

Behavioral Impact, Acceptability, and HIV Incidence Among Homosexual Men With Access to Postexposure Chemoprophylaxis for HIV

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Background: Little is known about the behavioral impact, acceptability, and incidence of HIV infection in persons with easy access to post-sexual exposure prophylaxis (PEP) to prevent HIV.

Methods: Participants were recruited from a well-characterized, high-risk HIV seronegative homosexual male cohort in Rio de Janeiro, Brazil, given a 4-day supply of zidovudine and lamivudine, and instructed to begin PEP immediately after an eligible exposure. For eligible exposures, an additional 24-day supply was provided. Reported behavior, PEP utilization, adverse events, and incident HIV infection were the main study outcomes. The observed and expected incidences of HIV infection were compared.

Results: Two hundred subjects were enrolled and followed for a median of 24.2 months. The median age was 28 years. PEP was initiated 109 times by 68 participants (34.0%). In comparison to reported behavior at baseline, reported high-risk sexual activities on average declined over time for both PEP and non-PEP users. There were no serious drug-related adverse events. There were 11 HIV seroconversions, 10 among non-PEP users and 1 that was a PEP failure. The

overall seroincidence was 2.9 per 100 person-years (95% CI = 1.4, 5.1). The expected number of new HIV infections and corresponding expected seroincidence based on the risk profile were 11.8 and 3.1, respectively ($P > 0.97$). The most commonly reported reasons for not initiating PEP among seroconverters were sex with a steady partner and not considering the exposure to be of sufficiently high risk to warrant PEP.

Conclusion: PEP was safe and did not appear to be associated with increases in reported high-risk behavior in our cohort. Ready access to PEP did not appear to substantially affect HIV transmission, suggesting a limited public health impact of this intervention.

Key Words: postexposure chemoprophylaxis, postexposure prophylaxis, HIV, HIV incidence, lamivudine, zidovudine

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Postexposure chemoprophylaxis (PEP) to prevent HIV infection is widely used in a variety of settings. In one retrospective case-control study of health care personnel, postexposure treatment with zidovudine was associated with an estimated 81% reduction in the risk of HIV infection, although the lack of a randomized trial does not allow firm conclusions about this intervention.¹ The efficacy of antiretroviral therapy in reducing maternal-infant transmission of HIV infection is also high, with some of the effect appearing to be due to postpartum chemoprophylaxis of the infant.^{2–4}

There are no data on the efficacy of chemoprophylaxis following sexual exposure to HIV, and animal studies showed mixed results.^{5,6} Despite this lack of information, PEP use after high-risk sexual exposures is advocated and often used,^{7–11} based primarily on data from the other settings in which it has been studied. However, the health care setting is usually associated with a single exposure, which makes the justification for providing chemoprophylaxis and compliance with the postexposure regimen relatively straightforward. This is in contrast to post-sexual exposure prophylaxis, for which the possibility of repeated exposures is more likely. The use of chemoprophylaxis

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laxis for sexual exposures has the potential to increase high-risk sexual behavior. This could theoretically negate any protective effect of the regimen, because the clinical protection provided by PEP in other settings has been shown to be incomplete.

There are also limited data on the acceptability, tolerability, safety, impact on sexual behavior, and HIV seroincidence among persons taking post-sexual exposure chemoprophylaxis. The purpose of this study was to examine these issues in a cohort of homosexual men who were provided with ready access to PEP.

METHODS

The institutional review boards of the Universidade Federal do Rio de Janeiro and of the University of Pittsburgh, as well as the Brazilian National Ethics Committee, approved the study. Participants for this study were recruited among HIV-seronegative, former participants of Projeto Praça Onze, a prospective HIV seroincidence study conducted from July 1995–June 1998 among high-risk men who have sex with men in Rio de Janeiro, Brazil. This cohort had a documented overall annual HIV seroincidence of 3.1%.¹² The present study was conducted between December 1998 and May 2001. Recruitment was accomplished by generating a list of potentially eligible former Praça Onze participants. Approximately 250 individuals were contacted by telephone and the first 202 eligible volunteers who agreed to participate were enrolled.

