

Prophylaxis Following Nonoccupational Exposure to HIV

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Introduction

Several programs and observational studies have been designed to offer postexposure prophylaxis (PEP) following exposure to HIV in a variety of nonoccupational settings, including consensual and nonconsensual sex and injection drug use. Separate, published--but unofficial--guidelines exist in the United States recommending the use of nonoccupational PEP following consensual sexual exposure ([1](#)) and sexual assault.[\(2\)](#) Massachusetts has policy and procedures in place to provide PEP following all such exposures,[\(3\)](#) Rhode Island has recently developed guidelines for nonoccupational PEP use,[\(4\)](#) and the states of New York and California have guidelines for the use of PEP following sexual assault.[\(5,6\)](#) In accordance with recent legislation, California is developing guidelines for PEP use following nonassault, nonoccupational exposures.

In 1998, the U.S. Centers for Disease Control and Prevention (CDC) published guidelines for the use of nonoccupational PEP that neither recommended nor discouraged its use.[\(7\)](#) Revised guidelines are currently undergoing review after a May 2001 consultation resulted in draft revisions. Internationally, several countries have official policies recommending nonoccupational PEP,[\(8\)](#) including France,[\(9\)](#) Italy,[\(10\)](#) Spain,[\(11\)](#) Switzerland,[\(12\)](#) Australia,[\(13,14\)](#) and South Africa.[\(15\)](#) This chapter summarizes the available data regarding nonoccupational PEP and discusses the practical issues involved in the implementation of such programs.

Efficacy and Related Background Data

Although there are no efficacy data directly supporting the use of nonoccupational PEP for sexual (mucosal) exposures, several related sets of data from occupational exposure, mother-to-child transmission, and animal studies support its biological plausibility ([Table 1](#)). However, the validity of generalizing results of nonmucosal exposures to mucosal exposures--because of differences in the mucosal immune response--remains uncertain.[\(16\)](#)

Occupational Exposure Studies

The 1987 approval of zidovudine (ZDV), the first agent available for the treatment of HIV infection, was followed by official consideration of antiretroviral therapy as prophylaxis following potential exposure to HIV. In 1990 the CDC published a statement that neither recommended nor discouraged such use following occupational exposures to HIV.[\(17\)](#) The 1995 presentation of a case-control study in health care

workers, which demonstrated a 79% reduction in the likelihood of HIV infection when ZDV was used following occupational exposure,(18) led to the 1996 revision of the CDC guidelines to recommend PEP following substantial occupational exposures.(19) The published study ultimately showed an 81% reduction in HIV infection when ZDV was used following occupational exposure, and this raised a number of questions regarding generalizability to nonoccupational exposures, the feasibility of providing nonoccupational PEP, and its safety and cost-effectiveness.(20)

Unfortunately, PEP following occupational exposure is not always effective.(20-26) In some cases, HIV infection has occurred despite rapid initiation of treatment and use of multidrug regimens. Transmission of drug-resistant virus, possible increased infectivity when hepatitis C virus is also transmitted, and late initiation or early discontinuation of PEP have also been hypothesized to explain some of these breakthrough infections.

Mother-to-Child Transmission Studies

Multiple studies of antiretroviral drugs used in pregnant women and/or their newborns have demonstrated efficacy in preventing mother-to-child transmission of HIV infection (Table 1).(27,28) Some of these studies have included drugs given to both the mother and the newborn,(29-33) some just to the mother,(34,35) and some to just to the newborn.(33,36-38) The New York State Department of Health analysis demonstrating efficacy even in those infants who only received ZDV within 48 hours after birth (9.2% compared to 26.6% transmission without PEP) suggests that there is likely a post- as well as a pre-exposure effect of antiretrovirals used in the prevention of mother-to-child transmission.(33) A second analysis of that data set suggests, as in animal studies, that earlier initiation of PEP in the infant is more effective.(38) As a result of this second analysis, New York State regulations require that maternal HIV antibody test results be available as soon as possible and no later than 48 hours after maternal blood draw or delivery for women who present without prenatal HIV testing. The first prospective study of antiretrovirals used only in the postnatal period to prevent mother-to-child transmission showed a transmission rate of 15.3% at 6 weeks in infants who were randomized to receive a combination of ZDV and nevirapine, compared to a transmission rate of 20.9% in infants randomized to nevirapine alone, suggesting that this combination PEP approach has some efficacy in preventing infection in infants.(36) A second prospective study of PEP in infants is underway in South Africa.(38) Preliminary data suggest that treating the infant with a single dose of nevirapine (11.6% PCR positive by 6 weeks) or 6 weeks of zidovudine (18% PCR positive by 6 weeks) may be partially effective in reducing HIV transmission, although the study is not yet complete.

