*Perspective*

# Occupational and Nonoccupational Postexposure Prophylaxis for HIV in 2009

*Data supporting the efficacy of HIV postexposure prophylaxis (PEP) come largely from a small number of older studies and case reports in health care workers, studies of transmission from infected mothers to their infants, and animal studies. These data also provide support for the current recommendations regarding duration of PEP and the window of time within which PEP should be started. Although much of the available data are from experience with older 2-drug regimens, newer potent 2- and 3-drug regimens are increasingly used in occupational exposure management, and drugs with mechanisms of action targeting early events in infection (eg, entry inhibitors, integrase inhibitors) may in the future become attractive options. Nonoccupational PEP remains controversial, although its feasibility and safety have been demonstrated in a number of programs. Existing recommendations generally call for its use within 72 hours of high-risk contact with a high-risk or HIV-infected source individual. This article summarizes a presentation on PEP for HIV infection made by Raphael J. Landovitz, MD, at the IAS–USA continuing medical education course held in Los Angeles in February 2009. The original presentation is available as a Webcast at www.iasusa.org.*

## Management of Occupational Exposure to HIV

Data from the Centers for Disease Control and Prevention (CDC) for the period 1985 to 2001 indicate that there were 57 confirmed HIV seroconversions in health care workers (HCWs) after occupational exposure to HIV and 138 cases of possible transmission in which HIV infection or AIDS occurred in workers with no known risk factors for HIV infection other than occupational exposure in which postexposure seroconversion was not documented (Table 1). The cases of transmission occurred primarily through percutaneous exposures involving punctures or cuts from sharp objects, mostly hollow-bore needles. However, transmission also occurred via mucous membrane and nonintact skin exposures, mostly to HIV-infected blood, but occasionally via concentrated laboratory virus or visibly bloody body fluids. Most cases of transmission occurred in HCWs who routinely have the most direct contact with HIV-infected patients or their blood—nurses, laboratory workers handling specimens, surgeons, health aides, and emergency medical technicians working in the field.

With regard to factors affecting risk of transmission, deep injury was associated with the greatest risk (adjusted odds ratio [OR], 15), with elevated risk also associated with the presence of visible blood on device (OR, 6.2), terminal illness of the source patient (OR, 5.6), and contact with a needle in the source patient's artery or vein (OR, 4.3). "Terminal illness of the source patient" in this analysis likely represents exposure to a high level of HIV viremia (the ability to measure viral load was not always available during the period covered by the analysis). Although the source person's viral load is likely a surrogate for transmission risk, the use of viral load for assessing risk in this regard has not yet been established. Low or undetectable viral load in the source person does not rule out the possibility of transmission.

The rationale for occupational and nonoccupational postexposure prophylaxis (PEP) comes from various analogous fields. Studies of HIV pathogenesis have demonstrated that systemic infection does not occur immediately after exposure to virus, presenting a "window of opportunity" for potential intervention. Generally, virus can be found in antigen-presenting cells translocating across the mucosa approximately 24 hours after acquisition of virus and in regional lymph nodes within 48 hours to 72 hours. Viremia is detectable in blood as early as 5 days after acquisition. Limited studies and case reports have provided data demonstrating the feasibility, safety, and efficacy of PEP in HCWs.

Evidence of efficacy also comes from studies of HIV transmission from mother to child. Although antiretroviral therapy is now standard care during pregnancy and delivery in an infected mother and postpartum in the neonate, the finding that administration of antiretroviral treatment to an infant within 48 hours after birth has approximately 65% efficacy in preventing transmission from an untreated, infected mother stands as an example of successful true postexposure prophylaxis in humans. In addition, animal data indicate that durable infection with simian immunodeficiency virus (SIV) can be prevented with antiretroviral treatment after intravenous, intravaginal, and transrectal inoculation.

A CDC case-control study in HCWs reported in 1997 remains the core research supporting PEP (Cardo et al, *N Engl J Med*, 1997). In this study, 33 HCWs infected with HIV via occupational exposure (94% with needlestick injuries, all hollow needles) were compared with 679 HCWs who had been exposed to the virus but did not seroconvert. Postexposure prophylaxis with zidovudine monotherapy had been given to 27% of case patients and 36% of control patients, and the reduction in risk associated with zidovudine

