Published in final edited form as:
Infect Dis Clin North Am. 2014 December ; 28(4): 601–613. doi:10.1016/j.idc.2014.08.005.

Prevention of HIV/AIDS: Post-Exposure Prophylaxis (including Healthcare Workers)

Susan E. Beekmann, RN, MPH and
Department of Internal Medicine, The University of Iowa College of Medicine, Iowa City, IA 52242, USA

David K. Henderson, MD[*]
Deputy Director for Clinical Care, Clinical Center, National Institutes of Health, Bethesda, MD 20892, USA

Keywords

HIV; postexposure prophylaxis; occupational exposure; nonoccupational exposure; HIV PEP

Although HIV incidence in the United States was relatively stable from 2006 to 2009, 48,100 new HIV infections were estimated to have occurred in 2009 in the U.S.[1] and 2.3 million new cases occurred globally in 2012.[2] Postexposure prophylaxis (PEP), which is designed to prevent HIV infection after an exposure, is one of a number of strategies for HIV prevention. PEP was first used after occupational HIV exposures in the late 1980's, with CDC issuing the first set of guidelines that included considerations regarding the use of antiretroviral agents for postexposure prophylaxis after occupational HIV exposures in 1990.[3] A case-control study of HIV seroconversion in healthcare workers (HCW) after percutaneous exposure published in 1997 provided the first evidence in humans that PEP with a single antiretroviral agent appeared to be protective against infection.[4] More recently, use of PEP has been extended to nonoccupational exposures, including following sexual contact or injection-drug use.[5] In this paper, we will provide a brief rationale for PEP, assessment of the need for PEP, and details of its implementation.

RATIONALE FOR PEP FOR EXPOSURES TO HIV

Biological Plausibility of PEP

The hypothesis underlying the administration of antiretroviral chemoprophylaxis is that postexposure treatment provided during a "window of opportunity" will attenuate initial HIV replication and prevent systemic HIV infection and allow time for a cellular immune

[*]Corresponding author: DHenderson@cc.nih.gov.

Disclosure statement: Neither SEB nor DKH have any disclosures

response. Dendritic cells in the mucosa and skin are believed to be the initial target for HIV infection or capture.[6] In a primate model, simian immunodeficiency virus (SIV) remained localized in association with dendritic cells underlying the site of vaginal inoculation for the first 24 hours after exposure to cell-free virus.[7] Within 24 to 48 hours, these cells appeared to migrate to regional lymph nodes and present SIV to T lymphocytes. Cell-free and cell-associated SIV was detected in the peripheral blood within 5 days after inoculation.

Productive HIV infection occurs in a sequence of events involving initial capture and/or infection of dendritic target cells near the exposure site with subsequent transmission of HIV to susceptible T cells in regional lymph nodes. Each step in this sequence is a potential target for intervention. Early antiretroviral treatment plausibly prevents infection by blocking the infection of T cells, presumably in the regional lymph nodes. Interrupting or delaying the productive infection of T cells could also allow time for the development of specific cellular immunity directed against HIV in the exposed individual.

Animal studies provide evidence for an important role for the cellular immune system in HIV PEP. Intact cellular immunity was required for successful PEP in one mouse retroviral model.[8] Putkonen and co-workers demonstrated robust specific cellular responses in macaques in which SIV infection was successfully prevented by postexposure prophylaxis.[9] These macaques developed a strong enough immune response that a second challenge with the same viral inoculum resulted in either no or significantly limited infection.

These data suggest that antiretroviral chemoprophylaxis administered soon after an exposure, in concert with cellular immunity, may prevent or inhibit systemic HIV infection. This preventive effect theoretically is caused by limiting proliferation of virus in dendritic cells in skin or in T cells in regional lymph nodes during the time in which the virus remains relatively localized. This effect may be bolstered by a robust cellular immune response.

Animal Models of PEP

In general, PEP is most likely to be effective in animal models in which the exposure inoculum is relatively low, when treatment is started soon after exposure (usually within 24 hours), and when treatment is continued for several days to weeks after inoculation.[10,11] In one study of SIV in macaques, all the animals receiving postexposure treatment for 28 days remained uninfected; only half the animals treated for 10 days remained uninfected; and none of the animals that received only 3 days of treatment were protected.[11] Similarly, delay in initiating prophylaxis was detrimental in this model. All of the animals that were treated within 24 hours of intravenous SIV infection remained uninfected, whereas only 50% of the animals that received treatment beginning 48 hours after infection and only 25% of the animals that received treatment beginning 72 hours after exposure were protected. Otten and colleagues demonstrated similar findings in a macaque study assessing postexposure prophylaxis after vaginal inoculation with HIV type 2.[12] All animals treated within 48 hours were protected, whereas only some of the animals that received the antiretroviral agent 72 hours after inoculation remained uninfected.