Animal Studies

Results from animal studies of PEP have provided data supportive of its probable efficacy in intravenous, oral, and vaginal simian immunodeficiency virus (SIV) and HIV-2 exposures, and these data have been instructive in terms of timing and duration of therapy (Table 1). In SIV models, nucleotide and nucleoside analogues have been protective in preventing infection in a majority of intravenously inoculated macaques when given early after exposure (within 24 hours is superior to 48 or 72 hours) and for

a 28-day course.(39-43) When provided to macaques following intravaginal exposure to HIV-2, the nucleotide analogue PMPA (tenofovir) was fully protective when treatment was initiated at 12 or 36 hours postinoculation (0 of 8 treated animals infected), and only partially effective at 72 hours (1 of 4 treated animals infected; 3 of 4 controls infected).(44) The 3 control animals seroconverted at 2 weeks and the experimental animal at 16 weeks postexposure, raising concerns about the possibility of delayed seroconversion and the need for adequate follow-up HIV antibody testing after administration of PEP. Studies in oral mucosal transmission models have shown efficacy of combined pre- and postexposure interventions, even with antiretroviral-resistant virus, raising questions about the mechanism of action of PEP in this setting.(45-47) Nonnucleoside reverse transcriptase inhibitors (NNRTIs) appear to be at least partially protective PEP agents in primate studies.(48,49)

Preliminary Human Data

For two important reasons, no prospective, randomized, controlled studies have been implemented to evaluate the efficacy of nonoccupational PEP. First, ethical concerns arise over withholding PEP given the convergence of supportive data. Second, evaluating the efficacy of an intervention aimed at reducing the risk of an already very low-risk exposure would require thousands of study subjects. Several observational studies of nonoccupational PEP following both consensual and nonconsensual exposures have been published or presented (Table 2). Although valuable, these studies were not designed to demonstrate efficacy.

PEP Studies in North America

CDC Registry

In June 1999, a CDC-sponsored registry began assessing the availability of nonoccupational PEP nationwide in the United States (Table 2). The objectives of the registry study include evaluating exposures that lead to PEP prescription, describing prescribed PEP regimens and adverse events, comparing seroconversion among those who do and do not receive PEP prescriptions, and providing data for a future case-control study to determine the efficacy of nonoccupational PEP. Initial findings were presented at the International AIDS Conference in Barcelona in 2002.(50)

Data were presented on 424 exposed patients, 92% with sexual exposures. There were 233 reports from Massachusetts and 146 from California, where PEP study sites have contributed data to the registry. There were 15 reports from New York, and nine additional states contributed between one and nine reports. Exposures included receptive anal sex (reported in 44% of cases), receptive oral sex (in 25%), receptive vaginal sex (in 23%), insertive anal sex (in 23%), and insertive vaginal sex (in 8%). Multiple exposures were reported. Twenty-nine percent reported knowing that the source of exposure was HIV infected.

Data from a 4- to 6-week follow-up were submitted for 160 patients (38%), 159 of

whom received PEP. Of these treated participants, 53% received three drugs, and 42% received two drugs. Zidovudine and lamivudine were included in 85% of regimens. Seventy-five percent of the 159 patients completed their initial regimen, 9% had the regimen modified, and 14% stopped early. Of the changes or discontinuations, 55% resulted from adverse effects.

Of the 160 patients with at least 4-6 weeks of follow-up data, 68% had an HIV test at 4-6 weeks, 13% had a test at 6 months, and 6% had a test at 12 months. One seroconversion was reported in an individual with multiple exposures involving a partner who had started antiretroviral therapy with a viral load of 180,000 copies/mL 2 weeks before the presenting exposure. The PEP regimen of stavudine and lamivudine was initiated 11 hours after an insertive anal exposure, and the HIV test was positive 2 months later. It is unclear if this was a PEP failure given the multiple additional exposures that occurred before, during, and after the PEP course. Investigators are attempting to improve the geographic representation of the sample and to increase data acquisition regarding exposed patients who do not take PEP.

Emergency Physician Practices, Attitudes, and Beliefs

A national survey of emergency medicine physicians and residents in the United States demonstrated that nonoccupational PEP is recommended most frequently following sexual assault (35%), followed by unintentional needlesticks (25%), and unprotected sex and shared injection drug use materials (<15%).⁽⁵¹⁾ Sixty-four percent felt it was feasible to provide PEP in the emergency department, although only 46% felt confident in prescribing appropriate drugs for PEP.

San Francisco

Feasibility Study

Four hundred and one exposed individuals and 64 of their source partners were enrolled in a feasibility study of nonoccupational PEP between October 1997 and May 1999 ([Table 2](#)).⁽⁵²⁾ The majority of participants were between 20 and 60 years old, male, and white. Approximately 50% presented following possible exposure via receptive anal intercourse, the highest-risk sexual exposure, and fewer than 5% after receptive oral intercourse with ejaculation, the lowest-risk exposure. Approximately 50% of exposed participants reported that their source partner was known to be HIV infected, and the majority of the remaining partners were men who have sex with men (MSM). Thus, the San Francisco study reached a population at high risk of acquiring HIV infection.

The mean time to initiating PEP medications was 33 hours. The majority of participants experienced some subjective toxicity, with fatigue, nausea, and headache being the most common. There were no significant laboratory toxicities. Adherence to the 28-day course of medication was nearly 80%.

There were no seroconversions in the first 6 months following PEP. Four participants

seroconverted in the second 6-month follow-up period.(53) All 4 of these individuals experienced ongoing high-risk behavior and multiple potential exposures. History and laboratory testing, including the detuned (sensitive/less sensitive) HIV antibody assay, suggested these infections all resulted from exposures after the presenting exposure. Six- and 12-month self-reported risk behaviors declined in approximately 80% of women and of MSM, and increased in only approximately 8% of participants in these groups.(54) Over 50% of heterosexual men reported no change in rates of risk behavior.

