Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis

Prepared by the U.S. Public Health Service Working Group
David T. Kuhar, MD[1]
David K. Henderson, MD[2]
Kimberly A. Struble, PharmD[3]
Walid Heneine, PhD[4]
Vasavi Thomas, RPh, MPH[4]
Laura W. Cheever, MD, ScM[5]
Ahmed Gomaa, MD, ScD, MSPH[6]
Adelisa L. Panlilio, MD[1]

[1]*Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease control and Prevention*
[2]*Office of the Deputy Director for Clinical Care, Clinical Center, National Institutes of Health*
[3]*Division of Antiviral Products, Center for Drug Evaluation and Research, Food and Drug Administration*
[4]*Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease control and Prevention*
[5]*HIV/AIDS Bureau, Health Resources and Services Administration*
[6]*Division of Surveillance, Hazard Evaluation, and Field Studies, National Institute for Occupational Safety and Health, Centers for Disease control and Prevention*

The material in this report originated in the National Center for Emerging and Zoonotic Infectious Diseases, Beth Bell, MD, Director; Division of Healthcare Quality Promotion, Denise M. Cardo, MD, Director

Corresponding preparer: David T. Kuhar, MD, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, CDC, 1600 Clifton Rd., NE, MS A-31, Atlanta, GA 30333. Telephone: 404-639-4000; Fax: 404-639-1244; E-mail: jto7@cdc.gov.

Summary

This report updates U.S. Public Health Service recommendations for the management of health-care personnel (HCP) who have occupational exposure to blood and/or other body fluids that might contain human immunodeficiency virus (HIV). Although the principles of exposure management remain unchanged, recommended HIV postexposure prophylaxis (PEP) regimens and the duration of HIV follow-up testing for exposed personnel have been updated. This report emphasizes the importance of primary prevention strategies, the prompt reporting and management of occupational exposures; adherence to recommended HIV PEP regimens when indicated for an exposure; expert consultation in management of exposures; follow-up of exposed HCP to improve adherence to PEP; and careful monitoring for adverse events related to treatment, as well as for virologic, immunologic and serologic signs of infection. To ensure timely postexposure management and administration of HIV PEP, clinicians should consider occupational exposures as urgent medical concerns, and institutions should take steps to ensure that staff are aware of both the importance of, and the institutional mechanisms available for, reporting and seeking care for such exposures.

Summary of Recommendations

---PEP is recommended when occupational exposures to HIV occur.

---Determine the HIV status of the exposure source patient to guide need for HIV PEP, if possible.

---Start PEP medication regimens as soon as possible after occupational exposure to HIV and continue them for a 4-week duration.

---New Recommendation--- PEP medication regimens should contain 3 (or more) antiretroviral drugs (listed in appendix A) for all occupational exposures to HIV.

---Expert consultation is recommended for any occupational exposures to HIV and at a minimum for situations described in Box 1.

---Provide close follow-up for exposed personnel (Box 2) that includes counseling, baseline and follow-up HIV testing, and monitoring for drug toxicity. Follow-up appointments should begin within 72 hours of an HIV exposure.

---New Recommendation--- If a newer 4th generation combination HIV p24 antigen-HIV antibody test is utilized for follow-up HIV testing of exposed HCP, HIV testing may be concluded at 4 months after exposure (Box 2). If a newer testing platform is not available, follow-up HIV testing is typically concluded at 6 months after an HIV exposure.

Introduction

Preventing exposures to blood and body fluids (i.e., 'primary prevention') is the most important strategy for preventing occupationally acquired human immunodeficiency virus (HIV) infection. Both individual healthcare providers and the institutions that employ them should work to ensure adherence to the principles of "Standard Precautions,"(1) including assuring access to and consistent use of appropriate work practices, work practice controls, and personal protective equipment. For instances in which an occupational exposure has occurred, appropriate postexposure management is an important element of workplace safety. This document provides updated recommendations concerning the management of occupational exposures to HIV.

The use of antiretrovirals as postexposure prophylaxis (PEP) for occupational exposures to HIV was first considered in guidelines issued by the Centers for Disease Control and Prevention (CDC) in 1990.(2) In 1996, the first U.S. Public Health Service (PHS) recommendations advocating the use of PEP after occupational exposure to HIV were published; these recommendations have been updated three times.(3-6) Since publication of the most recent guidelines in 2005, several new antiretroviral agents have been approved by the Food and Drug Administration (FDA), and additional information has become available regarding both the use and safety of agents previously recommended for administration for HIV PEP.

As a direct result of 7 years' experience with the 2005 guidelines, several challenges in the interpretation and implementation of those guidelines have been identified. Those challenges include difficulties in determining levels of risk of HIV transmission for individual exposure incidents; problems determining the appropriate use of two- versus three- (or more) drugs in PEP regimens; the high frequency of side effects and toxicities associated with administration of previously recommended drugs; and the initial management of healthcare personnel (HCP) with exposures to a source patient whose HIV infection status was unknown. The PHS working group has attempted to address both the new information that has been developed as well as the challenges associated with the practical implementation of the 2005 guidelines in this update.

This report encourages using HIV PEP regimens that are optimally tolerated, eliminates the recommendation to assess the level of risk associated with individual exposures to determine the

number of drugs recommended for PEP, modifies and expands the list of antiretroviral medications that can be considered for use as PEP, and offers an option for concluding HIV follow-up testing of exposed personnel earlier than 6 months postexposure. This report also continues to emphasize the following: 1) primary prevention of occupational exposures; 2) prompt management of occupational exposures and, if indicated, initiation of PEP as soon as possible after exposure; 3) selection of PEP regimens that have the fewest side-effects and are best tolerated by prophylaxis recipients; 4) anticipating and preemptively treating side effects commonly associated with taking antiretroviral drugs; 5) attention to potential interactions involving both drugs that could be included in HIV PEP regimens, as well as other medications that PEP recipients might be taking; 6) consultation with experts on postexposure management strategies (especially determining whether an exposure has actually occurred and selecting HIV PEP regimens, particularly when the source patient is antiretroviral treatment-experienced); 7) HIV testing of source patients (without delaying PEP initiation in the exposed provider) using methods that produce rapid results; and 8) counseling and follow-up of exposed HCP.

Recommendations concerning the management of occupational exposures to hepatitis B virus and/or hepatitis C virus have been published previously(5, 7) and are not included in this report. Recommendations for nonoccupational (e.g., sexual, pediatric, and perinatal) HIV exposures also have been published previously.(8-10)

Methods

In 2011, the Centers for Disease Control and Prevention (CDC) reconvened the interagency U.S. Public Health Service (PHS) working group to plan and prepare an update to the 2005 *U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis*.(6) The PHS working group^ was comprised of members from CDC, FDA, the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). Names, credentials, and affiliations of the PHS working group are listed in the "U.S. Public Health Service Working Group" section at the end of this

guideline. The working group met twice a month to monthly to create a plan for the update as well as draft the guideline.

A systematic review of new literature that may have become available since 2005 was not conducted; however, an initial informal literature search did not reveal human randomized trials demonstrating superiority of two- versus three- (or more) drug antiretroviral medication regimens as PEP or an optimal PEP regimen for occupational exposures to HIV. Because of the low risk for transmission associated with occupational exposures (i.e., approximately 0.3% per exposure when all parenteral exposures are considered together),(11) neither the conduct of a randomized trial assessing efficacy nor the conduct of trials assessing the comparative efficacy of two- versus three-drug regimens for postexposure prophylaxis is practical. In light of the absence of such randomized trials, CDC convened a meeting of the PHS interagency working group and an expert panel of consultants* in July 2011 to discuss the use of HIV PEP, and develop the recommendations for this update. The expert panel consisted of professionals in academic medicine considered to be experts in the treatment of HIV-infected individuals, the use of antiretroviral medications, and PEP. Names, credentials, and affiliations of the expert panel of consultants are listed in the "Expert Panel Consultants" section at the end of this guideline.

Prior to the July 2011 meeting, the meeting participants^* were provided an electronic copy of the 2005 guidelines, asked to review them, and to consider the following topics for discussion at the upcoming meeting: (1) the challenges associated with the implementation of the 2005 guidelines, (2) the role for ongoing risk stratification in determining the use of two- vs. three or more drug PEP regimens, (3) updated drug choices for PEP, (4) the safety and tolerability of

antiretroviral agents for the general population and pregnant or lactating HCP, and (5) any other topics in the 2005 guideline needed to be updated.

At the July 2011meeting, a CDC representative presented a review of the 2005 guideline recommendations, surveillance data on occupational exposures from the National Surveillance System for Healthcare Workers (NaSH),(12) and data from the National Clinicians Postexposure Prophylaxis Hotline (PEPline) on the numbers of occupational exposures to HIV managed annually, PEP regimens recommended, and challenges experienced with implementation of the 2005 guidelines. An FDA representative presented a review of the new medications that have become available since 2005 for the treatment of HIV-infected individuals, information about medication tolerability and toxicity, and the use of these medications during pregnancy. These presentations were followed by a discussion of the topics listed above.

Among the challenges discussed regarding implementation of the 2005 guidelines were the difficulties in determining level of risk of HIV transmission for individual exposure incidents which in turn determined the number of drugs recommended for HIV PEP. The consensus of the meeting participants^* was no longer to recommend exposure risk stratification (discussed in detail in the "Recommendations for the Selection of Drugs for HIV PEP" section of the guideline below). To update the drug choices for PEP, all drugs available for the treatment of HIV infected individuals were discussed with regards to tolerability, side effects, toxicity, safety in pregnancy and lactation, pills burden, and frequency of dosing. A hierarchy of recommended drugs/regimens was developed at the meeting and utilized in creating the PEP regimen recommendations (Appendices A and B) in these guidelines. Among other topics identified as needing an update were the acceptable HIV testing platforms available for source patient and

follow-up testing of exposed HCP, the timing of such testing, depending on the platform used, and the potential utility of source patient drug-resistance information/testing in PEP regimens.