Inclusion criteria were male gender; confirmed HIV seronegativity; reported homosexual or bisexual behavior; sexually active, defined as anticipated sexual activity in the next 6 months; willingness to use PEP after high-risk exposures; and age 18–35 years. Persons with high-risk exposures for HIV in the previous 48 hours; anemia, leukopenia, or hepatic enzyme abnormalities at baseline; or a history of allergy or intolerance to any of the study medications were excluded from the study.

The exposure of any mucous membrane (oral, urethral, anal) to blood or semen or vaginal secretions within 48 hours was considered to be eligible for PEP. The study regimen was zidovudine 300 mg and lamivudine 150 mg orally in a fixed-dose combination tablet twice daily for 28 days. This regimen was chosen because, at the time of the study, a 2-drug regimen was recommended for most HIV exposures that warrant PEP.¹³ All enrolled subjects were given a 4-day supply of the regimen at enrollment and instructed to begin chemoprophylaxis immediately after an eligible exposure and to return for evaluation within 96 hours of starting PEP. For exposures deemed to be eligible by study personnel, subjects were given an additional 24-day supply of medication to complete the 4-week regimen. Subjects were instructed to begin taking the study regimen immediately after eligible exposures and in no circumstances >48 hours after the exposure and to report symptoms consistent with severe toxicity. At the end of 4 week of therapy, subjects were evaluated for side effects and adher-

ence and given another 4-day supply of medication to be kept in case of another high-risk exposure. Participants who did not start PEP were instructed to return every 6 months for evaluation.

At each visit, a detailed history, including questions about high-risk behaviors, was taken and a physical examination with a focus on the presence of sexually transmitted diseases was performed. A laboratory evaluation to assess for potential medication toxicity was performed at the baseline, 12-month, and 24-month visits, and, for subjects who took PEP, following the completion of the 28 days of study medications. This assessment included a complete blood count, erythrocyte mean corpuscular volume, and hepatic enzyme tests. HIV serology was performed at every visit, including both regular visits and visits that involved PEP. PEP failure was defined as a documented HIV seroconversion that occurred within 2 months after the exposure for which PEP was taken. Conversely, seroconversions that occurred ≥ 2 months after the exposure for which PEP was taken were not considered as PEP failures. For participants who seroconverted during the study and who had previously used PEP, polymerase chain reaction was performed on blood samples obtained at the beginning and at the end of the PEP course to ensure that the subsequent seroconversion was unrelated to the exposure that led to PEP use. Additional laboratory evaluations were undertaken for persons who took PEP based on the occurrence of symptoms that could have been caused by the study medications or if there were other medical reasons to suspect an increased likelihood of PEP-related side effects (e.g., a history of pancreatitis).

Adherence to the study medications was estimated based on a detailed set of questions that were asked at the 28-day visit and the use of pill counts. During each visit, trained professionals provided pre- and posttest counseling, subjects were provided with condoms, and participation in safer sex workshops was offered. Pre- and posttest counseling included detailed individual discussions on what are considered to be high-risk exposures regardless of the type of partnership (steady or casual), the expected side effects of antiretroviral drugs, and the lack of data on the efficacy of PEP.

All laboratory tests were performed using commercial kits according to the manufacturers' instructions. Seroincident HIV infection (HIV seroconversion) was defined as HIV enzyme-linked immunosorbent assay (ELISA) seronegativity at the baseline visit with a subsequent positive ELISA and Western blot during a follow-up visit. Drug-resistant HIV was assessed for the 1 participant in whom PEP failed, using the TruPrep Extraction Kit for viral RNA according to the manufacturer's directions (Visible Genetics, Toronto, Canada).¹⁴ RNA was reverse transcribed, polymerase chain reaction amplified, and sequenced using the Trugene HIV-1 Genotyping Kit, also according to the manufacturer's directions (Visible Genetics).

