Introduction

Background and History

In the mid-1990’s, postexposure prophylaxis (PEP) was recognized as a safe and effective intervention to prevent the acquisition of HIV for healthcare workers exposed to HIV-contaminated blood or body fluids. In contrast, the use of nonoccupational PEP for a sexual or injection drug use HIV-related exposure has been more controversial. In 1997, the Centers for Disease Control and Prevention (CDC) concluded there was insufficient evidence regarding the efficacy of nonoccupational PEP to recommend either for or against its use, but in 2005 the CDC and the Department of Health and Human Services revised its position and issued nonoccupational PEP guidelines.[1] These guidelines were updated in 2016 by the CDC and Department of Health and Human Services.[2]

Although existing guidelines recommend PEP for non-occupational exposures to HIV, the actual use of nonoccupational PEP has not achieved widespread acceptance and implementation.[3] Strategies for preventing nonoccupational HIV acquisition include abstinence, consistent and correct use of condoms, mutually monogamous sex with a partner not infected with HIV, abstinence from injection drug use (or if this is not possible, then consistent use of sterile injection equipment), and daily use of HIV preexposure prophylaxis (PrEP).[2]

Despite decades of efforts to implement these risk-reduction programs, during the past decade approximately 38,000 new HIV infections have occurred annually in the United States.[4,5] In some instances, the need for nonoccupational PEP arises, due to condom breakage, condomless sex with a person later identified as HIV-positive, sharing injection equipment, sexual assault, or nonoccupational percutaneous injuries. Clinicians should view the use of nonoccupational PEP as one of many HIV prevention options. In addition, clinicians evaluating individuals for nonoccupational PEP should recognize these individuals may be candidates for future use of PrEP.

Challenges with Nonoccupational PEP

A number of challenges may arise during the initial evaluation of persons for nonoccupational PEP after sexual and other non-occupational exposures.

- With some exposures, the person seeking help may not actually know the HIV status (or any other information) of the source person.
- The exposure that brings the exposed person in for medical attention may not consist of an isolated event, but instead may be among multiple recent potential HIV exposure events; if this is the case, it is still necessary to assess the need for nonoccupational PEP for any significant exposures occurring within the last 36 to 72 hours (depending on which guidelines are being used).
Individuals often present for care more than 72 hours after the exposure. Certain sexual exposure events may involve concomitant exposures to other sexually transmitted pathogens, or hepatitis viruses with injection drug (or percutaneous needlestick) exposures. Some nonoccupational PEP cases involve persons recently sexually assaulted, which can involve additional medicolegal concerns and complications. From a practical perspective, insurers may not cover the cost of the 28-day course of nonoccupational PEP, or they may only partially cover the cost. In addition, some persons with a nonoccupational HIV exposure may not have insurance coverage or they may also choose not to submit claims through their insurance plan.

Nonoccupational PEP Guidelines

In 2016, the CDC and Department of Health and Human Services issued revised Nonoccupational PEP Guidelines. The Nonoccupational PEP Guidelines address a wide range of issues related to nonoccupational PEP, including initial evaluation, medication efficacy, potential medication risks and side effects, laboratory testing, recommended regimens, and monitoring. In addition, the use of PrEP has emerged as an important HIV prevention tool, and the Nonoccupational PEP Guidelines address transitioning from nonoccupational PEP to PrEP.

Nonoccupational PEP Expert Consultation

The evaluation and management of persons seeking care for nonoccupational PEP is complex, and decisions regarding whether to administer nonoccupational PEP often fall into zones of uncertainty. The National Clinician Consultation Center is a federally funded program that provides free, expert decision support for clinicians managing non-occupational exposures. Medical providers can access this free service via the Post-Exposure Prophylaxis PEPline at (888)-448-4911. The hours for PEPline phone consultation are 9 a.m.-9 p.m. Eastern Standard Time (EST) seven days a week. The PEPline can assist clinicians calling from the United States, but it is not a direct information or consultation service for patients.
Rationale for Providing Nonoccupational PEP

Due to ethical and logistical reasons, it is unlikely that a prospective randomized, placebo-controlled trial to evaluate nonoccupational PEP in humans will ever take place. In addition, human nonoccupational PEP studies are problematic because participants may have multiple exposures over the surveillance-testing period, making it difficult to discern the true benefit of nonoccupational PEP for a single exposure event. Thus, the rationale for providing nonoccupational PEP is based on extrapolation from use of PEP in other settings, animal studies, retrospective reviews, and observational trials.

Extrapolation from Occupational and Perinatal PEP Data

The rationale for nonoccupational PEP is based on the efficacy of PEP following occupational exposures to HIV. Most notably, in 1997, investigators reported findings from a case-control study involving healthcare workers who sustained needlestick injuries from source individuals who have HIV infection; this study demonstrated PEP with zidovudine, taken within 4 hours by most of the participants, reduced the risk of HIV seroconversion by 81%. In addition, several important perinatal transmission trials involving mothers with HIV infection have established the benefit of using PEP given to the mother during labor and to the baby following birth. For instance, a Ugandan study reported that administering single-dose nevirapine to mothers during labor and to their infants within 72 hours of birth reduced the vertical HIV transmission rate from 25.1% to 13.1%.

Based on these studies, in which PEP prevented HIV transmission in occupational and perinatal settings, PEP use was expanded to include injection drug use, nonoccupational percutaneous needlestick injuries, and sexual exposures. Meanwhile, ongoing trials have confirmed the efficacy of antepartum and intrapartum antiretroviral therapy to prevent mother-to-child HIV transmission, as well as the efficacy of extended antiretroviral prophylaxis for HIV-exposed infants to prevent breastfeeding transmission.

Animal Studies

The use of antiretrovirals for nonoccupational exposures is also partially derived from animal PEP studies. One of the earliest studies showed that tenofovir reduced the rate of seroconversion among macaques inoculated intravenously with simian immunodeficiency virus (SIV), with the greatest reduction in transmission achieved when prophylaxis was initiated as early as possible and continued for 28 days. A later study showed that tenofovir-based PEP is also effective in preventing HIV after intravaginal inoculation of female macaques with HIV-2: tenofovir prevented seroconversion all 8 of the female macaques exposed to HIV-2 when initiated within 12 to 36 hours.