After the expert consultation, the expert panelists received draft copies of these guidelines as they were updated and provided insights, information, suggestions, and edits, and participated in subsequent teleconferences with the PHS working group, to assist in developing these recommendations. Proposed recommendation updates were presented to the Healthcare Infection Control Practices Advisory Committee in November 2011(13) and June 2012(14) during public meetings. The PHS working group considered all available information, expert opinion, and feedback in finalizing the recommendations in this update.

Definition of Health-Care Personnel and Exposure

The definitions of HCP and occupational exposures are unchanged from those used in 2001 and 2005.(5, 6) The term HCP refers to all paid and unpaid persons working in healthcare settings who have the potential for exposure to infectious materials including body substances (e.g., blood, tissue, and specific body fluids), contaminated medical supplies and equipment, or contaminated environmental surfaces. HCP might include, but are not limited to, emergency medical service personnel, dental personnel, laboratory personnel, autopsy personnel, nurses, nursing assistants, physicians, technicians, therapists, pharmacists, students and trainees, contractual staff not employed by the healthcare facility, and persons not directly involved in patient care but potentially exposed to blood and body fluids (e.g., clerical, dietary, housekeeping, security, maintenance, and volunteer personnel). The same principles of exposure management could be applied to other workers with potential for occupational exposure to blood and body fluids in other settings.

An exposure that might place HCP at risk for HIV infection is defined as a percutaneous injury (e.g., a needlestick or cut with a sharp object) or contact of mucous membrane or nonintact skin (e.g., exposed skin that is chapped, abraded, or afflicted with dermatitis) with blood, tissue, or other body fluids that are potentially infectious. In addition to blood and visibly bloody body fluids, semen and vaginal secretions also are considered potentially infectious. Although semen and vaginal secretions have been implicated in the sexual transmission of HIV, they have not been implicated in occupational transmission from patients to HCP. The following fluids also are considered potentially infectious: cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid. The risk for transmission of HIV infection from these fluids is unknown; the potential risk to HCP from occupational exposures has not been assessed by epidemiologic studies in healthcare settings. Feces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus are not considered potentially infectious unless they are visibly bloody.(11)

Any direct contact (i.e., contact without barrier protection) to concentrated virus in a research laboratory or production facility requires clinical evaluation. For human bites, clinical evaluation must include the possibility that both the person bitten and the person who inflicted the bite were exposed to bloodborne pathogens. Transmission of HIV infection by this route has been reported rarely, but not after an occupational exposure.(15-20)

Risk for Occupational Transmission of HIV

Factors associated with risk for occupational transmission of HIV have been described; risks vary with the type and severity of exposure.(4, 5, 11) In prospective studies of HCP, the average risk for HIV transmission after a percutaneous exposure to HIV-infected blood has been

estimated to be approximately 0.3% (95% confidence interval [CI] = 0.2%--0.5%)(11) and after a mucous membrane exposure, approximately 0.09% (CI = 0.006%--0.5%).(21) Although episodes of HIV transmission after nonintact skin exposure have been documented, the average risk for transmission by this route has not been precisely quantified but is estimated to be less than the risk for mucous membrane exposures. The risk for transmission after exposure to fluids or tissues other than HIV-infected blood also has not been quantified but is probably considerably lower than for blood exposures.

Epidemiologic and laboratory studies suggest that multiple factors might affect the risk for HIV transmission after an occupational exposure.(22) In a retrospective case-control study of HCP who had percutaneous exposure to HIV, increased risk for HIV infection was associated with exposure to a larger quantity of blood from the source person as indicated by 1) a device (e.g., a needle) visibly contaminated with the patient's blood, 2) a procedure that involved a needle being placed directly in a vein or artery, or 3) a deep injury. The risk also was increased for exposure to blood from source persons with terminal illness, likely reflecting the higher titer of HIV in blood late in the course of acquired immunodeficiency syndrome (AIDS) Taken together, these factors suggest a direct inoculum effect (i.e., the larger the viral inoculum, the higher the risk for infection). One laboratory study that demonstrated that more blood is transferred by deeper injuries and hollow-bore needles lends further credence to the observed variation in risk related to inoculum size.(23)

Exposure to a source patient with an undetectable serum viral load does not eliminate the possibility of HIV transmission or the need for PEP and follow-up testing. While the risk of transmission from an occupational exposure to a source patient with an undetectable serum viral

load is thought to be very low, PEP should still be offered. Plasma viral load (e.g., HIV RNA) reflects only the level of cell-free virus in the peripheral blood; persistence of HIV in latently infected cells, despite patient treatment with antiretroviral drugs, has been demonstrated,(24, 25) and such cells might transmit infection even in the absence of viremia. HIV transmission from exposure to a source person who had an undetectable viral load has been described in cases of sexual and mother-to-child transmissions.(26, 27)

Antiretroviral Agents for PEP

Antiretroviral agents from six classes of drugs are currently available to treat HIV infection.(28) These include the nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), a fusion inhibitor (FI), an integrase strand transfer inhibitor (INSTI), and a chemokine (C-C motif) receptor 5 (CCR5) antagonist. Only antiretroviral agents approved by FDA for treatment of HIV infection are included in these guidelines, though none of these agents has an FDA-approved indication for administration as PEP. The rationale for offering antiretroviral medications as HIV PEP is based upon our current understanding of the pathogenesis of HIV infection and the plausibility of pharmacologic intervention in this process, studies of the efficacy of antiretroviral chemoprophylaxis in animal models,(29, 30) and epidemiologic data from HIV-exposed HCP.(22, 31) The recommendations in this report provide guidance for PEP regimens comprised of three (or when appropriate, more) antiretrovirals, consonant with currently recommended treatment guidelines for HIV infected individuals.(28)

Toxicity and Drug Interactions of Antiretroviral Agents

Persons receiving PEP should complete a full 4-week regimen.(5) However, previous results show a substantial proportion of HCP taking an earlier generation of antiretroviral agents as PEP frequently reported side effects,(12, 32-40) and many were unable to complete a full 4-week course of HIV PEP due to these effects and toxicities.(32-37) Because all antiretroviral agents have been associated with side effects (Appendix B),(28) the toxicity profile of these agents, including the frequency, severity, duration, and reversibility of side effects, is a critical consideration in selection of an HIV PEP regimen. The majority of data concerning adverse events have been reported primarily for persons with established HIV infection receiving prolonged antiretroviral therapy and therefore might not reflect the experience of uninfected persons who take PEP. In fact, anecdotal evidence from clinicians knowledgeable about HIV treatment indicates that antiretroviral agents are tolerated more poorly by HCP taking HIV PEP than by HIV-infected patients on antiretroviral medications. As side effects have been cited as a major reason for not completing PEP regimens as prescribed, the selection of regimens should be heavily influenced toward those that are best tolerated by HCP receiving PEP. Potential side effects of antiretroviral agents should be discussed with the PEP recipient, and, when anticipated, preemptive prescribing of agents for ameliorating side effects (e.g. anti-emetics, anti-spasmodics, etc.) may improve PEP regimen adherence.

In addition, the majority of approved antiretroviral agents might have potentially serious drug interactions when used with certain other drugs, thereby requiring careful evaluation of concomitant medications, including over-the-counter medications and supplements (e.g., herbals), used by an exposed person before prescribing PEP and close monitoring for toxicity of

anyone receiving these drugs.(28) PIs and NNRTIs have the greatest potential for interactions with other drugs. Information regarding potential drug interactions has been published and up-to-date information can be found in the *Guidelines for the use of antiretroviral agents in HIV-1 infected-adults and adolescents.*(28) Additional information is included in the manufacturers' package inserts. Consultation with a pharmacist or physician who is an expert in HIV PEP and antiretroviral medication drug interactions is strongly encouraged.

Selection of HIV PEP Regimens

Guidelines for treating HIV infection, a condition typically involving a high total body burden of HIV, recommend use of three or more drugs. Although the applicability of these recommendations to PEP is unknown, newer antiretroviral agents are better tolerated and have preferable toxicity profiles than agents previously used for PEP.(28) As less toxic and better tolerated medications for the treatment of HIV infection are now available, minimizing the risk of PEP noncompletion, and the optimal number of medications needed for HIV PEP remains unknown, the U.S. Public Health Services Working Group recommends prescribing three (or more) tolerable drugs as PEP for all occupational exposures to HIV. Medications included in an HIV PEP regimen should be selected to optimize side effect and toxicity profiles and a convenient dosing schedule to encourage HCP completion of the PEP regimen.

Resistance to Antiretroviral Agents

Known or suspected resistance of the source virus to antiretroviral agents, particularly to one or more of those that might be included in a PEP regimen, raises concerns about reduced PEP efficacy.(41) Drug resistance to all available antiretroviral agents has been reported, and cross-

resistance within drug classes occurs frequently.(42) Occupational transmission of drug-resistant HIV strains, despite PEP with combination drug regimens, has been reported.(43-45) If a source patient is known to harbor drug-resistant HIV, expert consultation is recommended for selection of an optimal PEP regimen. However awaiting expert consultation should not delay the initiation of HIV PEP. In instances of an occupational exposure to drug-resistant HIV, administration of antiretroviral agents to which the source patient's virus is unlikely to be resistant is recommended for PEP.

