Breastfeeding While Taking Lamivudine or Tenofovir Disoproxil Fumarate: A Review of the Evidence

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(See the Editorial Commentary by Rosenthal on pages 279–80.)

Lamivudine and tenofovir disoproxil fumarate (TDF) are both active against hepatitis B virus (HBV). Due to its potency, high genetic barrier to resistance, and safety during pregnancy, TDF may be useful to prevent HBV transmission from mother to child, which is the leading cause of transmission globally. Despite the safety record of lamivudine and TDF in pregnancy, the labels for both of these drugs recommend against their use during breastfeeding. In this review, we discuss the data regarding lamivudine and TDF use during pregnancy and breastfeeding and find that the exposure to the drug is lower from breastfeeding than from in utero exposure. Thus, the data do not support the contraindication to their use during breastfeeding.

Keywords. lamivudine; tenofovir; hepatitis B; breastfeeding.

Despite global promotion of hepatitis B immunization programs over the past 2 decades, chronic hepatitis B virus (HBV) infection and its complications, cirrhosis and hepatocellular carcinoma, remain an important medical problem affecting approximately 400 million people worldwide [1]. The major mode of transmission today is maternal–child despite recommendations for prophylaxis with monovalent HBV vaccine and hepatitis B immunoglobulin (HBIg) at birth. When vaccine and HBIg are administered according to World Health Organization (WHO) guidelines, failure of the current immunoprophylaxis regimen occurs in 8%–32% of mothers who have the highest risk of transmitting HBV—that is, women with HBV DNA approximately

10^7 IU/mL or higher [2]. For these women with high HBV DNA, antiviral therapy has been successful during the third trimester of pregnancy as an adjunct to HBV vaccine and HBIg, with studies suggesting very high efficacy with this strategy [3]. Continued antiviral therapy after delivery is needed in certain situations, for example, when anti-HBV treatment is necessary or to minimize flares postnatally while the immune system is returning to its prepregnancy state [4]. Although evidence has accumulated on the efficacy and safety of 2 anti-HBV drugs during pregnancy, tenofovir disoproxil fumarate (TDF) and lamivudine, their safety during breastfeeding has not been well studied. As a result, the drug labels do not recommend breastfeeding during the use of either of these drugs, which is problematic as breastfeeding is advantageous, especially in low-income countries where HBV is highly endemic. However, this recommendation is somewhat counterintuitive because infants are likely exposed to higher doses of drug in utero than they are through breast milk, but these drugs are recommended for use during pregnancy. Moreover, WHO human immunodeficiency virus (HIV) guidelines state that women who are HIV infected should

continue antiretroviral treatment while breastfeeding, with TDF as one of the recommended drugs (http://www.who.int/hiv/pub/guidelines/arv2013/art/artpregnantwomen/en/). With increasingly more data available from the HIV literature on lamivudine and TDF use during pregnancy and breastfeeding, it is necessary to summarize the evidence and reconsider the recommendation against the use of these medications during breastfeeding in HBV monoinfection, both because their use will likely increase in HBV-infected pregnant and lactating women and because the opportunity to breastfeed the infant is lost if it is not started soon after delivery. In this review, we evaluate the data regarding lamivudine and TDF use during pregnancy and breastfeeding.

LAMIVUDINE

Lamivudine, a nucleoside analogue, is used to treat HIV as well as chronic hepatitis B and has been safely given in HIV-infected pregnant women without increased risk of birth defects. Lamivudine is classified in the US Food and Drug Administration (FDA) pregnancy risk category C, meaning that "animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks." The Antiretroviral Pregnancy Registry has data on more than 4360 and 7072 women who have been exposed to lamivudine during their first and second/third trimesters, respectively, with newborn defect proportions of 3.1% and 2.9%, which are comparable to that of the general population. From these data, lamivudine appears to be safe in pregnancy.