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Table 1. Early Cases of Transmission of HIV to Health Care Workers, 1985 to 2001

| Occupation | Documented Transmission/ Possible Transmision |
|---|---|
| Nurse | 24/35 |
| Laboratory worker | 19/17 |
| Physician, nonsurgical | 6/12 |
| Physician, surgical | –/6 |
| Surgical technician | 2/2 |
| Dialysis technician | 1/3 |
| Other technician/ therapist | –/9 |
| Respiratory therapist | 1/2 |
| Health aide | 1/15 |
| Morgue technician | 1/2 |
| Housekeeper | 2/13 |
| Dental worker/dentist | –/6 |
| Emergency medical technician | –/12 |
| Other | –/4 |
| **Route of exposure** | **Documented cases** |
| Percutaneous (puncture/cut injury) | 48 |
| Mucocutaneous (mucous membrane or skin) | 5 |
| Percutaneous and mucocutaneous | 2 |
| Unknown | 2 |
| **Source of exposure** | **Documented cases** |
| Blood | 49 |
| Concentrated virus in laboratory | 3 |
| Visibly bloody fluid | 1 |
| Unspecified fluid | 4 |

Dashes indicate data not reported.
Adapted from Do et al, *Infect Control Hosp Epidemiol*, 2003.

use was calculated to be 81% (OR, 0.19; 95% CI, 0.02-0.52). In current practice, monotherapy would not be considered advisable, and the multidrug regimens now in use would be expected to provide even greater protective benefit. However, available data indicate that even multidrug therapy is not always successful in preventing infection. In a report on the first 21 known instances of failure of occupational PEP by the CDC, multidrug therapy was used in 5, including zidovudine plus didanosine in 2 HCWs, a 3-drug combination in 1, a regimen of zidovudine, didanosine, lamivudine, and indinavir in 1, and a combination of didanosine, stavudine, and nevirapine in 1, with all treatment started within 2 hours of exposure.

The adverse-effect profiles of PEP consisting primarily of lamivudine/zidovudine or the addition of early protease inhibitors (PIs) to lamivudine/zidovudine are shown in Figure 1 (Wang et al, *Infect Control Hosp Epidemiol*, 2000; Puro et al, CROI, 2002). The increase in adverse events with 3-drug treatment reflected in such data has contributed substantially to arguments that 2-drug combinations are preferred. The unproven correlate of that argument is that such toxicity compromises a PEP-taking patient's ability to complete the recommended 28-day treatment course, which is considered crucial to maximizing the potential for protective efficacy. Drugs used in more current regimens are better tolerated than were early combinations. A crucial component of maximizing the risk-to-benefit ratio of PEP is choosing to treat, and therefore to place at risk for adverse events, only the highest risk subset of exposures. Exposures with very small chances of transmitting infection likely fall on the disadvantageous side of a risk-benefit analysis; that is, the risks may outweigh the potential benefits.

The current recommendation for 28 days of prophylactic treatment is derived in large part from animal studies. A study in which 24 macaques were inoculated intravenously with SIV showed that PEP with (R)-9-(2-phosphonylmethoxypropyl)adenine (PMPA, tenofovir) initiated 24 hours after inoculation was associated with seroconversion in 50% of animals with 3 days of treatment, 25% with 10 days of treatment, and 0% with 28 days of treatment (Tsai et al, *J Virol*, 1998). With the potentially devastating consequences of a shorter course potentially providing less effective prophylaxis, this 28-day threshold has become standard. Ongoing studies in perinatal transmission may provide information about protective benefits of shorter courses of treatment that can be applied to adults.

In a similar macaque model, tenofovir prophylaxis was started 48 hours before or 4 hours or 24 hours after inoculation and continued for 28 days, with a control group left untreated after exposure. None of the animals receiving treatment and all control animals were infected (Tsai et al, *Science*, 1995). Additional findings with regard to exposure during birth in humans indicate protective benefit to the infant if treatment is started within 48 hours postpartum; the precise "cutoff" point after which PEP will not have any activity will likely never be delineated, but expert consensus clearly centers on the notion that PEP should be administered as soon as possible postexposure.

Taken together, these findings are the basis for current recommendations regarding the window of time after exposure during which prophylaxis should be initiated. To date, no evidence in humans indicates that treatment started after 48 hours is protective. However, most guidelines, including those by the World Health Organization, CDC and Department of Health and Human Services (DHHS), and the states of California, Massachusetts, and Rhode Island, recommend a window of 72 hours within which to start treatment; New York state has chosen to endorse a 36-hour window. A recent large, community-based cohort study of the safety, feasibility, and acceptance of PEP in men who have sex with men (MSM) showed that the median time to receipt of the first dose of treatment was 33 hours (interquartile range, 18-53 hours) (Kahn, *J Infect Dis,* 2001), indicating that approximately half of those exposed would be ineligible for treatment if a 36-hour window were used.