Information on whether a source patient harbors drug-resistant HIV may be unclear or unavailable at the time of an occupational exposure. Resistance should be suspected in a source patient who experiences clinical progression of disease, a persistently increasing viral load, or decline in CD4+ T-cell count despite therapy, or in instances in which a virologic response to therapy fails to occur. However, resistance testing of the source virus at the time of an exposure is impractical because the results will not be available in time to influence the choice of the initial PEP regimen. If, in the management of an occupational exposure to HIV, source patient HIV drug resistance is suspected, consultation with an expert in HIV management is recommended so that antiretroviral agents to which the source patients virus is unlikely to be resistant may be identified and prescribed. However, awaiting expert consultation should, again, not delay initiation of HIV PEP. If drug resistance information becomes available later in a course of PEP, this information should be discussed with the expert consultant for possible modification of the PEP regimen.

Antiretroviral Drugs During Pregnancy and Lactation

The decision to offer HIV PEP to a pregnant or breastfeeding healthcare provider should be based upon the same considerations that apply to any provider who sustains an occupational exposure to HIV. The risk of HIV transmission poses not only a threat to the mother, but also to the fetus and infant, as the risk of mother-to-child HIV transmission is markedly increased during acute HIV infection during pregnancy and breastfeeding.(46) However, unique considerations are associated with the administration of antiretroviral agents to pregnant HCP, and the decision to use antiretroviral drugs during pregnancy should involve both counseling and discussion between the pregnant woman and her healthcare provider(s) regarding the potential risks and benefits of PEP for both the healthcare provider and for her fetus.

The potential risks associated with antiretroviral drug exposure for pregnant women, fetuses and infants depend on the duration of exposure as well as the number and type of drugs. Information about the use of newer antiretroviral agents, administered as PEP to HIV-uninfected pregnant women, is limited. For reasons including the complexities associated with appropriate counseling about the risks and benefits of PEP, as well as the selection of antiretroviral drugs in pregnant women, expert consultation should be sought in all cases in which antiretroviral medications are prescribed to pregnant HCP for PEP.

In general, antiretroviral drug toxicity has not been shown to be increased in pregnancy. Conflicting data have been published concerning the risk of preterm delivery in pregnant women receiving antiretroviral drugs, particularly protease inhibitors;(47) in studies that have reported a positive association, the increase in risk was primarily observed in women who were receiving antiretroviral drug regimens at the time of conception and continued during pregnancy. Fatal(48)

and nonfatal(49) lactic acidosis has been reported in pregnant women treated throughout gestation with a combination of d4T and ddI. Prescribing this drug combination for PEP is not recommended. Physiologic changes that occur during pregnancy may alter antiretroviral drug metabolism, and, therefore, optimal drug dosing. The clinical significance of these changes is not clear, particularly when used for PEP in HIV-uninfected women. For details on antiretroviral drug choice and dosing in pregnancy, see *Recommendations for use of Antiretroviral drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.*(10)

Prospective data from the Antiretroviral Pregnancy Registry do not demonstrate an increase in overall birth defects associated with first trimester antiretroviral drug use. In this population, the birth defect prevalence is 2.9 per 100 live births, similar to the prevalence in the general population in the CDC's birth defect surveillance system (i.e., 2.7 per 100 live births).(50) Central nervous system defects were observed in fetal primates that experienced *in utero* efavirenz (EFV) exposure and that had drug levels similar to those representing human therapeutic exposure; however, the relevance of *in vitro* laboratory and animal data to humans is unknown.(10) While human data are reassuring,(51) one case of meningomyelocele has been reported among the Antiretroviral Pregnancy Registry prospective cases and data are insufficient to conclude that there is no increase in a rare outcome such as neural tube defect with first trimester EFV exposure.(50) For these reasons, we recommend that pregnant women not use EFV during the first trimester.(10) If EFV-based PEP is used in women, a pregnancy test should be done to rule out early pregnancy, and non-pregnant women who are receiving EFV-based PEP should be counseled to avoid pregnancy until after PEP is completed. HCP who care for women who receive antiretroviral drugs during pregnancy are strongly advised to report

instances of prenatal exposure to the Antiretroviral Pregnancy Registry (http://www.APRegistry.com). The currently available literature contains only limited data describing the long-term effects (e.g., neoplasia, mitochondrial toxicity) of *in utero* antiretroviral drug exposure. For this reason, long-term follow-up is recommended for all children who experienced *in utero* exposures.(10, 52, 53)

Antiretroviral drug levels in breast milk vary among drugs, with administration of some drugs resulting in high levels (e.g., lamivudine) while other drugs, such as protease inhibitors and tenofovir, are associated with only limited penetration into milk.(54, 55) Administration of antiretroviral triple drug regimens to breastfeeding HIV-infected women has been shown to decrease the risk of transmission to their infants and infant toxicity has been minimal. Prolonged maternal antiretroviral drug use during breastfeeding may be associated with increased infant hematologic toxicity,(56, 57) but limited drug exposure during 4 weeks of PEP may also limit the risk of drug toxicity to the breastfeeding infant. Breastfeeding should not be a contraindication to use of PEP when needed, given the high risk of mother-to-infant transmission with acute HIV infection during breastfeeding.(46) The lactating healthcare provider should be counseled regarding the high risk of HIV transmission through breast milk should acute HIV infection occur (in a study in Zimbabwe, the risk of breast milk HIV transmission in the 3 months after seroconversion was 77.6 infections/100 child-years).(58) To completely eliminate any risk of HIV transmission to her infant, the provider may want to consider stopping breastfeeding. Ultimately, lactating women with occupational exposures to HIV who will take antiretroviral medications as PEP must be counseled to weigh the risks and benefits of continued breastfeeding both while taking PEP, and while being monitored for HIV seroconversion.

Management of Occupational Exposure by Emergency Physicians

Many HCP exposures to HIV occur outside of occupational health clinic hours of operation, or at sites at which occupational health services are unavailable, and initial exposure management is often overseen by emergency physicians or other providers who are not experts in the treatment of HIV infection or the use of antiretroviral medications. These providers may not be familiar with either the PHS guidelines for the management of occupational exposures to HIV or with the available antiretroviral agents and their relative risks and benefits. Previous focus groups conducted among emergency department physicians who had managed occupational exposures to blood and body fluids in 2002(59) identified three challenges in occupational exposure management: evaluation of an unknown source patient or a source patient who refused testing, inexperience in managing occupational HIV exposures, and counseling of exposed workers in busy EDs. For these reasons, the U.S. Public Health Services Working Group recommends that institutions develop clear protocols for the management of occupational exposures to HIV, indicating a formal expert consultation (e.g. the in-house infectious diseases consultant, PEPline, etc.) mechanism, appropriate initial source patient and exposed provider laboratory testing, procedures for counseling the exposed provider, identifying and having an initial HIV PEP regimen available, and a mechanism for outpatient HCP follow-up. In addition, these protocols must be distributed appropriately and must be readily available (e.g. posted on signs in the emergency department, posted on a website, disseminated to staff on pocket-sized cards, etc.) to emergency physicians and any other providers who may be called upon to manage these exposure incidents.

Recommendations for the Management of HCP Potentially Exposed to HIV

Exposure prevention remains the primary strategy for reducing occupational bloodborne pathogen infections. However, when occupational exposures do occur, PEP remains an important element of exposure management.

HIV PEP

The recommendations provided in this report apply to situations in which a healthcare provider has been exposed to a source person who either has, or there is a reasonable suspicion of, HIV infection. These recommendations reflect expert opinion and are based on limited data regarding safety, tolerability, efficacy, and toxicity of PEP. If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued and no further HIV follow-up testing is indicated for the exposed provider. Because the great majority of occupational HIV exposures do not result in transmission of HIV, the potential benefits and risks of PEP (including the potential for severe toxicity and drug interactions, such as may occur with oral contraceptives, H_2-receptor antagonists, and proton pump inhibitors, among many other agents) must be considered carefully when prescribing PEP. HIV PEP medication regimen recommendations are listed in Appendix A, and more detailed information on individual antiretroviral medications is provided in Appendix B. Because of the complexity of selecting HIV PEP regimens, whenever possible, these recommendations should be implemented in consultation with persons who have expertise in the administration of antiretroviral therapy and who are knowledgeable about HIV transmission. Reevaluation of exposed HCP is recommended within 72 hours post-exposure, especially, as additional information about the exposure or source person becomes available.

Source Patient HIV Testing

Whenever possible, the HIV status of the exposure source patient should be determined to guide appropriate use of HIV PEP. Although concerns have been expressed about HIV-negative sources that might be in the so-called "window period" before seroconversion (i.e., the period of time between initial HIV infection and the development of detectable HIV antibodies), to date, no such instances of occupational transmission have been detected in the United States. Hence, investigation of whether a source patient might be in the "window period" is unnecessary for determining whether HIV PEP is indicated unless acute retroviral syndrome is clinically suspected. Rapid HIV testing of source patients facilitates timely decision-making regarding the need for administration of HIV PEP after occupational exposures to sources whose HIV status is unknown. FDA-approved rapid tests can produce HIV test results within 30 minutes, with sensitivities and specificities similar to those of first and second generation enzyme immunoassays (EIAs).(60) Third generation chemiluminescent immunoassays, run on automated platforms, can detect HIV specific antibodies two weeks sooner than conventional EIAs(60) and generate test results in an hour or less.(61) Fourth-generation combination p24 antigen-HIV antibody (Ag/Ab) tests produce both rapid and accurate results, and their p24 antigen detection allows identification of most infections during the "window period".(62) Rapid determination of source patient HIV status provides essential information about the need to initiate and/or continue PEP. Regardless of which type of HIV testing is employed, all of the above tests are acceptable for determination of source patient HIV status. Administration of PEP should not be delayed while waiting for test results. If the source patient is determined to be HIV-negative, PEP should be discontinued and no follow-up HIV testing for the exposed provider is indicated.

