Cumulative rates of viral breakthrough at 12 months after start of lamivudine treatment in patients with undetectable and persistently detectable HBV DNA levels (Kim 2007A)

Predictive factor during the initial 6 months of treatment	Cumulative rate of viral breakthrough** 12 months after LAM initiation	Unadjusted odds ratio and p value
Group 1 (undetectable HBV DNA) (n=204)	43 (21%)	6.86 (95%CI 2.40 to 19.62) for undetectable DNA risk of 21%; P<0.001*
Group 2 (persistently detectable HBV DNA) (n=17)	11 (63%)	

*****p values were analysed using the Mann-Whitney U-test and Fisher exact test to test for differences between the two groups.*
***Cumulative rate was calculated by the Kaplan-Meier method and log-rank test.*

Predictive factor – LAM resistance

One small prospective study (Franca 2007) of 28 HBeAg (+) and (-) patients were monitored monthly for the emergence of lamivudine resistant strain (YMDD mutant). Eight patients (29%) had viral breakthrough and all of them were related to the emergence of YMDD variants observed in 7, 21, and 35% of patients at 6, 12 and 18 months respectively. The emergence of lamivudine resistance was also associated with ALT flare (defined as an increase in ALT >3 x ULN from normal levels). This study was considered too small to draw reliable conclusions.

Resistance

Predictive factor: HBV DNA

One prospective study (N=85)(Thompson 2007) in a mixed HBeAg positive and negative population investigated the role of HBV DNA monitoring every 3 months in predicting lamivudine resistance (YMDD mutation on sequencing). The authors reported that no patient developed lamivudine resistance prior to 9 months of therapy; the proportion of patients who developed lamivudine resistance was 6%, 31% and 51% at 12, 24 and 48 months. In addition, detectable HBV DNA (10^5 copies/ml) at 6 months of lamivudine treatment was a predictor for early development of lamivudine resistance and the finding was statistically significant The risk ratio was derived from multivariable analysis, based on 11 covariates for 26 events, which gives a small event/covariate ratio; only 54 patients were included in the analysis (Table 283).

Table 283: Predictive value of detectable HBV DNA for LAM resistance in a group of 85 HBeAg positive and negative patients

	Outcome: development of LAM resistance (n=26)	
Predictive factors	Risk Ratio (95% CI)*	P-value*
Detectable DNA (>10^5 copies/ml) at 6 months of lamivudine treatment	4.73 (95%CI 1.49 to 15.0)	0.008

**Risk Ratio is given for the development of LAM resistance from a Cox proportional hazards model including the following variables: presence of G1896A mutation, persistent HBV DNA at 6 months, age, gender, ethnic background, baseline HBV DNA, baseline ALT levels, HBeAg status, fibrosis score, advanced fibrosis (F3/4), genotype, in a sample of 54 patients (the defined censor events for this analysis were development of LAM resistance (n=26), treatment cessation (n=27), continued therapy (n=29) or loss to follow up (n=3).*

12.1.3.8 Patients with CHB on adefovir treatment

Virologic response

Predictive factor: HBV DNA

One small retrospective study (Llop 2009) examined monitoring change in serum HBV DNA levels (measured as a mean decrease in log viral load or mean viral load decrease from baseline) at different time points (weeks 12 and 24) during adefovir (N=35) treatment in predicting virological responses (undetectable HBV DNA <200 copies/ml) at week 48 (Table 284, Table 285). At week 24, a decrease in viral load of 1 log had 93% sensitivity and 80% negative predictive values. HBV DNA decrease from baseline of ≤20% had 100% sensitivity and 100% negative predictive value. The authors concluded that a decrease in HBV DNA at week 12 and 24 can predict virologic response at 1 year in CHB patients treated with adefovir; however, there are very few patients and the results are regarded with caution.

Table 284: Differences in pattern of decrease in HBV DNA in responders versus nonresponders to adefovir (Llop 2009)

Predictive factors	Weeks	Virologic response at 1 year		
		Responders	Non responders	P value
Mean viral load decrease (in log)	4	1.6 (1.1)	0.8 (1.4)	0.2
	12	2.4 (1.1)	1.3 (1.3)	*0.03**
	24	2.6 (1.2)	1.3 (1.2)	*0.006**
Mean viral load decrease from	4	32.1 (17.6)	11 (21.9)	0.05
	12	46.6 (13.9)	19.9 (20)	*0.001**

Predictive factors	Weeks	Virologic response at 1 year		
baseline (%)	24	49.3 (12.7)	21.1 (19.8)	*<0.001**

**p values statistically significant (p<0.05). Categorical data were compared with Student's t-test (univariate analysis).*

Table 285: Area under the ROC curve at week 12 and 24 from treatment onset with adefovir (Llop 2009)

Adefovir	AUC
Viral load decrease from baseline (%)	
Week 12	0.83
Week 24	0.9
Decrease in log viral load	
Week 12	0.77
Week 24	0.79

12.1.3.9 Patients with CHB on entecavir treatment

Three prospective follow up studies (Lee 2001A, Jung 2010A, Chon 2011) were identified to compare different frequencies of monitoring tests in order to predict treatment response among previously treatment naïve patients with CHB receiving entecavir treatment.

The three included studies focused on different types of response to entecavir treatment and results are presented separately below by response type:

Virological response

Two prospective studies (Lee 2011A, Chon 2011) were found to test the association between the frequency of monitoring factors and virological response as assessed by undetectable HBV DNA for patients receiving entecavir treatment. However, these studies reported different thresholds of undetectable HBV DNA and different times in the frequency of monitoring factors so results are presented below separately for each study.

The Lee 2011A study presented separate multivariable analyses for HBeAg positive (n=59) and negative patients (n=42). This study investigated the predictive ability of monitoring tests at 3, 6 and 12 months (undetectable HBV DNA by PCR, mean HBsAg, HBsAg <3000 IU/ml at 3 months only) for assessing virological response (HBV DNA<50 copies/ml) at the end of 12 and 24 months of entecavir treatment (Table 286Table 287Table 288). Multivariable analyses were conducted based on the variables that were significant on univariate analysis (p<0.05): for the HBeAg positive patients, there were 4 covariates and 24 events for the 12 month virological response outcome and 8 covariates and 25 events for the 24 month outcome. For HBeAg negative patients, there were 2 covariates and 28 events for the 12 month outcome. There were no significant predictors for the outcome at 24 months.

Table 286: Value of predictive factors for the prediction of virological response at the end of 12 months of entecavir treatment in HBeAg positive patients with CHB (results of a multivariable analysis)

Predictive factors	Virological response (undetectable HBV DNA (by PCR) at 12 months		Odds ratio (95% CI) and P value*
	Virological response (n=24)	No virological response (n=35)	
Decline of HBV DNA by PCR, n (%) at 3 months			

Predictive factors	Virological response (undetectable HBV DNA (by PCR) at 12 months		Odds ratio (95% CI) and P value*
Undetectable HBV DNA (<50 copies/ml)	12 (50%)	2 (6.3%)	0.001
Detectable HBV DNA (>=50 copies/ml)	12 (50%)	33 (93,6%)	
HBV DNA by PCR, n (%) at 6 months			
Undetectable HBV DNA (<50 copies/ml)	12 (50%)	4 (11.4%)	0.092
Detectable HBV DNA (>=50 copies/ml)	12 (50%)	31 (88.6%)	
Mean HbsAg, log 10 IU/ml, mean (SD) - Baseline -3 months -6 months -12 months	 3.26 (1.11) 2.83 (1.07) 3.06 (0.97)	 3. 86 (1.01) 3.49 (0.89) 3.52 (0.78)	 0.423
HbsAg levels at 3 months, n (%)			
HbsAg <3000 IU/ml	17 (77.3%)	14 (43.8%)	OR 18.0 (95%CI 3.43 to 94.60) p =0.001
HbsAg >=3000 IU/ml	7 (22.7%)	21 (56.2%)	

** P value is derived from a multivariable analysis. Results were adjusted for decline of numbers with undetectable HBV DNA at 3 and 6 months, mean HbsAg (log10 IU/ml), HbsAg<3000 IU/ml at 3 months*
NS: non statistically significant

Table 287: Value of predictive factors for the prediction of virological response at the end of 24 months of entecavir treatment in HbeAg positive patients with CHB (results of a multivariable analysis)

Predictive factors	Virological response (undetectable HBV DNA (by PCR) at 24 months		Odds ratio and P value*
	Virological response (n=25)	No virological response (n=10)	
HBV DNA by PCR, n (%) at 3 months			
Undetectable HBV DNA (<50 copies/ml)	9 (39.1%)	0	0.686
Detectable HBV DNA (>=50 copies/ml)	14 (60.1%)	10 (100%)	
HBV DNA by PCR, n (%) at 6 months			
Undetectable HBV DNA (<50 copies/ml)	10 (40%)	0	0.408
Detectable HBV DNA (>=50 copies/ml)	15 (60%)	10 (100%)	
HBV DNA by PCR, n (%) at 12 months			
Undetectable HBV DNA (<50 copies/ml)	16 (64%)	0	0.998
Detectable HBV DNA (>=50 copies/ml)	9 (36%)	10 (100%)	
Mean HBsAg, log 10 IU/ml, mean (SD) - Baseline -3 months -6 months -12 months	 3.23 (1.11) 2.82 (1.09) 2.97 (1.00) 3.04 (0.82)	 4. 33 (0.76) 4.01 (0.40) 3.98 (0.38) 3.87 (0.25)	 0.218 0.982 0.253 0.219
HBsAg levels at 3 months, n (%)			
HBsAg <3000 IU/ml	17 (73.9%)	1 (11.1%)	OR 49.0 (95%CI 2.53 to 948.6)
HBsAg >=3000 IU/ml	8 (26.1%)	9 (88.9%)	

Predictive factors	Virological response (undetectable HBV DNA (by PCR) at 24 months		Odds ratio and P value*
			p=0.010

** P value is derived from a multivariable analysis. Results were adjusted for decline of numbers with undetectable HBV DNA at 3, 6 and 12 months, mean HBsAg (log10 IU/ml at baseline, 3, 6 and 12 months, HBsAg<3000 IU/ml at 3 months*

Table 288: Value of predictive factors for the prediction of virological response at the end of 12 months of entecavir treatment in HBeAg negative patients with CHB (results of a multivariable analysis)

Predictive factors	Virological response: Undetectable HBV DNA (by PCR) at 12 months		P value*
	Virological response (n=28)	No virological response (n=14)	
HBV DNA by PCR, n (%) at 3 months			
Undetectable HBV DNA (<50 copies/ml)	22 (78.6%)	8 (57.1%)	NS in univariate analysis
Detectable HBV DNA (>=50 copies/ml)	6 (21.4%)	6 (42.9%)	
HBV DNA by PCR, n (%) 6 months			
Undetectable HBV DNA (<50 copies/ml)	18 (64.3%)	2 (14.3%)	OR 11.12 (95%CI 1.89 to 65.31) P=0.008
Detectable HBV DNA (>=50 copies/ml)	10 (33.7%)	12 (85.7%)	
Mean HBsAg, log 10 IU/ml, mean (SD)			NS in univariate analysis
- Baseline	2.98 (0.79)	3. 22 (0.42)	
-3 months	3.05 (0.53)	3.16 (0.35)	
-6 months	3.18 (0.56)	3.24 (0.34)	
HBsAg levels at 3 months, n (%)			
HBsAg <3000 IU/ml	19 (70.4%)	11 (78.6%)	NS in univariate analysis
HBsAg >=3000 IU/ml	8 (19.6%)	3 (21.4%)	

** P value is derived from a multivariable analysis.;results were adjusted for liver cirrhosis, undetectable HBV DNA at 6 months*
NS: non statistically significant, figures in bold were statistically significant (P<0.05)

The Chon 2011 study investigated the role of frequency of testing of HBV DNA levels and HBV DNA reduction from baseline at 24 and 48 weeks to predict virological response (defined as undetectable HBV DNA below 12 IU/ml) at the end of 2 years of entecavir treatment. This study included a mixed population of HBeAg positive (72%) and HBeAg negative (28%) patients with CHB. After 2 years of entecavir treatment, 139/420 patients (79.4%) achieved a virological response.

Based on area under the ROC curve, the authors used the optimal cut off HBV DNA level at week 48 (partial virological response) to predict virological response at the end of 2 years of entecavir treatment; a HBV DNA level of 35IU/ml (2.24 log10 copies/ml), 174 copies/ml) was found to be the most optimal cut off point to predict virological response at 2 years.

Table 289: Distribution of patients at the end of 2 years of entecavir treatment by the optimal partial virological response (PVR) at week 48

	Patients with virological response N (%)	**Patients with no virological response** N (%)
Optimal cut off HBV DNA* at week 48		
>35 IU/ml (partial virological response)	10	31 (86.1%)

	Patients with virological response N (%)	**Patients with no virological response** N (%)
<= 35 IU/ml (favourable virological response)	129 (92.8%)	5

Positive predictive value was 96.3% and negative predictive value 75.6%. Optimal cut off point was determined by the maximal Youden index (sensitivity+ specificity-1)

The authors also narratively summarized that patients with partial virological response (PVR) (>35 IU/ml) at week 48 showed a significantly higher risk for detectable HBV DNA levels at the end of 2 years of entecavir treatment than those with favourable virological response at week 48 (<=35IU/ml) (OR 79.9- no information was given on the width of the confidence interval)

Serological response

Two studies were identified to test the association between predictor factors during treatment and serological response at the end of one year entecavir treatment for HBeAg positive patients with CHB. In one study (Lee 2011 A), serological response was assessed in terms of HBeAg loss or seroconverion, whereas the other study (Jung 2010A) defined serological response as the decrease in the HBsAg level>1 $\log_{10}$ IU/ml from baseline.