Of the 64 source partners, 50 were HIV positive.(55) Approximately 80% of this group had ever used antiretrovirals, and nearly 70% were using them at the time of enrollment. Nearly 50% had a plasma HIV RNA level of >1,000 copies/mL. Resistance rates for the various antiretrovirals ranged from 20% to 60%.

A recent analysis of two studies from San Francisco highlights the challenge of determining whether HIV seroconversion in the first few months following PEP is a result of failure of PEP to prevent infection or of other exposures that occurred either before or after PEP was initiated.(56) This is particularly challenging in the nonoccupational setting, where plasma samples from the potential source of exposure are rarely available to document transmission by testing for homology to the seroconversion virus. This study also highlights the challenges of designing an efficacy study of nonoccupational PEP given the difficulty of attributing infection to a specific exposure.

Sexual Assault

Survivors of sexual assault have been excluded from studies of nonoccupational PEP in San Francisco out of a desire to limit the burden on the survivor. PEP has been available through the Rape Treatment Center at San Francisco General Hospital. A 1998-1999 chart review revealed that 57% of those seen had documentation of being offered PEP, 32% of those accepted--38% of whom completed a 1-week follow-up visit and received the remainder of their medication course ([Table 2](#)).⁽⁵⁷⁾

Massachusetts

The Massachusetts Department of Public Health (MDPH) has supported several studies to assess the demand for, and the prescription of, PEP in Massachusetts. A 1998 survey of Massachusetts emergency departments (EDs) revealed that more than half had one or more requests for nonoccupational PEP in the previous year and that one-third of these patients were prescribed PEP medications ([Table 2](#)).⁽⁵⁸⁾ Only 15% of EDs had official, written protocols, and one-third had unwritten, informal protocols. There was significant variability among respondents in terms of acceptable timing to initiate PEP, indications for PEP, and medication regimens. Similarly, a provider survey conducted in 1998 revealed that of the 80 providers (representing 63 institutions), only 20% used written protocols.⁽⁵⁹⁾ Sixteen sites each reported having provided >100 PEP prescriptions, and the majority indicated they would like more formal training. It was partly based on these two data sets that the MDPH recognized that the demand for nonoccupational PEP existed, that clinical practices were inconsistent, and that clinical

guidance was needed.

As of October 2000, it has been the policy of the MDPH that nonoccupational PEP should be available and offered to all individuals with high-risk exposures.(3) The MDPH operates a 24-hour technical assistance hotline (for health care providers only) through the University of Massachusetts, assures access to clinical follow-up through multiple primary care centers, and provides reimbursement for 28 days of antiretroviral medications for the uninsured. More information may be found at: http://www.state.ma.us/dph/aids/guidelines/ca_exposure_nonwork.htm.

A structured nonoccupational PEP program and study have been available at the Fenway Community Health Center in Boston since September 1997 (Table 2).(60) As of 2002, 268 people had received PEP services, the majority of whom were white MSM who had had receptive anal (52.6%), oral (36.4%), or insertive anal (29.5%) intercourse. Approximately half of the patients received a three-drug PEP regimen. Only 46% of patients completed a 4-week course of PEP. One seroconversion has been reported (personal communication, Kenneth Mayer, July 2003).

Sexual Assault

A small program at Lawrence General Hospital in Lawrence, Massachusetts, reported on 83 sexual assault survivors who were evaluated for indications for PEP, of whom 34 were eligible and 15 began medications (Table 2).(61) Sixty-four percent completed their 28-day regimen of two nucleoside analogues.

Quebec, Canada

A survey of health care providers in the Quebec province mailed in November 1998 revealed frequent requests for PEP. Ninety of the responding 219 providers reported evaluating 875 patients and prescribing PEP to 43%.(62,63) Thirty-two percent presented with nonoccupational accidental needlestick exposures, not related to their own injection drug use. The majority received a three-drug regimen. An assessment of provider attitudes towards PEP prescription found that >90% would prescribe PEP for unprotected receptive anal or vaginal sex with a known HIV-positive partner, whereas only 20% (for vaginal exposures) to 40% (for anal exposures) would prescribe it for the same exposures if the partner's HIV status were unknown.

Vancouver, Canada

Canadian investigators have described the experience in British Columbia between April 1999 and November 2000, where PEP medications were distributed at >130 sites, mostly through EDs.(64) Guidelines were produced in March 1999 by the British Columbia Center for Excellence in HIV/AIDS. A 5-day starter kit is prescribed, containing three drugs for high-risk exposures (stavudine, lamivudine, and nelfinavir) and two drugs for moderate-risk exposures. Follow-up is provided by primary care providers who decide whether or not to provide the remaining 23 days of PEP treatment. A central pharmacist performs a final risk assessment and decides if the

regimen is to be continued.