Data analysis was performed using SAS version 6.12 (SAS Institute, Inc., Cary, NC). Comparisons between groups were analyzed using χ^2 tests for categorical variables and Wilcoxon rank sum tests for continuous variables. The comparison of the distribution of the number of male partners in the 6 months prior to the baseline interview to that of the 6 months prior to the last interview was performed by using the signed rank test. Behavior practices over time were examined using the McNemar test. To maximize sample size for the analyses examining the number of partners and sexual practices over time, we used the final interview individuals participated in for those participants who did not have a 24-month interview.

We calculated the total follow-up time for all subjects. Incidence rates are expressed as the incidence of seroconversion per 100 person-years of follow-up and exact 95% confidence limits were calculated. Because of the absence of a control group, there was no direct estimate of what the HIV incidence would have been in the study participants in the absence of a PEP program. However, study participants were recruited from a well-characterized HIV incidence study cohort, for which we had defined the incidence of and risk factors for HIV seroconversion.¹² We took the relationships between follow-up time, previously identified risk factors for new HIV infection, and HIV incidence observed in our noninterventonal study and applied them to the current cohort to produce an expected number of incident HIV cases in the absence of PEP. This was done by fitting a binomial regression model to our

first cohort's data with a complementary log (-log) link function that accounts for previously identified risk factors for incidence HIV infection in the cohort. Taking the coefficients from that model, we applied them to the covariate and follow-up patterns of our current study participants to calculate the expected number of HIV seroconversions and expected HIV seroincidence.

RESULTS

A total of 202 men were enrolled in the study. Two participants had no follow-up data and were excluded from further analysis. The analyses described are based on the remaining 200 subjects, who were followed for a total of 4585 person-months. The median follow-up time was 24.2 months. Ninety-four percent (n = 187) of the cohort was followed for 24 months or until seroconversion. Of the nonseroconverters who did not have a 24-month interview (n = 13), 7 (53.9%), 2 (15.4%), and 4 (30.8%) had their last interview at 6 months, 12 months, and 18 months, respectively. Sixty-eight participants (34.0%) took PEP in response to a high-risk behavior at least once, 86 (43.0%) did not take PEP despite reporting at least 1 instance of high-risk behavior; and 46 (23.0%) denied any high-risk behaviors during the study period. The demographic, behavioral, and HIV risk characteristics of these subjects are shown in Table 1. The 2 groups were comparable on age, race, education, income, risk behaviors at enrollment, illicit drug use, and hepatitis B seroprevalence. The non-PEP group had a

TABLE 1. Demographic and Behavioral Characteristics of the 200* Study Subjects at Baseline by Whether PEP Was Initiated at Least Once During the Study

Characteristic	PEP, n (%) (n = 68)	No PEP, n (%) (n = 132)	Total (n = 200)	P Value
Age y, median*	28	28	28	0.83
Race				
White	34 (50)	60 (45)	94 (47)	0.69
Black	15 (22)	26 (20)	41 (21)	
Mixed	3 (4)	11 (8)	14 (7)	
Other	16 (24)	35 (27)	51 (26)	
Completed high school, n (%)*	55 (81)	93 (70)	148 (74)	0.11
Income (Brazilian Reais per mo), median	445	480	465	0.57
Receptive anal sex last 6 mo	48 (71)	84 (64)	132 (66)	0.33
Unprotected receptive anal sex last 6 mo	23 (34)	34 (26)	57 (29)	0.23
Insertive anal sex last 6 mo	46 (68)	93 (70)	139 (70)	0.68
Unprotected insertive anal sex last 6 mo	20 (29)	39 (30)	59 (30)	0.98
History of gonorrhea last 6 mo*	7 (10)	32 (24)	39 (20)	0.02
Illicit drug use	8 (12)	17 (13)	25 (13)	0.82
Hepatitis B core antibody positive*	23 (34)	34 (26)	57 (29)	0.22

*Data were missing for 1 PEP user for age; 3 PEP users and 3 PEP nonusers for income; 1 PEP nonuser for history of gonorrhea; and 1 PEP user and 1 PEP nonuser for hepatitis B core antibody positivity.

slightly higher frequency of reported gonorrhea in the past 6 months prior to baseline (24 vs. 10%, $P = 0.02$).

