Updated US Public Health Service Guidelines for the Management of Occupational Exposures to Human Immunodeficiency Virus and Recommendations for Postexposure Prophylaxis

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This report updates US Public Health Service recommendations for the management of healthcare personnel (HCP) who experience 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 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. The following is a summary of recommendations: (1) PEP is recommended when occupational exposures to HIV occur; (2) the HIV status of the exposure source patient should be determined, if possible, to guide need for HIV PEP; (3) PEP medication regimens should be started as soon as possible after occupational exposure to HIV, and they should be continued for a 4-week duration; (4) new recommendation—PEP medication regimens should contain 3 (or more) antiretroviral drugs (listed in Appendix A) for all occupational exposures to HIV; (5) expert consultation is recommended for any occupational exposures to HIV and at a minimum for situations described in Box 1; (6) close follow-up for exposed personnel (Box 2) should be provided 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; and (7) new recommendation—if a newer fourth-generation combination HIV p24 antigen–HIV antibody test is utilized for follow-up HIV testing of exposed HCP, HIV testing may be concluded 4 months after exposure (Box 2); if a newer testing platform is not available, follow-up HIV testing is typically concluded 6 months after an HIV exposure.

Infect Control Hosp Epidemiol 2013;34(9):875-892

Preventing exposures to blood and body fluids (ie, 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, including ensuring 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. In 1996, the first US Public Health Service (PHS) recommendations advocating the use of PEP after occupational exposure to HIV were published; these recommendations have been updated 3 times. Since

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Received June 27, 2013; accepted June 27, 2013; electronically published August 6, 2013.

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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. These challenges include difficulties in determining levels of risk of HIV transmission for individual exposure incidents, problems determining the appropriate use of 2 versus 3 (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 and 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 after exposure. 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 that 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 and 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 (HCV) have been published previously and are not included in this report. Recommendations for nonoccupational (eg, sexual, pediatric, and perinatal) HIV exposures also have been published previously.

**METHODS**

In 2011, the CDC reconvened the interagency PHS working group to plan and prepare an update to the 2005 *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Post-exposure Prophylaxis.* The PHS working group was comprised of members from the CDC, the FDA, the Health Resources and Services Administration, and the National Institutes of Health. Names, credentials, and affiliations of the PHS working group members are listed as the byline 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 2-drug antiretroviral medication regimens versus those with 3 (or more) drugs as PEP or an optimal PEP regimen for occupational exposures to HIV. Because of the low risk of transmission associated with occupational exposures (ie, approximately 0.3% per exposure when all parenteral exposures are considered together), neither the conduct of a randomized trial assessing efficacy nor the conduct of trials assessing the comparative efficacy of 2-versus 3-drug regimens for PEP is practical. In light of the absence of such randomized trials, the CDC convened a meeting of the interagency PHS 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 “Expert Panel Consultants” at the end of this guideline.

Prior to the July 2011 meeting, the meeting participants were provided an electronic copy of the 2005 guidelines and asked to review them and consider the following topics for discussion at the upcoming meeting: (1) the challenges associated with the implementation of the 2005 guidelines, (2) the role of ongoing risk stratification in determining the use of 2-drug PEP regimens versus those with 3 or more drugs, (3) updated drug choices for PEP, (4) the safety and tolerability of antiretroviral agents for the general population and for pregnant or lactating HCP, and (5) any other topics in the 2005 guideline that needed to be updated.

At the July 2011 meeting, a CDC representative presented a review of the 2005 guideline recommendations, surveillance data on occupational exposures from the National Surveillance System for Healthcare Workers, and data from the National Clinicians’ Post-Exposure Prophylaxis Hotline (PEPline) on the number 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 to no longer recommend exposure risk stratification (discussed in detail in “Recommendations for the Selection of Drugs for HIV PEP” below). To update the drug choices for PEP, all drugs available for the treatment of HIV-infected individuals were discussed with regard to tolerability, side effects, toxicity, safety in pregnancy and lactation, pill burden, and frequency of dosing. A hierarchy of recommended drugs/regimens was developed at the meeting and utilized in creating the PEP regimen recommendations (Appendixes 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 and June 2012 during public meetings. The PHS working group considered all available information, expert opinion, and feedback in finalizing the recommendations in this update.