The analysis includes occupational, community, and sexual assault exposures to identify characteristics associated with the prescription of three vs two drugs and with 23-day follow-up after completion of the 5-day starter pack. Fifty-five percent of the 2,064 starter kits prescribed were for individuals sustaining an occupational exposure, 22% for community exposures, and 21% following sexual assault. Twenty-nine percent of exposed individuals knew or suspected the source of exposure was HIV infected. Twenty percent received three-drug starter kits. Community needlesticks (odds ratio [OR] = 1.89, 95% confidence interval [CI]: 1.42, 2.52), occupational mucocutaneous injuries (OR = 1.70, 95% CI: 1.14, 2.55), and being male (OR = 1.38, 95% CI: 1.10, 1.74) were associated with receiving three vs two drugs in a multivariate model. Thirty percent received the 23-day refill following the starter pack. Community sexual exposure (OR = 2.83, 95% CI: 1.41, 5.7), receiving a three-drug starter kit (OR = 2.61, 95% CI: 2.07, 3.29), having a community needlestick (OR = 1.75, 95% CI: 1.33, 2.29), and being male (OR = 1.24, 95% CI: 1.00, 1.53) were associated with receiving the 23-day follow-up prescription in a multivariate model.

The authors note that PEP is not always being appropriately prescribed in the British Columbia program; 50% of those receiving treatment did not qualify for PEP according to the guidelines. They conclude that "greater effort is needed to support health care providers in their assessment of HIV risk in order that they appropriately prescribe these potent medications."[\(64\)](#)

Sexual Assault

PEP is available for survivors of sexual assault in Vancouver, where acceptance has been reported at 28%, with 41% of participants returning for the first follow-up visit (at 2-5 days) ([Table 2](#)).[\(65\)](#) Only 11% of those who started PEP completed the 28-day medication course.

PEP Studies in South America

Brazil

A nonrandomized study of a high-risk cohort (annual HIV incidence of 3.4%) given PEP "starter packs" (medications to be initiated in the case of a potential exposure prior to evaluation by a clinician) has provided preliminary data suggesting efficacy in that setting, with 1 infection detected among 66 participants taking PEP (0.6 infections per 100 person-years) and 10 seroconversions in 131 non-PEP users (4.2 infections per 100 person-years), with a mean of 24.2 months of follow-up.[\(66\)](#) Importantly, no risk behavior data comparing the two groups have been presented, thus the difference in infection rates may reflect a difference in risk behavior between these two groups rather than an effect of PEP. The single seroconverter in the PEP group had a lamivudine-associated mutation in his plasma, but no data have been provided about the resistance pattern of the HIV from the potential source of infection to determine if

this was likely transmitted, or if it was acquired during the course of PEP ([Table 2](#)).

PEP Studies in Europe

A survey performed between September 1998 and February 1999 of 27 European countries showed that six countries had specific policies and procedures for nonoccupational PEP; information campaigns are present in two countries; and PEP is theoretically available in additional 12 countries.⁽⁸⁾

France

Official recommendations regarding nonoccupational PEP were instituted in April 1998, and several studies of PEP following consensual and nonconsensual sexual exposures have since been published or presented. Most recent presentations have noted that the majority of prescriptions for nonoccupational PEP in France are for low-risk exposures, and that the use of three drugs is associated with an unacceptably high incidence of severe adverse events.

A national surveillance system was instituted in July 1999, and, as of May 2000, 1,292 requests were reported for 100 hospitals.⁽⁶⁷⁾ The majority of the requests came from male patients (60%), with heterosexual exposures accounting for 66%. Only 24% of exposures were with a source known to be HIV infected. Seventy-six percent received PEP, with no significant difference if the HIV status of the source was known to be positive or unknown. The majority were given three drugs (76%). Forty-one percent were seen at 1 month, and 17% at 3 months. There were nine severe adverse events in this group, and the authors conclude that PEP is both overprescribed in low-risk situations and that fewer drugs should be used when it is prescribed.

Clinical investigators from France describe the impact of the 1998 French Ministry of Health guidelines offering PEP following injection drug use and consensual and nonconsensual sexual exposures through hospital EDs, with follow-up within 48 hours by a "PEP reference physician" appointed to validate occupational and nonoccupational risk assessment and PEP prescriptions.⁽⁶⁸⁾ They conducted surveys of hospital-based physicians in 1997 (1,604 physicians taking care of HIV-infected patients) and 1999 (571 PEP reference physicians), of whom 43% percent of the 1997 group and 54% of the 1999 group responded. PEP requests increased sevenfold (from 390 to 3,187), and prescriptions increased ninefold (from 165 to 1,835). In 1997, 74% of respondents reported no requests in the previous 12 months; in 1999, only 18% had received no requests. In the preguideline questionnaires, prescription attitudes were based more commonly on risk assessment (64% vs 33% in the postguideline period), whereas in the postguideline questionnaires, prescription attitudes were more highly influenced by patient request (41% vs 11% in the preguideline period.). These changes are consistent with the overall tone of the French guidelines, which state that "it is important to consider the perception of risk leading a person to request prophylaxis." Consistent with a willingness to prescribe for lower-risk exposures, the proportion of prescriptions for exposures from a source who was known to be HIV infected decreased from 78% to

41%.