The Lee 2011A study compared in a multivariable analysis the prognostic value of undetectable HBV DNA (<50 copies/ml) and HBsAg (measured as mean values and in a cut-off point of less than 3000 IU/ml) at 3, 6 and 12 months during treatment to predict HBeAg loss/seroconversion at the end of 12 and 24 months of entecavir treatment (Table 290Table 291). There were 8 covariates and 20 events at 12 months and 5 covariates and 18 events at 24 months.

Table 290: Frequencies of predictive factors by serological response at the end of 12 months of entecavir treatment for HBeAg positive patients with CHB

Predictive factors	**Serological response (HBeAg loss/seroconversion) at 12 months**		**Odds ratio (95%CI) P value***
	Serological response (n=20)	No serological response (n=39)	
HBV DNA by PCR, n (%) at 3 months			
Undetectable HBV DNA (< 2000 copies/ml	9 (47.4%)	5 (13.9%)	OR 4.43 (95%CI 1.03 to 19.16) p=0.046
Detectable HBV DNA	11 (52.6%)	34 (86.1%)	
HBV DNA by PCR, n (%) at 6 months			
Undetectable HBV DNA	9 (45%)	7 (17.9%)	0.884
Detectable HBV DNA			
Mean HBsAg, log 10 IU/ml, mean (SD) - Baseline -3 months -6 months -12 months	 2.98 (1.26) 2.72 (1.21) 2.85 (1.10)	 3. 79(0.83) 3.49 (0.79) 3.60 (0.60)	 0.629 0.601 0.550
HBsAg **levels at 3 months, n (%)**			
HBsAg <3000 IU/ml	16 (84.2%)	15 (42.9%)	OR 5.34 (95%CI 1.23 to 23.22) p=0.026
HBsAg >=3000 IU/ml	4	24	

**Results of the multivariable analysis adjusted results for the effect of mean Hb, mg/dl (SD), mean HBsAg (log10 IU/ml), HBsAg<3000 IU/ml at 3 months,* figures in bold were statistically significant (P<0.05)

Table 291: Frequencies of predictive factors by serological response at the end of 24 months of entecavir treatment for HBeAg positive patients with CHB

Predictive factors	Serological response (HBeAg loss/seroconversion) at 24 months		P value*
	Serological response (n=18)	No serological response (n=17)	
HBV DNA by PCR, n (%) at 3 months			
Undetectable HBV DNA	7 (43.8%)	2 (12.5%)	NS in univariate analysis
Detectable HBV DNA	11 (56.2%)	15 (87.5%)	
HBV DNA by PCR, n (%) at 6 months			
Undetectable HBV DNA	7 (38.9%)	3 (17.6%)	NS in univariate analysis
Detectable HBV DNA	11 (61.1%)	14 (82.4%)	
HBV DNA by PCR, n (%) at 12 months			
Undetectable HBV DNA	11 (61.1%)	5 (29.4%)	NS in univariate analysis
Detectable HBV DNA	7 (39.1%)	12 (70.6%)	
Mean HBsAg, log 10 IU/ml, mean (SD)			
- Baseline	2.98 (1.19)	4.14 (0.67)	0.046
-3 months	2.71 (1.27)	3.60 (0.65)	0.239
-6 months	2.85 (1.12)	3.73 (0.47)	0.239
-12 months	2.98 (0.93)	3.59 (0.49)	0.438
HBsAg **levels at 3 months, n (%)**			
HBsAg <3000 IU/ml	12 (75%)	6 (37.5%)	NS in univariate analysis
HBsAg >=3000 IU/ml	6 (25%)	11 (62.5%)	

Multivariable analysis showed that undetectable HBV DNA (<2000 copies/ml) and HBsAg< 3000 IU/ml at 3 months was an independent predictor of serological response (HBeAg loss/seroconversion) at 12 months.

The second study (Jung 2010A) presented results on the association between the cumulative incidence of predictive factors (ALT normalization, undetectable HBV DNA, HBeAg loss and seroconversion) during the one year of entecavir treatment and the serological response (decrease in the HBsAg level more than 1 $\log_{10}$ IU/ml from baseline) at the end of treatment for HBeAg positive previously treatment naïve patients with CHB. However, no further information was given on the frequency of measurements of predictive factors to predict treatment response.

12.1.3.10 Patients off treatment

Three studies (Wong 2004, Lee 2002, Lee 2003) were identified to investigate the predictive role of predictive factors on later response in patients with CHB off lamivudine treatment.

Virological response

One prospective cohort study (Lee, 2003) followed 46 out of 49 patients who had exhibited HBeAg loss/seroconversion during lamivudine therapy and agreed to receive extended lamivudine therapy for 6 to 12 months. This study investigated the role of HBV DNA levels at the time of lamivudine

discontinuation to predict virological relapse at 6 and 12 months post lamivudine treatment. Virological relapse was defined as post treatment reappearance of serum HBV DNA and/or HBeAg in two consecutive tests.

The authors reported that a higher proportion of patients with HBV DNA levels above 1000 copies/ml at the time of lamivudine discontinuation experienced virological relapse at 6 and 12 months post treatment (67% and 73% respectively) compared to patients with HBV DNA less than 1000 copies/ml (Table 292Table 293).

Table 292: Value of HBV DNA levels at discontinuation of lamivudine treatment for the prediction of relapse at 6 months post treatment in 46 patients who have HBeAg seroconverted during lamivudine treatment

	Cumulative relapse rates (at 6 months) (n=22)	Cumulative non relapse rates (at 6 months) (n=24)
HBV DNA level at time of lamivudine discontinuation (copies/ml)		
<200 (n=19)	5 (26%)	14 (74%)
200 – 1000 (n=12)	6 (50/%)	6 (50%)
>1000 (n=15)	11 (67%)	4 (33%)

Table 293: Value of HBV DNA levels at discontinuation of lamivudine treatment for the prediction of relapse at 12 months post treatment in 46 patients who have HBeAg seroconverted during lamivudine treatment

	Cumulative relapse rates (at 12 months) (n=25)	Cumulative non relapse rates (at 12 months) (n=21)
HBV DNA level at time of lamivudine discontinuation (copies/ml)		
<200 (n=19)	7 (37%)	12 (63%)
200 – 1000 (n=12)	7 (58%)	5 (42%)
>1000 (n=15)	11 (73%)	4 (27%)

Multivariable Cox proportional hazards analysis was conducted; covariates were not stated explicitly, but included age, time to HBeAg loss/seroconversion and HBV DNA levels at the time of lamivudine discontinuation, cirrhosis, history of previous interferon therapy. There were three independent predictors of relapse.

- For "higher HBV DNA levels" (not defined): OR 1.79 (95%CI 1.10 to 2.91)
- Time to HBeAg loss/seroconversion: OR 1.12 (95%CI 1.01 to 1.25) per month
- Age: OR 1.06 (95%CI 1.01 to 1.10) per year

12.1.3.11 Composite response

The study by Wong (2004) followed 34 out of 58 patients who had lamivudine resistance for at least 2 years after completing 5 years treatment with lamivudine, and investigated the role of ALT levels higher than twice the ULN and detectable HBV DNA (>10^6 copies/ml) as measured at the end of lamivudine treatment for predicting ALT flare. ALT flare was defined as equal or higher ALT levels than 5 times the ULN together with detectable HBV DNA in the follow up after stopping lamivudine.

The authors reported that ALT flare after stopping lamivudine treatment was significantly associated with the ALT level at the time of stopping lamivudine therapy (Table 60). The authors commented that as most (5/7) ALT flares occurred within 6 months after stopping lamivudine therapy, close monitoring in the first 6 months post treatment is essential, especially if ALT is elevated when lamivudine is stopped. However, this analysis was univariate and results may have been confounded by other factors, and the number of events was very small.

Another retrospective study (Lee 2002) in 42 HBeAg positive patients reported the association between HBV DNA levels measured at 2nd month of treatment and at the time of seroconversion with relapse within 6 months after lamivudine treatment. Relapse was defined as reappearance of serum HBV DNA and an increase in ALT at least 3 times the ULN within 6 months after the end of lamivudine treatment. Results from a univariate analysis showed that HBV DNA level at the second month of treatment was not related to relapse within 6 months. However, patients with HBV DNA levels more than 4.7 x 10^3 genomes/ml measured at the time of seroconversion were almost twice (OR 1.95 (1.42, 2.67) as likely to experience relapse within 6 months after the end of lamivudine treatment compared to patients whose HBV DNA levels were less than this threshold (Table 42).

Table 294: Value of HBV DNA levels at the 2nd month of treatment and at time of seroconversion for the prediction of relapse in 124 HBeAg positive patients

HBV DNA measured at 2nd month of treatment			
	Relapse within 6 months after lamivudine treatment	Odds ratio (95% CI) univariate	P value*
HBV DNA level (genomes/ml) at 2nd months of treatment			
>4.7 x 10^3	10/15 (66.7%)	1.524 (0.79-2.95)	0.2
<4.7 x 10^3	7/16 (43.8%)	1	
>10 x 10^3	7/12 (58.3%)	1.09 (0.58-2.1)	0.76
<10 x 10^3	10/19 (52.6%)	1	
>20 x 10^3	5/9 (55.6%)	1.02 (0.51-2.05)	0.96
<20 x 10^3	12/22 (54.5%)	1	
>50 x 10^3	2/4 (50%)	0.9 (0.51-2.05)	0.84
<50 x 10^3	15/27 (55.6%)	1	
HBV DNA (genomes/ml)measured at the time of seroconversion			
>4.7 x 10^3	5/5 (100%)	1.95 (1.42-2.67)	0.04
<4.7 x 10^3	19/37 (51.4%)	1	

* *P values were derived from a chi-square test, figures in bold were statistically significant (P<0.05)*

Another study (Wang 2010A) in HBeAg positive patients receiving lamivudine (N=125) who had been seropositive for HBsAg and HBeAg for more than 6 months and met the AASLD cessation criterion* were followed for a median of 24 months; 62/125 patients also received interferon alfa at the start of lamivudine treatment for 6 months. The population was divided into those who achieved HBeAg seroconversion (n=82) and those who achieved HBeAg loss (n=43) and then the incidence of subsequent relapse was monitored. Cumulative relapse rates up to 60 months after stopping lamivudine are shown inTable 295. Among the patients who achieved HBeAg seroconversion, 5 year cumulative relapse rates were calculated, stratifying by total treatment duration (< versus ≥18 months total treatment) (Table 296). The authors suggested that lamivudine cessation is a reasonable option for patients who maintained HBeAg seroconversion for a minimum of 6 months and whose total duration of treatment was at least 18 months.

*AASLD criterion: receiving ≥ 6 month additional lamivudine treatment after achieving HBeAg seroconversion/loss with undetectable HBV DNA by PCR assay and normal ALT plus an at least 12 month total

treatment duration for patients who underwent HBeAg seroconversion or an at least 18 month total treatment duration for those who underwent HBeAg loss.

Table 295: Cumulative relapse rate after lamivudine cessation at different follow up times (Wang 2010)

Follow up (months)	Group A (HBeAg seroconversion), n (%)	Group B (HBeAg loss), n (%)
1	0 (0)	0 (0)
2	9 (11)	8 (18.6)
3	12 (14.6)	10 (23.3)
4	13 (15.9)	12 (27.9)
6	17 (20.8)	12 (27.9)
9	18 (22.1)	14 (32.6)
12	19 (23.4)	15 (35)
18	20 (25)	16 (37.7)
24	20 (25)	16 (37.7)
36*	20 (25)	17 (41.1)
48	21 (29.4)	17 (41.1)
60	21 (29.4)	17 (41.1)

Table 296: Cumulative relapse rate stratified by total treatment duration in patients who achieved HBeAg seroconversion (N=82) (Wang 2010)

	5-year cumulative relapse rate*
<18 months total treatment	43/72 (60%)
≥ 18 months total treatment	3/10 (25.1%)

***log rank test p=0.002**

12.1.3.12 Children and young people with CHB

One retrospective small size study (Nagata 1999) in 22 patients investigated the role of detectable HBV DNA at different time periods during treatment with interferon alpha for predicting the virological response to this treatment (defined as undetectable HBV DNA and HBeAg seroconversion within 18 months of treatment completion) for HBeAg positive children (aged 2-14 years old). Unadjusted odds ratios were calculated from the data (Table 297).