PEP Use, Tolerability, and Safety

PEP was initiated a total of 109 times by 68 (34.0%) of the 200 participants. Of these, 100 (91.7%) were considered to involve eligible exposures and the 4-week course of PEP was prescribed. PEP was prescribed once for 49 (72.1% of the 68 PEP users) subjects, twice for 14 subjects (20.6%), 3 times for 2 subjects (2.9%), 4 times for 2 subjects (2.9%), and 9 times for 1 subject (1.5%).

Although at least 1 side effect was reported in 82% of the episodes of PEP use, nausea most commonly, the full 28-day regimen of PEP was completed for 89 (89.0%) of the eligible exposures, including the participant who seroconverted. The 11 (11.0%) noncompleted PEP courses correspond to 9 participants. Two did not come back to the study site to complete their day 28 visits, 1 participant with a history of pancreatitis was instructed to stop taking PEP because of an asymptomatic increase in pancreatic enzymes, and the other 6 stopped the medications because of nausea. Aside from the patient with elevated pancreatic enzymes, there were no clinically significant laboratory abnormalities among persons who took PEP.

There were 76 persons who reported at least 1 high-risk exposure but did not initiate PEP at the first follow-up visit, 65 at the 2nd visit, 66 at the 3rd visit, and 57 at the 4th visit. The most common reasons for not initiating PEP (≥ 1 possible response per participant) were sex with a steady partner ($n = 150$), participant did not consider the exposure to be of sufficiently high risk to warrant PEP (94), and concerns about side effects (23).

Risk Behaviors

Among PEP users, the median number of male partners in the 6 months before the baseline visit was 4 (range, 0–50), and 4 (range, 0–180) in the 6 months before the last visit ($P = 0.43$). For the PEP nonusers, the respective values were 2 (range, 0–40) and 2 (range, 0–100) ($P = 0.46$).

In comparison to reported behavior at baseline (i.e., before PEP availability), on average reported high-risk sexual activities declined over time for both PEP and non-PEP users (Fig. 1). For example, 32 (47.1%) of PEP users reported unprotected anal sex in the previous 6 months at the baseline visit vs. 27 (39.7%) at the last visit ($P = 0.35$). The corresponding values for non-PEP users were 48 (36.4%) and 32 (24.2%), respectively ($P = 0.008$). Similar patterns were seen for unprotected oral sex: 16 (23.5%) of PEP users reported this risk behavior at the baseline visit vs. 8 (11.8%) at the last visit ($P = 0.06$), with corresponding values for non-PEP users of 32 (24.4%) and 16 (12.2%), respectively ($P = 0.002$). The frequency of unprotected vaginal sex increased slightly, albeit nonsignificantly, over time for both PEP users (1.6 vs. 4.7%, $P = 0.16$) and non-PEP users (6.1 vs. 8.3%, $P = 0.26$). Al-

