Preventing HIV Infection After a Potential Sexual Exposure

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Postexposure prophylaxis (PEP) is now considered the standard of care after potential sexual HIV exposure. Appropriate antiretroviral drug regimens should be initiated as quickly as possible after unprotected receptive or insertive anal or vaginal intercourse, and possibly receptive oral intercourse with ejaculation, with an at-risk partner. PEP also includes counseling on risk reduction and adherence to therapy and referrals to mental health and substance abuse services as appropriate. Candidates for PEP should be tested at baseline for HIV antibodies, and HIV antibody testing should be performed serially until 6 months after the exposure. (*Infect Med.* 2007;24:239-246)

Key words: Postexposure prophylaxis ■ HIV ■ Antiretroviral drugs

Attempts to control the HIV pandemic through behavioral change alone (such as 100% condom use) have been inadequate to curb the spread of HIV. The use of antiretroviral medications to prevent HIV acquisition after sexual exposures is now recommended in many countries, including the United States.[1-4] However, antiretroviral agents are only one component of an intervention that also includes risk reduction and medication adherence counseling as well as the appropriate mental health services, substance abuse programs, and other HIV prevention services.

In 2005, the CDC revised its guidelines recommending the use of 28-day postexposure prophylaxis (PEP) antiretroviral regimens after sexual exposure to HIV. In the absence of data on the effectiveness of PEP, these recommendations were based on a combination of earlier evidence from studies on occupational exposures and prevention of mother-to-child transmission; animal studies; and preliminary observational studies of nonoccupational PEP in North America, Europe, and Australia. These studies suggested that PEP was reasonably well tolerated. Perhaps more important, there were no obvious increases in risk behaviors among either PEP users or community members who were aware of PEP. In this article, we will review the key components of PEP.

BACKGROUND

HIV infection is neither an inevitable nor an instantaneous consequence of exposure. After a percutaneous or mucous membrane exposure to HIV, a "window" of approximately 3 to 5 days exists before durable infection is established.[5] This interval affords an opportunity to potentially decrease the transmission risk, which is already very low, by using PEP. The average risk of HIV transmission after an occupational needlestick involving an HIV-infected source patient is about 0.3% (Table 1).[6]

In contrast, the average per-contact transmission rate after unprotected receptive anal intercourse is higher, at about 1% to 5%.[7-9] For unprotected insertive anal intercourse and receptive vaginal intercourse, this risk is about 0.1% to 1%, similar to the needlestick rate.[8-10] The per-contact transmission rate after unprotected insertive vaginal intercourse is generally less than 0.1%; it may be considerably higher (about 5%) with subtype E virus, although this subtype is uncommon in the United States.[10,11] Trauma, genital ulcer disease, and cervical ectopy may increase transmission rates.[12] The risk associated with receptive

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oral sex is difficult to quantify, although case reports suggest that HIV transmission infrequently occurs through oral sex.[9,13]

Nonoccupational PEP efficacy

No studies have evaluated the efficacy of PEP after sexual exposure to HIV. A placebo-controlled trial would not be ethical because of the known partial efficacy of PEP use following occupational health care worker exposures. An appropriately powered trial comparing 2 active interventions would be cost-prohibitive. However, supporting evidence has shown that antiretroviral agents can prevent HIV and simian immunodeficiency virus (SIV) transmission following occupational or perinatal exposures in humans and mucous membrane exposures in animal models, respectively.

Occupational PEP efficacy data are limited to a single case-control study that estimated an 81% risk reduction of HIV acquisition with the use of zidovudine monotherapy after a needlestick exposure.[6] Differences in exposure mode (mucous membrane in sexual exposure versus percutaneous in occupational exposure) result in different local immunological responses, obscuring the generalizability of occupational data to the nonoccupational setting. In the developed world, combined

antenatal, intrapartum, and postnatal treatment is recommended to optimally prevent vertical transmission of HIV from mother to child. However, substantial reduction of mother-to-child transmission is also realized only when the postnatal component is implemented.[14-16]

PEP is effective in macaque models after oral, vaginal, or intravenous SIV challenges. It is most effective when administered within 24 to 36 hours of exposure and continued for 28 days.[17-19] PEP has not been shown to be effective when initiated after 72 hours in these models.

PEP does not completely protect against HIV acquisition

Absolute PEP efficacy is unlikely in any context. Seroconversion despite antiretroviral use has occurred following occupational exposures, treatment to prevent mother-to-child transmission, and sexual exposures.[20,21] The fallibility of PEP is a useful reminder to practitioners and patients that biomedical prevention strategies are not substitutes for safer sex practices. Integration of PEP medication with behavioral interventions is crucial to maximizing the efficacy of PEP.