Table 297: Frequency of detectable HBV DNA (by hybridization and quantitative PCR) by virological response in a sample of 22 HBeAg children on interferon alpha treatment*

Detectable HBV DNA by hybridization and quantitative PCR	Virological responders within 18 months of treatment completion (n=10)	Virological non responders within 18 months of treatment completion (n=12)	Unadjusted odds ratio (95% CI)
Detectable HBV DNA at 4-7 weeks • by hybridisation • by quantitative PCR	 -8/10 -9/10	 -12/12 -12/12	3.95 (95%CI 0.14 to 108.09)
Detectable HBV DNA at 8-15 weeks			3.95 (95%CI 0.14 to

Detectable HBV DNA by hybridization and quantitative PCR	Virological responders within 18 months of treatment completion (n=10)	Virological non responders within 18 months of treatment completion (n=12)	Unadjusted odds ratio (95% CI)
• by hybridisation • by quantitative PCR	-2/10 -9/10	-12/12 -12/12	108.09)
Detectable HBV DNA at 16-24 weeks • by hybridisation • by quantitative PCR	 -1/10 -5/10	 -12/12 -12/12	29.00 (95%CI 1.36 to 616.60)
Detectable HBV DNA at 16-26 weeks • by hybridisation • by quantitative PCR	 -0/10 -5/10	 -11/12 -12/12	29.00 (95%CI 1.36 to 616.60)

**No statistical analysis was conducted by the authors.*

The authors concluded that monitoring of HBV DNA by quantitative PCR during interferon-alfa treatment may allow early prediction of response to interferon alpha, although that needs to be confirmed in a prospective study. Results should be interpreted with caution due to small sample size of the study.

12.1.4 Economic evidence

Published literature

There were no published studies that addressed this question

Unit costs

The unit costs of monitoring are provided below for consideration by the GDG

Pegylated interferon alfa 2a

Table 298: Monitoring for toxicity at 0, 2, 4, 12, 24 and 32 weeks.

Item	Cost	Cost source
Time with nurse – Band 7 for 20 minutes	£47.33	PSSRU*
Full blood count	£2.49	Shepherd 2006
Liver function test	£4.12	Shepherd 2006
ALT	£0..59	Expert opinion
Urea & electrolyte	£0.80	Expert opinion
Thyroid function test (at 12 weeks only)	£4.12	Shepherd 2006
Total	**58.86**	
*Based on a unit cost of £142 per hour of patient contact for a Band 7 nurse including the cost of qualifications.		

Table 299: Monitoring for response to therapy at 24 and 48 weeks

Item	Cost	Cost source
Time with specialist physician – Hepatologist for 20 minutes	£176	NHS Reference Costs**

Item	Cost	Cost source
HBeAg	£8.00	Expert opinion
HBV DNA	£40.00	Expert opinion
ALT	£0.59	Expert opinion
HBsAg quantitative	£5.00	Expert opinion
Total	**£230.00**	
**Based on the national average cost of a follow-up appointment with a consultant hepatologist.		

Nucleos(t)ides

Entecavir and Lamivudine

Table 300: Monitoring at weeks 0, 4, 12 and every 6 months thereafter

Item	Cost	Cost source
Time with nurse – Band 7 for 20 minutes	£47.33	PSSRU*
Full blood count	£2.49	Shepherd 2006
Liver function test	£1.03	Expert opinion
Renal function test	£0.80	Expert opinion
Blood clotting	£3.80	Shepherd 2006
HBV DNA	£40.00	Expert opinion
HBsAg qualitative (except at 4 weeks)	£5.00	Expert opinion
Total	**£100.45**	
*Based on a unit cost of £142 per hour of patient contact for a Band 7 nurse including the cost of qualifications.		

Table 301: Annual consultant appointment (at 48 weeks)

Item	Cost	Cost source
Time with specialist physician – Hepatologist for 20 minutes	£176	NHS Reference Costs**
HBeAg	£8.00	Expert opinion
Hepatitis B DNA	£40.00	Expert opinion
ALT	£0.59	Expert opinion
HBsAg quantitative	£10.00	Expert opinion
Total	**£235.00**	
**Based on the national average cost of a follow-up appointment with a consultant hepatologist.		

Adefovir and Tenofovir

Table 302: Monitoring at weeks 0, 4, 12 and every 6 months thereafter

Item	Cost	Cost source
Time with nurse – Band 7 for 20 minutes	£47.33	PSSRU*
Full blood count	£2.49	Shepherd 2006
Liver function test	£1.03	Expert opinion
Renal function test	£0.80	Expert opinion
Blood clotting	£3.80	Shepherd 2006
Phosphate	£0.60	Expert opinion

Item	Cost	Cost source
Urine test for protein/creatine ratio	£0.58	Expert opinion
HBV DNA	£40.00	Expert opinion
HBsAg qualitative (except at 4 weeks)	£5.00	Expert opinion
Total	**£101.63**	
*Based on a unit cost of £142 per hour of patient contact for a Band 7 nurse including the cost of qualifications.		

Table 303: Annual consultant appointment (at week 48)

Item	Cost	Cost source
Time with specialist physician – Hepatologist for 20 minutes	£176	NHS Reference Costs**
HBeAg	£8.00	Expert opinion
HBV DNA	£40.00	Expert opinion
ALT	£0.59	Expert opinion
HBsAg quantitative	£5.00	Expert opinion
Total	**£230.00**	
**Based on the national average cost of a follow-up appointment with a consultant hepatologist.		

Surveillance of patients who are active carriers

Table 304: Monitoring at 24 and 48 weeks

Item	Cost	
Time with nurse – Band 7 for 20 minutes	£47.33	PSSRU*
HBV DNA	£40.00	Expert opinion
ALT	£0.59	Expert opinion
HBeAg antibody	£8.00	Expert opinion
Total	**£95.92**	
*Based on a unit cost of £142 per hour of patient contact for a Band 7 nurse including the cost of qualifications.		

12.1.5 Evidence statements

12.1.5.1 Clinical evidence statements

For people in the immune tolerant phase of hepatitis B (detectable HBV DNA levels and normal ALT), there were two studies examining monitoring to predict future reactivation. One showed in multivariable analysis that ALT levels above 5 x ULN during that phase was predictive of future reactivation but gave no indication of frequency of monitoring (low quality evidence). Multivariable analysis in the other small study found no significant predictors for the time to future ALT elevation, but showed an increase in absolute ALT levels of about 8% at 3 months follow up (low quality evidence).

In people who are inactive carriers (HBeAg negative and normal ALT), two studies investigated monitoring ALT levels to predict future ALT flares or elevation. One study suggested a minimum period of monitoring of 3 months would identify about 90% of people with flares, but the evidence did not take into account censored patients (very low quality). Another small study suggested in

univariate analyses that HBV DNA levels above 10,000 copies/ml at 12 months could predict future ALT elevation; this threshold was not significant at 6 months (low quality). Other higher DNA thresholds predicted ALT elevations at earlier monitoring times, but at the expense of missing some people at risk (low quality evidence).

Eight studies examined monitoring in people with CHB who were receiving pegylated (or non-pegylated) interferon alfa (2a or 2b) treatment. There was variability across studies in the measures of response reported, in the interventions, in the predictors and thresholds used, and in the times of monitoring.

- Four studies reported multivariable analyses: one small study indicating that a 12 week decline in HBsAg was a predictor of sustained response, but this measure was not significant at 8 weeks (peg); another study (non-peg) that a change in DNA level was not a significant predictor of response at 8 weeks but a change in HBeAg at 8 weeks was significant; and another small study (non-peg) showed that a HBV DNA level of more than 5 log10 copies/ml at 12 weeks was an independent predictor of relapse, (all low quality evidence). The final small study (peg) reported a significant effect for HBV DNA decline at 4, 8 and 12 weeks and for HBsAg decline at 12 weeks, but no odds ratios or even p-values were given (very low quality evidence).
- Unadjusted analyses comparing predictions for values above versus below the thresholds allowed examination of trends: the body of evidence was consistent and suggested that monitoring after 8 weeks was the shortest time at which a significant predictive effect was found. Predictors included: a decrease of at least 90% in HBeAg levels at 8 and 12 weeks (non-peg); HBeAg levels of less than 10 IU/ml at 24 weeks (peg); HBV DNA levels of less than 5 log10 copies/ml at 24 weeks (peg); a decline and HBsAg levels above 0.5 log IU/ml (peg) (all low quality evidence).
- One large study identified patterns of response to peg interferon treatment and determined (in unadjusted analysis) that an early (0-4 weeks) decline of more than 1 log copies/ml or a delayed (4-32 weeks) decline of 2 log copies/ml HBV DNA predicted HBeAg loss at 24 weeks follow up post treatment (low quality).

Nine studies examined monitoring in people with CHB who were receiving lamivudine treatment. There was variability across studies in the measures of response reported, in the predictors and thresholds used, and in the times of monitoring.

- For response to treatment (HBeAg seroconversion and HBV DNA undetectable), one large retrospective study identified three HBeAg patterns based on monitoring at 2-monthly intervals and used multivariable analysis to examine the usefulness of these patterns in predicting response. A pattern of continuously decreasing HBeAg to more than 90% of pretreatment values was a strong independent predictor of response, in comparison with the group having a continuous decrease to 90% levels followed by a progressive increase or the group with no change/fluctuation in HBeAg levels (moderate quality evidence).
- In unadjusted analyses, comparing predictions for values above versus below various thresholds allowed examination of trends on response: the body of evidence was consistent and suggested that monitoring after 6 months was the shortest time at which a significant predictive effect was found. Predictors included: undetectable HBV DNA ($< 2.83 \times 10^5$ copies/ml) at 6 months (low quality); HBsAg > 3 log IU/ml at 6 months (very low quality)
- For viral breakthrough, unadjusted analyses compared predictions for values above versus below various thresholds allowed examination of trends on breakthrough: the body of evidence was consistent and all studies investigated monitoring after 6 months. Predictors included: decline of HBsAg < 0.7 log IU/ml at 6 months, (very low quality); persistently detectable HBV DNA $> 2.83 \times 10^5$ copies/ml at 6 months (low quality) but detectable HBV DNA > 6 IU/ml at 6 months was not a significant predictor (very low quality).

- For viral breakthrough, one large retrospective study identified three HBeAg patterns based on monitoring at 2-monthly intervals and used multivariable analysis to examine the usefulness of these patterns in predicting virological breakthrough. A pattern of a continuous decrease to 90% levels followed by a progressive increase was a strong independent predictor, as was a pattern of no change or fluctuation in HBeAg levels, both in comparison with a pattern of continuously decreasing HBeAg levels to more than 90% of pretreatment values (moderate quality evidence). In people having virological breakthrough in the breakthrough group, the change in HBeAg levels started to occur around 32 weeks of therapy.
- For resistance(YMDD mutation on sequencing), one small study used multivariable analysis to show that detectable HBV DNA (> 10^5 copies/ml) at 6 months of treatment was an independent predictor (low quality).

One small, retrospective study examined monitoring HBV DNA levels in people receiving adefovir. Univariate analysis suggested that a decrease of 1 log copies/ml at 12 and 24 weeks, but not at 4 weeks, was a significant predictor of virological response (very low quality evidence).

Two prospective studies investigated monitoring in people receiving entecavir treatment, but only one gave comparative results:

- One small study conducted multivariable analyses and showed that, in patients who were HBeAg positive, significant predictors of virological response at the end of 12 months were: undetectable HBV DNA below 50 copies/ml at 3 months, but not 6 months (p-value only) and HBsAg levels below 3000 IU/ml at 3 months. At 24 months treatment, the only significant independent predictor was HBsAg level below 3000 IU/ml at 3 months; undetectable HBV DNA was not a significant predictor. In patients who were HBeAg negative, HBV DNA was a significant predictor at 6 months but not 12 months (low quality) for virological response at 12 months (low quality evidence) and there were no significant predictors for the outcome at 24 months.
- For the outcome, serological response at 12 months, undetectable DNA levels below 2000 copies/ml were significant at 3 months, but not at 6 months, and so were HBsAg levels below 3000 at 3 months. For the outcome at 24 months, HBV DNA levels and HBsAg levels were not independent predictors at any time during treatment (very low quality evidence).

Three studies investigated people off-treatment, investigating monitoring to predict virological relapse at 6 and 12 months following discontinuation of lamivudine treatment in people who had achieved seroconversion /loss: one small study conducted a multivariable analysis and showed that 'higher' HBV DNA levels at the time of discontinuing treatment and the time to seroconversion/loss were significant independent predictors of virological relapse at 6 and 12 months post treatment (low quality). A univariate analysis in a small retrospective study suggested that HBV DNA level above 4.7 x 10^3 copies/ml at the time of seroconversion was a significant predictor of relapse (very low quality).

One very small, retrospective study in children showed in unadjusted analysis that detectable levels of HBV DNA at 16-24 weeks was a significant predictor of response to interferon alfa treatment , but measurements at 4-15 weeks were not significant (very low quality evidence)

12.1.5.2 Economic evidence statements

No economic evaluation was found on this question.

12.1.6 Recommendations and links to evidence

Recommendations	**Monitoring in people who do not meet criteria for antiviral treatment** **Adults with HBeAg-positive disease in the immune-tolerant and immune clearance phase** **74. Monitor ALT levels every 24 weeks in adults with HBeAg-positive disease who are in the immune-tolerant phase (defined by active viral replication and normal ALT levels [less than 30 IU/ml in males and less than 19 IU/ml in females]).** **75. Monitor ALT every 12 weeks on at least 3 consecutive occasions if there is an increase in ALT levels.**
Relative values of different outcomes	The GDG considered that monitoring of ALT and HBV DNA were equally important to assess when treatment needs to be initiated.
Trade off between clinical benefits and harms	For people in the immune tolerant phase of hepatitis B (detectable HBV DNA levels and normal ALT), there were two studies examining monitoring to predict future reactivation. One study showed in multivariable analysis that ALT levels above 5 x ULN during that phase was predictive of future reactivation but gave no indication of frequency of monitoring (low quality evidence). Multivariable analysis in the other small study found no significant predictors for the time to future ALT elevation, but showed an increase in absolute ALT levels of about 8% at 3 months follow up It was the GDG's opinion that if after 12 weeks of monitoring the ALT is still raised without any normalisation in HBV DNA level, then treatment will need to be started.
Economic considerations	The GDG considered the cost of performing serological testing at different intervals. Monitoring patients every 24 weeks was thought to be less costly and equally effective as monitoring every 12 weeks in patients with normal ALT levels. The cost of monitoring every 12 weeks was thought to be justified in people with elevated ALT levels in whom starting treatment may be required.
Quality of evidence	The evidence for predicting reactivation was considered to be low quality. Both of the studies had limitations: one prospective study (Chu 2007) employed a multivariable analysis of a Cox proportional hazard regression model, but had fewer than 10 events/covariate. The study was considered to be only partially applicable because it did not investigate frequency of monitoring. A second study was analysed appropriately, but data had to be extracted from univariate Kaplan Meier plots.
Other considerations	The recommendation was based on limited clinical evidence and GDG expert opinion. It was noted that what would be considered as a normal ALT level would differ between laboratories undertaking the test, and therefore it was not possible to give a specific level within the wording of the recommendation.