A systematic review and meta-analysis of PEP using pooled data of nonhuman primates across 18 studies (mostly involving intravenous inoculation with HIV) further substantiated the efficacy of PEP when initiated as soon as possible after HIV exposure. Studies in macaques have also demonstrated the efficacy of topical PEP for vaginal and rectal exposure to HIV, including a study that showed raltegravir gel protected female macaques against SIV infection when applied 30 minutes before or 3 hours after vaginal exposure.

Nonoccupational PEP Data in Humans

Although the human data on nonoccupational PEP is observational in nature and sample sizes have been inadequate to demonstrate a statistically significant reduction in HIV transmission, multiple studies involving men who have sex with men (MSM) suggest that nonoccupational PEP reduced the risk of HIV seroconversion. In addition, a feasibility study in San Francisco demonstrated that...
medical providers could identify and provide appropriate nonoccupational PEP after high-risk sexual and injection drug use-related exposures, as well as maintain exposed persons in care for the necessary follow-up period.[21] In another San Francisco study, investigators evaluated nonoccupational PEP effectiveness among persons with potential sexual or injection drug use exposures to HIV: of 702 people taking nonoccupational PEP, there were 7 (1%) seroconversions.[7] A detailed analysis of the 7 seroconversions revealed 3 of the 7 probably represented true nonoccupational PEP “failure” since these 3 individuals had no HIV exposures after initiating PrEP; the authors were unable to determine the exact cause for why they failed nonoccupational PEP.

Available data from reports of HIV transmission in persons who received nonoccupational PEP suggest that most HIV transmissions resulted from poor adherence while taking the nonoccupational PEP medications or from exposures to HIV that occurred after completing the 28-day nonoccupational PEP regimen.[22,23,24,25] In addition, one failure occurred in a 40-year-old woman in France who started PEP more than 72 hours after a high-risk sexual exposure.[26] Multiple studies involving sexual assault victims have demonstrated very low HIV transmission rates, but there were significant logistical problems in persons receiving nonoccupational PEP, including poor adherence and high rates of failure to return for follow-up care.[27,28,29,30,31]

**Rationale for Nonoccupational PEP in Persons Who Inject Drugs**

In the United States, persons who inject drugs make up less than 3% of the population, but accounted for approximately 10% of new HIV infections in 2010.[32] Although the percentage of new HIV infections attributed to injection drug use has decreased, the disproportionate number of new infections among persons who inject drugs likely involves the cooccurrence of sexual activities associated with increased HIV transmission risk (e.g. condomless sex, sex with multiple partners, and transactional sex), as well as overlapping social networks of risk groups.[33,34] Certain circumstances could arise whereby a person who injects drugs and normally uses safe injection practices has a high-risk exposure. Unfortunately, very limited data exist regarding the efficacy of nonoccupational PEP among persons who inject drugs.

The use of nonoccupational PEP after injection drug use exposures may have considerably different efficacy compared to sexual exposures and sparse data are available regarding the practical applications or efficacy of nonoccupational PEP in the setting of injection drug use. Of interest, however, one case report described a patient who inadvertently received a large-volume transfusion of HIV-infected blood, but early initiation of PEP prevented transmission of HIV.[35] Based on this, one might extrapolate that nonoccupational PEP could be effective following injection drug use-related exposures to HIV, particularly if started early.[36]
Evaluation for Nonoccupational PEP

Multiple factors influence the risk of HIV transmission in nonoccupational exposures to HIV. The initial evaluation of persons seeking care after potential nonoccupational exposures to HIV requires gathering information to determine whether nonoccupational PEP is indicated (Figure 3).[2] The initial evaluation, as recommended in the Nonoccupational PEP Guidelines, should address the following: (1) the HIV status of the potentially exposed person, (2) information related to the source person’s HIV status, (3) details regarding the type of exposure involved, (4) timing and frequency of the exposure(s), and (5) any available information related to antiretroviral therapy taken by the source patient if they are known to be infected with HIV.[2] In addition, the initial history intake should include the following:

- **Information on HIV Status of Person Potentially Exposed to HIV:** The first step in evaluating the exposure is to determine the HIV status of the person seeking medical care. Persons with established HIV infection should receive long-term continuous antiretroviral therapy, not a 28-day course of nonoccupational PEP. In the setting of a nonoccupational exposure to HIV, the HIV status of the exposed person should be determined as soon as possible, although HIV testing should not necessarily delay nonoccupational PEP initiation.

- **Information Related to Source Person’s HIV Status:** As part of the initial exposure evaluation, it is also important to determine whether the source person has HIV infection (or, if the status of the source is unknown, whether they are likely to have HIV infection). Often, the HIV status of the source person is not known (and not obtainable). The Nonoccupational PEP Guidelines recommend using nonoccupational PEP when the source person is known to have HIV infection; if HIV status of the source person is not known, the recommendation is to evaluate on a case-by-case basis, ideally in consultation with an expert.[2] When asking about information related to the source, it is important to ask whether other recent exposures occurred with this source (and/or other sources), as recent additional HIV-related exposures could potentially confound management decisions. Nevertheless, repeated exposures do not negate the need to assess whether the most recent exposure warrants nonoccupational PEP.