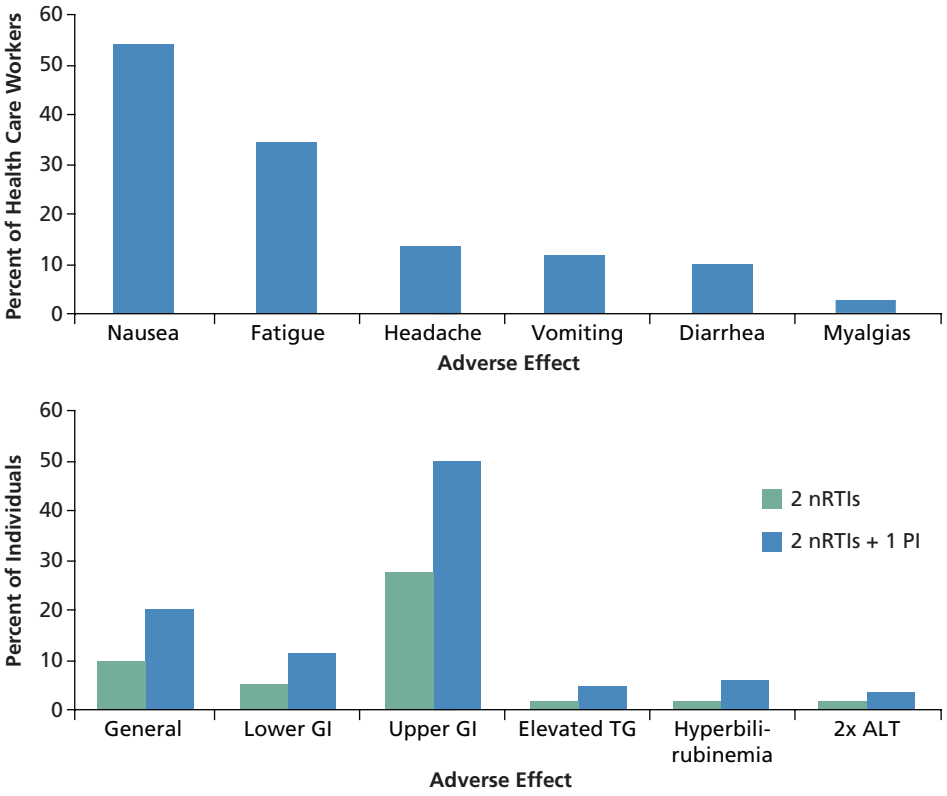



Figure **1.** Incidence of common adverse effects of postexposure prophylaxis (mainly lamivudine/zidovudine) in health care workers (top), and comparison between regimens of 2 nucleoside analogue reverse transcriptase inhibitors (nRTIs) (lamivudine/zidovudine) alone or in combination with early protease inhibitor (PI) regimens, mostly indinavir or nelfinavir (bottom). Top graph is adapted from Wang et al, *Infect Control Hosp Epidemiol*, 2000, and bottom adapted with permission from Puro et al, CROI, 2002. ALT indicates alanine aminotransferase; GI, gastrointestinal; TG,triglycerides.

## Management of Nonoccupational Exposure to HIV

There is considerable controversy over implementation of nonoccupational PEP (nPEP) strategies. To date, no placebo-controlled data are available on the efficacy of nPEP; the limited data that do exist on efficacy of PEP are from the occupational exposure literature. It is unlikely that controlled trials will be performed, both because current analogy to occupational exposures combined with the devastating nature of the outcome of seroconversion make placebo-controlled trials unethical, and active-controlled trials would have to be prohibitively large to demonstrate adequate power given that rates of seroconversion after sexual exposure in reality are quite low.

Data in the occupational exposure setting are not perfectly analogous to data in the sexual exposure setting for a number of reasons: the immunologic milieu of a mucosal exposure, especially a genital exposure, differs substantially from that in a percutaneous exposure, and viral loads and resistance patterns of virus in genital secretions differ from those in blood. In addition, repeated exposures are more common in the nonoccupational setting, and there are concerns that nPEP would become a "morning-after pill," although existing data do not support increased engagement in high-risk behaviors as a consequence of PEP availability. Moreover, source testing is frequently impossible, and in most cases the source individual's HIV serostatus is not known, further complicating triage decisions as to the risk-to-benefit ratio of PEP initation, even in the era of rapid testing availability.