Recommendations	**Adults with inactive chronic hepatitis B (immune-control phase)** **76. Monitor ALT and HBV DNA levels every 48 weeks in adults with inactive chronic hepatitis B infection (defined as HBeAg negative on 2 consecutive tests with normal ALT [less than 30 IU/ml in males and less than 19 IU/ml in females] and HBV DNA less than 2000 IU/mL).** o Consider monitoring more frequently (for example, every 12-24 weeks) in people with cirrhosis[xx] who have undetectable HBV DNA. **Children and young people** **77. Monitor ALT levels every 24 weeks in children and young people with HBeAg-positive disease who have normal ALT levels (less than 30 IU/ml for males and less than 19 IU/ml for females) and no evidence of significant fibrosis (METAVIR stage less than F2 or Ishak stage less than 3).** **78. Review annually children and young people with HBeAg-negative disease who have normal ALT (less than 30 IU/ml for males and less than 19 IU/ml for females), no evidence of significant fibrosis (METAVIR stage less than F2 or Ishak stage less than 3) and HBV DNA less than 2000 IU/ml.** **79. Review every 12 weeks children and young people with HBeAg-negative disease who have abnormal ALT (greater than or equal to 30 IU/ml for males and greater than or equal to 19 IU/ml for females) and HBV DNA greater than 2000 IU/ml.**
Relative values of different outcomes	The GDG considered that monitoring of ALT and HBV DNA levels were equally important as outcomes for people who are inactive carriers.
Trade off between clinical benefits and harms	In people who are inactive carriers (HBeAg negative and normal ALT), two studies investigated monitoring ALT levels to predict future ALT flares or elevation. One study suggested a minimum period of monitoring of 3 months would identify about 90% of people with flares, but the evidence did not take into account censored patients However, the GDG noted that the study population included a proportion of patients with significant liver fibrosis and that patients who suffered an ALT flare were more likely to have stage 2 or 3 fibrosis. The GDG felt that if it has been demonstrated that patients do not have significant fibrosis then ALT levels can be monitored less frequently. Another small study suggested in univariate analyses that HBV DNA levels above 10,000 copies/ml at 12 months could predict future ALT elevation; this threshold was not significant at 6 months (low quality). Below 10,000 copies/ml, only 2.9% patients had elevated ALT at 1 year and at 6 months.

xx As defined in recommendation 17

	Other thresholds (30,000 and 50,000 copies /ml were less discriminating (had smaller unadjusted odds ratios) and had increased proportions of patients below the threshold with elevated ALT (both levels had around 20% at 1 year). A threshold of 100,000 copies/ml was highly discriminating even at 6 months with 41% of patients above the threshold having elevated ALT, but the numbers of patients above this threshold was low. The GDG stated that at present most clinics in the UK would test HBV DNA yearly in this group of patients after a liver biopsy or non-invasive test that confirms there is minimal fibrosis and their HBV DNA level remains below10,000 copies/ml (<2000 IU/ml). A minority (approximately 1 in 20) of HBeAg negative patients will have active cirrhosis despite low levels of HBV DNA. The GDG stated that in order to classify patients into those having normal ALT and low HBV DNA levels, these tests will need to be done at least twice (within 6 months) after initial referral to understand the natural history of the disease.
Economic considerations	The GDG considered the cost of performing serological testing at different intervals. Monitoring patients was also concluded to be non-negotiable, particularly on pegylated interferon. Monitoring patients every 48 weeks was thought to be less costly and equally effective as monitoring every 12 weeks.
Quality of evidence	The evidence review included two studies: one prospective study that examined only the 43 people who had a flare and drew conclusions from this; it did not take into account any censoring. In addition, the GDG regarded this study as at least partly indirect evidence because of the presence of a proportion of people with significant liver fibrosis; the evidence was regarded as very low quality. Another fairly small prospective study (Feld 2007) reported time to event data, and produced univariate Kaplan Meier plots, without taking into account the other predictors identified by multivariable analysis. We calculated unadjusted odds ratios to compare the effect of above versus below the threshold, so these could have been confounded. This was, however, a well conducted study and was analysed appropriately, taking proper consideration of the fluctuating course of HBeAg negative disease; evidence was considered to be of low quality.
Other considerations	The recommendation was based on clinical evidence and GDG expert opinion. The GDG did not think there was a need to monitor the majority of patients more frequently than annually, but noted that if ALT levels were raised, the patient should be monitored more frequently. This took into account the fluctuating nature of negative disease. The GDG also considered another special case, that of people who had high transient elastography levels (≥11 kPa, indicating cirrhosis), but who also had undetectable HBV DNA levels (see LETR in chapter 8). These people would not be offered antiviral treatment unless their HBV DNA levels became detectable, but the GDG was concerned that an increase to detectable levels should be picked up quickly because of the risk of decompensation in people with cirrhosis. Therefore the GDG recommended more frequent monitoring in this group and suggested 12-24 weeks.

	Monitoring in people taking antiviral treatment
Recommendations	**Children, young people and adults taking peginterferon alfa-2a**

	80. Review injection technique and adverse effects weekly during the first month of treatment with peginterferon alfa-2a[yy]. **81. Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels) and thyroid function (and in children, weight and height) before starting peginterferon alfa-2a and 2, 4, 12, 24, 36 and 48 weeks after starting treatment to detect adverse effects[zz].** **82. Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting peginterferon alfa-2a at 12, 24 and 48 weeks after starting treatment to determine treatment response[aaa].** **Stopping peginterferon alfa-2a treatment** **Children and young people** **83. Consider stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and/or if HBsAg is greater than 20,000 IU/ml.** **Adults with HBeAg positive chronic hepatitis B and compensated liver disease – see recommendation 42** **Adults with HBeAg negative chronic hepatitis B and compensated liver disease** **84. Consider stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and HBsAg has not decreased, and consider second-line treatment in line with recommendation 48.**

yy At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

zz At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

aaa At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Relative values of different outcomes	The GDG considered that monitoring HBV DNA levels and HBsAg status during treatment with pegylated interferon were the most important predictors to direct whether to continue peginterferon therapy. Outcomes should be measured at least 6 months post treatment and virological response, serological response and the combination were all considered important, but loss of HBeAg and HBsAg loss were the best measures. The GDG made use of forest plots to look at trends across a number of outcomes. When examining stopping rules (because of a lack of response), the GDG considered whether the rule allowed discrimination between patients in predicting a treatment response (this meant having a statistically significant odds ratio for the presence versus the absence of the predictor). The GDG also required the negative predictive value (NPV) to be at least 95% in order to avoid stopping patients who might achieve a response; the GDG took into account the confidence interval around the odds ratio and the NPV.
Trade off between clinical benefits and harms	Several studies examined monitoring in people with CHB who were receiving pegylated (or non-pegylated) interferon alfa (2a or 2b) treatment. There was variability across studies in the measures of response reported, in the interventions, in the predictors and thresholds used, and in the times of monitoring. However, the body of evidence consistently showed the value of monitoring people who were on interferon based treatments. Most analyses were unadjusted for confounders, or were multivariable analyses with limitations, but generally showed that measurements at 12 weeks were equally as predictive as measurements at 24 weeks but that measurements at 8 weeks were less likely to be predictors of treatment response. The studies reported monitoring of HBsAg, HBV DNA and HBeAg as significant predictors. In HBeAg positive patients: • The evidence from one large study suggested that an HBsAg of <1500 IU/ml at 12 or 24 weeks is not as good as HBsAg < 20,000 IU/ml at predicting virological response post treatment, but the lower threshold is better for predicting HBsAg clearance (with the higher threshold not being statistically significant in discriminating patients at high and low risk). For HBeAg seroconversion at 24 weeks post treatment there was little difference between the thresholds and the NPV was only 73% • There did not appear to be a significant difference between B and C genotypes in this study for HBeAg seroconversion • Evidence from two studies showed that HBV DNA levels are reasonably good predictors of response, with a decline of 2 log or more giving reasonable discrimination, although the NPV is much less than 95% for HBeAg seroconversion. One large study in HBeAg positive patients investigated monthly serial measurements of HBV DNA in order to identify patterns of behaviour and their abilities to predict response. Five patterns of response to peg interferon treatment and determined (in unadjusted analysis) that an early (0-4 weeks) decline of more than 1 log copies/ml or a delayed (4-32 weeks) decline of 2 log copies/ml HBV DNA predicted HBeAg loss at 24 weeks follow up post treatment in comparison with a late response at 32-52 weeks or a post treatment response or no response. Analysis suggests that the best predictor includes both an early and a delayed decline (early decline > 1 log (up to 4

	weeks) plus delayed decline >2 log (up to 32 weeks)). For predicting HBsAg loss at 6 months post treatment, the early response pattern (up to 4 weeks) did not give sufficient discrimination and the NPV was not sufficiently high either. This was greatly improved when the delayed response was included. In HBeAg negative patients: • In three studies, the change in HBsAg level between baseline and 12 weeks does not, on its own, meet the requirements of a statistically significant odds ratio for an NPV of more than 95% with a narrow confidence interval. There was some evidence supporting better predictability of measurements at 24 weeks, but there was much uncertainty about this. The optimum level of HBsAg was unclear and would need to be investigated • A change of 2 log or more in HBV DNA on its own, at 12 weeks had relatively poor predictive value in validation studies (not statistically significant and NPV 75%) • One small study (Rijckborst 2010) derived a stopping rule for patients who had no decline in HBsAg and less than 2 log copies/ml decline in HBV DNA at 12 weeks. This stopping rule was not confirmed as highly effective in the same author's validation study (Rijckborst 2012) and even the original study had a wide confidence interval around the NPV (83 to 100%). • There may be an effect of genotype on the rule, but the evidence is too uncertain to have confidence in this. It is possible that the poorer discrimination of the rule in patients with non-D genotype is an artefact of smaller sample size One additional study (Lampertico 2012), conducted a multivariable analysis with a low number of events per covariate, and showed HBsAg level at 24 weeks (as a continuous predictor) to be the only monitoring marker of significance for predicting virological response; this was not a significant predictor at 12 weeks. The GDG took into account the known adverse events of peginterferon in considering when to stop treatment if patients had not responded.
Economic considerations	The GDG considered the cost of performing serological testing at different intervals. Monitoring patients every 24 weeks was thought to be less costly and equally effective as monitoring every 12 weeks. The GDG noted that quantitative HBsAg assays are now relatively low cost.
Quality of evidence	The quality of the evidence was generally low. Four studies included multivariable analyses, but there were often too few events for the number of covariates. Other studies reported sufficient information to calculate relative effects of above versus below particular thresholds, but these unadjusted analyses did not take into account other confounders and so were regarded as low quality evidence. However, overall the evidence was highly consistent which overcame some of the limitations of individual studies. One large study based on an RCT carried out serial measurements to identify patterns, but the analysis was unadjusted for confounders and the comparative analysis had to be considered to be low quality. When considering the stopping rules, the GDG found it useful to look at the asymmetric confidence interval around the NPV: in one instance the 95% confidence interval ranged from 80 to 100% around an NPV of 100%.
Other considerations	Recommendations were based on clinical evidence and GDG expert opinion.

The GDG was mindful that a first-line recommendation of peg interferon should be accompanied by accurate stopping rules appropriate to that therapy. This was particularly in view of the adverse effects associated with peg interferon. It would not be acceptable to subject the patient to adverse effects for no benefit. Continuing a patient on peg interferon when there was little chance of success would also risk progression of liver disease, which could be prevented by switching to second line nucleos(t)ides. On the other hand, the GDG wanted to maximise the likelihood that patients could achieve immune control using a single course of interferon, rather than having to be on nucleos(t)ides for the rest of their lives.

The GDG therefore considered carefully the evidence on existing stopping rules that have been developed specifically for people on peg interferon, in addition to stopping rules for antiviral therapy in general. The former have focussed on HBsAg levels during treatment as predictors of response, alongside HBV DNA changes during treatment.

The GDG recognised that the evidence base was relatively weak for stopping rules and that there were limitations to the evidence, notably the relatively few events, the lack of multivariable analysis and the selection of patients in the studies (only those with HBsAg measurements at appropriate times and people with 24 weeks follow up post treatment). These limitations applied, however, for all the candidate predictors for stopping.

Despite these limitations, the GDG noted that the evidence was consistent in favour of including HBsAg in the stopping rules.