- **Determination of Risk Related to Exposure:** The other key element of the initial nonoccupational PEP evaluation is to determine whether the exposure confers actual risk for HIV transmission (Table 1).[2,36] Nonoccupational PEP should only be used in the setting of “substantial risk for HIV acquisition”, defined as contact involving an area of the body known to be associated with HIV acquisition (vagina, rectum, eye, mouth or other mucous membranes, non-intact skin, or percutaneous needlestick injuries) with an infectious body fluid (e.g. blood, semen, vaginal secretions, rectal secretions, breast milk, or any body fluid visibly contaminated with blood). The risk of HIV transmission associated with nonoccupational exposures varies considerably by the type of sexual exposure, with receptive anal intercourse conveying the highest sexual risk.[2,36,37,38,39] Similarly, mucosal disruption in either the source person or the exposed person (as might occur with traumatic intercourse including sexual assault, or in the presence of ulcerative genital disease) increases risk of sexual HIV transmission: condom use markedly lowers the risk of transmission (Table 2).[36]

- **Timing of Risk Exposure:** It is important to determine the timing of exposure in persons seeking nonoccupational PEP. Available data suggest that PEP may not be effective if initiated beyond 72 hours after the exposure. Furthermore, PEP may not be the optimal long-term HIV prevention method for individuals who engage in activities involving frequent, recurrent HIV exposures, such as sex with an HIV-serodiscordant sex partners without consistently using condoms or regularly sharing needles or equipment with injecting partners; these individuals should receive intensive risk reduction counseling and may instead be better suited for PrEP.[2]

- **Source Person Antiretroviral Treatment Information:** If a source person is known to have HIV infection and takes antiretroviral medications, the provider should determine what medication the source takes, the most recent HIV RNA level, and if the source person has
developed resistance to any antiretroviral medications. The risk of HIV transmission is higher if the source person has advanced HIV disease or high HIV RNA levels.[40]
Recommended Antiretroviral Therapy for Nonoccupational PEP

Indication for Starting Antiretroviral Therapy

If the following criteria are met, a 28-day course of nonoccupational PEP is recommended:

- A person has had a nonoccupational exposure to blood, genital secretions, or other potentially infectious body fluids from a person known to be infected with HIV (if the HIV status of the source person is unknown, the recommendation is to evaluate on a case-by-case basis, ideally in consultation with an expert), and
- The exposure represents a substantial risk for HIV transmission, and
- The person seeks care within 72 hours of exposure

Note: Administering nonoccupational PEP with the goal of transitioning to PrEP can be considered beyond the 72-hour window in cases where multiple recent exposures to HIV have occurred more than 72 hours prior, but the most recent exposure occurred within the 72-hour window.

Three-Drug Regimens for Nonoccupational PEP

The Nonoccupational PEP Guidelines recommend using a three-drug combination in all cases when nonoccupational PEP is indicated. Although no evidence exists that a three-drug regimen is more effective than a two-drug regimen for nonoccupational PEP, the recommendation to use a three-drug combination is primarily based on data demonstrating that three-drug combination antiretroviral therapy achieves excellent virologic suppression as HIV treatment.

The Fenway Clinic in Boston reported their experience with the three-drug regimen raltegravir plus tenofovir DF-emtricitabine as nonoccupational PEP in 100 men who have sex with men and this regimen was well tolerated and had high completion rate; the most common adverse effects were diarrhea and abdominal discomfort (Figure 4). Although this study was not powered to demonstrate efficacy, no HIV transmissions were observed. In a similar study from Sydney, Australia, investigators enrolled 86 men who had sex with men to receive the same three-drug regimen of raltegravir plus tenofovir DF-emtricitabine for nonoccupational PEP; the regimen was well tolerated, adherence levels were high, completion rates were very high, and no HIV seroconversions occurred.

Preferred and Alternative Antiretroviral Regimens

The preferred nonoccupational PEP regimen for adult and adolescent patients age 13 years and older who have a baseline creatinine clearance of at least 60 mL/min consists of the fixed dose combination of tenofovir DF-emtricitabine combined with either raltegravir or dolutegravir (Table 3). See the safety information below regarding potential use of dolutegravir in women. The alternative regimen is tenofovir DF-emtricitabine plus darunavir plus ritonavir. At this time, the use of tenofovir alafenamide-emtricitabine is not recommended as an alternative to tenofovir DF-emtricitabine.

For adults and adolescents who have a baseline creatinine clearance less than 60 mL/min, the preferred and alternative regimens listed above should be modified by replacing tenofovir DF-emtricitabine with zidovudine and lamivudine; in this situation, the fixed-dose combination zidovudine-lamivudine should not be given in this situation so that doses of zidovudine and lamivudine can be adjusted individually based on renal impairment.

Use of Dolutegravir in Women for NonOccupational PEP

On May 18, 2018, an FDA Safety Alert was posted that warned of potential serious neural tube birth
defects in infants born to mothers who received dolutegravir at the time of becoming pregnant or early in the first trimester. Based on these findings, the CDC has made the following interim recommendations for the use of HIV PEP (occupational or nonoccupational) while the agency prepares a more detailed review of the evidence and recommendations.[44]

Health care providers prescribing PEP should avoid use of dolutegravir for:

- Non-pregnant women of childbearing potential who are sexually active or have been sexually assaulted and who are not using an effective birth control method; and,
- Pregnant women early in pregnancy since the risk of an unborn infant developing a neural tube defect is during the first 28 days.

The preferred PEP regimen for these women is raltegravir plus tenofovir DF-emtricitabine. Health care providers seeking advice can call the National Clinical Consultations Center’s PEPline at (888) 448-4911. The CDC currently recommends that prior to starting PEP all women of childbearing potential should have a pregnancy test performed. If the PEP regimen for a nonpregnant woman who has childbearing potential must include dolutegravir, she should use an effective birth control method until the PEP regimen is completed.

Medications Not Recommended

The antiretroviral medication abacavir, which is commonly used to treat HIV infection, is not recommended for nonoccupational PEP. Prior to receiving abacavir, all patients should have HLA-B*5701 testing; the HLA-B*5701 test is used to predict abacavir hypersensitivity, a potentially fatal reaction. The need to immediately administer nonoccupational PEP antiretroviral medications does not allow sufficient time to obtain results from HLA-B*5701 testing. In addition, the use of nevirapine for occupational PEP has been associated with life-threatening toxicity and therefore should never be used for nonoccupational PEP.[45]

Duration of Therapy

The Nonoccupational PEP Guidelines recommend that individuals who initiate antiretroviral therapy for nonoccupational PEP should complete a 28-day course.[2] Studies involving macaques have shown that PEP given for 28 days is more effective than 10 days, which is more effective than 3 days.[13] In addition, available data and experience with occupational postexposure prophylaxis support the use of a 28-day regimen.[8,46] From a conceptual standpoint, it is believed that PEP, in most instances, aborts a very early and limited HIV infection, rather than truly preventing any cell in the body from becoming infected with HIV. Thus, early initiation of nonoccupational PEP, when combined with a 28-day duration of therapy, is believed adequate to minimize tissue involvement and contain any local HIV replication while allowing sufficient time for localized immune responses to clear out the limited HIV infection.