DEFINITION OF HCP AND EXPOSURE

The definitions of HCP and occupational exposures are unchanged from those used in 2001 and 2005. 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 (eg, blood, tissue, and specific body fluids), contaminated medical supplies and equipment, and 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 (eg, 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 (eg, a needlestick or cut with a sharp object) or contact of mucous membrane or non-intact skin (eg, 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 are also 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 are also 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.

Any direct contact (ie, 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.

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. 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%) and that after a mucous membrane exposure to be approximately 0.09% (95% CI, 0.006%-0.5%). 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 that for blood exposures.

Epidemiologic and laboratory studies suggest that multiple factors might affect the risk of HIV transmission after an occupational exposure. 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 (eg, 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 (ie, 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 (eg, 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 6 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 the FDA for treatment of HIV infection are included in these guidelines, although none of these agents has an FDA-approved indication for administration as PEP. The rationale for offering antiretroviral medications as HIV PEP is based on 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 3 (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.2 However, previous results show that a substantial proportion of HCP taking an earlier generation of antiretroviral agents as PEP frequently reported side effects,32-40 and many were unable to complete a full 4-week course of HIV PEP due to these effects and toxicities.32-34 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 has 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 (eg, antiemetics and antispasmodics) 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 (eg, herbs), 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.29 Additional information is included in 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 the use of 3 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 PHS working group recommends prescribing 3 (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 1 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.\textsuperscript{42} Occupational transmission of drug-resistant HIV strains, despite PEP with combination drug regimens, has been reported.\textsuperscript{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 a decline in CD4\textsuperscript{T} cell count despite therapy and 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 source patient HIV drug resistance is suspected in the management of an occupational exposure to HIV, consultation with an expert in HIV management is recommended so that antiretroviral agents to which the source patient’s 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 breast-feeding healthcare provider should be based on the same considerations that apply to any provider who sustains an occupational exposure to HIV. The risk of HIV transmission poses a threat not only 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 breast-feeding.\textsuperscript{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 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 during pregnancy. Conflicting data have been published concerning the risk of preterm delivery in pregnant women receiving antiretroviral drugs, particularly PIs,\textsuperscript{46} 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\textsuperscript{48} and nonfatal\textsuperscript{49} lactic acidosis has been reported in pregnant women treated throughout gestation with a combination of stavudine and didanosine. 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.\textsuperscript{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 (ie, 2.7 per 100 live births).\textsuperscript{10} 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.\textsuperscript{10} While human data are reassuring,\textsuperscript{51} 1 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.\textsuperscript{46} For these reasons, we recommend that pregnant women not use EFV during the first trimester.\textsuperscript{10} If EFV-based PEP is used in women, a pregnancy test should be done to rule out early pregnancy, and nonpregnant 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 (eg, neoplasia and mitochondrial toxicity) of in utero antiretroviral drug exposure. For this reason, long-term follow-up is recommended for all children who experience in utero exposures.\textsuperscript{10,52,53}

Antiretroviral drug levels in breast milk vary among drugs,
with administration of some drugs resulting in high levels (eg, lamivudine), while other drugs, such as PIs and tenofovir (TDF), are associated with only limited penetration into milk. Administration of antiretroviral triple-drug regimens to breast-feeding 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 breast-feeding may be associated with increased infant hematologic toxicity, but limited drug exposure during 4 weeks of PEP may also limit the risk of drug toxicity to the breast-feeding infant. Breast-feeding 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 breast-feeding. 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 during the 3 months after seroconversion was 77.6 infections per 100 child-years). To completely eliminate any risk of HIV transmission to her infant, the provider may want to consider stopping breast-feeding. 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 breast-feeding both while taking PEP and while being monitored for HIV seroconversion.

