Seroconversion Following Nonoccupational Postexposure Prophylaxis against HIV

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Background. The efficacy of antiretroviral postexposure prophylaxis (PEP) against infection with human immunodeficiency virus (HIV) following occupational exposures has prompted the use of PEP after nonoccupational exposures. There are, however, important differences between occupational and nonoccupational exposures, and the effectiveness of PEP following nonoccupational exposure is unknown. We sought to describe the occurrence and circumstances of HIV seroconversion following nonoccupational PEP.

Methods. HIV uninfected individuals reporting potential sexual or injection drug use exposures to HIV in the preceding 72 h received a 28-day regimen of antiretroviral therapy and counseling in a nonrandomized trial. The level of HIV antibody was measured 12 weeks after PEP initiation.

Results. Of 877 exposed subjects, 702 were evaluable 12 weeks after exposure. Seroconversion was detected in 7 subjects (1%; 95% confidence interval, 0.4%–2%). Three seroconverters reported having no exposures after PEP initiation and, thus, probably represent evidence of chemoprophylactic failure. In the other 4 subjects, additional exposures to HIV after PEP initiation or detection of HIV RNA in plasma specimens obtained at baseline precluded determination of the source of seroconversion. No exposure source was available to assess genetic concordance with the seroconverter's virus.

Conclusions. As for occupational exposure, PEP is not completely effective in preventing HIV infection following nonoccupational exposure. Therefore, primary prevention remains essential. In contrast to the occupational setting, the potential source of exposure is rarely available for testing in the nonoccupational setting, and exposures are often not isolated. Thus, it is often impossible to determine whether seroconversion resulted from failure of PEP or from other exposures, posing difficulties for future comparative studies seeking to evaluate the effectiveness of PEP.

In a case-control study of health care workers, postexposure prophylaxis (PEP) with zidovudine was associated with an 81% reduction in the risk of HIV infection after percutaneous exposures [1]. The effectiveness of PEP in the occupational setting has prompted its use after nonoccupational sexual and injection drug use exposures, for which both feasibility and safety have been established [2–9]. However, the effectiveness of PEP after sexual or injection drug use exposures has not been evaluated, and there are several reasons why effectiveness after these exposures may differ from that after occupational exposure. These differences include time until PEP initiation, virus concentration, concomitant exposures to other pathogens, local trauma, and/or local immune response (in the case of mucosal sexual exposures). To begin to understand the effectiveness of PEP after sexual or injection drug use exposures, we describe the occurrence of and circumstances surrounding HIV seroconversion in the

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first 12 weeks after PEP initiation in a large group of exposed individuals in San Francisco.

METHODS

Study design. Men and women with a potential sexual or injection drug use exposure to HIV in the previous 72 h were enrolled in 1 of 2 studies of PEP: a previously reported feasibility study [5] in which all subjects received PEP in addition to 5 sessions of risk-reduction counseling (study 1, conducted during December 1997–April 1999); or a randomized risk-reduction counseling study, in which all subjects received PEP and either attended 2 or 5 risk-reduction counseling sessions (study 2, conducted during April 2001–October 2002). We combined these data for the purposes of describing HIV seroconversion in the first 12 weeks after PEP initiation, because the studies used the same subject-selection criteria, medication interventions, and behavioral and biological measurements. In each study, subjects were followed up for 52 weeks after receipt of PEP to determine adverse effects of therapy, adherence to treatment regimens, episodes of risk behavior, and HIV seroconversion. The current analysis was restricted to subjects who were evaluable at 12 weeks after enrollment.

Subjects. Individuals who believed they were HIV uninfected were eligible for participation if they reported having engaged in unprotected (no condom use or condom failure) receptive or insertive anal or vaginal intercourse or receptive oral intercourse with ejaculation, if they had shared injection drug use equipment, or if they had contact with a potentially infected body fluid on a mucous membrane or nonintact skin. The potential exposure must have occurred with a partner who was known to be HIV infected or who was a man who has sex with men, an injection drug user, a sex worker, or an anonymous partner.

Whenever possible, source-partners were recruited, as described previously [10]. Time was allotted during counseling sessions to discuss source partner recruitment. The potential benefits of recruiting source partners included discontinuing PEP if the source-partner was HIV antibody–negative and altering PEP regimens to include drugs that may be more efficacious. Counselors addressed concerns regarding regret, shame, guilt, personal responsibility, reluctance to cause stress in the source partner, and confidentiality. To help exposed index subjects find anonymous or casual acquaintances, counselors explored where the exposed subject and source partner had met, establishments that were frequented, and shared friends, among other resources. Source subjects were contacted directly by the index subject and not by study investigators or staff.

The Committee on Human Research at the University of California, San Francisco, approved the study protocols. Procedures for the study and for obtaining written informed consent were in accordance with the University of California, San Francisco, Committee on Human Research and the Helsinki Declaration of 1975, as revised in 1983.

Interventions. Subjects were given 2 nucleoside analogue reverse transcriptase inhibitors (either zidovudine plus lamivudine in a combination formulation of combivir, stavudine plus lamivudine, or stavudine plus didanosine), on the basis of the source subject's history of antiretroviral therapy, for 28 days. If the source subject's history of anitretroviral therapy was not available, combivir was given. A protease inhibitor, nelfinavir, was offered if the source subject reported having recently had a detectable plasma HIV RNA level while receiving treatment with antiretrovirals. A prescription was provided by telephone for callers who could not attend a same-day appointment. In study 1, telephone calls were answered 24 h per day, 7 days per week. In study 2, telephone calls were answered between 8 A.M. and 10 P.M., 7 days per week. Medications could be changed in response to adverse effects and/or newly discovered information regarding a source virus' antiretroviral resistance [10].

Study 1 included 5 sessions of risk-reduction counseling for all subjects [5]; in study 2, subjects were randomized to undergo 2 or 5 risk-reduction counseling sessions. The 2-session and 5-session counseling protocols in study 2, as well as the 5-session counseling protocol in study 1, had similar elements. The main difference between the 2 arms of the randomized study was in the amount of time available for development, implementation, rehearsal, and feedback of risk-reduction strategies. These 20–30-min sessions were individually tailored on the basis of social cognitive theory, incorporating strategies from motivational interviewing and coping-effectiveness training [11, 12]. The counselor evaluated the circumstances and determinants of the exposure and developed an individualized risk-reduction plan. The participant was then assisted in implementing the plan by means of skills training (e.g., sexual negotiation skills) or referral to specialized agencies (e.g., a substance abuse treatment center, if that was considered a factor).

Intensive adherence counseling was provided for all subjects in study 1 and for subjects randomized to the 5-session arm in study 2. Individuals randomized to the 2-session arm in study 2 received basic adherence counseling from the study clinician only. Subjects receiving intensive adherence counseling were trained by a counselor to use several adherence strategies. After clarifying the regimen, the counselor reviewed the rationale for each aspect of the regimen with the subject. The counselor then completed a checklist to identify problem areas that were used to assist in tailoring the regimen to the subject's lifestyle (e.g., by pairing medication-taking behaviors with behaviors that are likely to be performed), identifying and removing barriers, and creating a social environment conducive to adherence by reframing adherence to be consistent with broader social norms [13].

Laboratory evaluations. HIV antibody testing was performed at baseline and at week 12 after initiation of PEP. In subjects who developed HIV antibodies by week 12, stored plasma specimens obtained at baseline were tested for HIV RNA using the Versant HIV-1 RNA 3.0 Assay (Bayer) [14]. For subjects with detectable HIV RNA in stored samples of plasma, a third-generation HIV-1/HIV-2 antigen sandwich EIA with high IgM sensitivity (Abbott #3A77; Abbott Diagnostics) was also used to test stored plasma samples [15], and enzyme-linked immunospot (ELISPOT) assays were performed on stored PBMCs obtained at baseline. ELISPOT assays were performed in accordance with the Amplispot method, with the addition of IL-7 and IL-15 [16]. In these assays, pooled overlapping peptides spanning the HIV-1 Gag and cytomegalovirus pp65 proteins (BD Biosciences) were used to stimulate PBMCs in duplicate wells. As a positive control, staphylococcal enterotoxin B was added. ELISPOT plates were developed, as described elsewhere [17]. To determine the number of antigen-specific IFN-γ–producing cells, average spot numbers for negative control wells (containing cells and culture medium alone) were subtracted from averages for antigen-stimulated wells. Spot numbers were reported as IFN-γ spot-forming cells per 1×10^6 PBMCs. Genotypic antiretroviral resistance testing was performed on plasma samples with detectable HIV RNA using the TruGene Assay (Bayer). Phylogenetic testing of HIV was performed using neighbor-joining methods implemented in the Clustal W, version 1.4 [18].

Adherence and behavioral evaluations. Subjects were queried about missed doses of antiretroviral medications in each of the prior 4 days at weeks 1 and 4 after PEP initiation. A self-administered questionnaire regarding sexual behavior during the prior 6 months was completed at baseline by all participants, and an interview regarding sexual behavior since PEP initiation was conducted after the week-12 visit for participants who tested positive for HIV antibody.

RESULTS

Of 877 subjects who tested negative for HIV antibody for whom PEP was initiated after an eligible exposure, 702 subjects were evaluable 12 weeks after PEP initiation, among whom 7 HIV antibody seroconversions (1%; 95% CI, 0.4%–2%) were detected. Of these 702 subjects, 664 (94.6%) presented after a sexual exposure, 5 (0.7%) after both a sexual exposure and sharing of injection drug use equipment, 9 (1.3%) after an injection drug use exposure, and 9 (1.3%) after a nonrecreational needlestick injury. There were 667 male subjects (95%).

All seroconverters were men, and, compared with 50% of nonseroconverters, all presented after receptive anal intercourse ($P = .03$, by Fisher's exact test). Four seroconverters knew that their exposure-source partners were HIV-infected at enrollment. The remaining 3 seroconverters had not discussed HIV serostatus with their source partners. Although we sought to enroll source partners of seroconverters for laboratory testing (e.g., HIV phylogenetic testing), study recruitment was not successful in any of the seroconverter cases.

Antiretroviral prophylaxis. Seroconverters initiated PEP at a median of 45.5 h (range, 14–72.5 h) after exposure (table 1); the median time to PEP initiation for nonseroconverters was 32.5 h ($P = .11$, by Wilcoxon rank sum test). Of note, 3 seroconverters initiated PEP >55.5 h after exposure. There was

Table 1. Treatment and virologic characteristics of seroconverters following receipt of postexposure prophylaxis (PEP).

Seroconverter	Time to PEP initiation after exposure, h	Antiretroviral therapy	Medication adherence	Plasma HIV RNA level, copies/mL		Antiretroviral resistance mutations[a]
				At baseline	At seroconversion	
1	72.5	ddI and D4T	Poor[b]	<50	3381	None
2	67.5	ZDV and 3TC	Excellent[c]	<50	98,527	None
3	21	ZDV and 3TC, changed to D4T and 3TC[d]	Poor[e]	<50	>500,000	None
4	14	ZDV and 3TC	Excellent[c]	589 and 385[f]	>500,000	Baseline, none; week 12, M184V
5	55.5	ZDV and 3TC	Excellent[c]	<50	32,278	None
6	45.5	ZDV and 3TC	Fair[g]	<50	268,140	None
7	30.5	ZDV and 3TC, changed to D4T/3TC[d]	Excellent [c]	<50	258,599	None

NOTE. 3TC, lamivudine; D4T, stavudine; ddI, didanosine; ZDV, zidovudine.

[a] Primary mutations only.
[b] Missed 7 days of stavudine in first week.
[c] No missed doses.
[d] Medications were changed from ZDV and 3TC to D4T and 3TC.
[e] Missed approximately one-half of all medication dosages.
[f] After repeated testing.
[g] Missed 2 doses in first week.

Table 2. High-risk sexual behavior before and after receipt of postexposure prophylaxis (PEP).

Seroconverter	Risk behavior with an HIV-infected partner		Risk behavior with a partner with unknown HIV infection status	
	Before PEP[a]	After PEP[b]	Before PEP[a]	After PEP[b]
1	RAI (1) and IAI (2)	None	RAI (4) and IAI (5)	None
2	None	None	RAI (4) and IAI (4)	RAI (1)
3	None	None	RAI (1) and IAI (1)	ROI (3) and IAI (2)
4	RAI (3), IAI (1), and ROI (4)	None	RAI (8) and ROI (4)	None
5	None	None	RAI (1) and ROI (1)	None
6	RAI (1)	None	RAI (1)	None
7	RAI (1) and IAI (1)	RAI (5) and IAI (3)	None	None

NOTE. IAI, unprotected insertive anal intercourse; PEP, postexposure prophylaxis; RAI, unprotected receptive anal intercourse; ROI, unprotected receptive oral intercourse with ejaculation. Numbers in parentheses refer to the number of acts.

[a] In the 6 months prior to enrollment.

[b] Between enrollment and seroconversion.

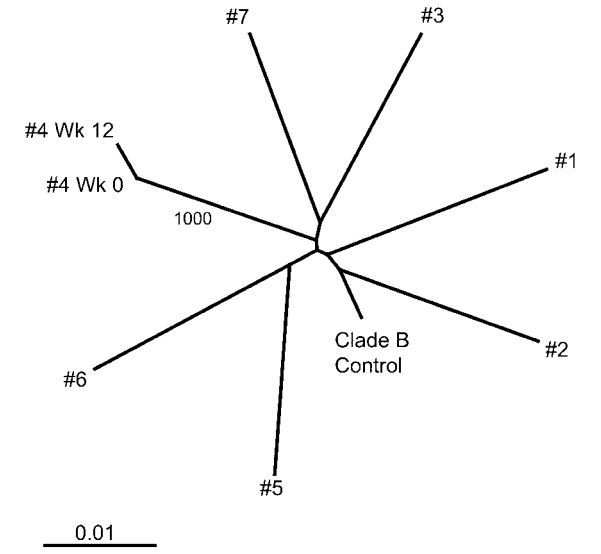
not a significant difference in the proportions of seroconverters (85.7%) and nonseroconverters (94.1%) who were initially prescribed combivir ($P = .4$), nor in the proportions who subsequently changed their PEP medication regimen. Fourteen subjects (2%) were prescribed nelfinavir; no seroconverters were in this group. All seroconverters completed the full 28-day course of therapy; however, at least 3 reported a substantial number of missed doses of medication. There were differences, which did not reach statistical significance, between the proportions of evaluable seroconverters and nonseroconverters who missed at least 1 dose of medication in the 4 days prior to the week-1 study visit (33% of seroconverters vs. 16% of nonseroconverters; $P = .3$) and the week-4 study visit (50% of seroconverters vs. 22% of nonseroconverters; $P = .4$).

Additional exposures to HIV. All seroconverters had other potential exposures to HIV in the 6 months preceding enrollment, in addition to the exposure that prompted study participation, including receptive anal intercourse (table 2). Four seroconverters reported exposures with partners whom they knew were HIV infected, and 6 reported exposures with partners whose HIV infection status they did not know. In the period between enrollment and seroconversion, 1 seroconverter reported exposures with HIV-infected partners and 2 seroconverters reported exposures with partners of unknown HIV infection status (table 2).

Plasma HIV RNA and resistance mutations. Six seroconverters had undetectable HIV RNA in stored plasma samples obtained at baseline and no resistance mutations in plasma samples obtained on seroconversion (table 1). One seroconverter had a low level of HIV RNA in his baseline plasma sample (589 and 385 copies/mL, on repeated testing), with no evidence of drug resistance, and a genotypic mixture at codon 184 in the seroconversion sample (table 1 and figure 1). Phylogenetic analysis confirmed that the virus at baseline and at seroconversion clustered together (figure 1). This individual initiated PEP 14 h after exposure and underwent baseline laboratory evaluation 3 days later. He reported multiple additional exposures with different partners in the 12 months prior to initiating PEP; however, information regarding timing was unavailable. A third-generation sandwich HIV antibody assay of his baseline plasma sample was nonreactive, and testing of PBMCs obtained at baseline revealed no cytotoxic T lymphocyte responses to HIV Gag but a vigorous response to cytomegalovirus pp65.

DISCUSSION

As is the case with occupational exposure [1, 19—25], PEP is not 100% effective after nonoccupational exposure. In our study, 3 seroconverters reported no additional HIV exposures after PEP initiation. Although it is possible that their infections resulted from additional exposures prior to presentation or from unreported exposures after PEP initiation, it is likely that these infections represent PEP failure. Without analysis of biological specimens obtained from potential infection sources, however, it is impossible to determine the infection source with certainty. Three other seroconverters reported continued unprotected sexual activity after PEP initiation that may have been the source of their infections. A final seroconverter had HIV RNA detected in plasma samples obtained at baseline. The presence of this HIV RNA may represent either failure of PEP to prevent infection or a preexisting infection resulting from another exposure prior to PEP initiation. The lack of humoral and cellular immune responses to HIV in this subject's blood



Seroconverter 4:	RT codon	182	183	184	185	186
	Baseline	CAA	TAC	ATG	GAT	GAT
		Q	Y	M	D	D
	Week 12	CAA	TAC	RTG	GAT	GAT
		Q	Y	M/V	D	D

Figure 1. *Top,* Phylogenetic analysis of protease and reverse-transcriptase sequences derived from seroconverter 4 indicates clustering of samples obtained at baseline and at week 12. The clustering of sequences is statistically supported by a bootstrap value of 1000 (i.e., 1000 trials were performed) and is consistent with viral evolution during postexposure prophylaxis, rather than superinfection. Sequences obtained from other seroconverters in this study serve as unrelated local controls. *Bottom,* Analysis of reverse-transcriptase codon 184 derived from seroconverter 4 at baseline and week 12 indicating appearance of the M184V mutation after receipt of postexposure prophylaxis. The standard International Union of Pure and Applied Chemistry code "R" is used to denote the mixture of sequences detected in the virus population at week 12. Lamivudine-resistant GTG coding for valine (V) was mixed with drug-susceptible ATG coding for methionine (M) at codon 184.

sample, which was obtained 3 days after PEP initiation, is evidence against the presence of a distant preexisting infection, but it cannot exclude a very recent preexisting infection.

The mechanisms of PEP failure cannot be determined with certainty from these data. However, in the 3 cases most likely to have involved PEP failure, therapy was initiated >45 h after the exposure. Animal studies show that earlier initiation of PEP is more effective than later initiation; in one study [26], the efficacy of PEP was greater when it was initiated 12 h and 36 h after exposure than when it was initiated 72 h after exposure, and, in a second study, efficacy was greater when PEP was initiated 24 h after exposure than when it was initiated 48 h or 72 h after exposure [27]. Some have interpreted the usual 72-h cutoff for eligibility for PEP that was established on the basis of these animal models and simian immunodeficiency virus–macaque pathogenesis models [28] to mean that exposed individuals have 72 h to decide whether to initiate PEP. Taken together, we feel that our findings should be used to encourage both physicians and exposed individuals to initiate PEP as quickly as possible. In addition, complete adherence to PEP regimens should be emphasized, especially considering that this healthy patient population may not be accustomed to taking medications. It may be helpful to call the individual after 1 or 2 days to reinforce adherence messages and to answer questions, because the individual may have been distressed during initial counseling. Finally, we have described seroconversions in individuals who did not know the HIV infection status of their source partner. Thus, we feel it is important to not limit PEP availability to persons who know that their source partner is HIV infected, if that partner has risk factors associated with HIV infection.

Although our findings suggest that PEP efficacy is <100% for nonoccupational exposures, we cannot estimate the efficacy of PEP in the absence of an untreated comparison group. The occurrence of seroconversion does not necessarily mean that PEP is ineffective after sexual exposures. Indeed, in a case-control study and in case reports, PEP failure after occupational exposures, for which the overall effectiveness of zidovudine is estimated to be 81%, has been described [1, 19–25]. On the other hand, the small number of seroconversions also does not mean that PEP is necessarily effective under these conditions. Per-contact HIV transmission rates among individuals not receiving HAART are low; they are estimated to be <0.1% after insertive anal, insertive vaginal, and receptive vaginal intercourse and ~1%–3% after receptive anal intercourse [29–35]. Considering the proportion of study subjects truly exposed to an HIV-infected partner and these per-contact transmission rates, it is possible that use of PEP had no impact on reducing the likelihood of HIV infection. Fortunately, other evidence continues to support the probability of the effectiveness of PEP initiated after sexual exposures, including animal models [26, 36–38] and prevention of mother-to-child transmission [39, 40].

Although we were not able to estimate the efficacy of PEP initiated after sexual exposures, we have contributed evidence that both ongoing exposures and the inability to test the exposure source present significant obstacles to answering this question. At a minimum, the frequency of post-PEP exposures will markedly increase sample size needs and/or require study of specialized populations, such as monogamous, HIV-infected discordant couples who have experienced an isolated condom failure. The time and costs involved in developing and conducting a PEP efficacy study, given the obstacles we have described, would be substantial. In the absence of data regarding

the efficacy of PEP initiated after sexual exposures, the decision to initiate PEP under these conditions must be based on extrapolation from evidence obtained under other conditions. We feel it is critical that individuals seeking PEP are informed about the uncertainty regarding its efficacy.

Our finding of probable seroconversion following nonoccupational PEP use reinforces the need for primary prevention of exposures. Even if PEP is highly but not completely effective, its availability could result in overall increases in HIV incidence, if availability promotes increases in high-risk sexual behavior. Although available data from San Francisco and Brazil suggest that use of PEP does not induce behavioral disinhibition, this may be a function of the high incidence of subjective adverse effects that have been observed and that may discourage further use of PEP [6, 7]. This may not be the case with less toxic regimens in the future. Thus, efforts to promote the accessibility of PEP should be balanced by resources to prevent exposure.

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