Consideration of HIV Resistance in Source Patient

If medical information is available regarding a source person known to be HIV-positive, the choice of nonoccupational PEP regimen should take into account the source person’s antiretroviral medication history, most recent HIV viral load, and prior resistance testing results. In the event the source person has possible or known antiretroviral drug resistance, expert consultation should be obtained to determine the optimal nonoccupational PEP regimen for the exposed individual.

Recommendation if Source Patient has an Undetectable HIV RNA Level

Multiple studies have shown that persons with HIV who consistently maintain undetectable serum HIV RNA levels do not sexually transmit HIV, even with condomless sex.[47,48,49] These studies led
to the concept of undetectable equals untransmittable, which is commonly referred to as "U=U".\[50\] The widespread support of the U=U concept mainly occurred after the 2016 publication of the Nonoccupational PEP Guidelines. As might be expected, the 2016 Nonoccupational PEP Guidelines do not specifically address whether or not to initiate nonoccupational PEP after an exposure to a source person with HIV infection who has a recent undetectable HIV RNA level.\[2\] Thus at the present time, there are no clear recommendations regarding use of nonoccupational PEP following sexual exposures to source persons with HIV who have consistently suppressed HIV RNA levels. This issue will need to be addressed in future nonoccupational PEP guidelines.

**Recommendation if Person Exposed to HIV is Receiving PrEP**

Persons who are receiving HIV preexposure prophylaxis (PrEP) with daily tenofovir DF-emtricitabine and are adhering to a daily regimen do not need nonoccupational PEP following exposure to HIV.\[51\] If an individual is receiving PrEP, but is not consistently taking PrEP on a daily basis, nonoccupational PEP might be indicated following an HIV exposure.\[51\] In this situation of sporadic PrEP use, the decision to initiate nonoccupational PEP should be made on a case-by-case basis and ideally with the help of expert clinical consultation.

**Expert Consultation**

The Nonoccupational PEP Guidelines provide recommendations for scenarios that warrant expert consultation related to nonoccupational HIV exposure events.\[2\] Expert consultation is recommended when the healthcare provider has limited experience with prescribing antiretroviral medications or is considering nonoccupational PEP for pregnant or breastfeeding women, children, or persons with renal dysfunction. In addition, consultation is indicated when the source person has known or suspected antiretroviral resistance. Expert consultation for these issues and any other guidance on Nonoccupational PEP can obtained by calling the National Clinician Consultation Center's Post-Exposure Prophylaxis PEPline at at 888-448-4911; this service is available 9 a.m.-8 p.m. Eastern Standard Time (EST) Monday through Friday and 11 a.m.-8 p.m. on weekends and holidays.
Laboratory Testing for Source and Exposed Persons

The Nonoccupational PEP Guidelines provide recommend baseline laboratory studies for the source and the exposure person as well as a schedule of laboratory tests for monitoring the exposed person (Table 4).[2] Initial HIV testing of the exposed individual should consist of an HIV-1/2 antigen-antibody test using a blood specimen (preferably using a rapid test), or antibody testing if HIV antigen-antibody testing is not available.[2] Oral HIV tests are not recommended. Although it is very important to confirm the negative HIV status of the individual presenting for nonoccupational PEP, most experts do not advocate ordering an HIV RNA level (on the exposed person) unless they have signs or symptoms that suggest an acute retroviral illness.

Baseline Laboratory Evaluation

The baseline laboratory evaluation should include the following tests for the individual exposed to HIV:[2]

- HIV Ag/Ab testing (or HIV antibody testing if Ag/Ab test unavailable)
- Serologic testing for hepatitis B virus (HBV) and hepatitis C virus (HCV)
- Site-specific screening for sexually transmitted infections (chlamydia, gonorrhea, syphilis)
- Pregnancy test and emergency contraception, as indicated
- Serum creatinine (for calculating estimated creatinine clearance)
- Hepatic aminotransferase levels

Follow-Up Laboratory Studies

The Nonoccupational PEP Guidelines recommend all persons seeking care for nonoccupational PEP need follow-up HIV testing at 4 to 6 weeks after exposure and at 3 months after exposure to determine if HIV transmission has occurred.[2] Ideally, the HIV-1/2 antigen-antibody test should be used, but HIV antibody testing is acceptable if the HIV-1/2 antigen-antibody test is not available. Persons who have an exposure to HIV should be instructed about the signs and symptoms associated with acute retroviral infection and asked to return for evaluation if these occur during or after nonoccupational PEP.[2] If the exposed person becomes hepatitis C antibody positive as a result of the original exposure, an additional HIV test should be conducted at 6 months postexposure.[2] Of note, HCV testing for susceptible exposed persons is recommended at baseline and at 6 months, but not at 4 to 6 weeks or 3 months. For exposed persons not immune to HBV at baseline, providers should ascertain HBV status of the source if possible and administer HBV postexposure prophylaxis as indicated. Follow-up HBV testing should then be conducted at 6 months.[2]
Nonoccupational PEP in Special Populations and Circumstances

The Nonoccupational PEP Guidelines identify additional considerations for certain special populations as outlined below.

Pregnant Women and Women of Childbearing Potential

The recommended regimens for nonoccupational PEP are generally considered safe during pregnancy. Several antiretroviral medications are considered problematic for use in pregnancy.