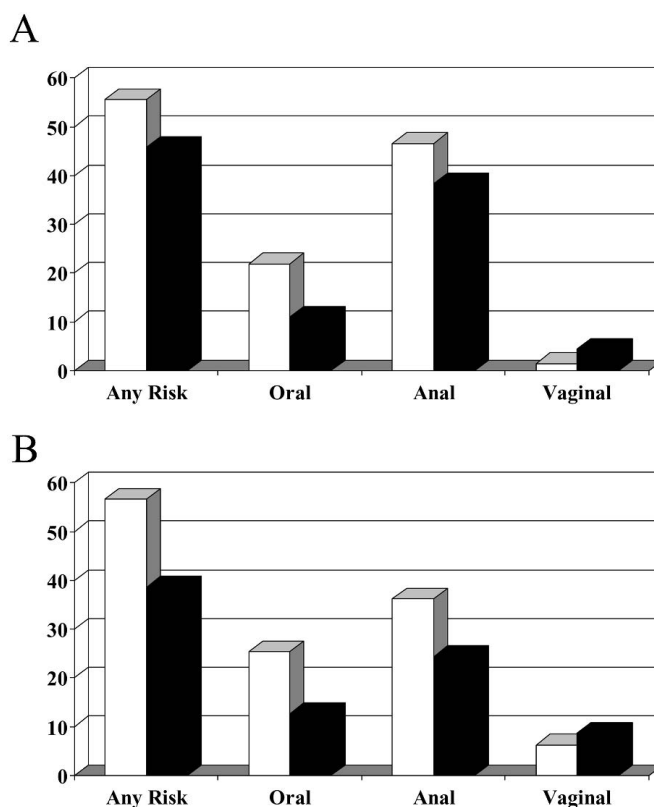


FIGURE 1. Self-reported high-risk behavior for PEP users (A) and non-PEP users (B), at the baseline visit (open bars) and last visit (closed bars). Eleven participants (5.5%) had the last follow-up interview at 6 months; 5 (2.5%) at 12 months; 6 (3.0%) at 18 months; and 178 (89.0%) at 24 months. "Oral," "anal," and "vaginal" refer to oral, anal, and vaginal sex, respectively, that was unprotected at least some of the time.

though reported high-risk behaviors declined over time among most study participants, some members of the cohort reported that their behaviors became more risky during the course of the study. For example, while 43 (21.5%) of the participants reported engaging in unprotected anal sex in the 6 months prior to baseline, but not in the 6 months prior to their last visit, there were 22 subjects (11.0%) who denied unprotected anal sex before baseline but reported unprotected anal sex in the 6-month period preceding their final interview ($P = 0.009$).

HIV Incidence

Eleven subjects had new HIV infections during the course of the study, for an overall seroincidence of 2.9 per 100 person-years (95% CI = 1.4, 5.1) (Table 2). Of the seroconverters, 10 had not taken PEP in response to a high-risk behavior and 1 had taken PEP immediately before seroconversion. This participant was seronegative at day 0 of PEP. On the last day of PEP, the Western blot was indeterminate but became positive

TABLE 2. Selected Characteristics of 11 Study Subjects With Incident HIV Infection at First Study Visit

Study No.	Age (y)	Education	Hepatitis B Seropositivity, Baseline Visit	Visit Seroconversion Observed (mo)	Exposure Description	Took PEP?*	Reason for Not Taking PEP
015	28	12 years	Negative	6	Unprotected oral and anal sex	No	Fixed partner, believed to be HIV-negative
017	22	3 years	Negative	12	Unprotected oral and anal sex	No	Didn't want people seeing take medication, friends advised against
022	26	University	Negative	6	Unprotected oral sex	No	Didn't consider exposure high risk, worried about side effects
027	28	8 years	Negative	6	Unprotected oral sex	No	Didn't consider exposure high risk, friends advised against, worried about side effects
078	26	8 years	Positive	12	Unprotected oral and vaginal sex	Yes	NA
095	32	University	Positive	24	Unprotected oral sex	No	Didn't consider exposure high risk
107	32	12 years	Positive	24	Unprotected oral and anal sex	No	Didn't consider exposure high risk
126	33	3 years	Negative	18	Unprotected oral and anal sex	No	Fixed partner, believed to be HIV-negative
148	27	8 years	Negative	12	Unprotected oral and anal sex	No	Fixed partner, believed to be HIV-negative
183	29	8 years	Positive	6	Anal sex with condom, condom broke	No	Not known
210	20	12 years	Negative	18	Unprotected oral and anal sex	No	Didn't consider exposure high risk

*As a result of high-risk exposure that resulted in HIV seroconversion. NA indicates not applicable.

over the next few weeks. Viral RNA was not detectable in plasma taken on day 0 of PEP use. Amplified viral RNA from plasma on the last day of PEP had the M184V mutation, which confers resistance to lamivudine.