Epidemiologic and Clinical Data Relevant to Occupational PEP

Studies of prevention of mother-to-child transmission, including AIDS Clinical Trial Group protocol 076,[13] indicated a protective effect of zidovudine which was attributable to a reduction in maternal HIV viral load (see chapter 1 of this issue).

In the CDC's retrospective case-control study of HCWs, zidovudine PEP was associated with an 81% reduction in the odds of infection after adjustment for relevant exposure risk factors.[4] This relatively small study was not designed to evaluate the merits of individual treatment regimens; thus, the effect of the drug regimen (dose, time to initiation, duration) on efficacy could not be determined. The study did not prove that treatment was effective, and limitations inherent in the design, including the small number of cases and the fact that cases and controls were not from the same cohort, must be considered.[14] Nevertheless, this study provided very suggestive epidemiologic evidence that zidovudine afforded some protection to exposed HCWs.

Antiretroviral chemoprophylaxis for occupational exposures to HIV has been in use in the United States since the late 1980s.[15] The numbers of occupational infections with HIV that have been reported to CDC have decreased steadily.[16] From 2000 to 2014, only a single case of occupational HIV infection was reported to CDC in 2010 (David Kuhar, CDC personal communication). Most have been well-documented parenteral exposures (usually needlesticks from hollow-bore needles) to blood from a source patient known to be HIV-infected. Several factors have likely contributed to this decrease, including the use of primary exposure prevention strategies resulting in fewer exposures; the efficacy of highly active antiretroviral therapy in lowering the viral burden in HIV-infected source patients (both reducing the likelihood of their hospitalization and decreasing their need for, and numbers of, invasive procedures that place HCWs at risk for exposures); reduced reporting to CDC as the epidemic has matured and as staff have become knowledgeable about appropriate interventions; less aggressive case finding by the CDC and other local and state public health officials; and the use of PEP for occupational exposures.

Prophylaxis failures following occupational needle stick exposures have been documented in at least 24 instances.[17–20] In more than 75% of the instances of failure, zidovudine was used as a single agent. Only six instances of failure in the context of occupational needle stick exposure have been reported in association with the use of multiple-agent prophylaxis regimens.[19–23] In 15 of the 24 instances of PEP failure, the source patient for the exposure had previously been treated with one or more anti-retroviral agents; thus, antiretroviral resistance possibly may, at least in part, explain the chemoprophylaxis failure. Additional factors may have contributed to these failures, including: exposure to high HIV inocula; delayed initiation of prophylaxis; failure to achieve adequate drug concentrations; and inadequate treatment duration.

ASSESSMENT OF THE NEED FOR OCCUPATIONAL AND NON OCCUPATIONAL PEP

Multiple factors should be considered when assessing an individual's need for PEP. First, prophylaxis should only be offered to individuals who are HIV-negative. Second, the type of

exposure must be assessed, as 'per-event' risk varies widely, depending on the exposure. Characteristics of the source patient are the final factors which need to be included in the initial risk assessment.

Baseline HIV Testing of Occupationally and Non-Occupationally Exposed Individuals

A negative result from an enzyme-linked immunosorbent assay (ELISA) for antibodies to HIV should be documented at the time of the initial assessment for both occupational and nonoccupational exposures. If possible, HIV antibody testing should be done with an FDA-approved rapid test kit with results available within one hour. HIV viral load testing may yield false positive results if viral load levels below 1000 copies/uL are detected, and so is not recommended for baseline testing in the absence of signs or symptoms of acute retroviral syndrome. Fourth-generation HIV tests, which detect p24 antigen as well as conventional HIV antibodies, may be used in place of HIV antibody tests. Early antigen recognition with these assays reduces the window period for detection by approximately five days.

Testing of the Source Patient

In occupational settings, the source patient can often be quickly tested with a rapid HIV test. With the possible exception of the setting in which a high index of suspicion exists for acute infection (e.g., source patient with risk factors and signs and symptoms consistent with acute retroviral syndrome), a negative HIV screening test obviates the need for PEP. Source patients should also be tested to assess hepatitis B and HCV serostatus, stage of disease, history of antiviral therapy, and viral load status for any/all of the bloodborne pathogens, if known. The source patient in nonoccupational exposures is rarely available for testing, so other epidemiologic factors must be considered. High-risk populations for which the toxicity and cost of PEP can be justified include: men who have sex with men, men who have sex with both men and women, commercial sex workers, injection-drug users, persons with a history of incarceration, persons from a country where the seroprevalence of HIV is at least 1%, and persons who have a sexual partner belonging to one of these groups.