HBeAg negative patients

In HBeAg negative patients, the GDG decided that HBsAg should not be used on its own for decision making, although noted the potential for a change of 1.0 log IU/ml at 24 weeks as a stopping rule in one small study. HBV DNA as a predictor on its own was also non-optimum, with a lack of statistical significance and relatively low NPV in the single validation study.

Within the Rijckborst 2012 validation study, neither a decline in HBV DNA of 2 log or more nor any decline in HBsAg were good individual predictors of response: for both, the odds ratio at 12 weeks was not statistically significant (i.e. not a predictor) and there was a relatively low NPV. On the other hand, validation of the proposed combination stopping rule (Rijckborst 2012) of a decline in HBV DNA of 2 log or more plus any decline in HBsAg at 12 weeks gave a significant odds ratio and an NPV of 95% (although the confidence interval around the NPV ranged from 75 to 100% - so there was uncertainty.

The GDG recognised the limitations of these studies, but wished to use the stopping rule that gave the best prediction. The combination of a decline in HBsAg level and a decline in HBV DNA of 2 log or more at 12 weeks was a better predictor than either measure alone, but the NPV was 95% in the validation study, and the GDG had some uncertainty about using the 12 week values. They also noted that the 24 week levels were as good predictors as at 12 weeks and took into account the cost of more frequent monitoring. Additionally, they drew on the low quality evidence from the Lampertico multivariable analysis, for which only HBsAg at 24 weeks was statistically significant, and the 12 week value was not. On the other hand, the GDG still wanted the option of decision making at 12 weeks and thought that, as further research is done, the 12 week rule would become more favoured. Therefore, the GDG made a research recommendation to investigate stopping rules, and recommended that clinicians consider stopping at 24 weeks and that patients

	are monitored at 12 and 24 weeks. This combination of recommendations did not preclude decision making at 12 weeks at the discretion of the clinician. The GDG was not confident that there was an effect of genotype D in the combination stopping rule, even though the odds ratio was not significant for the non-D genotype patients and was significant for the D genotype patients; this difference was as likely to be due to sample size issues as an effect of genotype. The GDG also took into account the fact that the cost effectiveness analysis for treatment ruled out genotyping. In HBeAg positive patients, there was evidence in favour of using HBsAg levels during treatment as predictors of response. HBsAg levels were better predictors of response than HBV DNA, mainly because of the higher NPVs in the former. The GDG was interested in the different patterns of HBV DNA decline in the the Borg 2006 study, and concluded that using measurements at 12 weeks as predictors for stopping treatment could mean that some patients would not have the opportunity for a delayed response. The GDG therefore agreed that the stopping rule should be applied at 24 rather than 12 weeks. The GDG decided that, in view of the limited evidence, a stopping rule that included either or both HBsAg and HBV DNA levels was the most conservative approach. The threshold of 20,000 IU/ml was selected for HBsAg rather than 1500 IU/ml because of the higher NPV for the former. The HBV DNA threshold was a decrease of 2 log or more. The GDG was mindful that stopping rules should be considered in conjunction with patient information on the different types of treatment for CHB, including awareness of the potential for short term (one-off) treatment with peg interferon versus potential for lifetime treatment with nucleo(t)sides, and side effects of drugs including resistance, and with reference to the patient's personalised care plan (Chapter 6).
Recommendations	**Children, young people and adults with compensated liver disease taking entecavir or lamivudine** **85. Monitor full blood count, liver function (including bilirubin, albumin and ALT) and renal function (including urea and electrolyte levels) in people with compensated liver disease before starting entecavir or lamivudine, 4 weeks after starting treatment and then every 3 months to detect adverse effects[bbb].** **86. Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting entecavir or lamivudine, 12, 24 and 48 weeks after starting treatment and then every 6 months to determine treatment response and medicines adherence[ccc].**

bbb At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

ccc At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in

87. **Monitor HBV DNA levels every 12 weeks in people with HBeAg-negative disease who have been taking lamivudine for 5 years or longer[ddd].**

Children, young people and adults with compensated liver disease taking tenofovir disoproxil

88. **Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels and urine protein/creatinine ratio), and phosphate levels in people with compensated liver disease before starting tenofovir disoproxil, 4 weeks after starting treatment and then every 3 months to detect adverse effects.**
89. **Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting tenofovir disoproxil, 12, 24 and 48 weeks after starting treatment and then every 6 months to determine treatment response and medicines adherence.**

Stopping nucloes(t)ide analogue treatments in HBeAg positive adults with compensated liver disease

90. **Consider stopping nucleoside or nucleotide analogue treatment 12 months after HBeAg seroconversion in people without cirrhosis.**

Stopping nucloes(t)ide analogue treatments in HBeAg negative adults with compensated liver disease

91. **Consider stopping nucleoside or nucleotide analogue treatment 12 months after achieving undetectable HBV DNA and HBsAg seroconversion in people without cirrhosis.**

Children, young people and adults with HBeAg or HBsAg seroconversion after antiviral treatment

92. **In people with HBeAg seroconversion after antiviral treatment, monitor HBeAg, anti-HBe, HBV DNA level and liver function at 4, 12 and 24 weeks after HBeAg seroconversion and then every 6 months.**
93. **Monitor HBsAg and anti-HBs annually in people with HBsAg seroconversion after antiviral treatment and discharge people who are anti-HBs positive on 2 consecutive tests.**

children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

ddd At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

	Children, young people and adults with decompensated liver disease who are taking entecavir or lamivudine **94. Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels and urine protein/creatinine ratio), blood clotting, HBV DNA level and HBeAg status in people with decompensated liver disease before starting entecavir or lamivudine and weekly after starting treatment to assess treatment response and adverse effects. When the person is no longer decompensated, follow the recommendations in 'Children, young people and adults with compensated liver disease taking entecavir or lamivudine'[eee].** **Children, young people and adults with decompensated liver disease who are taking tenofovir disoproxil** **95. Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels and urine protein/creatinine ratio) and phosphate, blood clotting, HBV DNA level and HBeAg status in people with decompensated liver disease before starting tenofovir disoproxil and weekly after starting treatment to assess treatment response and adverse effects. When the person is no longer decompensated, follow the recommendations in 'Children, young people and adults with compensated liver disease taking tenofovir disoproxil'[fff].**
Relative values of different outcomes	The GDG considered that monitoring HBV DNA levels and HBsAg status during treatment with nuclos(t)ides were the most important outcomes to direct whether to continue with treatment. For people receiving lamivudine in particular, the GDG was also interested in virological breakthrough.
Trade off between clinical benefits and harms	Nine studies examined monitoring in people with CHB who were receiving lamivudine treatment. There was variability across studies in the measures of response reported, in the predictors and thresholds used, and in the times of monitoring. However, all the studies investigating the predictive ability of different measurements showed similar trends, both for predicting response to treatment and for predicting virological breakthrough. For treatment response, the evidence was mainly represented by unadjusted analyses comparing the predictive ability of measurements above and below particular thresholds; all the studies investigated monitoring at 6 months. The body of evidence was consistent and suggested that monitoring could be used to good effect in predicting likely treatment response. One large retrospective study identified three HBeAg time patterns based on monitoring at 2-monthly intervals and used multivariable analysis to examine

eee At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

fff At the time of publication (June 2013), peginterferon alfa-2a and entecavir did not have a UK marketing authorisation for use in children for this indication, and tenofovir disoproxil did not have a UK marketing authorisation for use in children younger than 12 years for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

	the usefulness of these patterns in predicting response. A pattern of continuously decreasing HBeAg to more than 90% of pretreatment values was a strong independent predictor of response, in comparison with the group having a continuous decrease to 90% levels followed by a progressive increase or the group with no change/fluctuation in HBeAg levels (moderate quality evidence). Virological breakthrough is an increase in the HBV DNA levels in patients who have already achieved a response to treatment. It can be considered to be one of the first manifestations of drug resistance. Much of the evidence was from unadjusted analyses of various predictors, but there was again a consistent effect for predicting virological breakthrough. For viral breakthrough, the same large retrospective study identified three HBeAg patterns based on monitoring at 2-monthly intervals and used multivariable analysis to examine the usefulness of these patterns in predicting virological breakthrough. A pattern of a continuous decrease to 90% levels followed by a progressive increase was a strong independent predictor, as was a pattern of no change or fluctuation in HBeAg levels, both in comparison with a pattern of continuously decreasing HBeAg levels to more than 90% of pretreatment values (moderate quality evidence). The time dependence of HBeAg in the group of people with virological breakthrough showed that the upturn in HBeAg levels started to occur around 32 weeks of therapy. Evidence was obtained from one small prospective study conducted in people receiving entecavir. This carried out separately multivariable analyses in people who were HBeAg positive and negative and for virological and serological responses at 12 and 24 months of treatment. Significant predictors were HBV DNA below 50 copies/ml at 3 or 6 months and HBsAg levels below 3000 IU/ml at 3 months. Three studies investigated people off-treatment, investigating monitoring to predict virological relapse in people who had achieved seroconversion /loss following discontinuation of lamivudine treatment: one small study conducted a multivariable analysis and showed that 'higher' HBV DNA levels at the time of discontinuing treatment and the time to seroconversion/loss were significant independent predictor). A univariate analysis in a small retrospective study suggested that HBV DNA level above 4.7×10^3 copies/ml at the time of seroconversion was a significant predictor of relapse at 6 and 12 months.
Economic considerations	The evidence for children and young people was non existent, however the GDG felt that increased frequency of monitoring in children is necessitated by a different physiology and increased potency of treatments in children. Therefore side effects and efficacy of treatments are less certain, necessitating increased monitoring.
Quality of evidence	For the lamivudine studies, the quality of the evidence was mainly low or very low with much of the information coming from small studies that did not conduct multivariable analyses. The exception to this was a large retrospective study that investigated the effect of time dependent patterns of HBeAg measurements; this was considered to be of moderate quality. However, there were consistent trends across studies which give more confidence in the evidence. For the remaining studies, evidence quality was low or very low: the study in entecavir, although conducting multivariable analysis had a low ratio of events/covariates, and the adefovir study was too small to be reliable.
Other considerations	Recommendations were based on the clinical evidence and GDG experience and expert opinion. The GDG did not recommend lamivudine as an option for the treatment of patients with CHB because of the early selection of resistance evident by sequencing (Thompson, Hsieh) and because of the cross-resistance to entecavir. However, in the absence of early stopping rules for entecavir, those

	rules identified for lamivudine may be informative. In HBeAg (-) patients, there are no useful data informing when antiviral therapy should be stopped which needs further research. The GDG was also aware of other studies which suggested that approximately 10% of HBeAg positive patients lost HBsAg after 5 years of NA treatment. The GDG believed that treatment may be stopped in these patients as there are rare reports of reacquisition of HBsAg after HBsAg loss. However, the optimal duration of nucleotide treatment after loss of HBsAg is unknown. With regard to the stopping of nucleos(t)ide treatment because of HBeAg seroconversion, the GDG thought that 6 months was too short a period because of the relatively high reversion rate, and recommended that treatment should be continued for at least 12 months after HBeAg seroconversion. Patients should then be monitored 6-monthly for signs of reversion (raised HBeAg, HBV DNA and ALT). If HBV DNA and ALT levels meet the requirements for treatment (recommendations 27 and 28), the treatment recommendations apply. The GDG noted the lack of evidence on monitoring in children and people with decompensated disease and decided to adopt similar recommendations based on the indirect evidence in adults with compensated disease.

12.2 Surveillance testing for HCC

12.2.1 Introduction

Hepatocellular carcinoma (HCC) is the most common form of liver cancer. The main cause of HCC varies by country and population but hepatitis B and C are both significant causes worldwide. In countries where HBV is endemic it usually results in being the main cause of HCC[91] . HBV-associated cirrhosis is a strong risk factor for HCC but 30 to 50% of HCC associated with HBV occurs in the absence of cirrhosis [5]. Risk factors for the development of HCC include male gender, a long duration of CHB, previous seroreversion from anti-HBe to HBeAg, core promoter mutations, and co-infections especially with hepatitis C and hepatitis D viruses [29,71] In particular high levels of HBV replication persisting for up to 3 to 4 decades significantly increases the risk of developing HCC.

Two tests are commonly used for periodic surveillance for HCC; alpha-fetoprotein and ultrasound scanning and have been examined in randomised trials comparing surveillance with no surveillance (in which there is an impact of surveillance plus subsequent treatment on mortality)[16,111]. HBV carriers at high risk for the development of HCC are likely to require periodic screening with one or both of these tests.

12.2.2 Review question: When and how frequently should surveillance testing be offered to detect early hepatocellular carcinoma in people with chronic hepatitis B?

For full details see review protocol in Appendix C.

Table 305: PICO characteristics of review question

Protocol	

Protocol	
Population	Children, young people and adults with CHB infection (particularly those with cirrhosis)
Intervention	Ultrasound and/or serum alpha feto-protein assay at: - 12 monthly - 6 monthly - 3 monthly
Comparison	Ultrasound and/or serum alpha-fetoprotein assay at: - 12 monthly - 6 monthly - 3 monthly
Outcomes	1. Lesion or hepatocellular carcinoma ≤1, 2 and 3cm in diameter 2. Survival rate 3. All-cause mortality 4. Liver cancer staging 5. Hepatocellular carcinoma 6. Morbidity (end stage liver failure)

12.2.3 Clinical evidence

We searched for randomised and observational studies comparing different intervals of surveillance testing [ultrasound (US) and/or serum alpha fetoprotein (AFP)] in detecting early hepatocellular carcinoma (HCC) in people with chronic hepatitis B infection. Implicit in the investigation of surveillance frequency is that patients who are detected in the earlier stages of HCC can be treated earlier with potentially better chance of survival. The guideline does not, however, cover management of people with HCC.