Behavioral impact of PEP

The potential for increased risk taking is a concern with all bioprophy-

lactic strategies, including vaccines, microbicides, PEP, and preexposure prophylaxis (PrEP). If the perceived protection offered by PEP causes a rise in high-risk behavior, even fairly small increases in unsafe sexual practices could overwhelm its preventive benefit.[22] Fortunately, the available data suggest that access to or use of PEP does not result in an increase in risk behaviors.[23-27]

The greatest potential of nonoccupational PEP programs is to engage patients in comprehensive HIV prevention services. A 5-visit risk-reduction counseling program implemented in San Francisco as part of a PEP feasibility study was associated with a reduction in risk behavior sustained over 12 months.[25] Less intensive 2-session risk-reduction counseling may accomplish similar risk reductions in most persons seeking PEP.[28] Developing comprehensive programs in clinical practice will require commitment from private health care institutions and the public health sector in collaboration with community-based prevention programs.

Cost-effectiveness

PEP is cost-effective when targeted to at-risk populations after sexual exposures.[29,30] French guidelines have resulted in increased prescribing of PEP, often after exposures in which the source is not likely to be HIV-infected.[31] This untargeted program has not been shown to be cost-effective.[32] Overall program cost-effectiveness depends on the mix of exposure types within the program, the number of drugs used, and safety laboratory monitoring protocols. Mathematical modeling data suggest, in terms of cost-effectiveness, that 3-drug therapy is best reserved for situations in which baseline nucleoside resistance levels in the population exceed 15%.[33]

PEP cost-effectiveness analyses

Table 1 – Per-contact infection risk

Exposure	Per-contact transmission rate
Receptive anal intercourse	0.8% - 5%[7-9]
Insertive anal intercourse	< 0.1% - 1%[8,9]
Receptive vaginal intercourse	< 0.1% - 1%[10]
Insertive vaginal intercourse*	0.01% - 5.6%[10,11]
Occupational needlestick	0.3%[6]

*Subtype E HIV is associated with much higher per-contact transmission rates for insertive vaginal intercourse than are other subtypes.

have been limited to medication-related benefits and adverse effects and have not included costs and benefits of risk-reduction and adherence counseling. To be feasible, PEP programs should be integrated into existing care systems (testing, counseling, HIV medical care) and targeted at the at-risk populations.

WHEN TO OFFER PEP
WHO SHOULD BE OFFERED PEP?

PEP is intended for persons who are not HIV-infected; thus, potentially exposed persons who seek PEP should be tested at baseline for HIV antibodies. Initiation of treatment should not be delayed in the event of unknown baseline serostatus. If a baseline HIV antibody test result is positive, PEP should then be discontinued and the patient should be referred for expert care for chronic HIV infection.

When using rapid HIV testing to establish baseline HIV status in exposed persons, results should be confirmed by routine testing methods. PEP may still be initiated pending the test result; in this scenario, a 3-drug regimen should be used to avoid generation of resistant virus in case the person is already chronically HIV-infected.

PEP should be offered after an exposure that has the potential to transmit HIV infection with a known HIV-positive source partner or a source partner with unknown HIV status who is at reasonable risk for having HIV infection (Table 2). Local epidemiology can help determine the likelihood that an unknown source may be HIV-infected. A "knee-jerk" response of providing PEP after any sexual exposure should be avoided. The nature of the exposure and characteristics of the source patient need to be understood, although establishing them is time-intensive and requires skill in crisis management.[27,34]

Table 2 – Indications for postexposure prophylaxis

Indications and criteria	Comment
HIV status of exposed client • HIV-negative or untested or • Rapid test positive but confirmatory test pending	In the case of positive rapid test, may use 3-drug regimen pending confirmation.
Exposure type • Unprotected receptive or insertive anal or vaginal intercourse • Consider receptive oral sex with ejaculation	Any source genital secretion in contact with exposed mucous membrane or non-intact skin.
Exposure source HIV status • Known HIV infection • At high risk for HIV infection based on local epidemiology	Usually includes men who have sex with men, past or present injection drug users, and commercial sex workers and their partners. When this information is not known about the source, it may be reasonable to offer postexposure prophylaxis.
Timing •Within 72 hours of exposure	Postexposure prophylaxis should be initiated as soon as possible. Individual decisions need to be made in case of multiple exposures, when some are within and some outside 72 hours.