Timing and Duration of PEP

Animal studies have suggested that PEP is most effective when begun as soon as possible after the exposure and that PEP becomes less effective as time from the exposure increases,(29, 30) PEP should be initiated as soon as possible, preferably within hours of exposure. Occupational exposures to HIV should be considered urgent medical concerns and treated immediately. For example, a surgeon who sustains an occupational exposure to HIV while performing a surgical procedure should promptly scrub out of the surgical case, if possible, and seek immediate medical evaluation for the injury and PEP. Additionally, if the HIV status of a source patient for whom the practitioner has a reasonable suspicion of HIV infection is unknown and the practitioner anticipates that hours or days may be required to resolve this issue, antiretroviral medications should be started immediately rather than delayed.

Although animal studies demonstrate that PEP is likely to be less effective when started more than 72 hours postexposure,(30, 63) the interval after which no benefit is gained from PEP for humans is undefined. If initiation of PEP is delayed, the likelihood increases that benefit might not outweigh the risks inherent in taking antiretroviral medications. Initiating therapy after a longer interval (e.g., 1 week) might still be considered for exposures that represent an extremely high risk for transmission. The optimal duration of PEP is unknown; however, duration of treatment has been shown to influence success of PEP in animal models.(30) Because 4 weeks of PEP appeared protective in *in vitro*, animal(29, 30, 63, 64) and occupational(22) studies, PEP should be administered for 4 weeks, if tolerated.

Recommendations for the Selection of Drugs for HIV PEP

PHS no longer recommends that the severity of exposure be used to determine the number of drugs to be offered in an HIV PEP regimen, and a regimen containing three (or more) antiretroviral drugs is now recommended routinely for all occupational exposures to HIV. Examples of recommended PEP regimens include those consisting of a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone plus an integrase strand transfer inhibitor (INSTI), a protease inhibitor (boosted with ritonavir), or a non-nucleoside reverse transcriptase inhibitor. Other antiretroviral drug combinations may be indicated for specific cases (e.g. an exposure to a source patient harboring drug-resistant HIV), but should only be prescribed after consultation with an expert in the use of antiretroviral agents. No new definitive data exist to demonstrate increased efficacy of three-drug HIV PEP regimens, compared with the previously recommended two-drug HIV PEP regimens for occupational HIV exposures associated with a lower level of transmission risk. The recommendation for consistent use of three-drug HIV PEP regimens reflects (1) studies demonstrating superior effectiveness of three drugs in reducing viral burden in HIV-infected persons when compared with two agents,(28, 65, 66) (2) concerns about source patient drug-resistance to agents commonly used for PEP,(67, 68) (3) the safety and tolerability of new HIV drugs, and (4) the potential for improved PEP regimen adherence due to newer medications that are likely to have fewer side effects. Clinicians facing challenges such as antiretroviral medication availability, potential adherence and toxicity issues, or others associated with a three-drug PEP regimen, might still consider a two-drug PEP regimen in consultation with an expert.

The drug regimen selected for HIV PEP should have a favorable side effect profile as well as a convenient dosing schedule to facilitate both adherence to the regimen and completion of 4 weeks of PEP. Because the agents administered for PEP still can be associated with severe side effects, PEP is not justified for exposures that pose a negligible risk for transmission. Expert consultation could be helpful in determining whether an exposure constitutes a risk that would warrant PEP. The preferred HIV PEP regimen recommended in this guideline should be reevaluated and modified whenever additional information is obtained concerning the source of the occupational exposure (e.g., possible treatment history or antiretroviral drug resistance), or if expert consultants recommend the modification. Given the complexity of choosing and administering HIV PEP, whenever possible, consultation with an infectious diseases specialist or another physician who is an expert in the administration of antiretroviral agents is recommended. Such consultation should not, however, delay timely initiation of PEP.

PHS now recommends emtricitabine (FTC) plus tenofovir (TDF) (these two agents may be dispensed as Truvada®, a fixed-dose combination tablet) plus raltegravir (RAL) as HIV PEP for occupational exposures to HIV. This regimen is tolerable, potent, conveniently administered, and has been associated with minimal drug interactions. Additionally, although we have only limited data on the safety of RAL during pregnancy, this regimen could be administered to pregnant HCP as PEP (see discussion above). Preparation of this PEP regimen in single dose "starter packets," which are kept on-hand at sites expected to manage occupational exposures to HIV, may facilitate timely initiation of PEP.

Several drugs may be used as alternatives to FTC plus TDF plus RAL. TDF has been associated with renal toxicity,(69) and an alternative should be sought in HCP who have underlying renal

disease. Zidovudine (ZDV) could be used as an alternative to TDF and could be conveniently prescribed in combination with lamivudine (3TC), to replace both TDF and FTC, as Combivir®. Alternatives to RAL include darunavir (DRV) plus ritonavir (RTV), etravirine (ETV), rilpivirine (RPV), atazanavir (ATV) plus RTV, and lopinivir (LPV) plus RTV. When a more cost-efficient alternative to RAL is required, saquinivir (SQV) plus RTV could be considered. A list of preferred alternative PEP regimens is provided in Appendix A.

Some antiretroviral drugs are contraindicated as HIV PEP or should only be used for PEP under the guidance of expert consultants (Appendix A and B). Among these drugs are nevirapine (NVP), which should not be used and is contraindicated as PEP because of serious reported toxicities, including hepatotoxicty (with one instance of fulminant liver failure requiring liver transplantation), rhabdomyolysis, and hypersensitivity syndrome.(70-72) Antiretroviral drugs not routinely recommended for use as PEP because of the higher risk for potentially serious or life-threatening adverse events, include ddI and tipranavir (TPV). The combination of ddI and d4T should not be prescribed as PEP due to increased risk of toxicity (e.g., peripheral neuropathy, pancreatitis, and lactic acidosis). Additionally, abacavir (ABC) should only be used as HIV PEP in the setting of expert consultation, due to the need for prior HLA B57-01 testing to identify individuals at higher risk for a potentially fatal hypersensitivity reaction.(28) The fusion inhibitor, enfuvirtide (Fuzeon™, T20), is also not generally recommended as PEP, unless its use is deemed necessary during expert consultation, due to its subcutaneous route of administration, significant side effects, and potential for development of anti-T20 antibodies that may cause false-positive HIV antibody tests among uninfected patients.

When the source patient's virus is known or suspected to be resistant to one or more of the drugs considered for the PEP regimen, the selection of drugs to which the source person's virus is unlikely to be resistant is recommended; again, expert consultation is strongly advised. If this information is not immediately available, the initiation of PEP, if indicated, should not be delayed; the regimen can be modified after PEP has been initiated, whenever such modifications are deemed appropriate. For HCP who initiate PEP, re-evaluation of the exposed person should occur within 72 hours postexposure, especially if additional information about the exposure or source person becomes available.

Regular consultation with experts in antiretroviral therapy and HIV transmission is strongly recommended. Preferably, a process for involvement of an expert consultant should be formalized in advance of an exposure incident. Certain institutions have required consultation with a hospital epidemiologist or infectious diseases consultant when HIV PEP use is under consideration. At a minimum, expert consultation is recommended for the situations described in Box 1.

Resources for consultation are available from the following sources:

- PEPline at http://www.nccc.ucsf.edu/about_nccc/pepline/; telephone 888-448-4911;
- HIV Antiretroviral Pregnancy Registry at http://www.apregistry.com/index.htm ; Address: Research Park, 1011 Ashes Drive, Wilmington, NC 28405. Telephone: 800-258-4263; Fax: 800-800-1052; E-mail: registies@Kendle.com;
- FDA (for reporting unusual or severe toxicity to antiretroviral agents) at http://www.fda.gov/medwatch; telephone: 800-332-1088; address: MedWatch, The FDA

Safety Information and Adverse Event Reporting Program, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852;

- CDC's "Cases of Public Health Importance" (COPHI) coordinator (for reporting HIV infections in HCP and failures of PEP) at telephone 404-639-2050
- HIV/AIDS Treatment Information Service at http://aidsinfo.nih.gov.

Follow-Up of Exposed HCP

Importance of Follow-up Appointments

HCP who have experienced occupational exposure to HIV should receive follow-up counseling, postexposure testing, and medical evaluation regardless of whether they take PEP. Greater emphasis is placed upon the importance of follow-up of HCP on HIV PEP within 72 hours of exposure and improving follow-up care provided to exposed HCP (Box 2). Careful attention to follow-up evaluation within 72 hours of exposure can: 1) provide another (and perhaps less anxiety-ridden) opportunity to allow the exposed HCP to ask questions and for the counselor to make certain that the exposed HCP has a clear understanding of the risks for infection and the risks and benefits of PEP, 2) ensure that continued treatment with PEP is indicated, 3) increase adherence to HIV PEP regimens, 4) manage associated symptoms and side-effects more effectively, 5) provide an early opportunity for ancillary medications or regimen changes, 6) improve detection of serious adverse effects, and 7) improve the likelihood of follow-up serologic testing for a larger proportion of exposed personnel to detect infection. Closer follow-up should in turn reassure HCP who become anxious after these events.(73, 74) The psychological impact of needlesticks or exposure to blood or body fluid should not be underestimated for HCP. Exposed personnel should be advised to use precautions (e.g., use of

barrier contraception, avoid blood or tissue donations, pregnancy, and if possible, breastfeeding) to prevent secondary transmission, especially during the first 6-12 weeks postexposure. Providing HCP with psychological counseling should be an essential component of the management and care of exposed HCP.