Three-drug combination use, recommended in the guidelines, increased from 46% in 1997 to 83% in 1999. The authors reported 13 severe, reversible adverse events among patients receiving three antiretroviral agents for PEP, and refer to nine additional severe adverse events in an ongoing prospective PEP study. The events in the retrospective study included six cases of nephrolithiasis (associated with indinavir), three severe rashes (two associated with indinavir, one with nevirapine), two cases of drug-induced hepatitis (indinavir), one cholecystitis (nevirapine plus indinavir), and one hemolysis (indinavir). Indinavir was used in 47% of prescribed regimens; nelfinavir was used in 32%. The risk of a severe adverse event was 0.71%, apparently higher than estimates of the per-contact risk of acquiring HIV from lower-risk exposures such as receptive vaginal or insertive anal intercourse with an HIV-infected partner.

The French authors note that although PEP use is increasing, it is still only requested after a small minority of potential exposures. Consistent with other reports, the majority of requests are associated with sexual exposures, as opposed to those associated with injection drug use. The authors conclude that PEP should be restricted to those with well-documented exposures, as opposed to the less risky ones described in the 1999 survey, and that PEP regimens should more often include two rather than three drugs due to the substantial risk of serious toxicity observed in this retrospective study as well as in an ongoing prospective study in France.

A review of the experience in 11 hospitals that used zidovudine, lamivudine, and nelfinavir, showed that 26% were lost to follow-up within 2 days, and 57% of the remaining patients discontinued PEP after the source tested negative for HIV or they reevaluated their risk.⁽⁶⁹⁾ Ten percent of the remaining group discontinued medications due to adverse events, and an additional 25% discontinued just the nelfinavir. Three additional groups have presented their experiences with nonoccupational PEP in France ([Table 2](#)).⁽⁷⁰⁻⁷²⁾ Debab et al noted similar completion rates among occupationally and nonoccupationally exposed individuals seeking PEP, however there was a difference in adverse-event rates (59% in occupationally exposed vs 21% in sexually exposed).⁽⁷²⁾ Prevot et al noted that the HIV status of the source was known to be positive for those with occupational exposures more frequently than for those with nonoccupational exposures (74% vs 42%); however, PEP was instituted more commonly for nonoccupational exposures (21% vs 63%).

Sexual Assault

Unlike the North American experience with PEP in the context of sexual assault, two French groups reported significant acceptance rates, 74% and 95% ([Table 2](#)).^(73,74) Medication completion and follow-up rates, however, remained poor, at approximately 24-36%.

Other European Countries

Swiss guidelines have recommended nonoccupational PEP since 1997. A voluntary registry had received 115 reports as of December 1999, many for exposures with

sources of unknown HIV status (64%) and in the absence of behaviors associated with significant risk.(12) A registry of PEP prescriptions in Italy suggests that thus far the demand is small, but growing (Table 2). Spain also has guidelines recommending the use of nonoccupational PEP.(11) A group in London has routinely prescribed a regimen for both occupational and nonoccupational exposures containing full-course nevirapine, and found an unacceptable degree of serious hepato- and dermatotoxicity.(75)

PEP Studies in Australia

Nonoccupational PEP has been recommended and available in New South Wales since December 1998. The New South Wales recommendations were extended to all of Australia in 2001.(14) Data from eastern Australia collected between 1998 and 2002 were reported recently.(76) Eight hundred nineteen subjects were included, the majority of whom were MSM who had either receptive (66%) or insertive (31%) anal sex. Two hundred thirty-two sexual exposures and seven needle-sharing exposures occurred with a source partner who was known to be HIV infected. Sixty-six percent of prescriptions were for three or more drugs. Seventy-seven percent of subjects were followed at 4 weeks. Only approximately 50% were evaluated at 12 weeks, and 20% at 6 months. Two HIV seroconversions were detected in individuals who reported ongoing risk behavior. Although promising, and consistent with the feasibility study in San Francisco that followed a similar number of PEP recipients,(52) these data are not proof of efficacy.

PEP Studies in Africa

South Africa

The South African government presented guidelines for nonoccupational PEP use in April 2002, recommending that all rape survivors be provided a "comprehensive package of care...including counseling...on the risks of using antiretrovirals as preventative drugs, so they could make an informed choice. If they so choose (as is the case of needlestick injuries), they will be provided with such drugs in public health institutions."(15) A standardized national protocol has been developed for the treatment of adult sexual assault survivors with zidovudine and lamivudine.

A chart review was performed from a clinical practice that provides PEP to sexual assault survivors in Johannesburg.(77) Six hundred eighty-seven subjects were seen over a 4-year period, 16% of whom were HIV-infected at presentation. Although 435 subjects were given starter packs of PEP medications, no data are available regarding how many of these picked up the remaining prescription. One hundred seventy-three subjects were seen 6 or more weeks after initiating PEP, and there was one seroconversion (0.6%). Among 25 subjects who presented >72 hours after the assault, 9 followed-up, and 1 seroconverted. Although intriguing, these data are limited by lack

of information about who actually took PEP, limited follow-up, and a study design that does not permit analysis of efficacy.