We intended to investigate the question in 3 ways: the best type of study design is one that involves a test and treat approach, comparing two strategies in a randomised design: so that patients are randomised to surveillance frequency 1 plus appropriate treatment versus surveillance frequency 2 plus appropriate treatment, and the impact on patient outcomes is investigated.

In the absence of RCTs of this type, we investigated the predictive ability of surveillance at different frequencies on patient outcomes, using multivariable analysis adjusting for other confounders. This type of study may include treatment as a confounding factor.

Finally, we considered the comparison of different surveillance frequencies for the detection of HCC lesions of different sizes.

A total of four studies (two are abstracts) have been identified and included in this review, of which two are randomised studies and the remaining two are retrospective cohort studies.

One RCT compared 3 monthly intervals versus 6 monthly intervals of HCC surveillance and a second cluster RCT compared 4 monthly intervals versus 12 monthly intervals of HCC surveillance; both RCTs were in patients who did not have HCC. Two studies compared 6 monthly intervals versus 12 monthly intervals of HCC surveillance; both were retrospective studies in patients who had HCC. Because there was limited data on a solely chronic hepatitis B population, studies containing mixed populations have been included. All four studies contained mixed populations, including hepatitis B,

hepatitis C and other non-HBV or HCV conditions (e.g. non-alcoholic steatohepatitis, primary biliary cirrhosis, and autoimmune hepatitis). Patients with cirrhosis are at a very high risk of developing HCC. Two studies had cirrhotic populations and the cirrhotic status of patients was unclear in the remaining two studies. Because the aim of this review is to examine the optimal timing/frequency of HCC surveillance and HCC surveillance is widely applied in clinical practice, studies comparing surveillance with no surveillance have been excluded.

The evidence was meta-analysed and GRADE was applied, where possible. Otherwise, the results are summarised in a narrative form. Forest plots can be found in appendix G.

12.2.3.1 Summary characteristics of included studies

Adults with CHB infection

Table 306: Summary characteristics of included studies

Included studies Study design Setting	N	Patient characteristics	Group 1	Group 2	Length of F/U	Outcomes
Trinchet JC et al. 2011 RCT (multi centre) France and Belgium	1278	12.5% HBV patients (44% HCV, 39% alcohol, 2% hemochromatosis) Patients with compensated cirrhosis and without HCC	Ultrasound (US) with or without alpha fetoprotein (AFP) at 6 monthly (n=638)	US with or without AFP at 3 monthly (n=640)	Median 47 months	1. Cumulative rate of focal lesion ≤1cm at 5 years 2. Cumulative incidence of hepatocellular carcinoma (HCC) at 2 and 5 years 3. Survival rate at 2 and 5 years 4. Mortality (all-cause and individual causes) 5.
Kim DY et al. 2007 Retrospective study (abstract) South Korea	400	Mostly HBV patients (72.3%) with HCC Cirrhotic status unclear	US and AFP at 6 monthly (n=219)	US and AFP at 12 monthly (n=181)	N/A	1. Frequency of solitary HCC ≤3cm 2. Survival rate at 5 years
Santi V et al. 2010 Retrospective study	649	HCC patients (Child-Pugh class A or B) 9.1% HBV	US with or without AFP at 6 monthly (n=510)	US with or without AFP at 12 monthly (n=139)	N/A	1. Median observed survival 2. Survival rates at year 1, 3 and 5

Included studies Study design Setting	N	Patient characteristics	Group 1	Group 2	Length of F/U	Outcomes
Italy		patients 41.8% cirrhosis				
Wang JH et al. 2011 Cluster RCT Taiwan	744	Patients with HBV or HCV, without HCC (% cirrhosis unclear; % HBV patients unclear)	US and AFP at 4 monthly (n=387)	US and AFP at 12 monthly (n=357)	Max. 4 years	8. Frequency of HCC ≤2cm 9. Cumulative HCC incidence at 3 years 10. Cumulative survival rate at 4 years 11. Proportion of HCC

Children with CHB infection

No relevant studies have been identified.

12.2.3.2 Different intervals of hepatocellular carcinoma (HCC) surveillance in detecting early HCC in CHB infected adults

6 monthly versus 12 monthly intervals of HCC surveillance

Two retrospective studies (one of which is an abstract) compared HCC surveillance testing in detecting early HCC every 6 months versus every 12 months, however, in only one of these studies were the majority of patients infected with chronic hepatitis B (72%) (Kim et al. 2007) and the other study had an indirect population with only 9.1% CHB infected patients (mostly hepatitis C patients, approximately 60%) (Santi et al. 2010). About 42% of the population in the Santi et al. study had cirrhosis. Kim et al. diagnosed HCC by both ultrasound and alpha-fetoprotein measurement and Santi et al. diagnosed HCC by ultrasound with or without alpha-fetoprotein measurement. Both studies included patients with HCC. Only the Santi et al study reported a multivariable analysis for the predictive ability of different frequencies of surveillance.

Table 307 shows the survival rates at year 1, 3 and 5 reported by the studies.

Table 307: Survival rates reported by the studies

Study	Survival rate	n	6 monthly	n	12 monthly	P value
Kim et al. 2007	5 year	219	25%	181	16%	**0.006**
Santi et al. 2010	1 year	510	85.4%	139	40.1%	-
	3 year		80.6%		37.5%	-
	5 year		57.2%		21.1%	-

Santi et al. also reported a median observed survival of 45 months (95%CI 40-50) in the 6 monthly surveillance group, and 30 months (95%CI 24-36) in the 12 monthly surveillance group (p=0.001).

Table 308 shows the outcomes comparing 6 monthly versus 12 monthly intervals of HCC surveillance, reported by Santi et al.

Table 308: Comparison of outcomes in 6 monthly and 12 monthly intervals of HCC surveillance (Santi et al, 2010)

	n	Group 1 6 monthly surveillance	n	Group 2 12 monthly surveillance	P value
Solitary HCC ≤2cm	497	120 (24.1%)	137	7 (5.1%)	-
Solitary HCC ≤3cm		214 (43%)		29 (21.2%)	-
Median tumour size (range), cm (N=622)		2.5 (0.2-18)		3.3 (0.8-11)	**<0.001**

*Median observed survival adjusted for lead time (the length of time between detection of a disease and its usual clinical presentation and diagnosis) was reported in the 6 monthly HCC surveillance group but was not reported in the 12 monthly HCC surveillance group.

Multivariable analyses showed that 12 monthly intervals HCC surveillance was associated with a statistically significant increased risk of HCC beyond the very early stage (Table 309) and mortality (Table 310), compared to 6 monthly intervals HCC surveillance.

Table 309: Univariate and multivariate analysis for HCC beyond the very early stage (defined as solitary nodule >2cm or multinodular tumour with or without vascular invasion and/or metastases) in patients with HCC and 9% HBV (Santi et al. 2010)

	Univariate analysis P value	Multivariate* analysis Odds ratio (95%CI)
Surveillance		
Semiannual (6 monthly)	**<0.001**	1.0
Annual (12 monthly)		5.99 (2.57-13.98)
Alpha feto-protein		
≤20 ng/ml	0.091	1
21-200ng/ml		0.91 (0.59-1.41)
>200ng/ml		2.58 (1.17-5.69)

**Adjusted for age, platelet count, alpha-fetoprotein, Child-Pugh class and oesophageal varices*

Table 310: Univariate and multivariate analysis for mortality (Santi et al. 2010)

	Univariate analysis P value	Multivariate* analysis hazard ratio (95%CI)
Surveillance		
Semiannual (6 monthly)	**0.028**	1
Annual (12 monthly)		1.39 (1.05-1.82)
Alpha feto-protein		
≤20 ng/ml	**<0.001**	1
21-200ng/ml		1.32 (1.03-1.70)
>200ng/ml		1.77 (1.27-2.46)

**Adjusted for age, platelet count, alpha-fetoprotein, Child-Pugh class, cancer stage and all treatments other than OLT.*

Table 311: Comparison of 6 monthly versus 12 monthly intervals of hepatocellular carcinoma surveillance – clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 monthly HCC surveillance Frequency (%)	12 monthly HCC surveillance Frequency (%)	Relative Risk (95% CI)	Absolute	
% of patients with solitary hepatocellular carcinoma ≤3cm										
2 Kim 2007 Santi 2010	Observational studies	Very serious [a,b]	Very serious inconsistency [c]	Serious indirectness [d]	Serious imprecision [e]	350/716 (48.9%)	122/318 (38.4%)	RR 1.46 (1.24 to 1.73)	176 more per 1000 (from 92 more to 280 more)	VERY LOW
% of patients with solitary hepatocellular carcinoma ≤3cm (sensitivity analysis including studies with majority HBV patients)										
1 Kim 2007	Observational study	Very serious [a,b]	No serious consistency	No serious indirectness	Serious imprecision [e]	136/219 (62.1%)	93/181 (51.4%)	RR 1.21 (1.01 to 1.44)	108 more per1000 (from 5 more to 226 more)	VERY LOW
% of patients with solitary hepatocellular carcinoma ≤3cm (sensitivity analysis including studies with a small proportion of HBV patients)										
1 Santi 2010	Observational study	Serious [a]	No serious consistency	Serious indirectness [d]	No serious imprecision	214/497 (43.1%)	29/137 (21.2%)	RR 2.03 (1.45 to 2.85)	218 more per1000 (from 95 more to 392 more)	VERY LOW

(a) Retrospective design, prone to selection bias, lead time bias and length bias.
(b) Inadequate information on patient characteristics and unclear diagnostic method of hepatocellular carcinoma in one study (Kim 2007). Further information about the study will be requested from the authors [pending].

(c)Substantial heterogeneity, I^2=88% (p=0.004).
(d) Mostly hepatitis B patients (>70%) in one study and 9.1% hepatitis B patients in another study.
(e) The confidence interval is consistent with two clinical decisions; appreciable benefit and no appreciable benefit or harm.

6 monthly versus 3 monthly intervals of HCC surveillance

One multi-centre prospective randomised trial (Trinchet et al. 2011) of 1,278 patients with histologically confirmed compensated cirrhosis (100%). Patients were randomised into two groups, 6 monthly and 3 monthly intervals of HCC surveillance. 12.5% of the population were chronic hepatitis B patients, the remainder comprised of hepatitis C (44.1%) and other aetiologies of cirrhosis (including alcohol-related, autoimmune hepatitis etc).

Error! Not a valid bookmark self-reference. shows that survival rates in both groups were very similar at year 2 and 5. Table 313 shows different outcomes associated with HCC surveillance at 6 monthly and 3 monthly frequencies. An increased number of focal lesions ≤1cm in diameter was observed in the 3 monthly group compared to the 6 monthly group over 5 years (5-year cumulative incidence of 41% vs. 28%, respectively; p=0.002).

Table 312: Survival rates at 2 and 5 years after a median follow up of 47 months

	Group 1 (n=638) US at 6 months	**Group 2 (n=640) US at 3 months**	**P value**
Survival rate			
24 months	93.5%	95.8%	-
60 months	85.8%	84.9%	-

Table 313: Comparison of outcomes in 6 monthly and 3 monthly intervals of HCC surveillance, after a median follow up of 47 months

	Group 1 (n=638) US at 6 months	**Group 2 (n=640) US at 3 months**	**P value**
Cumulative incidence of first focal lesion			
24 months	13.2%	20.4%	-
60 months	32.8%	35.5%	-
Cumulative incidence of HCC			
24 months	2.7%	4%	-
60 months	12.3%	10%	-
Prevalence of HCC ≤3cm	70% (95%CI 59-81%)	79% (95% CI 69-90%)	-
Cumulative incidence of HCC ≤3cm	9.1%	7.8%	0.48
Diameter of the first focal lesion (mm)	N=156	N=178	
≤10	43 (28%)	73 (41%)	
11-20	78 (50%)	71 (40%)	
21-30	23 (15%)	23 (13%)	
31-50	7 (4%)	7 (4%)	
≥51	5 (3%)	4 (2%)	
Cumulative incidence of focal lesions ≤10mm in diameter			
60 months	28%	41%	**0.002**

Table 314: Comparing 6 monthly versus 3 monthly intervals of hepatocellular carcinoma surveillance – clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	6 monthly HCC surveillance Frequency (%)	3 monthly HCC surveillance Frequency (%)	Relative Risk (95% CI)	Absolute	
% of patients with hepatocellular carcinoma (median of 47 months follow up)										
1 Trinchet 2010	Randomised trial	No serious [a]	No serious inconsistency	Very serious indirectness [b]	Serious imprecision [c]	70/638 (11%)	53/640 (8.3%)	RR 1.32 (0.94 to 1.86)	27 more per 1000 (from 5 fewer to 71 more)	VERY LOW
Mortality (median of 47 months follow up)										
1 Trinchet 2010	Randomised trial	No serious [a]	No serious inconsistency	Very serious indirectness [b]	Serious imprecision [c]	82/638 (12.9%)	72/640 (11.3%)	RR 1.14 (0.85 to 1.54)	16 more per 1000 (from 17 fewer to 61 more)	VERY LOW
Mortality from liver failure (median of 47 months follow up)										
1 Trinchet 2010	Randomised trial	No serious [a]	No serious inconsistency	Very serious indirectness [b]	Serious imprecision [c]	34/638 (5.3%)	24/640 (3.8%)	RR 1.42 (0.85 to 2.37)	16 more per 1000 (from 6 fewer to 51 more)	VERY LOW
Mortality from hepatocellular carcinoma (median of 47 months follow up)										
1 Trinchet 2010	Randomised trial	No serious [a]	No serious inconsistency	Very serious indirectness [b]	Serious imprecision [d]	12/638 (1.9%)	17/640 (2.7%)	RR 0.71 (0.34 to 1.47)	8 fewer per 1000 (from 18 fewer to 12 more)	VERY LOW

(a) Adequate randomisation procedure and allocation concealment. Did not provide reasons for loss to follow up (small percentage of loss to follow up).
(b) Mixed population with a small proportion of chronic hepatitis B patients (12.5%).