Exposure Type and Risk of HIV Transmission

Pooled data from multiple studies following HCWs with occupational HIV exposures suggest that the average risk of HIV transmission associated with percutaneous exposures to blood-contaminated sharp objects that have been used on HIV-infected individuals is approximately 0.32% (Table 1).[24] The estimated risk of mucocutaneous transmission is 0.03%. The risk of infection associated with intact skin exposure to HIV is too low to be detected in these studies.

Nonoccupational risk of HIV transmission depends on the nature of the exposure (Table 1). The estimated risk of transmission following needle-sharing injection drug-use is higher than for any form of sexual exposure. The estimated risks associated with sexual exposures vary from 1.69% per act of male-to-female receptive anal intercourse[25] to 0.005% per act of insertive oral intercourse,[5] while only case reports have been received of female-to-female sexual transmission of HIV.[26] Per-act transmission probabilities are methodologically difficult to ascertain, as the time of seroconversion of the index case and the transmission to

the partner, the number of unprotected sex acts, duration of exposure to HIV, and potential HIV cofactors at the time of transmission are rarely known precisely.[25] Exposures warranting PEP include unprotected sex, protected sex with condom failure, intravenous drug use or other mucosal or wound exposure. Exposures involving the insertive oral partner do not require PEP.

In general, chemoprophylaxis is recommended for exposures known to confer a transmission risk. Chemoprophylaxis should be considered for exposures with a "negligible risk." Chemoprophylaxis *may not* be warranted for exposures that do not pose a known transmission risk. In this framework, treatment is recommended for all percutaneous exposures to HIV and for mucosal and non-intact skin exposures, especially those that that involve high titers of HIV (e.g., blood from patients with advanced HIV disease, high viral load, or low CD4+ counts). Treatment should be considered for small-volume, short-duration mucosal and non-intact skin exposure if the source patient is known or suspected to have a high circulating viral burden. In some institutions healthcare providers are give the option of electing prophylaxis for small-volume, short-duration mucosal and nonintact skin exposure. Though the associated risks for transmission are likely substantially smaller, some healthcare workers would prefer to take antiretroviral chemoprophylaxis to address even this smaller risk. Treatment is not indicated for most intact skin exposures. Occasionally a large volume intact-skin exposure might warrant consideration for prophylaxis (e.g., if a pheresis machine becomes disconnected with the pressure-pump engaged and the provider gets blood extensively on intact skin)

The actual risks associated with specific exposures to HIV are impossible to predict. Because the efficacy of PEP will likely never be demonstrated definitively in a clinical trial, and because the agents involved are associated with substantial toxic effects, PEP must be implemented with caution. Current USPHS guidelines are based on exposures to blood or other potentially infectious materials known to contain HIV, not materials of uncertain HIV status.[27]

Decisions about treatment when the source material is not known to contain HIV should be based on a careful risk assessment, including a determination of (1) the probability of HIV infection in the source patient; (2) the type of exposure and the associated risk of HIV transmission with such an exposure, if HIV was, in fact, present; and (3) the risks associated with treatment for the exposed individual. In many "source unknown" exposures, the risk of transmission is negligible, and treatment is simply not indicated. Only if the assessment suggests that the risk of HIV transmission outweighs the risk of treatment is it reasonable to initiate the basic treatment regimen until test results or other data become available.

The use of antiretroviral chemoprophylaxis for nonoccupational exposures has been investigated extensively.[5,28–36] The rationale for providing PEP in these cases is no different from that for providing prophylaxis for occupational exposures. Clinicians should evaluate the circumstances of each exposure, provide counseling about the risks for infection and secondary transmission, and provide up-to-date information about the potential risks and benefits of antiretroviral chemotherapy. In many instances, the care provider's primary role is one of reassurance, inasmuch as the risk for transmission associated with many such

community exposures may be quite small. Several reports describe instances in which HIV transmission has been associated with human bites.[37,38] Evaluation of the bitten individual should include baseline testing for preexisting HIV infection, an offer of PEP if the patient is exposed to HIV, and follow-up identical to that described for other parenteral HIV exposures. Perpetrators of sexual assault are considered to be a high-risk population for HIV infection and PEP should be offered for these cases.[39–41]

DETAILS OF IMPLEMENTATION OF PEP

In this section, we will first discuss the factors that should be considered when choosing a treatment regimen. We will also discuss adverse effects associated with PEP, the timing and duration of PEP, and finally the follow-up needed for HIV exposures.