What type of exposure warrants PEP?

Receptive or insertive anal or vaginal intercourse without a condom, or in the case of condom failure (slippage or breakage), are all exposures in which PEP should be offered, regardless of whether ejaculation occurred (Table 2). Receptive oral intercourse with ejaculation is considered in some guidelines to be sufficiently risky to warrant PEP use. Other mucous membrane or non-intact skin contact with any potentially infectious body fluid (such as ejaculate in the eye or on scratched or abraded skin) is similarly an indication for offering PEP.

Exposure source HIV status

PEP should be offered if an eligible exposure occurred with a source who is known to be HIV-positive. In the case of a source with unknown HIV status who belongs to a sociodemographic group at increased risk for HIV infection, such as men who have sex with men, injection drug users, and persons who have exchanged sex for money or drugs, guidelines recommend either always offering PEP or deciding on a case-by-case basis.

The HIV status of the source is often unknown. Attempts to gather source information by telephone often yield important data that may influence PEP initiation or discontinuation and regimen choice. If the exposure source reports being HIV-negative and/or can be tested rapidly and his or her HIV test results are negative, PEP can be discontinued. If the source reports symptoms that

suggest acute HIV seroconversion in the context of recent exposures, expert consultation should be sought before discontinuing PEP.

Initiation and duration of PEP

Animal study data suggest that PEP is more effective the earlier it is initiated.[17,19] Maximal benefit can likely be achieved when PEP is administered 24 to 36 hours after an exposure. Most guidelines use 72 hours postexposure as the cutoff beyond which PEP is not recommended. PEP should be taken for 28 days; treatment failures have occurred with 3- and 10-day PEP courses in animal models.[17]

PROVIDING PEP SERVICES WHAT MEDICATIONS SHOULD BE PROVIDED?

A known history or suspicion of drug resistance in the source virus should prompt expert consultation to determine the optimal regimen. Experts disagree about the best number and type of agents to use for PEP.[1-4] Treatment of chronic HIV infection currently mandates 3-drug combination therapy. However, the superiority of 3- over 2-drug combinations has not been demonstrated in the postexposure setting. The smaller viral burden after an exposure versus that in chronic infection supports the assertion that 2 drugs may be sufficient.

While 3-drug combinations probably cause more adverse effects than do 2-drug combinations, there is no evidence that a greater number of adverse effects result in higher rates of PEP discontinuation.[34-37] Two factors—increasing antiretroviral drug resistance prevalence among potential exposure sources and improved ease and tolerability of newer 3-drug combinations—may bolster support for the more routine use of 3-drug combinations.

Most guidelines are several years old and recommend agents that were in common use at the time. Newer agents may be preferable for dosing convenience and tolerability. Reasonable combinations of nucleoside analogs include zidovudine, tenofovir, or stavudine with lamivudine or emtricitabine. When available, fixed-dose combination pills are preferable.

Reasonable third-agent options include the protease inhibitors nelfinavir, indinavir, lopinavir/ritonavir, fosamprenavir, and atazanavir. Atazanavir should not be used with proton pump inhibitors and should be used cautiously with H_2 blockers. New York State guidelines advocate tenofovir as the third agent in combination with zidovudine and lamivudine.[4] Tenofovir and a combination of tenofovir and emtricitabine are being studied for potential PrEP based on macaque models.[38-40]

Efavirenz (in pregnant women or those who may become pregnant), abacavir, and combinations of stavudine and didanosine are not recommended because of toxicity concerns. Nevirapine is contraindicated because of potential fatal hepatic and cutaneous reactions, although there is some interest in use of a very short course of nevirapine as an adjunct to the standard regimen.[41,42]

The future roles of CCR5-receptor antagonists and integrase inhibitors will need to be assessed as these agents arrive in clinical use. Emergency contraception and sexually transmitted infection (STI) prophylaxis should be used as the clinical context dictates.

HIV testing

HIV antibody testing should be performed at baseline and at 3 and 6 months after exposure. Many guidelines recommend testing at 4 to 6 weeks as well. As a compromise, some offer the first posttreatment test at 2 to 3 months. Safety monitoring recommendations vary substantially across guidelines. Some favor testing only in the case of toxicity; others recommend measuring complete blood cell count, liver enzyme levels, and serum creatinine level at baseline, week 2, and weeks 4 to 6.

Decisions about routine laboratory testing should take into account the relative health of the population being served, the individual being treated, and the specific medications being prescribed. Hepatitis B and C screening, rapid plasma reagin, and other STI testing should be encouraged at baseline and in follow-up.

Psychosocial and behavioral interventions and support

Appropriate counseling and referrals are central to the success of a comprehensive PEP intervention.[25,34] All patients should receive HIV pre- and post-test counseling and adherence counseling. When possible, individualized risk-reduction counseling should be incorporated into the standard HIV counseling. HIV-specific counseling must be integrated with trauma counseling for sexual assault survivors. Substance use, mental illness, domestic violence, and other psychosocial needs should be addressed through referrals to appropriate services.

Proactive follow-up

PEP completion rates following occupational, consensual sex, and sexual assault exposures are poor in the absence of prospective follow-up via telephone or letter. Children and adolescents have even lower PEP completion rates after sexual assault, ranging from 15% to 52%.[43,44] Treatment of adolescent assault survivors is often further complicated by high rates of coexisting mental illness.[43]

Adherence to each dose of PEP medication is important and requires specific counseling.[34] Maxmizing PEP adherence and completion rates

requires proactive follow-up, adherence counseling, symptom management, and attention to mental health and substance abuse issues.

SERVICE DELIVERY

Persons at risk for HIV acquisition are diverse and have unique needs for services. Service delivery systems should provide rapid access to initial care, expert follow-up, and context-specific risk-reduction and adherence interventions. Identifying the ideal mechanism for rapid administration of PEP is a challenge. PEP may be initiated in an urgent care clinic or emergency department. Medication starter packs can be provided to at-risk persons with instructions about who to contact should they initiate PEP.[26] With adequate staffing, screening for PEP eligibility can be provided by telephone consultation, and initial PEP prescriptions can subsequently be phoned-in to local pharmacies after patient eligibility has been established.[34]

Many providers who care for patients after a potential exposure are unfamiliar with PEP, making easily accessible consultative services an attractive option. The National Clinician Consultation Services PEPline (888-448-4911) is intended only to provide technical support to health care providers for management related to occupational exposures. Nevertheless, it will help with nonoccupational exposure management. We recommend prospective telephone and/or mail contact for scheduling follow-up appointments, even after PEP completion, to ensure completion of follow-up HIV testing.

CONCLUSIONS

The PEP "moment" is a brief window of opportunity to make lasting interventions in persons at risk for HIV infection. The fear that drives someone who may have been exposed to HIV to seek a clinical inter-

vention can be parlayed into a motivator for behavior change. PEP is considered standard of care after potential sexual HIV exposures, although its use by both providers and patients is probably quite low. Appropriate drug regimens should be initiated as quickly as possible—certainly within 72 hours—after unprotected receptive or insertive anal or vaginal intercourse, and possibly receptive oral intercourse with ejaculation, with an at-risk partner (known HIV-infected or of unknown HIV status from a high-risk group such as men who have sex with men, injection drug users, and commercial sex workers). PEP should be continued for 28 days.

PEP services provide an opportunity to engage patients in risk-reduction counseling and provide access to prevention, mental health, substance abuse, and primary care services. The optimal "menu" of pre-

Table 3 – Interventions for postexposure prophylaxis

Intervention	Comment
Medications	Do not use nevirapine.
• Individualize in the case of known or suspected resistance	Efavirenz should not be used in pregnancy.
• Minimum of 2 nucleoside analogs	Seek expert consultation if
• Third drug options include a protease inhibitor or tenofovir	using abacavir or didanosine.
STI treatment or prophylaxis	
Emergency contraception	
Laboratory testing	See text for specific
• HIV antibody	considerations regarding
• Consider safety laboratory studies	timing of follow-up HIV
• Serological tests for hepatitis B and C	antibody tests and indications
• Serological test for syphilis	for safety laboratory studies.
• Tests for other STIs	
Counseling and referrals	Programs providing post-exposure prophylaxis must be
• Postexposure prophylaxis adherence counseling	able to provide or refer for all of these services.
• HIV pre- and post-test counseling	
• Individualized risk-reduction counseling	
• Substance use, mental health, domestic violence and other psychosocial concerns	

STI, sexually transmitted infection.

Therapeutic agents mentioned in this article

Abacavir

Atazanavir

Didanosine

Efavirenz

Emtricitabine

Fosamprenavir

Indinavir

Lamivudine

Lamivudine/zidovudine

Lopinavir

Nelfinavir

Nevirapine

Ritonavir

Stavudine

Tenofovir

Tenofovir/emtricitabine

Zidovudine

ventive services, counseling, and type and number of antiretrovirals is still being defined. ❖

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