Congo

Médecins Sans Frontières (Doctors Without Borders) initiated a PEP program in 2000 among sexual assault survivors in the Congo. They have prepared an unpublished report describing 329 survivors seen between February 2000 and February 2002.⁽⁷⁸⁾ The median age was 17 years (ranging 2 to 55 years), and 20% were <13 years old. Only 2 were male. The median time to presentation was one week following possible exposure; only 39.3% presented at <3 days. Delay to presentation was longer in older survivors, those assaulted by multiple perpetrators, and those whose perpetrator was a member of the military. Of 214 who received an HIV test at presentation, 9 were HIV infected. Among those testing HIV negative, 92% presenting within 72 hours were prescribed PEP (ZDV + 3TC). Additionally, 5 HIV-infected and 12 untested survivors were provided with PEP. The younger survivors were less likely to be given PEP due to difficulty in ascertaining what had happened during the assault. A 28-day course was completed by 65.7%, and 75.5% completed 21 days of PEP. No seroconversions were identified in the 33% of subjects who had a follow-up HIV test at 6 months. Among the 233 charts with medical information available, vulvar trauma was documented in 136 cases, vaginal trauma in 151, and anal trauma or infection in 10 cases.⁽⁷⁸⁾

Behavioral Data

Many studies of voluntary counseling and testing or risk reduction counseling have demonstrated reductions in subsequent risk-taking behavior and/or reduced sexually transmitted disease (STD) or HIV rates.⁽⁷⁹⁻⁸³⁾ Thus, integrating risk-reduction counseling into PEP programs may reduce the likelihood of future exposures as well as the risk of infection from the presenting exposure.^(52,54)

One of the most significant concerns about the use of nonoccupational PEP is that the availability of this secondary, biomedical intervention might reduce commitment to primary prevention strategies. Such a change was not seen in the San Francisco feasibility study, which found, to the contrary, that 74% of participants had a reduction in self-reported risk behaviors at 6 months after PEP initiation.⁽⁵⁴⁾ Nor was it seen in the Brazilian study, in which the proportion of participants reporting any risk exposure was reduced from 57% at baseline to 40% at 24 months ($p = .001$).⁽⁶⁶⁾

A cross-sectional survey of 104 serodiscordant couples in California showed that although more than two-thirds reported unprotected sex with their partner in the past 6 months, most respondents, regardless of serostatus, said that viral load testing and awareness of postexposure prevention had no effect on their condom use.⁽⁸⁴⁾ Likewise, two cross-sectional surveys performed among gay men in San Francisco in 1998 and 1999 (before and after a community-wide outreach campaign to recruit for a study of PEP) suggested that although general knowledge of PEP might be associated with increased rates of unprotected anal intercourse among HIV-positive (but not HIV-negative or untested) men, those men who actually knew that PEP was available in

their community did not report higher rates of risk behavior, regardless of HIV status.(85) Attitudes and beliefs regarding PEP were evaluated in a high-risk cohort of 183 MSM in Montreal in 1998-1999.(86) Fewer than 20% knew about PEP, and its use was very rare. Although there was a high level of belief in the effectiveness of PEP, most were still very concerned about the seriousness of HIV, and there was no apparent impact on risk behaviors.

Sexual Assault Data and Policy

State and international policies regarding the use of PEP in sexual assault have been described in the section above,(3,6,87) as have preliminary data regarding its use in a number of locations.(57,61,65,73,74,77,78) In general, it appears that acceptance of PEP in this setting in North American and European cohorts is relatively low, although one of the French groups described a very high degree of acceptance. The African studies to date do not describe the number of eligible subjects who are offered and accept PEP. Completion of medications and follow-up appear poor in North American and European cohorts and are incompletely described in the two available African studies.

Integrating a discussion of HIV transmission risk, HIV antibody testing, and the risks and benefits of taking PEP medications into a sexual assault evaluation and treatment session is fraught with challenges. Some programs elect not to offer HIV antibody testing until the first follow-up visit several days later in an attempt to minimize the emotional consequences of an already traumatic situation. The barriers to providing PEP in this setting have not been formally explored. Effective education and counseling strategies will need to be developed and tested in this setting, particularly in areas of high HIV incidence, where the risk of acquiring HIV from rape is significant.

Sexual Assault in the Context of High HIV Prevalence

The potential benefits of PEP are directly related to the risk of acquiring HIV infection from a given exposure. When the prevalence of HIV is high in the community, the likelihood of being exposed to HIV from a sexual assault increases. Sub-Saharan Africa suffers from the highest HIV prevalence rates of any region in the world. Antenatal surveillance data from South Africa suggest that HIV prevalence rates range as high as 30-50% in various provinces. Concomitant STDs and ulcerative genital disease are also common, increasing the likelihood of HIV transmission.

Rape is often associated with visible mucosal trauma and is usually associated with microtrauma even when no visible signs are evident. Adolescent and preadolescent girls with cervical ectopy are at increased risk of acquiring HIV compared to adult women. Although no data exist documenting the per-contact transmission rate of HIV in the context of sexual assault, numerous factors suggest that this rate might be substantially higher than per-contact transmission rates derived from studies of heterosexual partners.

A report (87) and commentary (88) in the *Lancet* highlighted the problem of rape in

girls and infants. In a cross-sectional, nationally representative survey of nearly 12,000 women in South Africa in 1998, 1.6% reported rape or attempted rape before the age of 15.⁽⁸⁷⁾ Some argue that one of the factors contributing to the rape of girls and infants is the "virgin cleansing myth" (the belief that having sexual intercourse with a virgin will cure HIV infection). Such myths have been perpetuated in other contexts and other cultures (eg, gonorrhoea in Scotland in the 1910s and 1920s), and it is unclear what influence the virgin cleansing myth truly has on risk behavior and HIV prevalence in Africa. Some have argued that the existence of the myth does not prove that the belief drives behavior, and that, in fact, we may not look deeply enough into the true causes of sexual assault if we assume that this behavior is driven primarily by the virgin cleansing myth. Although several organizations do provide PEP following sexual assault in South Africa, there are no published descriptions of the use of PEP for sexual assault survivors in a high-prevalence area such as sub-Saharan Africa. Initiation of a prospective study of PEP acceptance, adherence, and adverse effects among sexual assault survivors is planned in Cape Town in early 2004.