(c) The confidence interval is consistent with two clinical decisions; appreciable clinical benefit and no appreciable clinical benefit or harm.
(d) The confidence interval is consistent with three clinical decisions; appreciable benefit, no appreciable benefit or harm and appreciable harm.

4 monthly versus 12 monthly intervals of HCC surveillance

One cluster RCT (abstract) (Wang et al. 2011) of 744 patients (mixed population of HBV and HCV, unclear proportion) comparing HCC surveillance every 4 months with every 12 months. Ultrasound and alpha-fetoprotein were used for HCC surveillance. Table 315 shows no statistical difference in 4-year survival rate in the two groups; with a risk ratio (ignoring cluster effects) of 1.06 (95%CI 0.90 to 1.25). Compared with 12 monthly HCC surveillance, there were significantly more patients with tumour size ≤2cm in the 4 monthly group (p=0.003) (Table 316). There was no significant difference in cumulative 3-year hepatocellular carcinoma incidence between the two groups (p=0.198). A significantly greater proportion of patients in the 4 monthly intervals surveillance group had tumour size ≤2cm, compared to those in the 12 monthly intervals surveillance group (Table 316).

Table 315: Cumulative survival rate at 4 years

	Group 1 4 monthly surveillance (n=387)	**Group 2 12 monthly surveillance (n=357)**	**P value**
Survival rate 4 years	45.3%	42.7%	0.38

Table 316: Comparison of outcomes in 4 monthly and 12 monthly intervals of HCC surveillance (measured at 4 years follow up, unless specified)

	Group 1 4 monthly surveillance (n=387)	**Group 2 12 monthly surveillance (n=357)**	**P value**
HCC, n	24	15	-
Cumulative 3 year HCC incidence	11.7%	9.7%	0.198
Tumour size ≤2cm	-	-	**0.003**
Mean tumour size (SD), cm	1.9 (0.7)	2.9 (1.5)	**0.006**

Table 317: Comparing 4 monthly versus 12 monthly intervals of HCC surveillance – clinical study characteristics and clinical summary of findings

Quality assessment						Summary of findings				
								Effect		Quality
Authors	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	4 monthly HCC surveillance Frequency (%)	12 monthly HCC surveillance Frequency (%)	Relative Risk (95% CI)	Absolute	
% of patients with hepatocellular carcinoma (4 years follow up)										
1 Wang 2011	Cluster randomised trial	Serious [a]	No serious inconsistency	Serious indirectness [b]	Serious imprecision [c]	24/387 (6.2%)	15/357 (4.2%)	RR 1.48 (0.79 to 2.77)	20 more per 1000 (from 9 fewer to 74 more)	VERY LOW
% of patients surviving (4 years follow up)										
1 Wang 2011	Cluster randomised trial	Serious [a]	No serious inconsistency	Serious indirectness [b]	Serious imprecision [c]	175/387 (45.3%)	152/357 (42.7%)	RR 1.06 (0.90 to 1.25	26 more per 1000 (from 43 fewer to 107 more)	VERY LOW

(a) no information on patient characteristics; unclear diagnostic method of hepatocellular carcinoma. Further information about the study will be requested from the authors [pending].
(b) Mixed population of hepatitis B and C (proportions unclear). Further information about the study will be requested from the authors [pending].
(c) The confidence interval is consistent with two clinical decisions; appreciable benefit and no appreciable benefit or harm.

12.2.4 Economic evidence

Published literature

One study was identified that evaluated the cost-effectiveness of surveillance testing to detect early hepatocellular carcinoma (HCC) in people with chronic hepatitis B.[92] This study is summarised in the economic evidence profile below (Table 318).

The HTA study suggests that 6 monthly surveillance is cost effective compared with annual surveillance with serum AFP triaging and possibly with AFP and ultrasound given a slightly higher threshold of £30,000 per QALY gained. This goes some way towards suggesting that more frequent surveillance in patients with cirrhosis could be cost effective. The study did not evaluate the cost effectiveness of 3 monthly programmes so it is difficult to draw conclusions on the cost effectiveness of 3 monthly versus 6 monthly surveillance. However, because 6 monthly surveillance with US and AFP is over the £20,000 per QALY threshold, it is unlikely that 3 monthly surveillance with US and AFP would be cost effective but it may be cost effective if it managed to pick up many more cancers at an early stage.

The study was, however, limited by the data available, the main inputs for the model were not meta analysed due to the fact that there were no studies to meta analyse. The study did not examine shorter than 6 monthly surveillance strategies, such as 3 month intervals in cirrhotic patients which limits the paper's ability to answer this question. It did not focus on non-cirrhotic patients. The analysis is diluted by the fact that HBV-infected patients represented only a subgroup in the analysis and that some of the more advanced statistics were only performed on the population as a whole and not on the HBV population specifically.

The question remains unanswered by the economic evidence presented here, but it does suggest that 6 monthly surveillance is superior than 12 monthly surveillance for HCC in Hep B infected patients with cirrhosis at a threshold of £20-30,000 per QALY. The question of what to do with non-cirrhotic patients is not answered by any of this evidence.

Table 318: Economic evidence profile: Surveillance testing to detect early hepatocellular carcinoma (HCC) in people with chronic hepatitis B

Study	Applicability	Limitations	Other comments	Incremental cost vs previous strategy	Incremental effects	Cost effectiveness (£ per QALY)	Uncertainty
Thompson 2007 [92]	Partially applicable [(a)]	Minor limitations [(b)]	Study was a well conducted analysis of HCC surveillance in	Intvn 2 vs 1: £2,100	Intvn 2 vs 1: 0.211	Intvn 2 vs 1: 10,200	The cost effectiveness acceptability curve shows that 6 monthly

Study	Applicability	Limitations	Other comments	Incremental cost vs previous strategy	Incremental effects	Cost effectiveness (£ per QALY)	Uncertainty
			cirrhotic patients. **Intvn 1:**No surveillance **Intvn 2:** Annual surveillance using AFP triage (Alpha-fetoprotein test as a triage test leading to more sensitive tests.) **Intvn 3:**Annual surveillance using ultrasound alone **Intvn 4:** Annual surveillance using AFP and ultrasound **Intvn 5:** 6-monthly surveillance using AFP triage **Intervention 6:** 6-monthly surveillance using ultrasound alone **Intervention 7:** 6-monthly surveillance using AFP and ultrasound	Intvn 3 vs 2: £2,500 Intvn 4 vs 3: £3,100 Intvn 5 vs 4: £3,400 Intvn 6 vs 5: £4,000 Intvn 7 vs 6: £4,700	Intvn 3 vs 2: 0.208 Intvn 4 vs 3: 0.261 Intvn 5 vs 4: 0.310 Intvn 6 vs 5: 0.306 Intvn 7 vs 6: 0.358	Intvn 3 vs 2: Dominated Intvn 4 vs 2: Extended dominated Intvn 5 vs 2: 12,700 Intvn 6 vs 5: Dominated Intvn 7 vs 5: 26,800	surveillance with US and AFP is only cost effective in 10% of the simulations when using a £20,000 per QALY threshold. The AFP triage strategy at 6 months is the cost effective strategy at £20,000 per QALY threshold. The analysis showed similar results in PSA and deterministic results.

(a) Paper did not look at the possibility of 3 monthly surveillance in cirrhotic patients, population was only partially applicable.
(b) There was a lack of meta-analysed data, the threshold used was £30,000, above the usual cost effectiveness threshold applied by NICE guideline

Unit costs

Surveillance method	Cost (from 2007 HTA) [92]
Ultrasound	£50 (£26 to £100)
Alpha-fetoprotein	£4 (£2 to £8)

Source/Note: *Average based on the costs reported by the hospitals where the mild hepatitis C trial was conducted.*[102]

12.2.5 Evidence statements

12.2.5.1 Clinical evidence statements

6 monthly versus 12 monthly intervals of HCC surveillance

One observational study of 400 patients (72% hepatitis B; unclear cirrhotic status) suggested that 6 monthly intervals of HCC surveillance (ultrasound and alpha-fetoprotein) maybe beneficial for identifying a greater proportion of patients with solitary HCC ≤3cm compared to 12 monthly intervals of HCC surveillance (VERY LOW QUALITY).

One observational study of 634 patients (9.1% hepatitis B; 42% patients with cirrhosis) showed that 6 monthly intervals of HCC surveillance (ultrasound +/- alpha-fetoprotein) is beneficial for identifying a greater proportion of patients with solitary HCC ≤3cm compared to 12 monthly intervals of HCC surveillance (VERY LOW QUALITY).

3 monthly versus 6 monthly intervals of HCC surveillance

One randomised study of 1278 patients with compensated cirrhosis (12.5% hepatitis B) suggested that 3 monthly intervals of HCC surveillance (ultrasound +/- alpha-fetoprotein) may be neither beneficial nor harmful on the following outcomes, compared to 6 monthly intervals of HCC surveillance at a median follow up of 47 months:

- Proportion of patients with hepatocellular carcinoma (VERY LOW QUALITY)
- Mortality (VERY LOW QUALITY)
- Mortality from liver failure (VERY LOW QUALITY)
- Mortality from HCC (VERY LOW QUALITY)

4 monthly versus 12 monthly intervals of HCC surveillance

One cluster randomised study of 744 patients (mixed population of hepatitis B and C, proportions unclear; unclear cirrhotic status) suggested that 4 monthly intervals of HCC surveillance (ultrasound and alpha-fetoprotein) may be neither beneficial nor harmful in reducing the proportion of patients with hepatocellular carcinoma, compared to 12 monthly intervals of HCC surveillance at 4 years of follow up (VERY LOW QUALITY).

12.2.6 Recommendations and Links to evidence

Recommendations	**96. Perform 6-monthly surveillance for HCC by hepatic ultrasound and alpha-fetoprotein testing in people with significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage**

	greater than or equal to 3) or cirrhosis. **97. In people without significant fibrosis or cirrhosis (METAVIR stage less than F2 or Ishak stage less than 3), consider 6-monthly surveillance for HCC if the person is older than 40 years and has a family history of HCC and HBV DNA greater than or equal to 20,000 IU/ml.** **98. Do not offer surveillance for HCC in people without significant fibrosis or cirrhosis (METAVIR stage less than F2 or Ishak stage less than 3) who have HBV DNA less than 20,000 IU/ml and are younger than 40 years.**
Relative values of different outcomes	The GDG addressed this question in 3 ways: (1) comparing test and treat strategies and their impact on patient outcomes; (2) the predictive ability of surveillance at different frequencies on patient outcomes; and (3) the effect of frequency on the detection of HCC lesions of different sizes (diagnosis). The GDG recognised that approach 2 could be confounded by treatments given. They considered the following outcomes to be critical for decision making. • All-cause mortality • Overall survival • Lesion or hepatocellular carcinoma <1,2 and 3 cm in diameter • The GDG noted that the third approach to the question relied on ultrasound findings and/or alpha fetoprotein levels being accurate diagnostic tests of HCC, and also assumed that the very small lesions would grow into larger HCC lesions giving rise to a poor prognosis. On the other hand, the accuracy of the tests was not expected to directly influence the effect of frequency on patient outcomes: if the tests were not sufficiently accurate, the discrimination between frequencies would be reduced. Therefore, the GDG placed greater weight on the patient outcomes.
Trade off between clinical benefits and harms	Performing hepatocellular carcinoma surveillance at appropriate time intervals in high risk chronic hepatitis B infected patients, particularly those with cirrhosis, can detect early nodules of a certain size or diameter. This allows clinicians to perform further diagnostic testing for hepatocellular carcinoma and detect early stages of HCC. This leads to earlier treatment and may improve overall survival. The GDG noted that this form of cancer develops quickly and may be asymptomatic until later stages, at which point the prognosis is poor. Therefore, it is important to detect nodules while still small for treatment to be effective. There are potential issues when considering the appropriate intervals for HCC surveillance. If the intervals are too long, this may delay diagnosis of hepatocellular carcinoma and affect survival. If HCC surveillance is more frequently performed there will be an associated increase in cost. In addition, small lesions are more difficult to detect using ultrasound and may not develop into malignant HCC. Therefore, too frequent surveillance intervals could be inaccurate. Evidence from one RCT in a (compensated) cirrhotic population with 12.5% CHB showed no clinically important difference in terms of all cause mortality or HCC mortality, but there were more lesions ≤1cm diameter detected in the 3 monthly surveillance group. In a second cluster RCT, patients in the 12 monthly surveillance group had a larger mean tumour size (and fewer patients with tumour size ≤2cm) compared to those in the 4 monthly surveillance group. There was potential for a clinically important difference in survival at 4 years, favouring the 4 monthly surveillance. Evidence from one retrospective cohort study in patients with HCC suggested that 6 monthly HCC surveillance could detect a larger proportion of patients