The official recommendation of the CDC on nPEP, published in 2005, is "The provision of antiretroviral drugs to prevent HIV infection after unanticipated sexual or injection drug-use exposure might be beneficial. For persons seeking care < 72 hours after nonoccupational exposure to . . . a person known to be HIV infected . . . a 28-day course of highly active antiretroviral therapy is recommended. Antiretroviral medications should be initiated as soon as possible after exposure." In practice, nPEP is becoming an increasingly common strategy, although there are important operational difficulties in locating nPEP services within 72 hours in many settings (including Los Angeles County; Landovitz et al, *Clin Infect Dis*, 2009). For all patients, local hospital emergency departments may not be comfortable with administration of antiretroviral medications, and follow-up is made more difficult, especially for uninsured patients, who lack, as yet, an HIV diagnosis and thus are not likely to be eligible for state drug-assistance programs to pay for PEP medications. The CDC launched and then closed a voluntary registry for practitioners administering nPEP, and no further data from this initiative are available. Safety and feasibility of nPEP programs, mostly in MSM, have been demonstrated in initiatives in the United States in San Francisco, Boston, and Los Angeles; in the European cities Amsterdam and Paris; as well as in Brazil.

The CDC has estimated risk of acquisition per 10,000 exposures to an infected source (Table 2). Many believe that these estimates are too low, with other data for receptive anal intercourse, for example, suggesting 3% to 5% risk per exposure (rather than the CDC estimate of 0.5%). Recent meta-analysis data suggest that sexual transmission rates, at least via heterosexual intercourse, may be up to 8-fold higher than previously reported and that the commonly cited values should be thought of as "lower bounds" for the risk of transmission (Powers et al, *Lancet Infect Dis*, 2008). Most guidelines recommend that nPEP should be instituted for patients presenting within 72 hours of an index event of anal or vaginal intercourse (some recommendations include receptive oral intercourse with ejaculation) with no condom or condom failure in which the source individual is

Table 2. Centers for Disease Control and Prevention Estimates of HIV Transmission Risk per 10,000 Exposures to Infected Source

| Route | Estimated Number of Transmitted Infections per 10,000 Exposures (% Risk) |
|---|---|
| Blood transfusion | 9000 (90%) |
| Needle-sharing injection-drug use | 67 (0.67%) |
| Receptive anal intercourse | 50 (0.5%) |
| Percutaneous needlestick | 30 (0.3%) |
| Receptive penile-vaginal intercourse | 10 (0.1%) |
| Insertive anal intercourse | 6.5 (0.065%) |
| Insertive penile-vaginal intercourse | 5 (0.05%) |
| Receptive oral intercourse | 1 (0.01%) |
| Insertive oral intercourse | 0.5 (0.005%) |

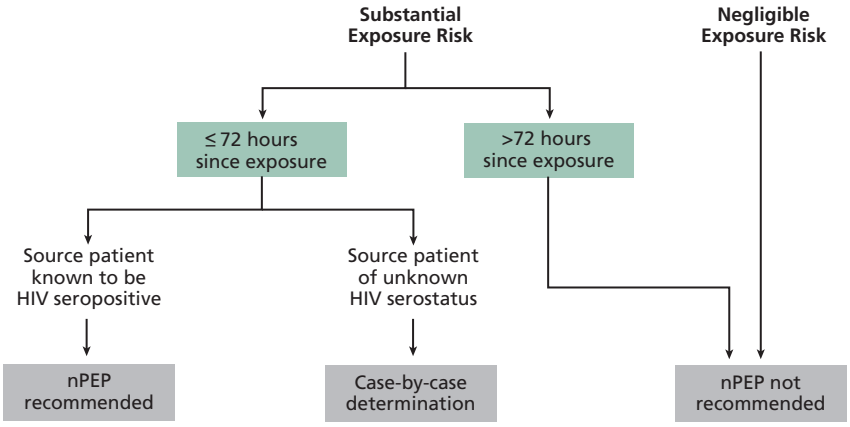
Adapted from Centers for Disease Control and Prevention, *Morb Mortal Wkly Rep*, 2005.

known to be HIV-seropositive or is an individual with unknown HIV serostatus engaging in high-risk behavior. The CDC has issued a flow diagram assisting clinicians in making PEP-initiation triage decisions (Figure 2). In brief, the guidelines recommend treatment for cases involving exposure of mucous membranes or nonintact skin to genital fluids, breast milk, or visibly bloody secretions within 72 hours.