Children and Adolescents

Consideration for prescribing PEP to children and adolescents is beyond the scope of this chapter, but has been addressed by others.^(6,89,90)

Conception

PEP has been requested and used in the setting of artificial insemination when the donor was found to be HIV infected ⁽⁹¹⁾ and for serodiscordant couples. There have been no published reports of the proactive use of PEP in this setting, but occasional requests for this intervention should be anticipated.

Cost-Effectiveness

Several papers have evaluated the cost-effectiveness of PEP and suggested that such cost-effectiveness may be limited to the highest-risk exposures (eg, receptive anal intercourse) with known HIV-positive partners.⁽⁹²⁻⁹⁷⁾ A recent publication reports on a retrospective cost analysis combined with model-based effectiveness estimates of the San Francisco PEP study.^(52,98) The study costs included, but were not limited to, HIV antibody testing and counseling, other laboratory testing, and antiretroviral medications. The main outcome measure was the "cost-utility ratio" (ie, the ratio of net program costs to the total number of quality-adjusted life-years (QALYs) saved by the program. The average cost per client was US\$1,222. The overall PEP program prevented an estimated 1.26 HIV infections, saved 11.74 QALYs, and averted US\$281,206 in future HIV-related medical care costs. The overall cost-utility ratio was US\$14,467 per QALY saved. Among men reporting receptive anal intercourse, the savings in averted HIV-related medical care costs exceeded the cost of the program.

For the overall study population, HIV PEP was cost-effective by conventional standards.

Harder to capture in such analyses is the potential positive impact of changes in risk behavior that might result from an exposed person reaching out for help, accessing a program that provides PEP, and perhaps receiving risk-reduction counseling and care for mental health and substance abuse issues. Where PEP fits into an overall prevention strategy is open to debate, and the questions may be different if PEP includes counseling and referrals in addition to medications.

Considerations for Use of PEP

Timing

Animal models of HIV acquisition and of PEP interventions suggest that PEP will be more effective the sooner it is started.(43,44) A 72-hour time limit for the initiation of PEP is reasonable given the evidence suggesting that PEP is not effective if initiated more than 72 hours postexposure ([Table 3](#)).

Exposure Risk

(Also refer to [Table 3](#))

If indeed PEP is effective following mucosal and other nonoccupational exposures, then those at highest risk of acquiring HIV infection from their specific exposure would be expected to benefit most from PEP. Potentially exposed individuals should be assisted in evaluating their risk, using a hierarchy of risk where receptive anal intercourse is riskier than insertive anal intercourse and receptive vaginal intercourse, which are riskier than insertive vaginal intercourse, which is riskier than receptive oral sex with ejaculation.(99-103) Other mucosal exposures, such as eye exposures, and exposures of nonintact skin to potentially infected body fluids, should also be considered.(104) The average risk of HIV infection from each of these exposure types should be presented within the context of the risk from an occupational needlestick involving a source known to be HIV infected (ie, approximately 0.3%, for which PEP is often recommended).(20) By comparison, the average per-contact risk of transmission for unprotected receptive anal intercourse is approximately 1-5%; for unprotected insertive anal intercourse and receptive vaginal intercourse, this risk is approximately 0.1-1%; and for unprotected insertive vaginal intercourse, it is <0.1%.(100-103,105) The risk associated with receptive oral sex with ejaculation is difficult to quantify, although numerous case reports suggest that HIV transmission does infrequently occur through oral sex.(106,107)

Additional factors that might enhance transmission, such as trauma, genital ulcer disease, or cervical ectopy, should also be considered,(108) and it should be noted that there is some geographic variation--possibly associated with the distribution of subtypes (clades) of HIV-1--in the relative risk of transmission by different

routes.(109,110) Injection drug use exposures may carry a higher transmission risk than occupational needlestick injuries, although the viability of HIV in syringes and drug use equipment is difficult to assess.(111-113)

To evaluate the likelihood that the source of exposure is HIV infected, local risk demographics must be taken into strong consideration. Exposed individuals who feel safe doing so should be encouraged to speak with their source partner about HIV status and risk.

When Is PEP Not Indicated?

PEP is not indicated for perceived exposures of negligible or no conceivable risk (eg, kissing, oral-anal contact, mutual masturbation without skin breakdown, bites not involving blood, cunnilingus not involving blood exposure, receptive oral intercourse without ejaculation [although pre-ejaculate in the presence of oral pathology may carry nonnegligible risk], insertive oral sex, etc.) PEP is also not indicated for high-risk behaviors with a person of extremely low likelihood of being HIV infected. Clinicians should be willing to decline requests for PEP and provide supportive counseling and referrals in these situations. In some situations (eg, a needlestick from a discarded syringe), the risk is simply not known, and individual judgment must be used.