	with HCC ≤3cm diameter (suitable candidate for curative treatments/ liver transplantation, according to the Barcelona Clinical Liver Cancer and Milan criteria). In the same study, 12 monthly HCC surveillance was associated with a 39% increased risk of mortality compared to 6 monthly HCC surveillance, using multivariable analysis. In addition, the GDG agreed that chronic hepatitis B infected patients with significant fibrosis or cirrhosis should be offered HCC surveillance regardless of age and other risk factors, as significant fibrosis or cirrhosis is such a substantial risk factor for hepatocellular carcinoma. Hepatocellular carcinoma also occurs in non-cirrhotic hepatitis B patients; however, the prevalence is relatively low. Therefore, HCC surveillance should not be considered in this group of patients unless they have other risk factors.
Economic considerations	Shorter surveillance intervals must be weighed against the cost of testing and the risk of developing the disease for some populations. There are two modalities of surveillance testing for HCC: imaging and serologic. In England and Wales, ultrasonography (US) and serum AFP has been the mainstay method for surveillance of HCC. Based on the clinical evidence, the GDG agreed that 6 month surveillance intervals lead to improved outcomes compared to surveillance testing every 12 months. According to the economic evidence, 6 month intervals are also likely to be more cost-effective than 12 month intervals at a threshold of £20, 000 per QALY gained. Based on expert opinion, the GDG agreed that surveillance testing is likely to be most cost-effective in populations that are at an increased risk of developing HCC. In less risky populations, it is unlikely to represent an effective use of NHS resources. Based on the clinical evidence, the group agreed that a shorter surveillance interval (e.g. 3 months) would double costs without improving outcomes and therefore should not be recommended.
Quality of evidence	Data of most included studies are based on mixed (indirect) populations, with small proportions of hepatitis B patients except for one study (Kim 2007), which included over 70% hepatitis B patients. There was one randomised trial (Trinchet et al 2011) comparing 3 with 6 months intervals, and one cluster randomised trial (Wang 2011) comparing 4 with 12 months. The remaining studies were observational studies of very low quality (Kim 2007; Santi 2010). Studies particularly of retrospective design are prone to selection bias and lead time bias. Two studies have taken lead time bias into account in the statistical analysis (Santi 2010 and Trinchet 2011). There is limited data examining the optimal interval of hepatocellular carcinoma in the hepatitis B population. Authors were contacted for further information (e.g. general information about the study, subgroup data if any) about the published articles/abstracts.
Other considerations	No study has been identified for children. Two studies examined HCC surveillance using both ultrasound and alpha-fetoprotein and the remaining two studies examined HCC surveillance using ultrasound with or without alpha-fetoprotein measurement. The GDG considered that both ultrasound and alpha-fetoprotein are currently used in clinical practice. The accuracy of ultrasound is highly dependent on the operator and alpha-fetoprotein level fluctuates greatly; therefore, the combination of the two could enhance the accuracy of the detection of early hepatocellular carcinoma. The GDG also took into consideration further information in the Trinchet 2011 RCT regarding very small HCC lesions: these were sometimes difficult to identify (for example, in the presence of fibrosis and fatty infiltration), and did not always develop into more advanced cancers. The GDG therefore placed more reliance on the effect of frequency on mortality in determining

	appropriate surveillance times. For this reason, they did not wish to recommend a periodicity of less than 6 months, because they thought that the increased incidence of "HCC" at shorter times, with its preponderance of lesions less than 10mm, could be unreliable. However, the GDG considered that a 6 month period was appropriate and decided that the very low quality evidence - showing a significant effect on mortality of 6 versus 12 monthly surveillance - was consistent with their experience. They were of the opinion that development of HCC lesions from very small to untreatable could occur in 12 months and they wanted to avoid this possibility by recommending a 6 month surveillance frequency. Finally, the guideline does not make recommendations for the subsequent management of detected HCC lesions, but it is likely that further monitoring/testing would take place before treatment. The GDG considered persistently high HBV DNA replication, age and family history of HCC to be relatively important risk factors that might trigger HCC surveillance. Age is an important factor as it is a surrogate to reflect the duration of infection and the extent of accumulated liver damage. The decision to consider surveillance for those without significant fibrosis or cirrhosis over the age of 40 was based on GDG clinical expert opinion as it was agreed that although HCC can occur in younger patients, the efficacy of offering HCC surveillance to all patients less than 40 years is likely to be low. Persistently high HBV DNA viral load indicates active disease and progressive liver damage and therefore risk of developing HCC is elevated. The GDG thought that family history of HCC is a well-established high risk factor for HCC. The GDG considered other factors that should be taken into account when assessing individual patients, as they influence the risk of developing hepatocellular carcinoma include ethnicity (risk of hepatocellular is greater in people of African or Asian family origin) and duration of infection, (risk higher in those neonatal and childhood infection). The GDG also recognised that there are some at-risk groups that may deviate from the recommendations and clinical opinion is needed by physicians when assessing individual patients.

13 Acronyms and abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
Anti - HBe	Hepatitis B e antigen antibody
Anti - HBs	Hepatitis B surface antigen antibody
Anti – HCV	Hepatitis C virus antibody
Anti – HDV	Hepatitis Delta virus antibody
Anti – HIV	Human immunodeficiency virus antibody
GGT	Gamma-glutamyl transferase
HBeAg	Hepatitis B e antigen
HBIG	Hepatitis B immune globulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis Delta virus
HIV	Human immunodeficiency virus
NUCs	Nucleos(t)ides

14 Glossary

Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Acute	A short sharp illness that may be severe but from which most people will recover from in a few weeks without lasting effects.
Albumin	The main protein in human blood, manufactured by the liver. Low albumin levels are an indication of liver damage.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
ALT	Stands for alanine aminotransferase, a liver enzyme that enters the blood following liver damage. An ALT test is used to monitor and assess the degree of damage in patients infected with chronic HBV.
Antigen	A substance (it may be part of a virus) which is recognised by the body as foreign so the body's immune defence can react by producing antibodies
Antibody	A specific immunoglobulin (protein) produced by the body as part of a defence reaction against an invading substance (antigen).
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm
Ascites	Accumulation of fluid in the cavity which surrounds the bowel, leading to enlarged, swollen and painful abdomen
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
AST	Stands for aspartate aminotransferase, a liver enzyme but less specific to the liver than ALT
Autoimmune	A type of disease causing the body's immune system to attack another part of the body
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.

Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Bile	A yellow/green fluid made by the liver to help digest foods containing fat and cholesterol
Bilirubin	A breakdown product of haemoglobin. Increases of bilirubin in the blood can indicate liver disease, especially in disease of the bile ducts
Blinding	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case-series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Cirrhosis	Where inflammation and fibrosis have spread to disrupt the shape and function of the liver. Even with no signs or symptoms of liver disease, the working capacity of liver cells has been badly impaired and they are unable to repair the liver. This is permanent cell damage and can lead to liver failure or liver cancer.
Chronic	An illness that lasts a long time (more than six months), possibly for the rest of a person's life
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of

	exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Co-infection	Being infected with more than one virus at the same time
Comorbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Compensated disease	Where medical treatment has counterbalanced damaged liver function. Decompensated disease is where treatment can no longer counterbalance severely damaged liver fundtion, leading to liver failure.
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Consensus methods may used when there is a lack of strong evidence on a particular topic.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) – in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness	An economic study design in which consequences of different

analysis (CEA)	interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Credible Interval	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Encephalopathy	Disturbed brain function leading to mental confusion and memory loss
Enzyme	A substance, usually a protein, produced by the body to help speed up a chemical reaction (which can be measured with liver function tests).
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.
EQ-5D (EuroQol-5D)	A standardise instrument used to measure a health outcome. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is

	obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Fibrosis	Where scar tissue is formed in an inflamed liver. Fibrosis can take a variable time to develop and, even with scar tissue present, the liver keeps on functioning quite well. However, continued build up of scar tissue may lead to cirrhosis
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Fulminant	A type of disease with rapid onset and follows a short, severe course.
Gastroenterologist	A doctor who specialises in treating digestive diseases
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Glycogen	Stored in the liver and muscles, glycogen is the way the body stores carbohydrates. It is easily changed back to glucose when the body needs energy quickly.
Gold standard See 'Reference standard'.	GRADE / GRADE profile A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
HAV	Stands for Hepatitis A virus

HBsAg seroconversion	The development of antibodies against HBsAg is known as HBsAg seroconversion. It signifies clearance of HBsAg and resolution of the chronic infection.
HBV	Stands for Hepatitis B Virus
HBV DNA	HBV DNA level, or 'viral load', is an indicator of viral replication. Higher HBV DNA levels are usually associated with an increased risk of liver disease and hepatocellular carcinomaHCC. HBV DNA level typically falls in response to effective antiviral treatment
HCC	Stands for hepatocellular carcinoma, also called hepatoma. With biliary tree cancer, HCC is one of the two main types of primary liver cancer.
HCV	Stands for Hepatitis C Virus
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life (HRQoL)	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Hepatic	Anything related to the liver
Hepatic artery	The artery that carries blood to the liver, pancreas, gallbladder, stomach and duodenal portion of the small intestine.
Hepatitis	Any inflammation of the liver known as hepatitis, whether its cause is viral or not. A sudden inflammation of the liver is known as acute hepatitis. Where inflammation of the liver lasts longer than six months the condition is known as chronic hepatitis.
Hepatitis B e antigen (HBeAg)	Hepatitis B e antigen (HBeAg) is an indicator of viral replication, although some variant forms of the virus do not express HBeAg (see 'HBeAg-negative chronic hepatitis B' below). Active infection can be described as HBeAg-positive or HBeAg-negative according to whether HBeAg is secreted.
HBeAg-negative	HBeAg-negative hepatitis B is a form of the virus that does not cause infected cells to secrete HBeAg. People can be infected with the HBeAg-negative form of the virus from the beginning, or the viral mutation can emerge later in the course of infection in people initially infected with the HBeAg-positive form of the virus.
HBeAg seroconversion	HBeAg seroconversion occurs when people infected with the HBeAg-positive form of the virus develop antibodies against the 'e' antigen. The seroconverted disease state is referred to as the 'inactive HBV carrier state' when HBeAg has been cleared, anti HBe is present and HBV DNA is undetectable or <2000 IU/ml. Once seroconversion has taken place, most people remain in the inactive HBV carrier state (immune control phase). However, increasing HBV DNA and recurrent hepatitis after seroconversion indicate the emergence of the HBeAg-negative strain of the virus (immune escape phase).

Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antigen (HBsAg) is a viral protein detectable in the blood in acute and chronic hepatitis B infection.
Hepatocyte	A liver cell
Hepatologist	A doctor who specialises in liver disease
Heterogeneity Or lack of homogeneity.	The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Immunoglobulins	Large proteins found in body fluids and cell tissues that bind to invading organisms, such as bacteria or viruses, to destroy them.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inflammation	The first response of the immune system to infection, commonly characterised by heat, swelling, pain and tenderness.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
Incremental cost effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention to treat analysis (ITT)	A strategy for analysing data from a randomised controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomisation and which may reflect non-adherence to the protocol.

Intervention	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Intraoperative	The period of time during a surgical procedure.
Jaundice	A condition in which the whites of the eyes go yellow and in more severe cases the skin also turns yellow. This is caused by the build up of bilirubin (containing yellow pigment) which is normally disposed of by the liver.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by 1- specificity.
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV) [In screening/diagnostic tests:]	A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct.
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening

	in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Oesophagus	The gullet. This important part of the digestive system is a tube through which food and liquid travels from the mouth to the stomach.
Opportunity cost	The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
P-value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Perioperative	The period from admission through surgery until discharge, encompassing the pre-operative and post-operative periods.
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Polypharmacy	The use or prescription of multiple medications.
Positive predictive value (PPV)	In screening/diagnostic tests: A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct. It is calculated as follows:
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	For diagnostic tests. The proportion of patients with that particular test result who have the target disorder (post test odds/[1 + post-test odds]).
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	For diagnostic tests. The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a

	range of services provided by general practitioners, nurses, dentists, pharmacists, opticians and other healthcare professionals.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Publication bias	Also known as reporting bias. A bias caused by only a subset of all the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (e.g. only outcomes or sub-groups where a statistically significant difference was found.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Quick Reference Guide	An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC)	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity Is plotted against 1-specificity. A perfect test will have a

curve	positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Reporting bias	See publication bias.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.
Sensitivity	Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the proportion of true cases that the test detects. See the related term 'Specificity'
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models

	based on decision analytical techniques (For example, Monte Carlo simulation).
Seroconversion	A change in the blood test so that something related to the virus appears. This may be an antigen, an antibody or the virus itself.
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).
Specificity	The proportion of true negatives that a correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Treatment allocation	Assigning a participant to a particular arm of the trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.
Varices	Dilated (expanded) and protruding blood vessels that run along the wall under the lining of the upper part of the stomach and lower end of the gullet,
Viral load	The amount of virus in the blood
Virus	A microscopic particle that infects living cells by getting inside them and replicating. Viruses cannot reproduce by themselves and can only multiply from within the cells of their living host.

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Appendices A–O are in a separate file.