Lamivudine diffuses freely across the placenta from the maternal circulation to the fetal circulation and is secreted in breast milk (Table 1) [5–10]. Several studies have investigated lamivudine levels in breastfed infants. In the Breastfeeding, antiretrovirals, and nutrition study from Malawi, 30 mother–infant pairs demonstrated that the lamivudine concentration in breastfed infants was only 3.7% of the mother's level despite the fact that lamivudine was concentrated in breast milk [11]. A recent Kenyan study of HIV-infected mothers treated with antiretroviral therapy from gestational week 34 to 6 months postpartum measured infant lamivudine concentrations at different time points [12]. The median maternal plasma lamivudine concentration was 508 ng/mL (interquartile range [IQR], 290–800 ng/mL) and the median breast milk lamivudine concentration was 1214 ng/mL (IQR, 862–1651 ng/mL). Interestingly, the median concentration of lamivudine in the infant at delivery was 67 ng/mL and steadily decreased to 24 ng/mL and below the limit of detection, at 6 and 24 weeks post delivery, respectively, even though the infants were breastfeeding. The investigators calculated that the daily dose to the infants via breast milk was 2% that of the recommended dose for treatment for HIV in infants >3 months of age. Thus, despite the fact that lamivudine is concentrated in the breast milk, it is not as efficiently absorbed by the infant through that route compared with the transplacental route. This study demonstrates that the infant is exposed to significantly higher amounts of lamivudine in utero than via breastfeeding. These infant serum concentrations are similar to findings from a study in Botswana [9]. In another study, Moodley et al examined 20 pregnant South African women and found that concentrations of lamivudine at birth were similar in maternal, cord, and neonatal serum, supporting free passage of lamivudine across the placenta [6]. Breast milk concentrations were higher, but they concluded that, given the volume of breast milk ingested by a neonate, the amount of lamivudine ingested is negligible. It should also be noted that one study found lower lamivudine levels in breast milk than in maternal serum [13].

TENOFOVIR DISOPROXIL FUMARATE

Because tenofovir has poor bioavailability, it is conjugated to disoproxil fumarate and administered as the prodrug, TDF. This prodrug has adequate oral bioavailability and is converted to tenofovir, a nucleotide analogue, in vivo. TDF is effective for the treatment of HIV and chronic hepatitis B. Due to its high efficacy against HBV, its low potential for the development of drug-resistant HBV, and its excellent safety record in pregnancy in HIV-infected women, TDF is a promising candidate to

Table 1. Concentration of Lamivudine In Vivo

First Author	Sample Size	Lamivudine Dose, mg	Concentration in Maternal Serum, µg/L	Concentration in Umbilical Cord, µg/L	Concentration in Amniotic Fluid, µg/L	Concentration in Infant Serum, µg/L	Concentration in Breast Milk, µg/L
Moodley [6]	20	300, 150	301	432	1830	330	900
Mandelbrot [7]	57	300	302	. . .	1747	240	. . .
Chappuy [8]	67	2 mg/kg of body weight	450	400	1680	. . .	. . .
Yeh [5]	14	300	271	216	931	. . .	. . .
Shapiro [9]	20	300	678	. . .	. . .	28	1828
Giuliano [10]	40	300	200	. . .	. . .	. . .	400

be used in pregnant women to prevent mother-to-child transmission of HBV. TDF has been classified as FDA pregnancy risk category B, which means that "animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women." No increase in birth defects has been reported in 1982 first-trimester exposure cases and 959 second/third-trimester exposure cases from the Antiretroviral Pregnancy Registry. However, the effect on long-term growth outcome is unknown.

Tenofovir readily crosses the placenta; however, its concentration in maternal blood is about 3 times higher than in cord blood [14, 15] (Table 2). In consideration of the safety of TDF in breastfeeding mothers, it is worthwhile to review data from pregnancy because there are limited data on breastfeeding and because levels of tenofovir are higher in utero than via breastfeeding [16]. Overall, studies in both animals and humans suggest that TDF is safe in pregnancy. In pregnant monkeys given doses with an area under the curve (AUC) about 25-fold higher than obtained with doses given to humans, there were no gross abnormalities in the offspring, but there was a slight reduction in fetal bone porosity observed within 2 months of maternal therapy [17]. A female rhesus macaque, who was given continuous tenofovir from her birth and throughout her pregnancies, had 3 infants with normal growth and development for up to 5 years despite the fact that the tenofovir dose was 4- to 6-fold higher than human doses [18].