Based on the risk profile of the study participants and the experience of our previous cohort study, the expected number of new HIV infections was 11.8 ($P > 0.97$ compared with the observed 11 infections), for an expected seroincidence of 3.1 per 100 person-years ($P > 0.97$ compared with the observed seroincidence of 2.9).

DISCUSSION

In this study, PEP was not associated with an increase in reported high-risk behavior. In fact, reported high-risk behaviors declined slightly for the cohort as a whole. An obvious limitation of self-reported behavior is the tendency to underreport high-risk activities.¹⁵ However, we have no evidence to indicate that the frequency of underreporting would change over time, and our findings are similar to the findings of other studies.¹⁶⁻¹⁸

Frequent use of PEP was uncommon in this cohort, despite the easy access to PEP that we provided. Of the 200 sub-

jects studied, only around a third initiated PEP ≥ 1 time. Of the 68 who started PEP because of an eligible exposure, >90% initiated PEP no more than 2 times during the 2 years of the study and <5% used PEP ≥ 4 times. These data are encouraging because they indicate that the provision of easy access to PEP did not lead to frequent overuse in this population. In addition, the PEP regimen used in this study was relatively safe, with no serious adverse events. In fact, the combination of zidovudine and lamivudine appears to be safer and more tolerable than some other PEP regimens.^{7,8}

We observed 11 HIV seroconversions during the study period, only 1 of which was a PEP failure. The study design and the relatively small number of seroconversions do not allow conclusions about the effectiveness of PEP in preventing infection. Nonetheless, the fact that there was only 1 PEP failure is encouraging. Since viral RNA was not detected on day 0 of PEP use and the source case was not identified, it was not possible to determine if the mutation associated with lamivudine resistance present on the last day of PEP use was due to primary or acquired resistance.

The finding that all but 1 of the seroconverters had not taken PEP in response to a high-risk behavior before serocon-

version and the reasons for not taking PEP indicate that subjects in our cohort often underestimated their risk of acquiring HIV. High-risk behavior with a steady partner, believed by participants to place them at low risk, was the most common reported reason for not starting PEP after a high-risk exposure. However, 3 seroconversions were attributed to sex with a steady partner. Upon closer scrutiny, in 2 instances, the steady partners admitted to having had sex outside of the relationship. The 3rd admitted to having misinformed his partner about his HIV serostatus.

The data from this study argue against establishing a public health PEP program in our population with the aim of having a major impact on HIV transmission. The observed seroincidence of nearly 3%, similar to what would have been expected in the absence of PEP, argues against a major impact of our intervention. One possible explanation for the lack of apparent impact despite only 1 PEP failure is that the 109 exposures for which PEP was taken represent a small proportion of the total eligible exposures that occurred during the study. In addition, the programmatic infrastructure that would be needed to administer such a program would be substantial. Given that the intervention appeared to have little impact on HIV seroincidence, the risk of adverse events, and the potential for PEP-induced drug-resistant HIV, such an investment does not seem warranted. It is possible that additional education about when to initiate PEP could have resulted in a lower HIV incidence. We doubt this, however, because the HIV knowledge of this cohort is high.¹⁹

This study was designed as a pilot project to determine the feasibility of providing PEP for a population of men with documented high HIV seroincidence. As such, it did not include a control group without access to PEP, nor did we attempt to measure the number of potential exposures to HIV that did not lead to PEP use, which severely limits our ability to draw firm conclusions on the behavioral impact of the intervention or to assess its potential efficacy. Nonetheless, the data from this study, in combination with data on the effectiveness of PEP in other settings, suggest that the provision of PEP is appropriate for individuals with high-risk sexual exposures who seek health care and wish to receive antiretroviral drugs.^{10,20-23}

In summary, PEP following sexual exposure was found to be safe and was not associated with an increase in reported high-risk behaviors. Only 1 PEP failure was observed. However, the occurrence of new HIV infections did not differ from what had been previously observed in this cohort in the absence of PEP, suggesting a limited public health impact of this intervention.

APPENDIX

Praça Onze Study Team

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