- **Dolutegravir**: As noted above, the use of dolutegravir has been associated with potential serious neural tube birth defects in infants born to mothers who received dolutegravir at the time of becoming pregnant. The CDC recommends that health care providers prescribing PEP medications should avoid use dolutegravir in pregnant women early in pregnancy as the risk of developing a neural tube defect from dolutegravir occurs during the first 28 days of pregnancy.[44]
- **Efavirenz**: Due to the risk of potential teratogenicity, efavirenz is classified as FDA pregnancy Category D and should be avoided during the first trimester of pregnancy or in women with childbearing potential.
- **Stavudine plus Didanosine**: The combination of stavudine and didanosine should not be used due to the risk of lactic acidosis.
- **Indinavir**: Indinavir should be avoided due to the risk of nephrolithiasis.
- **Nevirapine**: The medication nevirapine should never be used for PEP due to risk of severe hepatotoxicity. Furthermore, because the efficacy of hormonal contraception can be altered by some antiretroviral medications, women using such methods should be advised to use a secondary form of contraception (i.e. barrier methods) while taking nonoccupational PEP.
- **Darunavir plus Ritonavir**: Among the preferred and alternative recommended regimens for nonoccupational PEP, only darunavir boosted with ritonavir causes significant drug interactions with oral contraceptives.

Specific information is not provided in the guidelines regarding use of antiretroviral regimens for nonoccupational PEP in women who are breastfeeding. Expert consultation should be obtained for these cases.

Children and Adolescents

In many pediatric/adolescent nonoccupational PEP cases, expert consultation will be necessary. In the current Nonoccupational PEP Guidelines, the preferred regimen for children aged 4 weeks to less than 2 years of age is a 3-drug regimen of oral zidovudine and lamivudine plus either raltegravir or lopinavir-ritonavir, all adjusted for age and weight. For children aged 2 to 12 years, the preferred regimen is tenofovir DF plus emtricitabine plus raltegravir (dosed according to age and weight).[2]

For children age 13 and older with normal renal function, the adult and adolescent preferred and alternative nonoccupational PEP regimens can be used.[2]

Sexual Assault Survivors

Survivors of sexual assault may be less likely to seek care for nonoccupational PEP and may require additional psychological support, clinical follow-up, and adherence counseling. Testing and treatment for other sexually transmitted infections, emergency contraception evaluation, and supportive counseling are also highly recommended in cases of sexual assault.

Inmates

The Nonoccupational PEP Guidelines recommend that correctional facilities establish HIV prevention
programs. Elements should include confidential and voluntary HIV testing, risk reduction services, and nonoccupational PEP protocols. The Federal Bureau of Prisons published a clinical practice guideline based on the 2005 CDC Nonoccupational PEP guidelines and recommends that each facility develop its own protocol, but the CDC recommends that the most updated guidelines be used whenever possible.

HIV Postexposure Prophylaxis in Mass Casualty Events

In response to concerns for a potential mass casualty event within the United States, the Centers for Disease Control and Prevention convened a working group to address management of blood-borne pathogen exposure in persons who are injured in bombings and other mass-casualty events, as well as for emergency responders in these catastrophic events. This particular situation does not fall neatly under the guidelines for either occupational or nonoccupational PEP. Accordingly, a separate document was published in 2008, which specifically addresses postexposure prophylaxis for HIV, hepatitis B, hepatitis C, and tetanus in the setting of mass casualties. Postexposure prophylaxis for HIV is not routinely indicated for persons exposed to blood or tissue in bombings or mass-casualty events. In certain situations, however, nonoccupational PEP might be indicated if the risk for HIV exposure was determined to be high, such as with bombing of a research facility with HIV-infected blood specimens or culture vials growing HIV. If postexposure prophylaxis is indicated, the same principles of timing, laboratory testing, and antiretroviral medication selection should apply.
Initial Medication Prescription and Follow-up after Evaluation

Initial Medication Prescription and Timely Follow-Up

The guidelines recommend that providers should consider giving an initial prescription for 3 to 7 days of antiretroviral medication (e.g. a starter pack) or providing a prescription for an entire 28-day course. Ideally, at the initial visit, the facility would supply the starter pack medication or the full 28-day supply of medication, both to minimize any delay in receiving the first dose and to address any barriers that could prohibit the patient from filling the prescription. In addition, prior to leaving the facility, the person evaluated for nonoccupational PEP should have an early follow-up visit scheduled to assess adherence to nonoccupational PEP, monitor for toxicity, and provide any additional counseling or education that might be needed.[2] If this individual receives only a 3 to 7 day supply of antiretroviral medication, coordination of timely follow-up is essential to ensure the patient does not run out of medication.

Challenges to Follow-Up

A recent study reported significant patient attrition between initial emergency department visit for nonoccupational PEP and first follow-up clinic appointment.[6] Only about half of nonoccupational PEP patients attended their follow-up appointment, and less than a quarter of those initially started on nonoccupational PEP completed the full 28-day regimen. Older age and self-pay status predicted lower rates of follow-up and poor adherence; women were less likely than men to complete the full course of nonoccupational PEP.

HIV Prevention Counseling

Patients who are evaluated for nonoccupational PEP should receive HIV prevention counseling. This includes counseling on risk-reduction behaviors (e.g. using a barrier method with sex partners, not sharing equipment used to inject drugs) and referral to local community resources, if available). At follow-up visits, healthcare providers should assess for ongoing risk behaviors, provide additional counseling, and connect patients with services as needed.
Transitioning to Preexposure Prophylaxis

Preexposure Prophylaxis (PrEP)

Multiple studies conducted in recent years have demonstrated that daily use of PrEP (most commonly given as a fixed-dose combination of tenofovir DF-emtricitabine) protects against HIV infection among heterosexuals at high risk for HIV acquisition,[53,54,55,56] men who have sex with men (MSM) and transgender women,[54,57,58] and persons who inject drugs.[59] These studies show that PrEP is a feasible and effective HIV prevention strategy that may be more protective than repeated courses of nonoccupational PEP.