Postexposure Testing

HIV testing should be used to monitor HCP for seroconversion after occupational HIV exposure. After baseline testing at the time of exposure, follow-up testing should be performed at 6 weeks, 12 weeks, and 6 months after exposure. Use of fourth generation HIV Ag/Ab combination immunoassays allow for earlier detection of HIV infection.(60, 62, 75) If a provider is certain that a fourth generation combination HIV Ag/Ab test is used, HIV follow-up testing could be concluded earlier than 6 months after exposure. In this instance, an alternative follow-up testing schedule could be used (e.g., baseline testing, 6 weeks, and then concluded at 4 months after the exposure). Extended HIV follow-up (e.g., for 12 months) is recommended for HCP who become infected with HCV after exposure to a source who is co-infected with HIV and HCV. Whether extended follow-up is indicated in other circumstances (e.g., exposure to a source co-infected with HIV and HCV in the absence of HCV seroconversion or for exposed persons with a medical history suggesting an impaired ability to mount an antibody response to acute infection) is unknown. Although rare instances of delayed HIV seroconversion have been reported,(76, 77) adding to an exposed persons' anxiety by routinely extending the duration of postexposure follow-up is not warranted. However, decisions to extend follow-up in a particular situation should be based on the clinical judgment of the exposed person's health-care provider and should not be precluded because of HCP anxiety. HIV tests should also be performed on any exposed

person who has an illness compatible with an acute retroviral syndrome, regardless of the interval since exposure. A person in whom HIV infection is identified should be referred to a specialist who has expertise in HIV treatment and counseling for medical management. Health-care providers caring for persons who have occupationally acquired HIV infection should report these cases to their state health departments and to CDC's COPHI coordinator at telephone 404-639-2050.

Monitoring and Management of PEP Toxicity

If PEP is used, HCP should be monitored for drug toxicity by testing at baseline and again 2 weeks after starting PEP. In addition, HCP taking antiretrovirals should be evaluated if any acute symptoms develop while on therapy. The scope of testing should be based on medical conditions in the exposed person and the known and anticipated toxicities of the drugs included in the PEP regimen. Minimally, laboratory monitoring for toxicity should include a complete blood count and renal and hepatic function tests. If toxicities are identified, modification of the regimen should be considered after expert consultation. In addition, depending on the clinical situation, further diagnostic studies may be indicated (e.g., monitoring for hyperglycemia in a diabetic whose regimen includes a PI).

Exposed HCP who choose to take PEP should be advised of the importance of completing the prescribed regimen. Information should be provided about: potential drug interactions and prescription/nonprescription drugs and nutritional supplements that should not be taken with PEP or require dose or administration adjustments, side effects of prescribed drugs, measures (including pharmacological interventions) that may assist in minimizing side effects, and methods of clinical monitoring for toxicity during the follow-up period. HCP should be advised

that evaluation of certain symptoms (e.g., rash, fever, back or abdominal pain, pain on urination or blood in the urine, dark urine, yellowing of the skin or whites of the eyes, or symptoms of hyperglycemia (e.g., increased thirst or frequent urination) should not be delayed. Serious adverse events[§] should be reported to FDA's MedWatch program.

Reevaluation and Updating of HIV PEP Guidelines

As new antiretroviral agents for treatment of HIV infection and additional information concerning early HIV infection and prevention of HIV transmission become available, the PHS Interagency Working Group will assess the need to update these guidelines. Updates will be published periodically as appropriate.

^U.S. Public Health Service Working Group: Laura W. Cheever, MD, ScM, (HRSA); Ahmed Gomaa, MD, ScD, MSPH, (CDC); David K. Henderson, MD, (NIH); Walid Heneine, PhD, (CDC); David T. Kuhar, MD, (CDC); Adelisa L. Panlilio, MD (CDC); Kimberly A. Struble, PharmD, (FDA); Vasavi Thomas, RPh, MPH , (CDC)

***Expert Panel Consultants:** Judith Aberg, MD, FIDSA, FACP, New York University; Joseph Eron, MD, University of North Carolina, Chapel Hill; Ronald Goldschmidt, MD, University of California, San Francisco; Mark Russi, MD, MPH, Yale University; Michael S. Saag, MD, University of Alabama, Birmingham ; Michael L. Tapper, MD, Lennox Hill Hospital

Competing Interests

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Information included in these recommendations might not represent FDA approval or approved labeling for the particular product or indications in question. Specifically, the terms "safe" and "effective" might not be synonymous with the FDA-defined legal standard for product approval.

References

1. Siegel JD, Rhinehart E, Jackson M, Chiarello L. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Health Care Settings. *Am J Infect Control.* 2007;35(10 Suppl 2):S65-164.
2. CDC. Public Health Service statement on management of occupational exposure to human immunodeficiency virus, including considerations regarding zidovudine postexposure use. *MMWR Recomm Rep*. 1990;39(RR-1):1-14.
3. CDC. Update: provisional Public Health Service recommendations for chemoprophylaxis after occupational exposure to HIV. *MMWR Morb Mortal Wkly Rep.* 1996;45(22):468-80.
4. CDC. Public Health Service guidelines for the management of health-care worker exposures to HIV and recommendations for postexposure prophylaxis. *MMWR Recomm Rep.* 1998;47(RR-7):1-33.
5. CDC. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. *MMWR Recomm Rep.* 2001;50(RR-11):1-52.
6. Panlilio AL, Cardo DM, Grohskopf LA, Heneine W, Ross CS. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. *MMWR Recomm Rep.* 2005;54(RR-9):1-17.
7. Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention. Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2011;60(RR-7):1-45.
8. Smith DK, Grohskopf LA, Black RJ, Auerbach JD, Veronese F, Struble KA, et al. 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 Recomm Rep*. 2005;54(RR-2):1-20.
9. Havens PL; American Academy of Pediatrics Committee on Pediatric AIDS. Postexposure prophylaxis in children and adolescents for nonoccupational exposure to human immunodeficiency virus. *Pediatrics.* 2003;111(6 Pt 1):1475-89.
10. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Published 2012; Accessed August 23, 2012.
11. Bell DM. Occupational risk of human immunodeficiency virus infection in healthcare workers: an overview. *Am J Med.* 1997;102(5B):9-15.
12. CDC. The National Surveillance System for Healthcare Workers (NaSH): Summary Report for Blood and Body Fluid Exposures, Data Collected From Participating Healthcare Facilities (June 1995 through December 2007). http://www.cdc.gov/nhsn/PDFs/NaSH/NaSH-Report-6-2011.pdf. June 2011.
13. Department of Health and Human Services, Centers for Disease Control and Prevention, editors. Meeting Minutes: Healthcare Infection Control Practices Advisory Committee (HICPAC). http://www.cdc.gov/maso/facm/pdfs/HICPAC/2011110304_HICPAC_MINUTES.pdf. November 2011. Washington D.C.
14. Department of Health and Human Services, Centers for Disease Control and Prevention, editors. Meeting Minutes: Healthcare Infection Control Practices Advisory Committee (HICPAC). http://www.cdc.gov/maso/facm/pdfs/HICPAC/2012061415_HICPAC_MINUTES.pdf. June 2012. Atlanta, GA.

15. Wahn V, Kramer HH, Voit T, Bruster HT, Scrampical B, Scheid A. Horizontal transmission of HIV infection between two siblings. *Lancet*. 1986;2(8508):694.
16. Anonymous. Transmission of HIV by human bite. *Lancet*. 1987;2(8857):522.
17. Richman KM, Rickman LS. The potential for transmission of human immunodeficiency virus through human bites. *J Acquir Immune Defic Syndr.* 1993;6(4):402-6.
18. Vidmar L, Poljak M, Tomazic J, Seme K, Klavs I. Transmission of HIV-1 by human bite. *Lancet.* 1996;347(9017):1762.
19. Deshpande AK, Jadhav SK, Bandivdekar AH. Possible transmission of HIV Infection due to human bite. *AIDS Res Ther.* 2011;8:16.
20. Andreo SM, Barra LA, Costa LJ, Sucupira MC, Souza IE, Diaz RS. HIV type 1 transmission by human bite. *AIDS Res Hum Retroviruses.* 2004;20(4):349-50.
21. Ippolito G, Puro V, De Carli G; The Italian Study Group on Occupational Risk of HIV infection. Arch Intern Med. The risk of occupational human immunodeficiency virus infection in health care workers: Italian Multicenter Study. *Arch Intern Med.* 1993;153(12):1451-8.
22. Cardo DM, Culver DH, Ciesielski CA, Srivastava PU, Marcus R, Abiteboul D, et al.; Centers for Disease Control and Prevention Needlestick Surveillance Group. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. *N Engl J Med.* 1997;337(21):1485-90.
23. Mast ST, Woolwine JD, Gerberding JL. Efficacy of gloves in reducing blood volumes transferred during simulated needlestick injury. *J Infect Dis.* 1993;168(6):1589-92.
24. Furtado MR, Callaway DS, Phair JP, Kunstman KJ, Stanton JL, Macken CA, et al. Persistence of HIV-1 transcription in peripheral-blood mononuclear cells in patients receiving potent antiretroviral therapy. *N Engl J Med.* 1999;340(21):1614-22.
25. Ibanez A, Puig T, Elias J, Clotet B, Ruiz L, Martinez MA. Quantification of integrated and total HIV-1 DNA after long-term highly active antiretroviral therapy in HIV-1-infected patients. *AIDS.* 1999;13(9):1045-9.
26. Sturmer M, Doerr HW, Berger A, Gute P. Is transmission of HIV-1 in non-viraemic serodiscordant couples possible? *Antiviral therapy.* 2008;13(5):729-32.
27. Tubiana R, Le Chenadec J, Rouzioux C, Mandelbrot L, Hamrene K, Dollfus C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis.* 2010;50(4):585-96.
28. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Published 2012. Accessed September 17, 2012
29. Shih CC, Kaneshima H, Rabin L, Namikawa R, Sager P, McGowan J, et al. Postexposure prophylaxis with zidovudine suppresses human immunodeficiency virus type 1 infection in SCID-hu mice in a time-dependent manner. *J Infect Dis.* 1991;163(3):625-7.
30. Tsai CC, Emau P, Follis KE, Beck TW, Benveniste RE, Bischofberger N, et al. Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIVmne infection depends critically on timing of initiation and duration of treatment. *J Virol.* 1998;72(5):4265-73.
31. Henderson DK. Human Immunodeficiency Virus in Health Care Settings. In: GL Mandell, JE Bennett, R Dolin, editors. *Principles and Practice of Infectious Diseases.* 7 ed. New York: Elsevier, 2009. p. 3753-70.