**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 has HIV infection or for whom there is 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, H2-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, these recommendations should, whenever possible, be implemented in consultation with persons who have expertise in the administration of antiretroviral therapy and who are knowledgeable about HIV transmission. Re-evaluation of exposed HCP is recommended within 72 hours after 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 who might be in the so-called window period before seroconversion (ie, the period of time between initial HIV infection and the development of detectable HIV antibodies), no such instances of occupational transmission have been detected in the United States to date. 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).\(^40\) Third-generation chemiluminescent immunoassays, run on automated platforms, can detect HIV-specific antibodies 2 weeks sooner than conventional EIAs\(^40\) 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.\(^42\) 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 medical evaluation for the injury and PEP. Furthermore, if the practitioner anticipates that hours or days may be required to determine 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 (eg, possible treatment history or antiretroviral drug resistance) or if expert consultants recommend the modification. Given the complexity of choosing and administering HIV PEP, consultation with an infectious diseases specialist or another physician who is an expert in the administration of antiretroviral agents is recommended whenever possible. Such consultation should not, however, delay timely initiation of PEP.

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 (eg, possible treatment history or antiretroviral drug resistance) or if expert consultants recommend the modification. Given the complexity of choosing and administering HIV PEP, consultation with an infectious diseases specialist or another physician who is an expert in the administration of antiretroviral agents is recommended whenever possible. Such consultation should not, however, delay timely initiation of PEP.

The PHS now recommends emtricitabine (FTC) plus TDF (these 2 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, and conveniently administered, and it has been associated with minimal drug interactions. Additionally, al-
Box 1: Situations for Which Expert Consultation for Human Immunodeficiency Virus (HIV) Postexposure Prophylaxis (PEP) Is Recommended

Delayed (ie, later than 72 hours) exposure report
• Interval after which benefits from PEP are undefined

Unknown source (eg, 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

Breast-feeding 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 1 or more of the drugs considered for PEP, selection of drugs to which the source person’s virus is unlikely to be resistant is 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 (eg, gastrointestinal symptoms and others) are 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 (eg, 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.

though we have only limited data on the safety of RAL during pregnancy, this regimen could be administered to pregnant HCP as PEP (see the 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, and an alternative should be sought for HCP who have underlying renal disease. Zidovudine could be used as an alternative to TDF and could be conveniently prescribed in combination with lamivudine, to replace both TDF and FTC, as Combivir. Alternatives to RAL include darunavir plus ritonavir (RTV), etravirine, rilpivirine, atazanavir plus RTV, and lopinavir plus RTV. When a more cost-efficient alternative to RAL is required, saquinavir 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 be used for PEP only under the guidance of expert consultants (Appendixes A and B). Among these drugs are nevirapine, which should not be used and is contraindicated as PEP because of serious reported toxicities, including hepatotoxicity (with 1 instance of fulminant liver failure requiring liver transplantation), rhabdomyolysis, and hypersensitivity syndrome. Antiretroviral drugs not routinely recommended for use as PEP because of the higher risk for potentially serious or life-threatening adverse events include didanosine and tipranavir. The combination of didanosine and stavudine should not be prescribed as PEP due to increased risk of toxicity (eg, peripheral neuropathy, pancreatitis, and lactic acidosis). Additionally, abacavir should be used as HIV PEP only 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. The FI 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 1 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, reevaluation of the exposed person should occur within 72 hours after exposure, 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,
Box 2: Follow-Up of Healthcare 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 (eg, use of barrier contraception and avoidance of blood or tissue donations, pregnancy, and, if possible, breast-feeding) to prevent secondary transmission, especially during the first 6–12 weeks after exposure.

For exposures for which postexposure prophylaxis (PEP) is prescribed, HCP should be informed regarding the following:

- Possible drug toxicities (eg, rash and hypersensitivity reactions that could imitate acute HIV seroconversion and the need for monitoring)
- Possible drug interactions
- 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 the following:

- HIV testing at baseline and at 6 weeks, 12 weeks, and 6 months after exposure; alternatively, if the clinician is certain that a fourth-generation combination HIV p24 antigen–HIV antibody test is being utilized, then HIV testing could be performed at baseline, 6 weeks after exposure, and 4 months after exposure
- Complete blood counts and renal and hepatic function tests (at baseline and 2 weeks after exposure; further testing may be indicated if abnormalities are detected)

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

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:

- 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.
- The CDC’s Cases of Public Health Importance (COPHI) coordinator (for reporting HIV infections in HCP and failures of PEP) at telephone number 404-639-2050.

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 on 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 (eg, use of barrier contraception and avoidance of blood or tissue donations, pregnancy, and, if possible, breast-feeding) to prevent secondary transmission, especially during the first 6–12 weeks after exposure. 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 (eg, testing at baseline and 6 weeks after exposure, then concluding testing at 4 months after exposure). Extended HIV follow-up (eg, for 12 months) is recommended for HCP who become infected with HCV after exposure to a source who is coinfected with HIV and HCV. Whether extended follow-up is indicated in other circumstances (eg, for exposure to a source coinfected 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, adding to an exposed person’s 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 healthcare provider and should not be precluded because of HCP anxiety. HIV tests should also be performed for 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. Healthcare providers caring for persons who have occupationally acquired HIV infection should report these cases to their state health departments and to the CDC’s COPHI coordinator at telephone number 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 receiving 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 (eg, 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 pharmacologic 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 (eg, 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 [eg, increased thirst or frequent urination]) should not be delayed. Serious adverse events should be reported to the 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 interagency PHS working group will assess the need to update these guidelines. Updates will be published periodically as appropriate.

EXPERT PANEL CONSULTANTS

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ACKNOWLEDGMENTS

We thank Lynne M. Mofenson, MD (National Institutes of Health), for providing expert assistance with drafting the section of the guideline titled “Antiretroviral Drugs during Pregnancy and Lactation” as well as S. Michele Owen, PhD (Centers for Disease Control and Prevention [CDC]), and Bernard M. Branson, MD (CDC), for providing expert assistance with drafting the sections titled “Source Patient HIV Testing” and “Postexposure Testing.” We also acknowledge contributions from John T. Brooks, MD (CDC), Kenneth Dominguez, MD, MPH (CDC), and David Kim, MD (CDC).

Potential conflicts of interest. The expert panel consultants report the following competing interests: J.A. has a board membership with and has received funding from Bristol-Myers Squibb, Janssen, Merck, and ViiV; J.E. has consulted for Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck, and ViiV and has received grant funding from Bristol-Myers Squibb, GlaxoSmithKline, Merck, and ViiV; M.S.S. has consulted for Bristol-Myers Squibb, Gilead, Janssen, Merck, and ViiV and has received grant funding from Bristol-Myers Squibb, Gilead, Merck, and ViiV; M.L.T. owns Merck stock. All other authors report no conflicts of interest relevant to this article.

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

Information included in these recommendations might not represent US Food and Drug Administration (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.
**APPENDIX A**

<table>
<thead>
<tr>
<th>Table A1. Human Immunodeficiency Virus (HIV) Postexposure Prophylaxis (PEP) Regimens</th>
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<tbody>
<tr>
<td><strong>Preferred HIV PEP Regimen</strong></td>
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<tr>
<td>Raltegravir (Isentress; RAL) 400 mg PO twice daily</td>
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<tr>
<td>Plus</td>
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<tr>
<td>Truvada, 1 PO once daily</td>
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<tr>
<td>(Tenofovir DF [Viread; TDF] 300 mg + emtricitabine [Emtriva; FTC] 200 mg)</td>
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**Alternative Regimens**

(Each alternative is a complete fixed-dose combination regimen, and no additional antiretrovirals are needed: Striibld (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)

**NOTE.** For consultation or assistance with HIV PEP, contact the National Clinicians’ Post-Exposure Prophylaxis Hotline at telephone number 888-448-4911 or visit its website at http://www.nccc.ucsf.edu/about_nccc/pepline/. DF, disoproxil fumarate; PO, per os.

a The alternatives regimens are listed in order of preference; however, other alternatives may be reasonable based on patient and clinician preference.
b For drug dosing information, see Appendix B.