PEP Interventions

(Also refer to [Table 4](#))

Which Medications and for How Long?

There is no consensus about how many drugs to use for nonoccupational PEP, although the animal data supporting a 28-day course is compelling.(43) As the only human PEP data from the occupational setting demonstrated the effectiveness of ZDV, many attempt to include ZDV in nonoccupational PEP regimens. Some believe that two drugs will provide adequate potency in a prophylactic setting, which involves an inoculum much smaller than the amount of virus present in an infected individual initiating treatment. Others are concerned about providing the maximum potential antiviral potency and advocate the addition of a third drug, despite increased cost and the potential for additional toxicity. Data from a French study suggest that there is significant toxicity associated with three-drug regimens, whereas the San Francisco feasibility study found two-drug regimens to be generally well tolerated.(52,68) Toxicity associated with full-course nevirapine has resulted in recommendations against its use in PEP, although short-course nevirapine remains strongly recommended for the prevention of mother-to-child transmission of HIV.(114) Nevirapine is under consideration for use in pre-exposure prevention studies and a recent pharmacokinetics study suggests that twice-a-week or every-other-day dosing provides adequate blood levels.(115) Since the approval by the U.S. Food and Drug Administration of the nucleotide analogue tenofovir for treatment of HIV, interest in its use for PEP has been increasing. Tenofovir has been the most studied agent in animal

PEP models, and has been effective in a very short course when the first dose was provided prior to the exposure. Tenofovir is currently being used in studies of pre-exposure prevention in humans.

Although it is clear that transmission of drug-resistant HIV occurs, the mechanisms involved in the prophylactic effect of antiviral medications, and the importance of resistance, are less clear.(116-121) To complicate matters, plasma HIV resistance patterns do not always represent the resistance patterns of virus isolated from genital secretions.(122-129) Mother-to-child transmission studies have provided inconsistent results regarding the importance of drug resistance in prophylaxis failures.(130-133)

It is reasonable to assume that antiretroviral resistance matters, and it is important to construct, when possible, a PEP regimen to which the virus involved is unlikely to be resistant. When the source partner's antiretroviral medication history and corresponding HIV viral load measurements are known, PEP medications can be selected based on deductions of existing resistance. In the feasibility study conducted in San Francisco, about half of the HIV-positive sources who enrolled in the study had detectable HIV RNA, and resistance rates among the various drugs and classes ranged from 20% to 60%.(55) A clinician with expertise in antiviral resistance and cross-resistance should be consulted when the source's medication history is known.

Laboratory Testing

HIV antibody testing should be performed at the time of presentation and 6 months after the exposure. It is reasonable to repeat the test at 2-3 months postexposure as well, as the majority of HIV seroconversions will occur within that time period. A case of delayed seroconversion in a treated monkey suggests that delayed seroconversion may happen in the context of human PEP, although this has never been reported in either the occupational or nonoccupational setting.(44) Unless the patient develops symptoms and signs consistent with acute HIV infection, HIV RNA testing should not be performed, as the specificity characteristics of these tests are not satisfactory in a diagnostic setting.(134-137) The odds of a false-positive test result are significant in a setting of low pretest probability and may outweigh any potential benefit of detecting HIV viremia during the brief period prior to seroconversion.(138,139)

STD and hepatitis testing should be considered in patients presenting for PEP. Safety laboratory studies should be tailored to the specific individual and probably do not need to be routinely performed. Immunizations for hepatitis A and B should be offered as well.

Counseling

The provision of PEP should always include HIV pre- and posttest counseling, with an emphasis on identifying the emotional and social factors that may have contributed to the risk episode. It is helpful to explore the incident in contrast to a time when the person was able to maintain lower-risk behavior. The second step is to explore the pattern of behavior: Was this an isolated event, episodic, or part of a regular pattern? Developing a specific, client-centered risk-reduction plan and appropriate referrals is

the third key component. In follow-up visits, the risk-reduction plan should be reviewed and reevaluated, and the outcome of prior referrals assessed.

Summary

Occupational PEP is widely recommended and utilized, and a growing body of related evidence in the areas of mother-to-child transmission and animal exposures suggests that PEP use following nonoccupational exposures may be effective in reducing the likelihood of transmission. As with occupational exposures, the risk of acquiring HIV from a specific exposure should be assessed to determine if the costs and risks associated with PEP are warranted. Two-drug regimens appear to offer a reasonable safety profile. Although the addition of a third drug may be warranted in the case of suspected antiviral resistance, the routine use of three drugs may be associated with an unacceptable rate of significant adverse events. PEP should not be viewed as a simple "morning-after" approach to HIV prevention, but should be provided with risk reduction counseling to help prevent future exposures.

A national 24-hour hotline assists clinicians in the management of occupationally exposed health care workers (<http://www.ucsf.edu/hivcntr/PEpline/>). A similar resource that would also provide patient referrals for care is needed to assist in the care of people with potential nonoccupational exposures to HIV. As noted in the Massachusetts Emergency Department survey and McCausland et al, (51) demand for nonoccupational PEP exists. The diversity of practice patterns suggests the need for evidence-based practice guidelines.(58) The CDC is currently considering a revision of their guidelines that may provide clearer recommendations regarding the treatment of people with possible nonoccupational exposures to HIV.

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