32. Wang SA, Panlilio AL, Doi PA, White AD, Stek M, Jr., Saah A. Experience of healthcare workers taking postexposure prophylaxis after occupational HIV exposures: findings of the HIV Postexposure Prophylaxis Registry. *Infect Control Hosp Epidemiol.* 2000;21(12):780-5.
33. Swotinsky RB, Steger KA, Sulis C, Snyder S, Craven DE. Occupational exposure to HIV: experience at a tertiary care center. *J Occup Environ Med.* 1998;40(12):1102-9.
34. Parkin JM, Murphy M, Anderson J, El-Gadi S, Forster G, Pinching AJ. Tolerability and side-effects of post-exposure prophylaxis for HIV infection. *Lancet.* 2000;355(9205):722-3.
35. Puro V. Post-exposure prophylaxis for HIV infection. Italian Registry of Post-Exposure Prophylaxis. *Lancet.* 2000;355(9214):1556-7.
36. Lee LM, Henderson DK. Tolerability of postexposure antiretroviral prophylaxis for occupational exposures to HIV. *Drug Saf.* 2001;24(8):587-97.
37. Russi M, Buitrago M, Goulet J, Calello D, Perlotto J, van Rhijn D, et al. Antiretroviral prophylaxis of health care workers at two urban medical centers. *J Occup Environ Med.* 2000;42(11):1092-100.
38. Garb JR. One-year study of occupational human immunodeficiency virus postexposure prophylaxis. *J Occup Environ Med.* 2002;44(3):265-70.
39. Grime PR, Ris L, Binns C, Carruthers JR, Williams S. Pan-Thames survey of occupational exposure to HIV and the use of post-exposure prophylaxis in 71 NHS trusts. *J Infect.* 2001;42(1):27-32.
40. Puro V, DeCarli G, Soldani F, et.al. Adverse drug reactions associated with PEP. Presented at: 10th Conference on Retroviruses and Opportunistic Infections, 2003, Boston. Poster No. 711.
41. Beltrami EM, Cheingsong R, Heneine WM, Respess RA, Orelien JG, Mendelson MH, et al. Antiretroviral drug resistance in human immunodeficiency virus-infected source patients for occupational exposures to healthcare workers. *Infect Control Hosp Epidemiol.* 2003;24(10):724-30.
42. Johnson VA, Calvez V, Gunthard HF, Paredes R, Pillay D, Shafer R, et al. 2011 update of the drug resistance mutations in HIV-1. *Topics in antiviral medicine.* 2011;19(4):156-64.
43. Hawkins DA, Asboe D, Barlow K, Evans B. Seroconversion to HIV-1 following a needlestick injury despite combination post-exposure prophylaxis. *J Infect.* 2001;43(1):12-5.
44. Beltrami EM, Luo CC, de la Torre N, Cardo DM. Transmission of drug-resistant HIV after an occupational exposure despite postexposure prophylaxis with a combination drug regimen. *Infect Control Hosp Epidemiol.* 2002;23(6):345-8.
45. Perdue B, Rufael DW, Mellors J, Quinn T, Margolick J. HIV-1 Transmission by a Needle-stick Injury Despite Rapid Initiation of Four-Drug Postexposure Prophylaxis. Presented at: 6th Conference on Retroviruses and Opportunistic Infections; 1999, Chicago
46. Lockman S, Creek T. Acute maternal HIV infection during pregnancy and breast-feeding: substantial risk to infants. *J Infect Dis.* 2009;200(5):667-9.
47. Kourtis AP. Antiretroviral drug use during pregnancy and risk of premature delivery: is there a connection? *J Infect Dis.* 2010;201(7):978-80.
48. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Infect.* 2002;78(1):58-9.
49. Mandelbrot L, Kermarrec N, Marcollet A, Lafanechere A, Longuet P, Chosidow D, et al. Case report: nucleoside analogue-induced lactic acidosis in the third trimester of pregnancy. *AIDS.* 2003;17(2):272-3.
50. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 July 2011. Wilmington, NC: Registry Coordinating Center, 2011

51. Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS.* 2011;25(18):2301-4.
52. Blanche S, Tardieu M, Benhammou V, Warszawski J, Rustin P. Mitochondrial dysfunction following perinatal exposure to nucleoside analogues. *AIDS.* 2006;20(13):1685-90.
53. Thorne C, Newell ML. Safety of agents used to prevent mother-to-child transmission of HIV: is there any cause for concern? *Drug Saf*. 2007;30(3):203-13.
54. Mirochnick M, Thomas T, Capparelli E, Zeh C, Holland D, Masaba R, et al. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrob Agents Chemother.* 2009;53(3):1170-6.
55. Benaboud S, Pruvost A, Coffie PA, Ekouevi DK, Urien S, Arrive E, et al. Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2. *Antimicrob Agents Chemother*. 2011;55(3):1315-7.
56. Shapiro RL, Hughes MD, Ogwu A, Kitch D, Lockman S, Moffat C, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *N Engl J Med.* 2010;362(24):2282-94.
57. Dryden-Peterson S, Shapiro RL, Hughes MD, Powis K, Ogwu A, Moffat C, et al. Increased risk of severe infant anemia after exposure to maternal HAART, Botswana. *J Acquir Immune Defic Syndr.* 2011;56(5):428-36.
58. Humphrey JH, Marinda E, Mutasa K, Moulton LH, Iliff PJ, Ntozini R, et al. Mother to child transmission of HIV among Zimbabwean women who seroconverted postnatally: prospective cohort study. *BMJ.* 2010;341:c6580.
59. Panlilio AL, Sinkowitz-Cochran R, Grady MA, Cardo DM. Barriers to and facilitators of implementing U.S. Public Health Service (PHS) guidelines on occupational exposure management by emergency physicians. Presented at: 13th Annual Meeting of the Society for Health-care Epidemiology of America, 2003, Arlington, VA. Abstract no. 240.
60. Masciotra S, McDougal JS, Feldman J, Sprinkle P, Wesolowski L, Owen SM. Evaluation of an alternative HIV diagnostic algorithm using specimens from seroconversion panels and persons with established HIV infections. *J Clin Virol.* 2011;52 Suppl 1:S17-22.
61. Branson BM. The future of HIV testing. *J Acquir Immune Defic Syndr.* 2010;55 Suppl 2:S102-5.
62. Chavez P, Wesolowski L, Patel P, Delaney K, Owen SM. Evaluation of the performance of the Abbott ARCHITECT HIV Ag/Ab Combo Assay. *J Clin Virol.* 2011;52 Suppl 1:S51-5.
63. Otten RA, Smith DK, Adams DR, Pullium JK, Jackson E, Kim CN, et al. Efficacy of postexposure prophylaxis after intravaginal exposure of pig-tailed macaques to a human-derived retrovirus (human immunodeficiency virus type 2). *J Virol.* 2000;74(20):9771-5.
64. Tsai CC, Follis KE, Sabo A, Beck TW, Grant RF, Bischofberger N, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl)adenine. *Science.* 1995;270(5239):1197-9.
65. Gulick RM, Mellors JW, Havlir D, Eron JJ, Gonzalez C, McMahon D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med.* 1997;337(11):734-9.
66. Hirsch M, Steigbigel R, Staszewski S, Mellors J, Scerpella E, Hirschel B, et al. A randomized, controlled trial of indinavir, zidovudine, and lamivudine in adults with advanced human immunodeficiency virus type 1 infection and prior antiretroviral therapy. *J Infect Dis.* 1999;180(3):659-65.
67. Wheeler WH, Ziebell RA, Zabina H, Pieniazek D, Prejean J, Bodnar UR, et al. Prevalence of transmitted drug resistance associated mutations and HIV-1 subtypes in new HIV-1 diagnoses, U.S.-2006. *AIDS.* 2010;24(8):1203-12.
68. Kim D, Wheeler W, Ziebell R, Johnson J, Prejean J, Heneine W, et al. Prevalence of Transmitted Antiretroviral Drug Resistance among Newly-diagnosed HIV-1-infected Persons, US, 2007.

Presented at: CROI 2010: 17th Conference on Retroviruses and Opportunistic Infections, 2010, San Francisco.

69. Scherzer R, Estrella M, Li Y, Deeks SG, Grunfeld C, Shlipak MG. Association of tenofovir exposure with kidney disease risk in HIV infection. *AIDS.* 2012;26(7):867-875.
70. Cattelan AM, Erne E, Salatino A, Trevenzoli M, Carretta G, Meneghetti F, et al. Severe hepatic failure related to nevirapine treatment. *Clin Infect Dis.* 1999;29(2):455-6.
71. Johnson S, Baraboutis JG. Adverse effects associated with use of nevirapine in HIV postexposure prophylaxis for 2 health care workers. *JAMA.* 2000;284(21):2722-3.
72. CDC. Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures--worldwide, 1997-2000. *MMWR Morb Mortal Wkly Rep.* 2001;49(51-52):1153-6.
73. Armstrong K, Gorden R, Santorella G. Occupational exposure of health care workers (HCWs) to human immunodeficiency virus (HIV): stress reactions and counseling interventions. *Soc Work Health Care.* 1995;21(3):61-80.
74. Meienberg F, Bucher HC, Sponagel L, Zinkernagel C, Gyr N, Battegay M. Anxiety in health care workers after exposure to potentially HIV-contaminated blood or body fluids. *Swiss Med Wkly.* 2002;132(23-24):321-4.
75. Bentsen C, McLaughlin L, Mitchell E, Ferrera C, Liska S, Myers R, et al. Performance evaluation of the Bio-Rad Laboratories GS HIV Combo Ag/Ab EIA, a 4th generation HIV assay for the simultaneous detection of HIV p24 antigen and antibodies to HIV-1 (groups M and O) and HIV-2 in human serum or plasma. *J Clin Virol.* 2011;52 Suppl 1:S57-61.
76. Ridzon R, Gallagher K, Ciesielski C, Ginsberg MB, Robertson BJ, Luo CC, et al. Simultaneous transmission of human immunodeficiency virus and hepatitis C virus from a needle-stick injury. *N Engl J Med.* 1997;336(13):919-22.
77. Ciesielski CA, Metler RP. Duration of time between exposure and seroconversion in healthcare workers with occupationally acquired infection with human immunodeficiency virus. *Am J Med.* 1997;102(5B):115-6.

BOX 1. Situations for Which Expert Consultation for Human Immunodeficiency Virus (HIV) Postexposure Prophylaxis (PEP) is Recommended

Delayed (i.e., later than 72 hours) exposure report
- Interval after which benefits from PEP are undefined

Unknown source (e.g., needle in sharps disposal container or laundry)
- Use of PEP to be decided on a case-by-case basis
- Consider severity of exposure and epidemiologic likelihood of HIV exposure
- Do not test needles or other sharp instruments for HIV

Known or suspected pregnancy in the exposed person
- Provision of PEP should not be delayed while awaiting expert consultation

Breastfeeding in the exposed person
- Provision of PEP should not be delayed while awaiting expert consultation

Known or suspected resistance of the source virus to antiretroviral agents
- If source person's virus is known or suspected to be resistant to one or more of the drugs considered for PEP, selection of drugs to which the source person's virus is unlikely to be resistant recommended
- Do not delay initiation of PEP while awaiting any results of resistance testing of the source person's virus

Toxicity of the initial PEP regimen
- Symptoms (e.g. GI symptoms and others) often manageable without changing PEP regimen by prescribing antimotility or antiemetic agents
- Counseling and support for management of side effects is very important as symptoms are often exacerbated by anxiety.

Serious medical illness in the exposed person
- Significant underlying illness (e.g. renal disease) or an exposed provider already taking multiple medications may increase the risk of drug toxicity and drug-drug interactions

Expert consultation can be made with local experts or by calling the National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline) at 888-448-4911.

BOX 2. Follow-Up of Health-Care Personnel (HCP) Exposed to Known or Suspected Human Immunodeficiency Virus (HIV)-Positive Sources

Counseling (At the time of exposure, and at follow-up appointments) Exposed HCP should be advised to use precautions (e.g., use of barrier contraception, avoid blood or tissue donations, pregnancy, and if possible, breastfeeding) to prevent secondary transmission, especially during the first 6–12 weeks postexposure.

For exposures for which PEP is prescribed, HCP should be informed regarding:

- possible drug toxicities (e.g. rash and hypersensitivity reactions which could imitate acute HIV seroconversion and the need for monitoring)
- possible drug interactions, and
- the need for adherence to PEP regimens.

Early Reevaluation after Exposure Regardless of whether a healthcare provider is taking PEP, reevaluation of exposed HCP within 72 hours after exposure is strongly recommended, as additional information about the exposure or source person may be available

Follow-up Testing and Appointments Follow-up testing at a minimum should include:

- HIV testing at baseline, 6 weeks, 12 weeks, and 6 months postexposure; Alternatively, if the clinician is certain that a 4th generation combination HIV p24 antigen-HIV antibody test is being utilized, then HIV testing could be performed at baseline, 6 weeks, and concluded at 4 months postexposure.
- Complete Blood counts, Renal and Hepatic Function Tests (At baseline and 2 weeks postexposure; further testing may be indicated if abnormalities were detected)

HIV testing results should preferably be given to the exposed healthcare provider at face to face appointments

APPENDIX A: HIV Postexposure Prophylaxis Regimens

PREFERRED HIV PEP REGIMEN
Raltegravir (Isentress®; RAL) 400mg PO Twice Daily Plus Truvada™,1 PO Once Daily [Tenofovir DF (Viread®; TDF) 300mg + emtricitabine (Emtriva™; FTC) 200mg]

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. Prescribers unfamiliar with these agents/regimens should consult physicians familiar with the agents and their toxicities.)*^**	
Raltegravir (Isentress®; RAL)	Tenofovir DF (Viread®; TDF) + emtricitabine (Emtriva™; FTC); available as Truvada™
Darunavir (Prezista®; DRV) + ritonavir (Norvir®; RTV)	Tenofovir DF (Viread®; TDF) + lamivudine (Epivir®; 3TC)
Etravirine (Intelence®; ETR)	Zidovudine (Retrovir™; ZDV; AZT) + lamivudine (Epivir®; 3TC); available as Combivir®
Rilpivirine (Edurant™; RPV)	Zidovudine (Retrovir®; ZDV; AZT) + emtricitabine (Emtriva™; FTC)
Atazanavir (Reyataz®; ATV) + ritonavir (Norvir®; RTV)	
Lopinavir/ritonavir (Kaletra®; LPV/RTV)	
The following alternative is a complete fixed-dose combination regimen and no additional antiretrovirals are needed: Stribild™ (elvitegravir, cobicistat, tenofovir DF, emtricitabine)	

ALTERNATIVE ANTIRETROVIRAL AGENTS FOR USE AS PEP ONLY WITH EXPERT CONSULTATION^
Abacavir (Ziagen®; ABC)
Efavirenz (Sustiva®; EFV)
Enfuvirtide (Fuzeon™; T20)
Fosamprenavir (Lexiva®; FOSAPV)
Maraviroc (Selzentry®; MVC)
Saquinavir (Invirase®; SQV)
Stavudine (Zerit®; d4T)

ANTIRETROVIRAL AGENTS GENERALLY NOT RECOMMENDED FOR USE AS PEP
Didanosine (Videx EC®; ddI)
Nelfinavir (Viracept®; NFV)
Tipranavir (Aptivus®; TPV)

ANTIRETROVIRAL AGENTS CONTRAINDICATED AS PEP
Nevirapine (Viramune®; NVP)

--- For consultation or assistance with HIV PEP, contact PEPline at telephone 888-448-4911 or visit their website http://www.nccc.ucsf.edu/about_nccc/pepline/. DF, disoproxil fumarate; PO, per os.

*The alternatives regimens are listed in order of preference, however, other alternatives may be reasonable based upon patient and clinician preference.

^For Drug Dosing Information, see Appendix B

APPENDIX B:
Information on HIV Postexposure Prophylaxis Medications*^

Drug Name	Drug Class	Dosing (Dosage Form)	Advantages	Disadvantages
Abacavir (Ziagen®; ABC)	Nucleoside Reverse Transcriptase Inhibitor (NRTI)	ABC : 600 mg daily (available as a 300 mg tablet) Also available as component of fixed-dose combination Epzicom®, dosed daily (300mg 3TC + 600mg ABC) Trizivir®, dosed twice daily (150mg 3TC + 300mg ABC + 300mg AZT)	Take without regard for food	Potential for life-threatening ABC hypersensitivity reaction (rash, fever, nausea, vomiting, diarrhea, abdominal pain, malaise, respiratory symptoms) in patients with HLA-B*5701; requires patient testing prior to use which may not be available nor practical prior to initiating PEP
Atazanavir (Reyataz®; ATV)	Protease Inhibitor (PI)	ATV: 300 mg + RTV: 100 mg once daily (Preferred dosing for PEP^) ATV: 400 mg once daily without RTV (Alternative dosing-may not be used in combination with TDF) (available as 100, 150, 300, and 200 mg capsules)	Well tolerated	Indirect hyperbilirubinemia and jaundice common Skin rash Nephrolithiasis Potential for serious or life-threatening drug interactions that may affect dosing Absorption depends on low pH; Caution when coadministered with H2 Antagonists, antacids, and proton pump inhibitors PR interval prolongation

				Caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation Must be given with food
Darunavir (Prezista®; DRV)	PI	DRV: 800 mg once daily + RTV: 100 mg once daily (Preferred dosing for PEP^) DRV: 600 mg twice daily + RTV: 100 mg twice daily (Alternative dosing) (available as 75, 150, 400, and 600 mg tablets)	Well tolerated	Rash (DRV has sulfonamide moiety) Diarrhea, nausea, headache Hepatotoxicity Potential for serious or life-threatening drug interactions that may affect dosing Must be given with food and with RTV
Efavirenz (Sustiva®; EFV)	Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)	EFV: 600 mg daily (available as 50, 200 mg capsules and 600 mg tablets) Also available as component of fixed-dose combination Atripla®, dosed daily (200mg FTC + 300mg TDF + 600mg EFV)	Available as a complete regimen dosed once per day	Rash Neuropsychiatric side effects (e.g., dizziness, somnolence, insomnia, or abnormal dreaming) common; severe psychiatric symptoms possible (dosing before bedtime might minimize these side effects); use with caution in shift workers Do not use during pregnancy; Teratogen in

				nonhuman primates Potential for serious or life-threatening drug interactions that may affect dosing May cause false-positive results with some cannabinoid and benzodiazepine screening assays Take on an empty stomach
Elvitegravir (EVG)	Integrase Strand Transfer Inhibitor (INSTI)	Available as a component of fixed-dose combination Stribild™, dosed daily (150mg EVG + 150mg cobicistat + 300mg TDF + 200mg FTC)	Well tolerated Available as a complete regimen dosed once per day	Diarrhea, nausea, headache Nephrotoxicity; should not be administered to individuals with acute or chronic kidney injury or those with eGFR<70 Cobicistat is a pharmacokinetic enhancer to increase EVG exposures, has no antiviral activity, but is a potent CYP3A inhibitor Potential for serious or life-threatening drug interactions Must be given with food
Emtricitabine (Emtriva™; FTC)	NRTI	200 mg once daily (available as 200 mg capsule) Also available as	Well tolerated Minimal toxicity Minimal drug	Rash perhaps more frequent than with 3TC Hyperpigmentatio

		component of fixed-dose combination Atripla®, dosed daily (200mg FTC + 300mg TDF + 600mg EFV) Complera™, dosed daily (25mg RPV+ 300mg TDF + 200mg FTC) Stribild™, dosed daily (150mg EVG + 150mg cobicistat + 300mg TDF + 200mg FTC) Truvada™, dosed daily (200mg FTC + 300mg TDF)	interactions Take without regard for food	n/skin discoloration If the PEP recipient has chronic hepatitis B, withdrawal of this drug may cause an acute hepatitis exacerbation
Enfuvirtide (Fuzeon™; T20)	Fusion Inhibitor (FI)	T20: 90 mg (1 ml) twice daily by subcutaneous injection (available as Single-dose vial, reconstituted to 90 mg/ml)		Local injection site reactions occur in almost 100% of patients Never studied among antiretroviral-naïve or HIV-negative patients False-positive EIA HIV antibody tests might result from formation of anti-T20 antibodies that cross-react with anti-gp41 antibodies Twice-daily injection
Etravirine (Intelence®; ETR)	NNRTI	200 mg twice daily (available as 100mg and 200mg tablets)	Well tolerated and has not had the same frequency of CNS side effects reported as EFV	Rash (including SJS) and hypersensitivity (sometimes with organ dysfunction, including hepatic failure) Nausea

				Potential for serious or life-threatening drug interactions that may affect dosing Must be given with food
Fosamprenavir (Lexiva®; FOSAPV)	PI	FOSAPV: 1400 mg daily + RTV: 100 mg once daily (Preferred dosing for PEP) FOSAPV: 1400 mg twice daily without RTV (Alternative dosing) (available as 700 mg tablets)	Well tolerated	Diarrhea, nausea, vomiting, headache, skin rash (FOSAPV has sulfonamide moiety) Potential for serious or life-threatening drug interactions that may affect dosing Oral contraceptives decrease FOSAPV concentrations Take with food if given with RTV
Lamivudine (Epivir®; 3TC)	NRTI	3TC : 300 mg once daily (Preferred dosing for PEP) 3TC : 150 mg twice daily (Alternative dosing) (available as a 150 or 300 mg tablet) Also available as component of fixed-dose combination generic lamivudine/zidovudine, dosed twice daily (150mg 3TC + 300mg AZT) Combivir®, dosed twice daily (150mg 3TC + 300mg AZT) Epzicom®, dosed daily	Well tolerated Minimal toxicity Minimal drug interactions Take without regard for food	If the PEP recipient has chronic hepatitis B, withdrawal of this drug may cause an acute hepatitis exacerbation

		(300mg 3TC + 600mg ABC) Trizivir®, dosed twice daily (150mg 3TC + 300mg ABC + 300mg AZT)		
Lopinavir/ritonavir (Kaletra®; LPV/RTV)	PI	Kaletra®: 400/100 mg = 2 tablets twice daily (Preferred dosing for PEP) Kaletra®: 800/200 mg = 4 tablets once daily (Alternative dosing) (available as 200/50 mg tablets)	Take without regard to food	GI intolerance, nausea, vomiting, diarrhea are common PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or receiving other drugs with similar effect. Potential for serious or life-threatening drug interactions that may affect dosing
Maraviroc (Selzentry®; MVC)	CCR5 Coreceptor Antagonist	MVC: 300 mg twice daily (dose may need adjustment by expert consultant if on concomitant CYP3A inducers) (available as 150 and 300 mg tablets)	Well tolerated	Abdominal pain, cough, dizziness, musculoskeletal symptoms, pyrexia, rash, orthostatic hypotension Hepatotoxicity which may present with an allergic reaction including rash. Requires HIV tropism testing of source virus before treatment to ensure CCR5 tropic virus and efficacy, which

				may not be available nor practical prior to initiating PEP Potential for serious or life-threatening drug interactions that may affect dosing Dose adjustments for MVC required when given with potent CYP3A inhibitors or inducers
Raltegravir (Isentress®; RAL)	INSTI	400 mg twice daily (available as 400 mg tablet)	Well tolerated Minimal drug interactions Take without regard for food	Insomnia, nausea, fatigue, headache, severe skin and hypersensitivity reactions have been reported
Rilpivirine (Edurant™; RPV)	NNRTI	25 mg once daily (available as 25mg tablets) Also available as component of fixed-dose combination Complera™, dosed daily (25mg RPV + 300mg TDF + 300mg FTC)	Well tolerated and fewer rashes and fewer discontinuations for CNS adverse effects compared to EFV Available as a complete regimen dosed once per day	Depression, insomnia, rash, hypersensitivity, headache Potential for serious or life-threatening drug interactions that may affect dosing Caution when coadministered with H2 antagonists and antacids Coadministration with proton pump inhibitors is contraindicated Use RPV with caution when coadministered with a drug having a known risk

				of torsades de pointes. Must be given with food
Saquinavir (Invirase®; SQV)	PI	SQV: 1,000 mg + RTV: 100 mg twice daily (Preferred dosing for PEP) (available as 500 mg tablets)	Well-tolerated, although GI events common	GI intolerance, nausea, diarrhea, headache Pretreatment ECG recommended SQV/r is not recommended for patients with any of the following conditions: (1) congenital or acquired QT prolongation; (2) pretreatment ECG >450 msec; (3) on concomitant therapy with other drugs that prolong QT interval; (4) complete AV block without implanted pacemakers; (5) risk of complete AV block. PR and QT interval prolongations, torsades de pointes has been reported Potential for serious or life-threatening drug interactions that may affect dosing Must be given with food
Stavudine (Zerit®; d4T)	NRTI	d4T : 40 mg twice daily if body weight is >60 kg d4T : 30 mg twice	Take without regard for food	GI side effects include diarrhea and nausea

		daily if body weight is <60 kg (available as 15, 20, 30, and 40 mg tablets)		Hepatotoxicity, neurologic symptoms (e.g. peripheral neuropathy), and pancreatitis
Tenofovir DF (Viread®; TDF)	NRTI	300 mg once daily (available as 300 mg tablet) Also available as component of fixed-dose combination Atripla®, dosed daily (200mg FTC+ 300mg TDF + 600mg EFV) Complera™, dosed daily (25mg RPV + 300mg TDF + 200mg FTC) Stribild™, dosed daily (150mg EVG + 150mg cobicistat + 300mg TDF + 200mg FTC) Truvada™, dosed daily (200mg FTC + 300mg TDF)	Well tolerated Take without regard for food	Asthenia, headache, diarrhea, nausea, vomiting Nephrotoxicity If the PEP recipient has chronic hepatitis B, withdrawal of this drug may cause an acute hepatitis exacerbation Drug interactions
Zidovudine (Retrovir®; ZDV; AZT)	NRTI	AZT : 300 mg twice daily (available as 100 mg capsule or 300 mg tablet) Also available as component of fixed-dose combination generic lamivudine/zidovudine, dosed twice daily (150mg 3TC + 300mg AZT) Combivir®, dosed twice daily (150mg 3TC + 300mg AZT) Trizivir®, dosed twice daily (150 mg 3TC +	Take without regard for food	Side effects (especially nausea, vomiting, headache, insomnia, and fatigue) common and might result in low adherence Anemia and neutropenia

		300mg ABC + 300mg AZT)		

*This Appendix does not provide comprehensive information on each individual drug. For detailed information, please refer to individual drug package inserts. AV, atrioventricular; CNS, central nervous system; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EIA, enzyme immunoassay; GI, gastrointestinal; SJS, Stevens-Johnson syndrome.

^Certain antiretroviral agents such as protease inhibitors have the option of once or twice daily dosing depending on treatment history and use with ritonavir. For PEP the selection of dosing and schedule is to optimize adherence while minimizing side-effects where possible. This table includes the preferred dosing schedule for each agent and in all cases, with the exception of Kaletra, the once daily regimen option is preferred for PEP. Twice daily administration of Kaletra is better tolerated with respect to GI toxicities compared to the once daily regimen. Alternative dosing and schedules may be appropriate for PEP in certain circumstances, and should preferably be prescribed by individuals experienced in the use of antiretroviral medications.