Nonoccupational PEP, like occupational PEP, can fail. A patient of the author's presented at 50 hours after receptive anal intercourse and was started on a 28-day regimen of zidovudine/lamivudine plus ritonavir-boosted lopinavir. The patient claimed 100% adherence and no new exposures but tested HIV-seropositive at 5 months postexposure, with wild-type virus and a low viral load. He was subsequently lost to follow-up. A recently published, well-characterized case report suggests that seroconversion through antiretroviral prophylaxis does not obligate the acquisition of drug-resistant virus (as many assumed would be the case) and may portend slower clinical progression and lower virologic set points (Prada et al, *JAIDS*, 2008). This observation needs further validation in larger cohorts and clinical trials before it can be routinely accepted, and it likely is dependent on many viral and host-related factors.

Controversy continues over whether 2-drug or 3-drug regimens are preferred. Mathematical modeling suggests using a 3-drug regimen if baseline antiretroviral drug resistance in the source patient population is greater than 15% (Bassett et al, *Clin Infect Dis*, 2004). For 2-drug regimens, dual nucleoside analogue reverse transcriptase inhibitors (nRTIs) are recommended; the most experience is with zidovudine/lamivudine, but there is increasing use of and safety data with tenofovir/emtricitabine (Mayer et al, *JAIDS*, 2008). With regard to which drugs to add for 3-drug combinations, nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs) are not recommended because of their associated risk of hepatotoxicity, particularly for nevirapine. Efavirenz should also be avoided because of the potential emergence of NNRTI resistance. Ritonavir-boosted PIs are attractive options, particularly in cases of high-risk exposure.

HIV entry inhibitors and integrase inhibitors are potentially attractive on the basis of their mechanisms of action; both target an early stage of HIV replication and therefore likely affect early infection pathogenesis. In a case report involving the entry inhibitor maraviroc, a medical student was exposed via a small-gauge needle puncture to a multidrug-resistant virus from a source patient who was taking a regimen of tenofovir, ritonavir-boosted lopinavir, fosamprenavir, and enfuvirtide (plasma HIV RNA level, 3.8 $\log_{10}$ copies/mL) (Mechai et al, *J Med Virol*, 2008). The student received PEP with tenofovir, lamivudine, fosam-




**Substantial Risk for HIV Exposure**

*Exposure of:*
vagina, rectum, eye, mouth, or other mucous membrane, nonintact skin, or percutaneous 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-infected

**Negligible Risk for HIV Exposure**

*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 serostatus of the source

Figure 2. The Centers for Disease Control and Prevention (CDC) flow diagram for nonoccupational postexposure prophylaxis (nPEP) decision making. Adapted from CDC, *Morb Mortal Wkly Rep*, 2005.

prenavir, and maraviroc and remained HIV-seronegative at 6-month follow-up with no adverse events.

There have been 2 case reports of use of the integrase inhibitor raltegravir (Siegel et al, *AIDS*, 2008). In one, a surgical resident was exposed to multidrug-resistant virus from a source patient (plasma HIV RNA level, 215,000 copies/mL) via scalpel laceration and received emtricitabine/tenofovir, ritonavir-boosted atazanavir, and raltegravir. Development of jaundice prompted rapid discontinuation of the ritonavir-boosted atazanavir, with no additional adverse events observed. In the other case, a laboratory technician was exposed via puncture with a capillary tube containing HIV-infected blood and received emtricitabine/tenofovir, ritonavir-boosted darunavir, and raltegravir with no adverse events. Both patients were HIV-seronegative at 6-month follow-up.

A larger case series presented recently suggests a salutary safety profile of emtricitabine/tenofovir plus raltegravir in MSM after potential sexual exposure to HIV (Mayer et al, IAC, 2009). Although such limited case reports and case series neither confirm nor refute efficacy, they contribute important safety information about the use of such drugs in HIV-seronegative at-risk populations and increase confidence in their safety profiles in an era when the use of nevirapine as part of PEP regimens was also mechanistically attractive but ultimately shown to have unacceptable safety issues when used in this capacity.

## Conclusion

Generally, management of exposure to HIV should include risk assessment of the event to determine likelihood of transmission; discussion of PEP with antiretroviral drugs; emotional and psychological counseling and support; counseling on safe-sex practices during the period of monitoring; and close medical follow-up with repeat serologic testing.

In patients with nonoccupational exposure, practitioners should take advantage of "the PEP moment" to discuss risk-reduction behavior with the exposed patient; make appropriate referrals to substance-abuse, domestic-violence, or mental health support services; and initiate other sexually transmitted disease testing or treatment and hepatitis screening as necessary. During follow-up, practitioners should maintain vigilance for signs and symptoms of acute HIV infection. It remains unclear who will pay for nPEP treatment and management, particularly for uninsured patients.

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## Suggested Reading


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