**APPENDIX B**

<table>
<thead>
<tr>
<th>Table B1. Information on Human Immunodeficiency Virus (HIV) Postexposure Prophylaxis (PEP) Medications</th>
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<tbody>
<tr>
<td><strong>Drug name</strong></td>
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<tr>
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<tr>
<td>Abacavir (Ziagen; ABC)</td>
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<td>Drug name</td>
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<tr>
<td>Atazanavir (Reyataz; ATV)</td>
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<td>Darunavir (Prezista; DRV)</td>
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<td>Efavirenz (Sustiva; EFV)</td>
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<td>Elvitegravir (EVG)</td>
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<td>Drug name</td>
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<tr>
<td>Emtricitabine</td>
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<td>Drug name</td>
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<td>Lopinavir/ritonavir</td>
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<tr>
<td>Maraviroc (Selzentry; MVC)</td>
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<td>Raltegravir (Isentress; RAL)</td>
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<tr>
<td>Rilpivirine (Edurant; RPV)</td>
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<td>Saquinavir (Invirase; SQV)</td>
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TABLE B1 (Continued)

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Drug class</th>
<th>Dosing (dosage form)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Stavudine (Zerit; d4T)</td>
<td>NRTI</td>
<td>d4T: 40 mg twice daily if body weight is &gt;60 kg d4T: 30 mg twice daily if body weight is &lt;60 kg Available as 15-, 20-, 30-, and 40-mg tablets</td>
<td>Take without regard for food</td>
<td>GI side effects include diarrhea and nausea Hepatotoxicity, neurologic symptoms (eg, peripheral neuropathy), pancreatitis</td>
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<tr>
<td>Tenofovir DF (Viread; TDF)</td>
<td>NRTI</td>
<td>300 mg once daily; available as 300-mg tablet Also available as component of fixed-dose combination Atripla, dosed daily (200 mg of FTC + 300 mg of TDF + 600 mg of EFV) Complera, dosed daily (25 mg of RPV + 300 mg of TDF + 200 mg of FTC) Strivil, dosed daily (150 mg of ETV + 150 mg of cobicistat + 300 mg of TDF + 200 mg of FTC) Truvada, dosed daily (200 mg of FTC + 300 mg of TDF)</td>
<td>Well tolerated Take without regard for food</td>
<td>Asthenia, headache, diarrhea, nausea, vomiting Nephrotoxicity; should not be administered to individuals with acute or chronic kidney injury or those with eGFR &lt;60 If the PEP recipient has chronic hepatitis B, withdrawal of this drug may cause an acute hepatitis exacerbation Drug interactions</td>
</tr>
<tr>
<td>Zidovudine (Retrovir; ZDV; AZT)</td>
<td>NRTI</td>
<td>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 (150 mg of 3TC + 300 mg of AZT) Combivir, dosed twice daily (150 mg of 3TC + 300 mg of AZT) Trizivir, dosed twice daily (150 mg of 3TC + 300 mg of ABC + 300 mg of AZT)</td>
<td>Take without regard for food</td>
<td>Side effects (especially nausea, vomiting, headache, insomnia, and fatigue) common and might result in low adherence Anemia and neutropenia</td>
</tr>
</tbody>
</table>

NOTE. 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; cGFR, estimated glomerular filtration rate; EIA, enzyme immunoassay; GI, gastrointestinal; SJS, Stevens-Johnson syndrome.

* Certain antiretroviral agents, such as PIs, 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 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 with 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.

REFERENCES


In the September 2013 issue of the journal, in the article by Kuhar et al (Kuhar DT, Henderson DK, Struble KA, Heneine W, Thomas V, Cheever LW, Gomaa A, Panlilio AL, US Public Health Service Working Group. Updated US Public Health Service guidelines for the management of occupational exposures to human immunodeficiency virus and recommendations for postexposure prophylaxis. Infect Control Hosp Epidemiol 2013;34(9):875–892), there are 3 errors. In Appendix Table B1, row 1 ("Abacavir"), column 3 ("Dosing (dosage form)"), "300 mg daily" is incorrect; the correct dosing is 600 mg daily. Also in Appendix Table B1, row 17 ("Tenofovir DF"), column 5 ("Disadvantages"), the text immediately following "Nephrotoxicity" ("should not be administered to individuals with acute or chronic kidney injury or those with eGFR <60") should be deleted. Finally, the correct affiliation for author Ahmed Gomaa is Division of Surveillance, Hazard Evaluation, and Field [not "Health"] Studies, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, Ohio. The authors regret these errors.