In July 2012, the FDA approved tenofovir DF-emtricitabine for use as PrEP in individuals with ongoing high risk of HIV acquisition. The PrEP Clinical Practice Guideline recommend that individuals with frequent and multiple exposures to HIV, such as MSM who report condomless anal sex with a partner who has HIV infection, should not be managed with repeated courses of nonoccupational PEP, but instead strongly considered for PrEP. Clinicians with questions about PrEP can call the National Clinician Consultation Center’s Pre-Exposure Prophylaxis PrEPline at 1-855-448-7737 for expert consultation. The PrEPline is available Monday – Friday, 11 a.m.–6 p.m. EST.

Transitioning from Nonoccupational PEP to PrEP

Many individuals who present for nonoccupational PEP following a sexual or injection drug use exposure may be excellent candidates for PrEP, particularly if they report ongoing activities associated with increased risk for HIV acquisition. The PrEP Clinical Practice Guideline recommend that persons receiving a 28-day course of nonoccupation PEP should be evaluated for transitioning to PrEP if (1) they have repeatedly sought nonoccupational PEP, and/or (2) they engage in behaviors that result in frequent, recurrent exposures to HIV that would require sequential or near-continuous courses of nonoccupational PEP.[51]

Persons taking nonoccupational PEP who are deemed appropriate candidates to receive PrEP can immediately transition to PrEP after completing the 28-day course of nonoccupational PEP.[51] The transition from nonoccupational PEP to PrEP should occur without a gap, but prior to the transition, documentation of HIV-negative status should be obtained, preferably with an HIV-1/2 antigen-antibody test.[51] To practically achieve a transition without allowing a gap, the recommended 4 to 6 week follow-up HIV testing should be preformed several days earlier than normal (several days prior to the end of the 28-day course of nonoccupational PEP). The approach of immediate transition will diminishes the risk of HIV acquisition among individuals who have significant ongoing risk. There is no definitive evidence that receipt of nonoccupational PEP delays HIV seroconversion.[2]
Concerns with Nonoccupational Postexposure Prophylaxis

Toxicity of Antiretroviral Therapy

Initial concerns about severe side effects and pharmacological toxicities in otherwise healthy persons have been ameliorated by the use of less toxic, well-tolerated antiretroviral agents.\cite{60}

Use of Nonoccupational PEP and Drug Resistance Mutations

Selection of drug-resistant HIV can potentially result from the use of nonoccupational PEP. The development of HIV drug resistance during receipt of nonoccupational PEP is highly unlikely because few individuals receiving nonoccupational PEP will develop HIV infection and emergence of new resistant strains would be uncommon following a 28-day course of a potent three-drug antiretroviral nonoccupational PEP regimen. Nonoccupational PEP should not be withheld due to theoretical concerns about the potential selection of drug-resistant HIV.

Use of Nonoccupational PEP and Changes in High-Risk Behavior

Some clinicians have expressed concern that availability of nonoccupational PEP could theoretically result in behavioral disinhibition among individuals at risk for HIV infection.\cite{3} Multiple studies involving MSM have shown that risk behavior does not necessarily increase after individuals receive nonoccupational PEP.\cite{21,61,62} In one study in San Francisco, 72% of nonoccupational PEP recipients reported a decrease in risk behavior over the next 12 months, 13% reported no change, and 14% reported an increase in risk behavior; in that study, 17% of participants requested a repeat course of nonoccupational PEP within the following year.\cite{61} In a separate study, investigators reported that 12% of individuals requested a second course of nonoccupational PEP within 6 months of the initial nonoccupational PEP course.\cite{21} In a study that specifically examined whether the knowledge of nonoccupational PEP availability would lead to an increase in risk behavior, there was no difference in risk behavior among men who have sex with men exclusively and who knew about nonoccupational PEP versus those who had never heard of it.\cite{62} Taken together, the available data suggest that receipt of nonoccupational PEP (consisting of both antiretroviral prophylaxis and counseling) does not increase HIV risk behaviors nor has it been linked to an increase in HIV prevalence. Of note no studies have been published that have examined changes in injection drug use patterns among persons who inject drugs who have received a course of nonoccupational PEP.
Summary Points

- Nonoccupational PEP represents an important tool in the arsenal of HIV prevention but remains an underutilized strategy.
- As a whole, there is a body of data that supports use of nonoccupational PEP and indicates it may reduce the risk of HIV infection after nonoccupational exposures to HIV.
- The use of antiretroviral medications for nonoccupational PEP is recommended for HIV-negative persons following an exposure that has a substantial risk for HIV acquisition, if started within 72 hours of the exposure.
- A 28-day course of three-drug antiretroviral medications is recommended for nonoccupational PEP.
- The preferred nonoccupational PEP regimen for adult and adolescents aged 13 years and older who have a baseline creatinine clearance of at least 60 mL/min consists of the fixed dose combination of tenofovir DF-emtricitabine plus either raltegravir or dolutegravir.
- The person exposed to HIV should have baseline laboratory studies that include HIV testing, screening for sexually transmitted infections, serum creatinine, aspartate aminotransferase (AST) and alanine transaminase (ALT) levels, testing for viral hepatitis, and a pregnancy test (if indicated).
- Expert consultation should be sought for all situations that fall outside the scope of the guidelines, including situations when exposure to drug-resistant HIV has occurred. Consultation can be obtained through local expertise (if available) or by calling the National Clinician Consultation Center’s Post-Exposure Prophylaxis Hotline (PEPline) at 888-448-4911.
- All patients seeking care for nonoccupational PEP should have follow-up HIV testing at 4 to 6 weeks and again at 3 months to determine if HIV infection has occurred. The fourth-generation combination HIV p24 antigen-HIV antibody test is preferred for all testing. Additional HIV testing should be conducted at 6 months if the exposure resulted in HCV transmission.
- Nonoccupational PEP has not been linked to high rates of adverse side effects, selection of resistant HIV virus, or increases in risky behaviors.
- Some patients who seek nonoccupational PEP should be evaluated as potential candidates to receive PrEP following completion of nonoccupational PEP. The transition from occupational PEP to PrEP, if warranted, should occur without a gap.
Citations


[PubMed Abstract]

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   [PubMed Abstract]

   [CDC]

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References


Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. [AIDSinfo] -


Figures

Figure 1 Tenofovir for Postexposure Prophylaxis following SIV-1 Inoculation of Macaques

In this study, investigators inoculated 24 macaques with simian immunodeficiency virus (SIV) and then instituted various postexposure prophylaxis regimens with tenofovir, which is (R)-9-(2-phosphonylmethoxypropyl).