Choosing a Regimen for PEP

Several factors influence the selection of antiretroviral drugs for prophylaxis regimen: (1) the type of exposure and the estimated risk of HIV transmission associated with the exposure; (2) the probability that drug-resistant virus strains are present in the source patient; (3) the safety profile and likelihood of the individual's adherence to the proposed treatment regimens; and (4) the cost of the agents.

CDC has recently published its fourth update of Public Health Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis.[27] Since publication of the previous update in 2005,[20] several novel antiretroviral agents have been granted FDA approval. In addition, investigators have amassed substantial experience regarding the safety and toxicity of these agents administered for prophylaxis for both occupational and nonoccupational exposures. CDC and its expert consultants identified several challenges in the use and interpretation of the 2005 guidelines and addressed these issues in the 2013 recommendations.[27] Despite the fact that no data demonstrate increased efficacy of three-drug HIV PEP regimens when compared with two-drug regimens, the 2013 guidelines recommend the routine administration of three agents for PEP and no longer recommend attempting to characterize the level of risk for HIV transmission for discrete exposures. CDC now recommends the combination of raltegravir, tenofovir, and emtricitabine as the "preferred" regimen for postexposure prophylaxis, though not all experts agree. Some individuals emphasize the importance of the cost of these regimens and still favor a protease inhibitor as the third component of the regimen.[42] For alternative regimens, the 2013 guidelines recommend use of three agents (e.g., two nucleoside reverse transcriptase inhibitors and either an integrase strand transfer inhibitor, a "ritonavir-boosted" protease inhibitor, or a non-nucleoside reverse transcriptase inhibitor (Table 2). These alternative regimens may be indicated in unique clinical circumstances, but should be prescribed only after consultation with an expert experienced in the use of antiretrovirals and knowledgeable about the exposure.[27]

The 2013 CDC guidelines characterize three antiretroviral agents as "generally not recommended for use" in postexposure prophylaxis (didanosine, nelfinavir and tipranavir), and one agent, nevirapine, as "contraindicated" for use in prophylaxis. Nevirapine has been used extensively to treat HIV infection, but is known to have a greatly increased associated

with severe cutaneous and hepatic toxicity for males with CD4 counts > 400 cells/ul and females with CD4 counts > 250 cells/uL, counts which most persons who are candidates for PEP would be expected to have., Thus nevirapine is a poor choice for PEP and in fact is contraindicated.[43–47]

HIV resistance is an increasing concern, with resistance to all antiretroviral drugs reported as well as transmission of resistant strains.[48–52] Before treatment, 8–18% of HIV infected persons have resistance to one or more antiretroviral drugs, and such resistance mutations adversely affect therapeutic response to the relevant drugs. If the source patient's resistance pattern for currently circulating virus is known, that information should guide selection of the PEP regimen. Drug resistance is most likely to be present among patients with high viral loads who are not responding to treatment or do not adhere to the treatment regimen. Unfortunately, if the resistance profile of the patient's virus has not been tested, clinical predictions about drug resistance are neither sensitive nor specific. Special genotypic and phenotypic tests to detect HIV resistance often are not readily available to provide immediate support for prophylactic treatment decisions. When drug resistance is suspected, PEP regimens should be based on the same principles used to select drugs for HIV-infected patients in whom treatment is failing. Many experts recommend a minimum of three agents that include the use of at least two drugs that the source patient has not taken in the recent past (i.e., preceding 30 days). If the resistance is likely to involve an entire class of antiretroviral drugs (e.g., protease inhibitors), including agents from other classes makes implicit sense.