In humans, a case report from Japan noted blunted fetal biparietal diameter and femur length in an infant whose mother received 4 weeks of TDF starting at 35 weeks of gestation [19]. However, it is difficult to attribute these abnormalities to TDF as it is a single case report and the mother only received a short course of TDF in late pregnancy. The majority of human studies report no evidence of impairment of growth or bone health with in utero exposure to TDF [20, 21]. A recent study of HIV-infected women in Africa showed that TDF use in 248 pregnant women did not increase the risk for kidney disease, birth defects, or growth abnormalities in their infants [22]. In a systematic review of 903 infants whose mothers had received TDF for >2 weeks and most of them for several months during pregnancy, there was no increased risk of birth abnormalities [23]. Furthermore, the review showed no effect on fetal growth, but one study showed slightly lower infant height at age 1 year [24], the

significance of which is unclear. This review did not reveal any effects on bone health, but the data on that were limited. Bone health in the infant is a concern because TDF affects bone mineral density in adults when the drug is given long term [25]. Siberry et al looked at 74 infants in the United States exposed to TDF for at least 8 weeks and 69 infants not exposed to TDF. The TDF-exposed infants had significantly lower average whole-body bone mineral content compared with unexposed infants (56.0 vs 63.8 g, respectively) [26]. However, the clinical significance and long-term importance of this finding is unclear.

The limited data on tenofovir excretion into breast milk demonstrate that the infants receive low doses of tenofovir via breastfeeding. Breast milk samples were collected at various time points from 5 Ivorian women administered 1 tablet of nevirapine (200 mg) plus 2 tablets of TDF (300 mg)/emtricitabine (200 mg) at the start of labor and 1 tablet of TDF/emtricitabine daily for 7 days postpartum [16]. The median maximal tenofovir concentration in breast milk was 14.1 ng/mL, which is lower than in maternal serum or cord blood. Thus, given the amount of milk ingested by the infant, the median amount of tenofovir ingested would be 0.03% of the recommended neonatal dose. Another study from Malawi and Brazil found that levels of tenofovir in breast milk 2 days after a single 600-mg TDF dose during labor were 6.3–17.8 ng/mL [27]. These data corroborate findings from animals. A study of 2 nursing rhesus macaques demonstrated that the peak tenofovir concentrations in breast milk were approximately 2%–4% of those detected in serum, with milk AUC values being approximately 20% of the serum values [28]. The authors concluded that the low tenofovir concentrations observed in breast milk of lactating macaques are unlikely to be toxic for the infant. The same authors had reported previous studies demonstrating a favorable safety profile of prolonged daily treatment of infant macaques with a dose of tenofovir (10 mg/kg subcutaneously) that is much higher than the daily amount of tenofovir likely to be ingested and absorbed from breast milk [29].

CONCLUSIONS

Lamivudine and TDF are both active against hepatitis B and safe to both the mother and the fetus during pregnancy, with the majority of data on pregnancy coming from HIV-monoinfected women. Although data are more limited on these drugs during breastfeeding, the data are consistent in demonstrating low total exposure of the drugs to the breastfed infant. It appears difficult to justify that these drugs can be recommended during pregnancy but contraindicated during breastfeeding. In fact, WHO recommends the use of both agents for HIV-infected breastfeeding mothers. For HBV, both of these drugs, especially TDF, may prove useful to prevent mother-to-infant transmission of HBV and may need to be continued for at least a

Table 2. Concentration of Tenofovir In Vivo

First Author	Sample Size	Tenofovir Dose, mg	Concentration in Maternal Serum, ng/mL	Concentration in Umbilical Cord, ng/mL
Flynn [14]	13	600	234	76
	15	900	456	68
Hirt [15]	38	300	310	100

short period of time after delivery to prevent maternal flares of liver inflammation when the immune system recovers from pregnancy and responds to the HBV infection [4]. Furthermore, breastfeeding provides multiple benefits to the infant, especially in low-income settings, which is precisely where HBV endemicity is the highest, and if breastfeeding is not started soon after delivery, the opportunity to breastfeed is lost. Thus, our review of the existing data suggests that lamivudine and TDF should not be contraindicated during breastfeeding; however, long-term studies of infants breastfed while their mothers were receiving lamivudine or TDF are warranted. Reconsideration should be given to the current contraindication of lamivudine and TDF during breastfeeding. This may result in a formal re-evaluation of the evidence and, if deemed necessary, additional studies to generate more data on this important drug safety issue.

Notes

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