<table>
<thead>
<tr>
<th>Study Hour</th>
<th>SIV Inoculation</th>
<th>Start PEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>48</td>
</tr>
<tr>
<td>48</td>
<td></td>
<td>72</td>
</tr>
</tbody>
</table>

Study Features

- N = 24 macaques
- Randomized to 6 treatment arms
- SIV inoculated intravenously
- SIV dose 10x 50% infective dose
- PEP started at 24, 48, or 72 hours
- PEP duration: 3, 10, or 28 days
- PEP regimen: Tenofovir (PMPA) SQ
- Analyzed for antibody and viremia

Tenofovir (PMPA) = (R)-9-(2-phosphonylmethoxypropyl) adenine
Among animals that received placebo, all became infected with simian immunodeficiency virus (SIV). The most effective tenofovir prevention regimen consisted of early initiation of tenofovir (at 24 hours) and long duration of postexposure prophylaxis (28 days).

Figure 3 Algorithm for Evaluation and Treatment of possible nonoccupational HIV exposures


Substantial risk for HIV acquisition

≤72 hours since exposure

Source patient known to be HIV positive

nPEP recommended

Source patient of unknown HIV status

Case-by-case determination

≥73 hours since exposure

Negligible risk for HIV acquisition

nPEP Not recommended

Substantial Risk for HIV Acquisition

Exposure of
Vagina, rectum, eye, mouth or other mucous membrane, nonintact skin, or precutaneous contact

With
Blood, semen, vaginal secretions, rectal secretions, breast milk, or any body fluid that is visibly contaminated with blood

When
The source is known to be HIV-positive

Negligible Risk for HIV Acquisition

Exposure of
Vagina, rectum, eye, mouth or other mucous membrane, intact or nonintact skin, or percutaneous contact

With
Urine, nasal secretions, saliva, sweat, or tears if not visibly contaminated with blood

Regardless
Of the known or suspected HIV status of the source
Figure 4 Symptoms Associated with Raltegravir plus Tenofovir DF-Emtricitabine for Nonoccupational PEP

This graph shows the side effect profile of 100 men who have sex with men who received raltegravir plus tenofovir DF-emtricitabine for nonoccupational PEP. The most common adverse effects were diarrhea and abdominal pain.

### Table 1.

**Estimated Per-Act Probability of Acquiring HIV from an Infected Source, by Exposure Act**

<table>
<thead>
<tr>
<th>Exposure Type</th>
<th>Rate for HIV Acquisition per 10,000 Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parenteral</strong></td>
<td></td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>9,250</td>
</tr>
<tr>
<td>Needle sharing during injection drug use</td>
<td>63</td>
</tr>
<tr>
<td>Percutaneous (needlestick)</td>
<td>23</td>
</tr>
<tr>
<td><strong>Sexual</strong></td>
<td></td>
</tr>
<tr>
<td>Receptive anal intercourse</td>
<td>138</td>
</tr>
<tr>
<td>Insertive anal intercourse</td>
<td>11</td>
</tr>
<tr>
<td>Receptive penile-vaginal intercourse</td>
<td>8</td>
</tr>
<tr>
<td>Insertive penile-vaginal intercourse</td>
<td>4</td>
</tr>
<tr>
<td>Receptive oral intercourse</td>
<td>Low</td>
</tr>
<tr>
<td>Insertive oral intercourse</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Biting</td>
<td>Negligible</td>
</tr>
<tr>
<td>Spitting</td>
<td>Negligible</td>
</tr>
<tr>
<td>Throwing body fluids (including semen or saliva)</td>
<td>Negligible</td>
</tr>
<tr>
<td>Sharing sex toys</td>
<td>Negligible</td>
</tr>
</tbody>
</table>

*Factors that may increase the risk of HIV transmission include sexually transmitted diseases, acute and late-stage HIV infection, and high viral load. Factors that may decrease the risk include condom use, male circumcision, antiretroviral treatment, and preexposure prophylaxis. None of these factors are accounted for in the estimates presented in the table.

^HIV transmission through these exposure routes is technically possible but unlikely and not well documented.

Source:

- Centers for Disease Control and Prevention: U.S. Department of Health and Human Services. Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, and Other Nonoccupational Exposure to HIV - United States, 2016. [CDC](https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6524a1.htm)
## Table 2.

### Relative Risks of Factors that Alter Per-Act HIV Transmission Risk for Sexual Exposures*

<table>
<thead>
<tr>
<th>Cofactor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factors that Increase Transmission Probability</strong></td>
<td></td>
</tr>
<tr>
<td>High plasma viral load ($\log_{10}$ copies/mL)</td>
<td>2.89</td>
</tr>
<tr>
<td>Genital ulcer disease</td>
<td>2.65</td>
</tr>
<tr>
<td>Acute versus asymptomatic stage of disease</td>
<td>7.25</td>
</tr>
<tr>
<td>Late versus asymptomatic stage of disease</td>
<td>5.81</td>
</tr>
<tr>
<td><strong>Factors that Decrease Transmission Probability</strong></td>
<td></td>
</tr>
<tr>
<td>Use of antiretrovirals by HIV-infected partner</td>
<td></td>
</tr>
<tr>
<td>Early versus delayed</td>
<td>0.08</td>
</tr>
<tr>
<td>Received treatment versus no treatment</td>
<td>0.08</td>
</tr>
<tr>
<td>Preexposure Prophylaxis of HIV-Uninfected Partner</td>
<td></td>
</tr>
<tr>
<td>Among heterosexual couples</td>
<td>0.29</td>
</tr>
<tr>
<td>Among men who have sex with men</td>
<td>0.56</td>
</tr>
<tr>
<td>Among injection drug users</td>
<td>0.52</td>
</tr>
<tr>
<td>Condom use</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Male Circumcision (heterosexual partners)</strong></td>
<td></td>
</tr>
<tr>
<td>HIV-uninfected partner is male</td>
<td>0.50</td>
</tr>
<tr>
<td>HIV-uninfected partner is female</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>Male circumcision (men who have sex with men)</strong></td>
<td></td>
</tr>
<tr>
<td>Insertive partner is HIV-uninfected partner</td>
<td>0.27</td>
</tr>
<tr>
<td>Receptive partner is HIV-uninfected partner</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*For a detailed description of data and factors used to generate estimates, see original table in article referenced below.