Timing and Duration of PEP

Treatment should be initiated as soon as possible after exposure. In most animal studies, efficacy is reduced when treatment is delayed for more than 24 hours.[11] Nonetheless, both occupational and nonoccupational exposures to HIV should be regarded as urgent medical concerns. When indicated, chemoprophylaxis should be started as soon as practical (i.e., within a few hours). When consultation is needed to select the best regimen, beginning the basic or expanded regimen until additional information is available may be the best course of action, rather than delaying the start of treatment. If local expertise is not available, additional resources for clinicians who need consultative assistance are listed in Table 3. The optimal duration of chemoprophylaxis is not known. A 4-week regimen is currently recommended.[27]

Adverse Effects of PEP

Adverse effects have been associated with all agents and regimens used for PEP. The frequency, severity, duration, and reversibility of side effects are important considerations in formulating a prophylactic treatment regimen. Unusual or serious and unexpected toxic effects of antiretroviral drugs should be reported to the manufacturer and the FDA (see Table 3). Although use of these drugs in the postexposure setting has become the standard of care, no agent has been approved or labeled for postexposure chemoprophylaxis for HIV exposures; therefore, all such use must be considered "off-label."

Much of the information about prophylactic treatment side effects was derived from studies of HCWs who took zidovudine alone, usually at doses higher than the currently recommended dose.[53] More than 50% of those treated reported at least one side effect, and about 30% stopped treatment because of symptoms. HCWs who took regimens that included two or more antiretroviral drugs experienced frequent side effects. In almost every instance, side effects ceased when treatment was stopped.

Side effects associated with HIV chemoprophylaxis are similar to (although strikingly more substantial than) those observed in HIV-infected patients, and most can be managed symptomatically (e.g., acetaminophen for headache and myalgia; prochlorperazine for nausea; antimotility drugs for diarrhea). These adverse effects can decrease rates of adherence and completion of PEP regimens. Regular contact with the individual on PEP as frequently as possible is important to encourage course completion. Because these complications occur so commonly and because they can often be managed effectively with the symptomatic medications described above, practitioners may wish to provide prescriptions for these agents with instructions, to “take this drug if you develop nausea, this one for diarrhea, etc.”

Follow-up Assessments for HIV PEP

In addition to baseline HIV testing, serologic testing for a documented HIV exposure is usually performed 6 weeks, 12 weeks, and 6 months after exposure.[27] Sequential testing is useful to allay fears, to document seronegativity, and, in rare instances, to diagnose HIV infection. Testing for more than 6 months is not routinely recommended, although individuals who become infected with hepatitis C (HCV) after exposure to a source who is coinfected with HIV and HCV should be tested again at 12 months.[27] Testing performed using fourth generation combination antigen/antibody immunoassay permits earlier detection of HIV infection. The 2013 CDC guidelines indicate that, if fourth generation HIV tests are used, HIV follow-up testing could be concluded at 4 months after the exposure.[27]

Symptoms of acute retroviral infection (e.g., fever, lymphadenopathy, pharyngitis, rash, headache, profound fatigue) have been associated with approximately 80% of reported occupational infections, even when PEP was administered.[54] For this reason, all HIV-exposed persons should be advised to return for evaluation and HIV testing if an illness suggestive of the acute retroviral syndrome occurs. HIV antibody tests may be negative or indeterminate during early phases of the seroconversion illness. Immunoblot or viral load tests (quantitative HIV RNA polymerase chain reaction) may be more sensitive methods for detecting early infection should it be suspected, but are *not* indicated in the routine management of HIV exposures.

Individuals who elect to receive PEP after HIV exposure should return 48 to 72 hours after initiation of treatment for routine evaluation for signs and symptoms of drug toxicity and to make certain that all questions and concerns are addressed. The exposed patient should next be seen no later than 2 weeks after initiation of therapy and some practitioners prefer weekly evaluations for the first month. The clinician evaluating the patient should obtain a careful history, perform a focused physical examination, and obtain relevant laboratory tests appropriate to the drug regimen. As a general rule, a complete blood cell count and renal and

hepatic chemical function tests are indicated. A random blood glucose measurement and a lipid profile should be considered whenever a protease inhibitor is included in the regimen.

Exposed individuals receiving PEP should be advised of the importance of completing the prescribed regimen. Many experts recommend use of barrier protection during sexual contact with partners and avoidance of shared blood-contaminated fomites (i.e. razors and toothbrushes). Exposed individuals receiving PEP should be provided information about potential drug interactions and what medications not to take while taking the prophylactic drug regimen; the side effects of the drugs that have been prescribed and measures to minimize these effects; and methods of clinical monitoring for toxicity during the follow-up period. They should be alerted to the need for immediate evaluation of symptoms of the seroconversion illness and of symptoms suggestive of serious toxicity (e.g., back or abdominal pain, pain on urination or blood in the urine, and symptoms of hyperglycemia, such as increased thirst or frequent urination).

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Key Points

- HIV postexposure prophylaxis is intended to prevent HIV infection after an exposure.
- HIV postexposure prophylaxis is one of a number of strategies for HIV prevention.
- PEP was first used after occupational HIV exposures.
- A case-control study of HIV seroconversion in healthcare workers after percutaneous exposure published in 1997 provided the first evidence in humans that PEP with a single antiretroviral agent appeared to be protective against infection.
- Use of PEP has been extended to nonoccupational exposures, including following sexual contact or injection-drug use.

Table 1

Estimated peer-act risk for acquisition of HIV, by exposure route*

Exposure route	Risk for 10,000 exposures to an infected source
Blood transfusion	9,000
Needle-sharing injection-drug use	67
Receptive anal intercourse	50
Percutaneous needle stick	30
Receptive penile-vaginal intercourse	10
Insertive anal intercourse	6.5
Insertive penile-vaginal intercourse	5
Mucous membrane exposure (e.g. splash)	3
Receptive oral intercourse	1
Insertive oral intercourse	0.5

* Estimates of risk for transmission from sexual exposures assume no condom use. Modified from CDC. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: Recommendations from the U.S. Department of Health and Human Services. *MMWR* 2004;54(No. RR-2):1–20.

Table 2

Recommended PEP for all occupational exposures to HIV

Preferred HIV PEP Regimen	
raltegravir (Isentress®) 400 mg PO twice daily Plus tenofovir DF (Viread®) 300 mg + emtricitabine (Emtriva™) 200 mg [Truvada™, 1 PO once daily]	
Alternative Regimens (May combine one drug or drug pair from the left column with 1 pair of nucleoside/nucleotide reverse transcriptase inhibitors from the right column)	
Raltegravir (Isentress®)	Tenofovir DF (Viread®) + emtricitabine (Emtriva™); available as Truvada
Darunavir (Prezista®) + ritonavir (Norvir®)	Tenofovir DF (Viread®) + lamivudine (Epivir®)
Etravirine (Intelence®)	Zidovudine (Retrovir™) + lamivudine (Epivir®); available as Combivir
Rilpivirine (Edurant™)	Zidovudine (Retrovir™) + emtricitabine (Emtriva)
Atazanavir (Reyataz®) + ritonavir (Norvir®)	
Lopinavir/ritonavir (Kaletra®)	
Stribild™ (elvitegravir, cobicistat, tenofovir DF, emtricitabine) [a complete fixed-dose combination regimen with no additional antiretrovirals needed]	
Alternative Antiretroviral Agents for Use as PEP ONLY with Expert Consultation	
Abacavir (Ziagen®)	
Efavirenz (Sustiva®)	
Enfuvirtide (Fuzeon™)	
Fosamprenavir (Lexiva®)	
Maraviroc (Selzentry®)	
Saquinavir (Invirase®)	
Stavudine (Zerit®)	
Antiretroviral Agents Generally Not Recommended for Use as PEP	
Didanosine (Videx EC®)	
Nelfinavir (Viracept®)	
Tipranavir (Aptivus®)	
Antiretroviral Agents Contraindicated as PEP	
Nevirapine (Viramune®)	

Modified from Kuhar DT, Henderson DK, Struble KA, Heneine W, Thomas V, Cheever LW, Gomaa A, Panlilio AL. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. *Infect Control Hosp Epidemiol* 2013;34(9):875–92.

TABLE 3

Management of HIV Exposure and PEP: HIV Postexposure Prophylaxis Resources and Registries

National HIV/AIDS Clinicians' Consultation Center: Postexposure Prophylaxis Hotline (PEPline)	Phone: 888-448-4911 Web site: http://www.nccc.ucsf.edu/about_nccc/pepline/
Antiretroviral Pregnancy Registry	Phone (US and Canada): 800-258-4263 or (FAX) 800-800-1052 Phone (International): 910-679-1598 Web site: http://www.apregistry.com Address: Research Park, 1011 Ashes Drive, Wilmington, NC 28405
U.S. FDA's MedWatch (for reporting unusual or severe toxicity to antiretroviral agents)	Phone: 800-332-1088 Web site: www.fda.gov/medwatch/
CDC's Cases of Public Health Importance (COPHI) coordinator (for reporting HIV infections in HCWs and failures of PEP)	Phone: 404-639-2050

Modified from Kuhar DT, Henderson DK, Struble KA, Heneine W, Thomas V, Cheever LW, Gomaa A, Panlilio AL. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. *Infect Control Hosp Epidemiol* 2013;34(9):875–92.