Source:

### Table 3. 2016 CDC and HHS Guidelines for Nonoccupational Exposure to HIV

**Preferred and Alternative 28-Day Regimens for Nonoccupational PEP\(^a, b\)**

**Adults and adolescents aged ≥13 years, including pregnant women, with normal renal function (creatinine clearance ≥60 mL/min)**

**Preferred Regimens:**
- Raltegravir (400 mg twice daily) plus tenofovir DF-emtricitabine (300-200 mg once daily)
- Dolutegravir (50 mg once daily) plus tenofovir DF-emtricitabine (300-200 mg once daily)

**Alternative Regimen:**
- Darunavir (800 mg once daily) plus ritonavir (100 mg once daily) plus tenofovir DF-emtricitabine (300-200 mg once daily)

**Adults and adolescents aged ≥13 years with renal dysfunction (creatinine clearance ≤59 mL/min)**

**Preferred Regimens:**
- Raltegravir (400 mg twice daily) plus zidovudine (dose adjusted) plus lamivudine (dose adjusted)
- Dolutegravir (50 mg once daily) plus zidovudine (dose adjusted) plus lamivudine (dose adjusted)

**Alternative Regimen:**
- Darunavir (800 mg once daily) plus ritonavir (100 mg once daily) plus zidovudine (dose adjusted) plus lamivudine (dose adjusted)

\(^a\)These recommendations do not reflect current Food and Drug Administration-approved labeling for antiretroviral medications listed in this table.

\(^b\)Ritonavir is used in clinical practice as a pharmacokinetic enhancer to increase the trough concentration and prolong the half-life of darunavir, lopinavir, and other protease inhibitors. Ritonavir is not counted as a drug directly active against HIV in the above “3-drug” regimens.

\(^a\)The dose adjustments for zidovudine and lamivudine are made based on degree of renal function.

**Source:**
Table 4.

**nPEP: Recommended Laboratory Monitoring of Source and Exposed Persons**

<table>
<thead>
<tr>
<th>Test</th>
<th>Source</th>
<th>Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>HIV Ag/Ab testing&lt;sup&gt;a&lt;/sup&gt; (or antibody testing if Ag/Ab test unavailable)</td>
<td>√</td>
<td></td>
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<tr>
<td></td>
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<tr>
<td>Hepatitis B serology, including: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody</td>
<td>√</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hepatitis C antibody test</td>
<td>√</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis serology&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonorrhea&lt;sup&gt;f&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Chlamydia&lt;sup&gt;f&lt;/sup&gt;</td>
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<td></td>
</tr>
<tr>
<td>Pregnancy&lt;sup&gt;h&lt;/sup&gt;</td>
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<td></td>
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<td></td>
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<tr>
<td>Serum creatinine (for calculating estimated creatinine clearance)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Alanine transaminase, aspartate aminotransferase</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>HIV viral load</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>HIV genotypic resistance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For persons prescribed:
- Tenofovir DF-emtricitabine + raltegravir
- Tenofovir DF-emtricitabine + dolutegravir

For all persons with HIV infection confirmed at any visit

Abbreviations: Ag/Ab, antigen/antibody combination test; HIV, human immunodeficiency virus; nPEP, nonoccupational postexposure prophylaxis; tenofovir DF, tenofovir disoproxil fumarate.

<sup>a</sup> Any positive or indeterminate HIV antibody test should undergo confirmatory testing of HIV infection status.

<sup>b</sup> For all persons considered for or prescribed nPEP for any exposure.
<table>
<thead>
<tr>
<th>Test</th>
<th>Source</th>
<th>Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Baseline</td>
<td>4-6 Weeks after exposure</td>
</tr>
</tbody>
</table>

For all persons considered for or prescribed nPEP for any exposure

b Only if hepatitis C infection was acquired during the original exposure; delayed HIV seroconversion has been seen in persons who simultaneously acquire HIV and hepatitis C infection.

c If exposed person susceptible to hepatitis B at baseline.

d If exposed person susceptible to hepatitis C at baseline.

e If determined to be infected with syphilis and treated, should undergo serologic syphilis testing 6 months after treatment

Testing for chlamydia and gonorrhea should be performed using nucleic acid amplification tests. For patients diagnosed with a chlamydia or gonorrhea infection, retesting 3 months after treatment is recommended.
- For men reporting insertive vaginal, anal, or oral sex, a urine specimen should be tested for chlamydia and gonorrhea.
- For women reporting receptive vaginal sex, a vaginal (preferred) or endocervical swab or urine specimen should be tested for chlamydia and gonorrhea.
- For men and women reporting receptive anal sex, a rectal swab specimen should be tested for chlamydia and gonorrhea.
- For men and women reporting receptive oral sex, an oropharyngeal swab should be tested for gonorrhea.

g If not provided presumptive treatment at baseline, or if symptomatic at follow-up visit.

h If woman of reproductive age, not using effective contraception, and with vaginal exposure to semen.

i eCrCl = estimated creatinine clearance calculated by the Cockcroft-Gault formula; eCrClCG = [(140 – age) x ideal body weight] ÷ (serum creatinine x 72) (x 0.85 for females).

j At first visit where determined to have HIV infection.

Source:
