Post Exposure Prophylaxis as a Biobehavioral HIV Prevention Intervention (PEP)

FINAL REPORT

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Sponsors:	GlaxoSmithKline (GSK) Friends Research Institute (FRI) City of Los Angeles AIDS Coordinators Office
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Running Head:	PEP

Project Timeline and Goals

Project Title: Post-Exposure Prophylaxis as a Biobehavioral HIV Prevention Intervention

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Project Milestones	Date
Initial Approval by Friends IRB	12/11/2000
Initial Approval by UCLA HSPC	3/29/2001
Initial Approval by RAND IRB	11/28/2000
Date of Consent for the First Participant	4/16/2001
Date of Consent for the Last Participant	1/3/2002
Date of Last Follow-up Activities	12/20/2002
Date of Drug Accountability (need from Dr. Moe)	1/25/2003
Date of This Report	4/30/2003

[1] ARC grant awarded to Dr. Shoptaw on 8/8/2000.
[2] Grant from City of Los Angeles in the amount of $50,000 to cover costs for promotion of the project
[3] Grant from GSK provided all clinical medicines and $7,500 to cover costs for promotional materials
[4] Assistance from RAND in the form of personnel costs for behavioral risk reduction counseling.

RATIONALE

Epidemiological studies document that in contrast to other parts of the United States, HIV-infection in Los Angeles County is associated with male-to-male sexual behaviors (80% of cases). Only 7% of AIDS cases locally are due to injection drug use behaviors (LA County HIV Epidemiology Program, 2002), while 43.9% of cases are due to drug injection in New York City (CDC Wonder, 2003). Los Angeles County remains the second highest concentration of AIDS cases nationwide (Los Angeles County Prevention Plan, 2002), indicating that a large number of individuals become HIV infected due to high-risk sexual behaviors. New increases in HIV infection rates among young men who have sex with men (MSM; LA County HIV Epidemiology Program, 2002) suggest that prior adherence to safer sex protocols is failing, particularly among youth. Some suggest that HIV is increasingly believed to be a chronic illness, especially by young MSM (Dilley, Woods, & McFarlad, 1997; Lert, 2000). Clearly the need for progress in HIV prevention is essential.

One avenue of prevention used in extremely high-risk exposure situations among health care workers is the biomedical intervention of post-exposure prophylaxis (PEP). Healthcare workers exposed to HIV within the workplace are urged to begin PEP treatment with 2- or 3-drug antiretroviral therapy instituted immediately, an intervention that reduces the probability of HIV seroconversion by approximately 70% (CDC, 1998a). Effectiveness for antiretroviral post-exposure prophylaxis (PEP) therapy is directly associated with time-to-initiation following an exposure event, with maximal benefit observed when therapy is started within 36 hours and with any benefit at all observed when started within 72 hours (Cotton, 1998).

PEP treatment, though standard of care for health care workers who experience occupational exposure, has not been recommended for individuals who experience potential HIV exposure following high-risk sexual activity with a partner of infected or unknown serostatus (Pinkerton et al., 1998). The Center for Disease Control and Prevention recommends that clinicians be circumspect when considering antiretroviral treatments for non-occupational exposure to HIV, maintaining that "…medical treatment after sexual, injecting-drug-use, or other nonoccupational HIV exposure is likely to be a relatively ineffective method for preventing HIV infection compared with preventing exposure in the first place (CDC, 1998b)." Correspondingly, outside select clinicians who provide biomedical prevention interventions after potential exposure to HIV as a for-fee-service, there are no current publicly funded programs that provide this treatment. Public HIV prevention services in Los Angeles County provide exclusively behavioral interventions, which target reductions in behaviors that might transmit HIV and thereby reduce future infections. It remains unknown whether providing post exposure prophylaxis following a potential HIV exposure due to non-occupational reasons is a feasible intervention within the diverse and broad County of Los Angeles.

CDC recommendations for differential treatment of individuals exposed to HIV in the workplace versus non-occupational settings have little basis in empiricism. Infectivity of HIV is consistently low, with risks for HIV seroconversion following a single event being very low in any setting. Risks for becoming infected with HIV after a single episode of needle stick exposure are estimated at 0.67% (Kaplan and Heimer, 1992). Risks for single episodes of receptive anal intercourse are estimated at 0.1%-3%, while the risks per episode of receptive vaginal

intercourse are estimated at 0.1%-0.2% (Mastro and de Vincenzi, 1996; Varghese et al., 2002). Factors can increase single episode transmission risks, such as rectal or vaginal inflammation, or co-infection with chlamydia, gonorrhea, syphilis, or ulcerative genital lesions (Wasserheit, 1992). Risks for HIV infection for the partner receiving body fluids during oral sex also are important (Dillon et al., 2000) and may be exaggerated by open sores or ulcers in the oral cavity during the episode. Yet, these are statistical concepts. It remains impossible to predict whether any specific sexual episode with a partner who is HIV-infected (or presumed infected) will result in a new infection. Also consistent across work and recreational settings is that individuals can experience potential for future exposures with HIV, particularly when there is little to no change in behavior.

The CDC and other medical professionals remain circumspect when considering the use of PEP following potential sexual exposure due to a widely held belief that these individuals regularly engage in high-risk behaviors and are unlikely to change their risk behaviors. Moreover, PEP medications are toxic and even among highly motivated healthcare workers who received the intervention, most reported side effects; a substantial number (24%-36%) discontinue the treatment due to those side effects (CDC, 1998b). Concerns over cost-efficiency (Pinkerton, Holtgrave, & Bloom, 1998) also exist, especially over the potential for increasing risk behaviors should one incorporate PEP into a coordinated HIV prevention strategy on a community-wide basis. Up to now, HIV-uninfected individuals had little knowledge as to where to seek medical care for prophylaxis after potential sexual or drug-related exposures to HIV.

STUDY OBJECTIVES

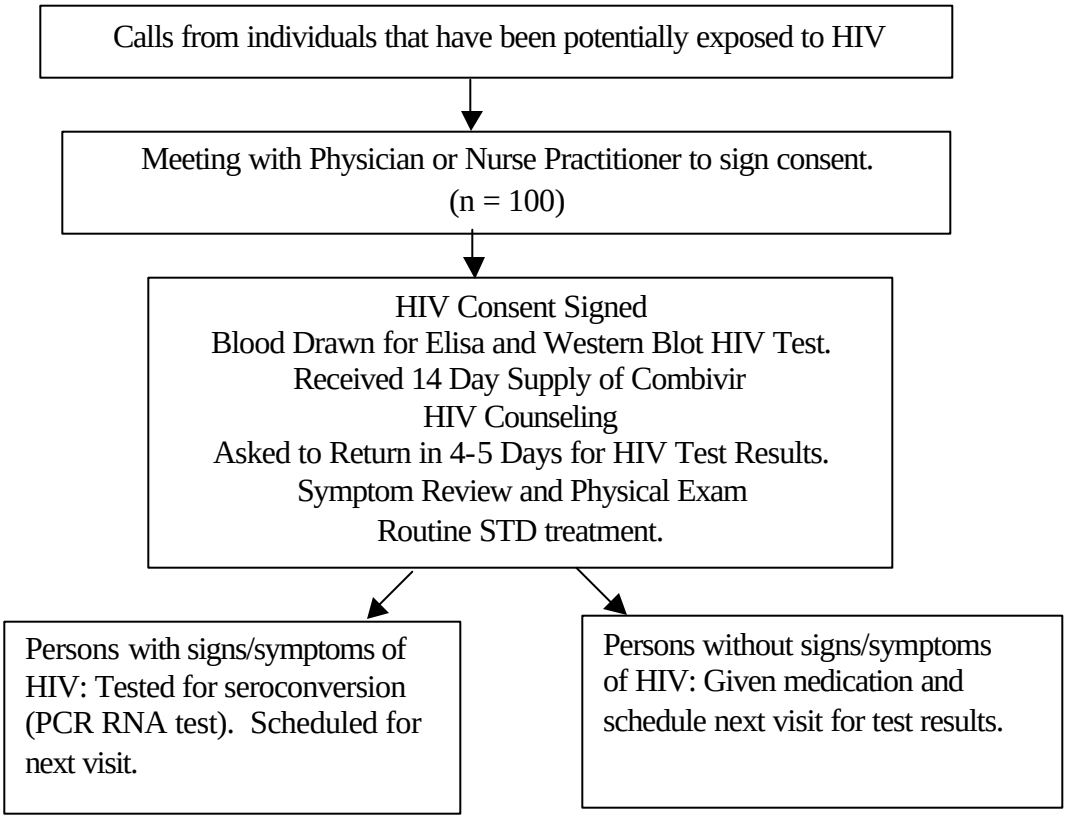
This project evaluated the feasibility of providing PEP within 72 hours of potential exposure to HIV following high-risk sexual or drug use events as part of comprehensive biobehavioral HIV prevention service for 100 individuals. The primary outcome was the feasibility of the intervention since there existed no data to indicate the demand for non-research-based PEP services in Los Angeles. If PEP following non-occupational exposure were to be incorporated into the mix of prevention programs within Los Angeles County, some documentation of the size of the demand would be necessary. Evaluation of the efficacy of PEP following sexual exposure to HIV is outside the resources of this project. For the purposes of this study, feasibility was defined as the proportion of patients that completed the PEP medication regimen divided by the number of patients that began a PEP medication regimen within 72 hours of a potential HIV exposure from sexual and drug related behaviors. Participants received a 28-day supply of antiretroviral medical intervention (Combavir – AZT+3TC) that was integrated with medical follow-up visits and individual behavioral HIV risk reduction counseling. It was hypothesized that the provision of PEP would be feasible and that the combination of medication and behavioral risk reduction counseling with the PEP would reduce the number of high-risk sexual and drug use behaviors from baseline levels to longer-term follow-up evaluations.

METHOD

Study Design

The design for this feasibility study featured an open-label strategy for delivering the medication in order to ensure access to active treatment and to measure the demand for the intervention and the practicality of delivering the medical with a behavioral risk reduction counseling program in combination (see Figure 1). This feasibility study allowed the physician maximal freedom for tailoring the specific antiretroviral treatment regimen to each individual, within the guidelines of the algorithm specified. The specific treatment regimen was tailored to each individual by Dr. Ardis Moe (co-PI) to maximize therapeutic potential and to limit side effects. Although risks for adverse events from taking antiretroviral medications were likely, all participants were informed of these risks relative to the potential benefit of the medications on an ongoing basis. HIV testing was indicated at baseline, 6-weeks, 12-weeks and 6-months after beginning PEP. For those participants who tested HIV negative, but were in the process of HIV seroconversion, there existed a potential risk for developing resistance to the PEP medications prior to initiation of formal HIV medical care, thereby potentially eliminating a treatment option. As soon as HIV test results were available, participants were asked to return to verify that PEP was their best potential treatment option.

Figure 1: Study Activity Flow-Chart



Participants

Participants were males and females of all ethnicities who reported recent (within 72 hours) potential HIV exposures following non-occupational events with persons known or suspected to be infected with HIV. Participants were required to report a high-risk potential sexual exposure to HIV, including: (in descending order of risk) (a) unprotected receptive anal

intercourse; (b) unprotected receptive vaginal intercourse; and (c) unprotected receptive oral intercourse in which the individual has open mouth wounds, ulcers, or inflamed mucosa that would provide viral entry points; or (d) a high-risk potential drug-related exposure to HIV, which involves sharing of injection equipment without sterilizing between uses. The sexual or injection partner in the high-risk event must have been known to be HIV-infected or of unknown serostatus, and presumed positive. Potential participants were excluded if they were unwilling to provide written informed consent for this treatment research project. They were also excluded if they were less than 18 years of age, presently incarcerated, pregnant or lactating, or known or strongly suspected to have had exposure to HIV that is resistant to AZT and/or 3TC.

Study Sites

In order to be increase the number of the potential individuals from different geographical areas throughout the Los Angeles area who could access PEP, two sites were used. Despite primary and extensive recruitment efforts being focused on the South Central Los Angeles site, all 100 participants were seen at Friends Health Center in Hollywood.

1. Friends Health Center
   6769 Lexington Ave
   Hollywood, CA 90038
   (323) 460-6910

2. Friends at Mount Carmel
   801 W. 70th Street
   Los Angeles, CA 90044
   (323) 565-2850

Procedure

Recruitment. Recruitment strategies included a multifaceted approach that involved word of mouth, specially developed recruitment materials posted in high-risk environments (e.g., cruising parks, sex clubs, tearooms, drug use areas), published in gay magazines and alternative newspapers, and distributed to general health care providers for HIV-uninfected men and women (e.g., STD clinics; County health clinics). As part of this recruitment effort, the City of Los Angeles AIDS Coordinator's Office initiated a city-wide publicity campaign describing the availability of PEP under this research protocol for individuals who have recent potential exposure to HIV (see Appendix A). Recruitment materials advised interested participants to phone the toll-free clinic number (888) 995-8880, to schedule an immediate appointment with a physician or nurse practitioner to discuss the appropriateness for starting PEP therapy.

Informed Consent. For participants who reported a high-risk potential HIV exposure, a session was scheduled with the study physician as soon as possible (including weekends) after the telephone call inquiring about the PEP study. During this session, participants were informed by the physician investigator of the nature of the study, the procedures to be conducted, the risks and benefits to PEP treatment, including the risks for seroconversion in the presence *and* in the absence of PEP, the voluntary nature of the research participation, the availability of alternative

treatments, and a description of the investigators involved. Participants were encouraged to ask questions of the physician or nurse practitioner and once resolved, s/he was asked to provide written informed consent. Following provision of written informed consent, participants began the initial procedures to evaluate for the appropriateness of PEP.

*Regulatory Oversight***.** Three oversight bodies reviewed the procedures for this project to ensure safe study participation: (1) the West Coast IRB for Friends Research Institute; (2) the UCLA Human Subjects Protection Committee for Medical Research; and (3) the IRB for RAND. All study activities were conducted in compliance with the Belmont Report and the Declaration of Helsinki regarding the rights of subjects in medical research.

Study Activities. Following collection of informed consent, participants began a pre-HIV test counseling session with an HIV counselor certified by Los Angeles County. During this counseling session, the individual provided consent for HIV testing, and received information on testing procedures including descriptions of the drawing of blood and the interpretation of the results. As PEP medications are suspected to be most effective within the 36 hours after a potential HIV exposure and no rapid HIV test was available (the OraSure QuickTest was not yet available), standard ELISA/Western Blot testing was conducted. In the absence of testing results, all participants were presumed to be uninfected. The testing procedure involved provision of a blood sample, drawn by medical personnel, using universal precautions. An ELISA HIV test was conducted to determine the presence or absence of HIV antibodies in the blood, and a Western Blot test was used to confirm these results (see Figure 1). At the end of the initial visit with the physician, participants who enrolled took their first dose of study medication, were given a 14-day supply to take home, and were scheduled for a return visit in one week. For participants who tested positive to HIV antibodies, study medication was discontinued immediately and these individuals received referrals to HIV medical care.

Antiretroviral Treatment Regimen. All participants engaged in a thorough discussion of the risks and benefits of the medications, potential drug interactions, as well as possible hypersensitivity reactions to the medications with a physician investigator at the first visit. During the initial visit, participants were given a 14-day supply of medication, and were scheduled for a follow-up visit in one week. All participants also received a pill tray and counseling regarding medication adherence strategies at this time. At Week 1, a second 14-day supply of medication was distributed, and initial lab reports were reviewed. Reports of adherence and side effects of medications were evaluated at Weeks 1, 2, 3, and 4. In addition, liver and kidney functioning tests were drawn at Weeks 2 and 4. During each visit, labs drawn during the previous visit were reviewed with the participant.

Study Measures

Physical exam: All participants reporting sexual exposure to HIV began with a targeted history and physical examination. Those reporting injection exposures were required to show recent "track marks." This evaluation process was used to verify participant appropriateness for inclusion in the PEP project. ***HIV test:*** Participants determined to have been potentially exposed to HIV within the last 72 hours underwent HIV testing using ELISA and Rapid Blot Test methods (2 10 cc serum samples). ***Safety panel:*** A blood safety panel (15 cc) including CBC

with differential, electrolytes, renal function, liver enzyme, and liver function tests were taken at the initial visit and on Weeks 2, and 4. ***Risk assessment***: High-risk sexual and drug use behaviors (lifetime and in the last 30 days) were recorded from participant self-report using a modified version of the Behavioral Questionnaire. ***Follow-up assessments (Week 1, 2, 3, 4, 6, 12,and 26)***: The following was repeated at the referenced follow-up points: Repeated targeted history and physical examination; HIV test at Weeks 6, 12, and 26 (three 10 ml lavender top – HIV Elisa, Western Blot, HIV-PCR), Behavioral Questionnaire (see Table 1). To increase follow-up rates, we provided $25 in grocery gift certificates for completing each of Week 12 and Week 26 assessments.

Table 1: Study Activity Timeline

	Baseline	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 6**	**Wk 12**	**Wk 26**
HIV Blood Test*	X				X	X	X	X
Safety Panel	X		X		X			
Modified BQA	X				X	X	X	X
Physical Exam	X							
Risk Reduction Education	X	X	X	X	X			

*May have been repeated more frequently if determined necessary by physician

Interventions

Risk Reduction Education. Risk reduction education was initiated by the behavioral counselor, which included providing information and literature on signs and symptoms of acute HIV seroconversion for the patient to review and keep for future reference. HIV risk reduction counseling was incorporated into each clinic visit and included educating the patient about the modes of HIV transmission and the relative risks for transmission with differing behaviors. This risk reduction education program, based on the *Project Light* manual was condensed from 7 sessions into 5, to meet the visit regimen of this study. These sessions were conducted by the non-medical staff members of each site in individual sessions, and included presentation of prevention and/or treatment materials, lasting approximately 30-45 minutes. Those participants who were interested in seeking additional treatment were facilitated in securing that care at local resources.

Therapeutic Regimens. All study drugs were supplied by GlaxoSmithKline and provided at no cost to study participants. As noted above, PEP medications were prescribed using two drug antiretroviral combinations, i.e., Combivir (AZT + 3TC). Study drugs and their prescriptions follow: Zidovudine (AZT) – 300 mg bid for 28 days; Lamivudine (3TC) – 150 mg bid for 28 days.

Zidovudine (AZT) is a synthetic nucleoside analogue of thymidine and inhibits HIV reverse transcriptase activity both by competing for utilization with the natural substrate and by its incorporation into viral DNA. The most serious side effects from taking AZT is a possible liver toxicity that can include severe anemia, particularly in patients with advanced HIV disease. Long-term use of AZT can cause serious side effects that include myopathy (muscle pain) and

myositis (disease or inflammation of a muscle); hepatomegaly (enlargement of the liver); and lactic acidosis (a rare and severe elevation of lactic acid that can possibly cause death). The frequency and severity of side effects from using AZT are greater in patients who have advanced HIV disease. Many side effects from taking AZT are similar to those of HIV disease itself. In clinical trials of asymptomatic HIV infected people taking AZT , the most common side effects were headache, tiredness/malaise, nausea and vomiting, anorexia (loss of appetite), and dizziness. Participants were advised to tell their doctor about any liver or kidney disease prior to taking Zidovudine. In addition, AZT is known to interact with many medications. Participants will be screened at admission and throughout the protocol to ensure that they consult with their treating physician if they are taking any of the following medications: ganciclovir, interferon-alpha, bone marrow suppressive drugs or drugs that interfere with the number and/or function of red or white blood cells, probenecid, phenytoin, methadone, fluconazole, atovaquone, and valproic acid.

Lamivudine (3TC) is a synthetic nucleoside analog whose principal mode of action is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analog. The most serious (and rare) side effect to taking 3TC, which may occur in mono- or combotherapy is lactic acidosis (see above). Serious side effects may occur more frequently for people who also have severe liver problems, including late stage hepatitis. More common and less serious side effects for those who take 3TC (usually in combination with AZT) include headache, tiredness/fatigue, fevers/chills, nausea and vomiting, diarrhea, anorexia (loss of appetite), abdominal cramps and pain, neuropathy, insomnia (sleeping problems), dizziness, sadness/depression, coughs, rashes, and pain.

Neither of these medications, either taken alone or in combination, are a cure for HIV infection. Neither have any of these medications, either taken alone or in combination, been shown to reduce the risks of transmitting HIV to others through sexual contact or blood contacts. Long-term effects of taking these medications are unknown at this time, but this risk was somewhat reduced by taking these medications for only 28 days. In addition, there is some evidence that taking these medications with alcohol or non-nicotine/caffeine substances may have increase likelihood for cardiomyopathy (Monsuez et al., 2000) and pancreatitis and liver dysfunction (Whitfield et al., 1997).

Toxicity Assessments. Toxicity of the treatments was assessed by the physician at each clinic visit using the toxicity scale of the AIDS Cooperative Trials Group (ACTG). Patients with any drug toxicity assessed at grade 2 or higher were followed weekly until resolution. There were no grade 3 or 4 toxicity events.

Biosafety Considerations. As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, and blood products, appropriate blood and secretion precautions were used by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the CDC.

RESULTS

Recruitment Efforts

A Community Advisory Board (CAB) set up for this project included representatives from many service agencies as well as individuals who were HIV-infected to assist in the development of the project and in creating recruitment materials. The CAB met 18 times between 10/12/00 and 7/25/01. On average, approximately 13 members of the CAB attended each meeting. Table 2 lists the agencies and the number of people from those agencies of members that participated in at least 1 CAB meeting. The CAB advised that all recruitment materials and activities focus primarily on the South Los Angeles area, given disproportionate increases in HIV-infection rates among people of color. Two outreach workers staged a multifaceted outreach effort that included conducting informational in-services for clinical sites, providing posters and postcards for local area businesses, posting advertisements in newspapers and magazines, releasing full articles about the project in the Los Angeles Times and The Wave (two local area newspapers), as well as visiting high risk areas (i.e. well-known parks and bath houses) around Los Angeles to pass out palm cards and place posters (see Appendix A for copies of recruitment postcards). Advertisements were developed in both English and Spanish, and both Anglo and ethnic models were used in each. Different advertisement messages were developed for the South Los Angeles and Hollywood target areas (see Appendix A). Spanish speaking staff members were available to answer calls from potential participants at all times, and a total of 2 monolingual Spanish-speaking participants enrolled to the project. Outreach efforts successfully yielded brisk enrollment, and 100 participants were enrolled between April 2001 and January 2002. In addition, a high-visibility newspaper report was published regarding the study on August 6, 2001 (see Appendix A).

Table 2: Agency representation at Community Advisory Board meetings

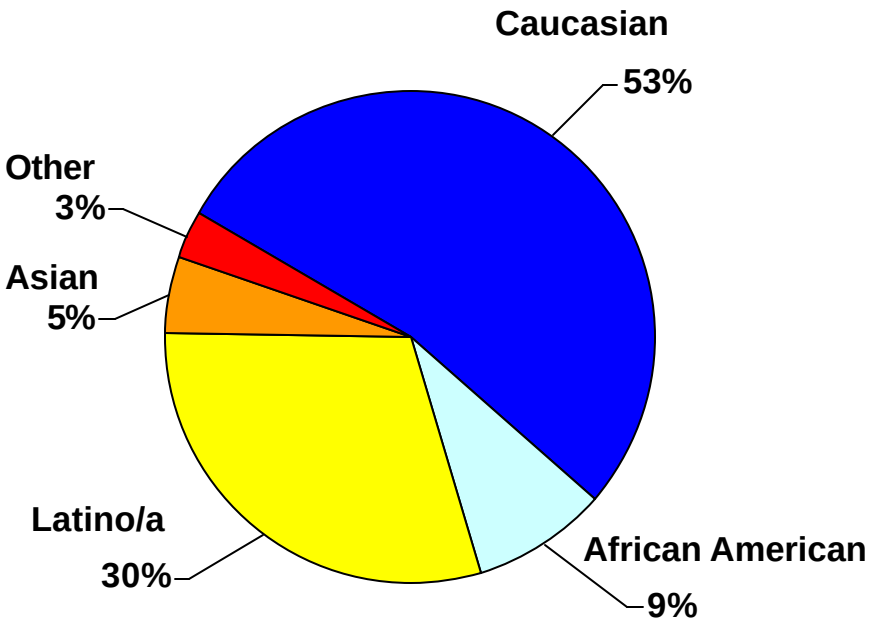
Agency	Members Attending
Friends Research Institute, Inc.	13
Van Ness Prevention Recovery House/Prevention Division	7
RAND	5
City of Los Angeles AIDS Coordinators' Office	4
Adult Industry Medical Healthcare Foundation	2
Community Members	2
Bienestar	2
Palms Residential Facility	2
Homeless Healthcare	2
Tarzana Treatment Center	1
UCLA	1
USC	1
UCSF	1

Demographic and Drug Use Characteristics.

Participants were 100 potentially HIV-infected individuals in the Los Angeles area. The average participant was a middle-classed, working man who experienced an atypical sexual experience in which he likely was exposed to HIV. In total, 95% of participants were men, with an average age of 31.76 years (SD = 7.53). Participants self-identified predominantly as homosexual (63.0%), with 19% identifying as heterosexual, 9% bisexual, and 9% not responding. Fifty percent of participants reported being single at the time they joined the study, although 40% did not respond to this question on their admission form. The ethnicity of the participants is depicted in Figure 2. Most participants had completed some college education, and averaged 14.72 years (SD = 2.32) of school, earning an average of $2,870 (SD = $2,095) in monthly income. The vast majority of the sample seeking care was employed (66%). There were no re-enrollments in this study, although two individuals had received PEP previously from other programs (USC and San Francisco).

A total of 81% of participants reported previous HIV testing experiences an average of 10.8 months (SD=18.6) prior to joining the study, with 24% (n=19) having been tested in the previous month. Most of those tested, were tested between 1 and 6 months prior to entering the study (39%; n=32), and 21% (n=17) were tested between 6 months and 1 year. Only 16% (n=13) of those previously HIV tested had been tested over a year prior to entering the study.

Figure 2: Ethnicity of Participants

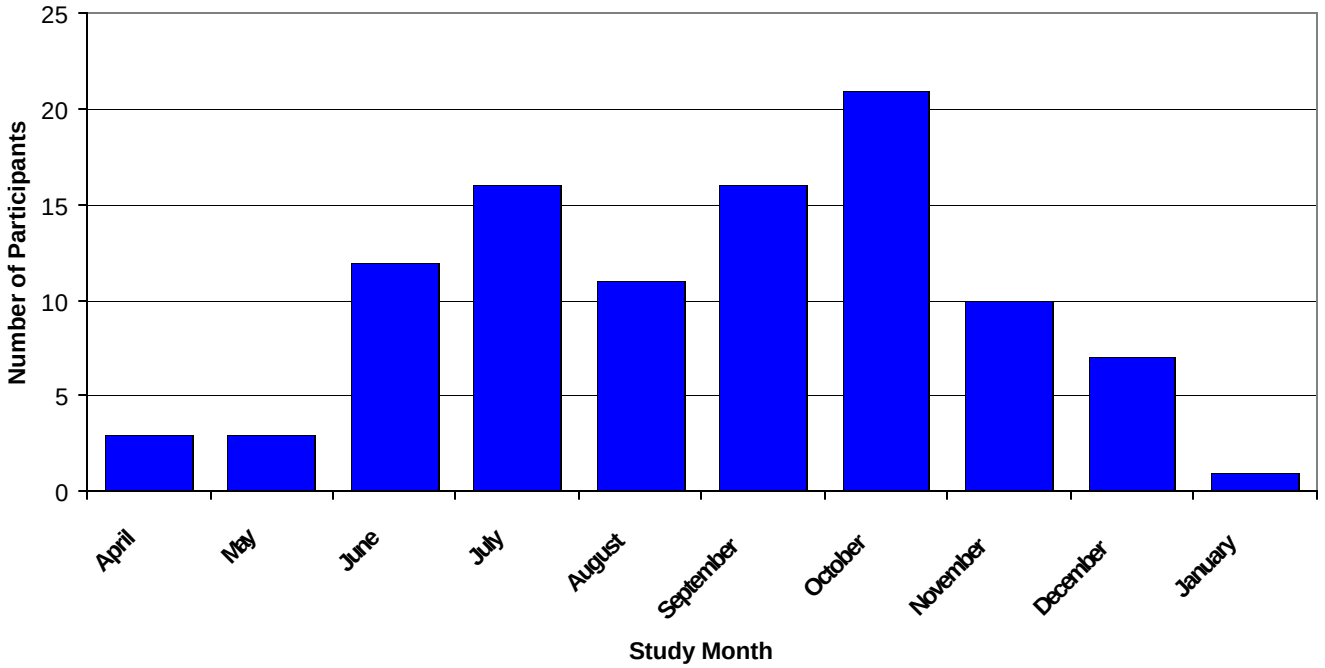


Participant Enrollment and Study Progress

Participants who phoned seeking this care generally were responding to posters announcing the study or to referrals from the California AIDS hotline and the Los Angeles Gay and Lesbian Center. Relatively few inquiries about PEP were fielded from individuals living within the South Los Angeles areas. Instead, inquiries from individuals who identified as being from the South Los Angeles areas often mentioned seeing our posted materials and inquired about free HIV testing facilities located near them. Many mentioned events that occurred outside the 72-hour window, acknowledging that it took some time to work up the courage to inquire about the study.

Most participants enrolled to the study on Mondays, with a good percentage enrolling on Tuesdays and Wednesdays, and the remaining portion distributed throughout the rest of the week. Although 92% of participants lived within the City of Los Angeles, there were 4% from distant Los Angeles County areas (i.e. Sun Valley), and 4% more that came from outside of Los Angeles County altogether (i.e. San Francisco, San Diego, and Orange County). Despite concentration of outreach and recruitment resources on the South Los Angeles areas, none were treated at the South Los Angeles clinic. All participants sought care at the Hollywood location. Figure 3 presents the number of enrollments to the PEP study each month throughout the active recruitment period.

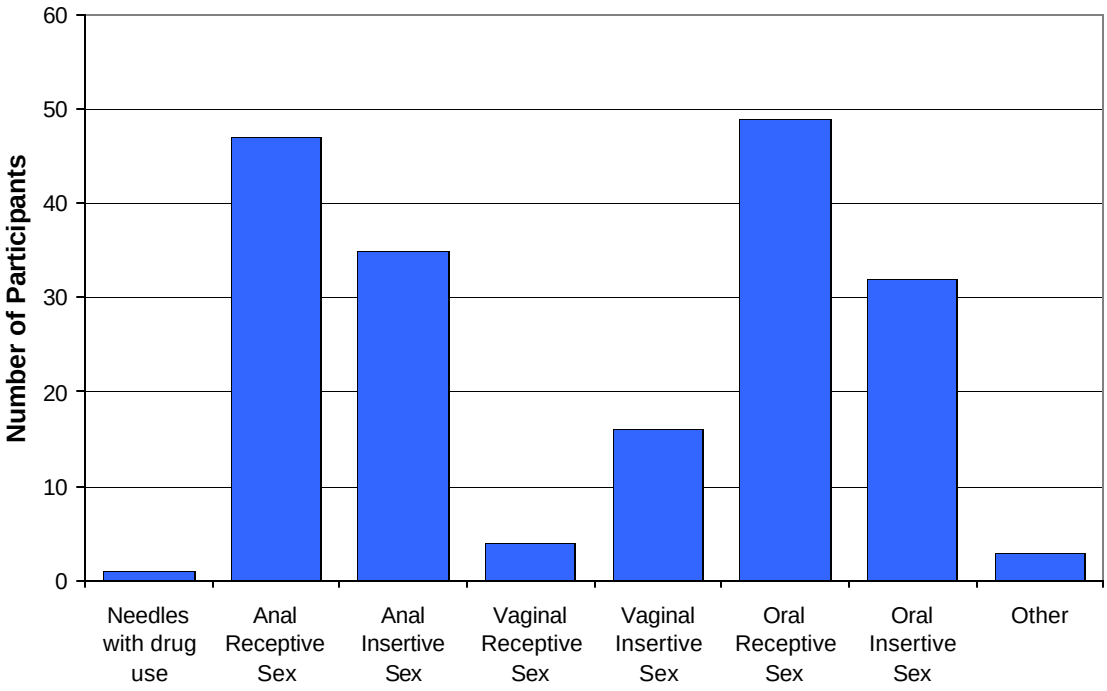
Figure 3: Enrollment of Study Participants by Study Month



Index Exposure Events

People enrolled to this study for a variety of reasons. Figure 4 depicts the types of potential HIV exposures that participants reported at study entry. Categories were not mutually exclusive, and 58% of participants entered the study reporting multiple risk factors from a particular exposure (e.g., both anal receptive and insertive intercourse). The most common types of potential HIV exposures reported were anal and oral receptive and insertive sexual contact with individuals known or suspected to be HIV infected, with most of these occurring with male-to-male sexual behaviors. Although 23% of participants reported using condoms at the time that they thought they were potentially exposed, 18 of those who used condoms (or 78.3%) reported that the condom failed. Four participants mentioned deception on the part of their partners to the point that they were unsure or unaware whether there was a condom used at the time of sexual contact. As can be seen from Figure 4, HIV exposure events generally carried high likelihood for HIV exposure and were not simply representative of the "worried well." In addition, a total of 45% of participants reported using alcohol and/or drugs at the time of their potential exposure, with 25% using alcohol, 12% using methamphetamine, 4% using ecstacy, 5% using cocaine, 5% using marijuana, 2% using GHB, and 3% using multiple drugs.

Figure 4: Number of Subjects Reporting Specific HIV Risk Behaviors at Study Entry

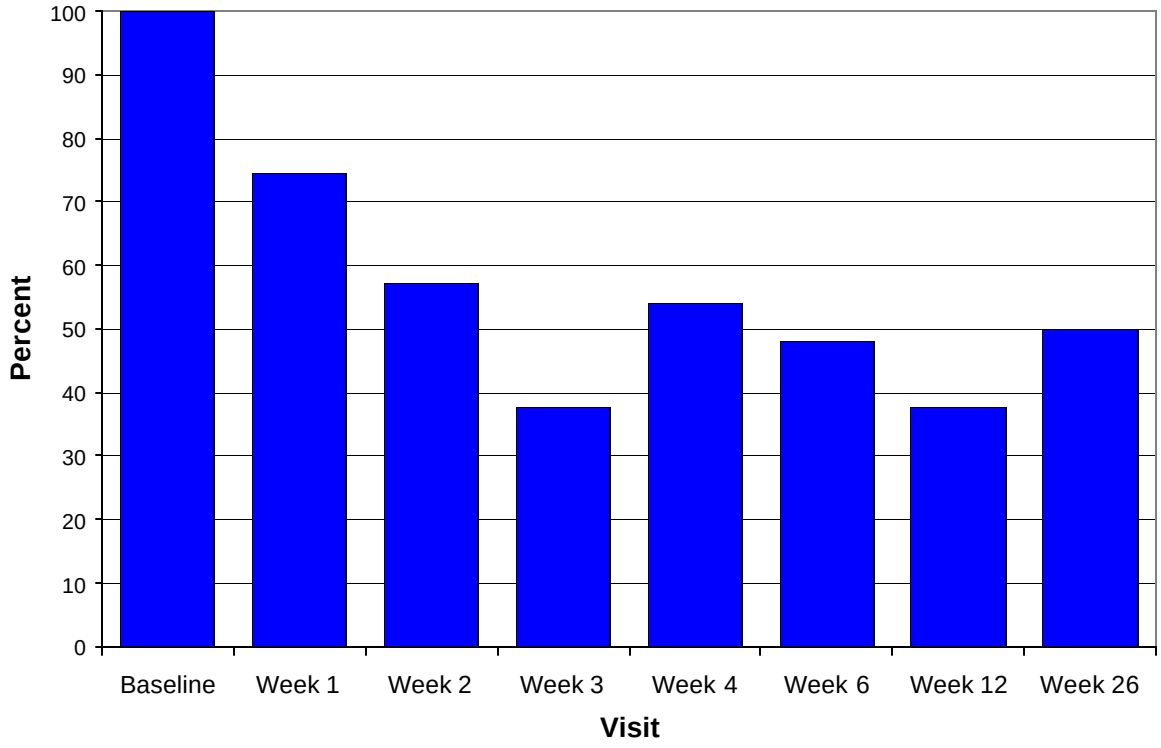


Feasibility Analysis

This project defined feasibility as the proportion indicated by the number of participants who completed the PEP medication divided by the number of participants who initiated PEP. Results showed that 85 participants were dispensed the full 28-day supplies of PEP medication. Of these 85, 21 (24.7%) participants either returned unused medication, or informed study staff that they missed doses of the medication. That left a total of 64 participants (65.3%) who are believed to have completed the 28-day regimen of medication, out of 98 total participants. Medication adherence was confirmed by a physical pill count conducted by the study nurse at each visit. Two participants were found to be HIV-positive at their baseline HIV-antibody test and, therefore, were not offered the full medication protocol. Thus, those two participants were removed from all subsequent data analyses. Participants took an average of 49.4 (88.39%) pills overall, out of a total possible of 56 pills.

Participants were less consistent with attendance at follow-up visits for behavioral counseling than for medication visits. Participants clearly were more interested in the medication aspects of this biobehavioral trial, as indicated by high attendance for visits at baseline and week 1 when medication was dispensed (see Figure 5). By the end of the trial, 48 of the participants returned to complete their 6-month follow-up visits. A total of 7 individuals withdrew consent (7.1%) following entry to the study and receipt of their study medications. This corresponded to a follow-up rate of only 52.8% at study end.

Figure 5: Retention of Participants (in percentage) at Each Study Visit



Outcomes from PEP Intervention

As noted, two of the 100 participants enrolled to the study believing they were HIV-negative, were, in fact, HIV-positive. As soon as testing results were available, these individuals were contacted and facilitated in entering HIV medical care.

A total of 81% of 98 study participants received all 28 days of study medication. The remainder did not receive all 28 days of study medication for the following reasons:

- 9% quit study medication due to side effects;
- 5% quit study medications because they failed to return to clinic;
- 2% quit because their partner tested HIV negative;
- 2% were withdrawn due to testing HIV positive at entry;
- 1% quit study medications due to lost pills.

Risk Behaviors. One concern to using PEP for non-occupational exposure events, is that it may encourage high-risk activities due to the belief that there is an effective biomedical protective intervention to use after high-risk sexual events. In this project, however, participants reported a reduction in risk behaviors (See Table 3) over the evaluation period. Participants reported having significantly fewer sexual partners in the past 30 days from the baseline to subsequent time points. Participants also reported reductions (although not significant) in the amount of receptive oral and anal sex that they were having from the baseline to subsequent time points. Unfortunately, the degree to which participants actually reported using condoms during sex also did not change as a result of their participation, and Figure 10 shows the percent of condom use among participants at each time point.

Table 3: Reported 30-Day Sexual Risk Behaviors by Study Visit

	SEXUAL RISK BEHAVIORS IN PAST 30 DAYS			
STUDY VISIT	**Number of Sexual Partners* % or M (± SD)**	**Times Unprotected Receptive Oral % or M (± SD)**	**Times Unprotected Receptive Anal % or M (± SD)**	**Percent of Time Used Condoms % or M (± SD)**
Baseline (n=85)	3.5 (3.9)	0.7 (3.0)	0.3 (1.2)	42.2 (38.3)
Week 4 (n=31)	1.9 (1.6)	0.2 (0.6)	0.0 (0.2)	38.8 (40.3)
Week 6 (n=35)	2.0 (1.8)	0.1 (0.2)	0.0 (0.2)	48.9 (45.1)
Week 12 (n=24)	1.4 (1.2)	0.1 (0.3)	0.0 (0.2)	16.9 (34.0)
Week 26 (n=32)	1.9 (1.7)	0.1 (0.3)	0.0 (0.0)	43.3 (44.4)

*****Significant reduction over time; $F(4, 202) = 4.43$, $p<.002$

Adverse Experiences

Over the treatment period, we observed one serious adverse event. This involved a participant who became suicidal over subsequent high-risk sexual behaviors that followed the index event that resulted in his PEP intervention. The individual was taking study medication when he experienced this psychiatric instability. The physician investigator notified the police of the participant's threats, who then transported the individual to an inpatient psychiatric facility.

Review of the record showed that this participant had a history of psychiatric instability and the event was determined "not related" to the study medication. As expected, participants frequently reported adverse experiences to the medical staff. A total of 79**%** of participants reported at least one side effect of the medication.

DISCUSSION

Our findings demonstrate that the feasibility for providing PEP in Los Angeles is quite high. Most participants are interested primarily in treatment using antiretroviral medications, with only minor interest in behavioral risk counseling interventions, even when implemented concurrent with the medications. We observed no seroconversions over the follow-up period for those with whom we were able to contact. However, it is possible that some number of individuals lost to follow-up became HIV positive. Findings also show that if offered, there will be vigorous demand for a PEP intervention in the areas of Los Angeles County where gay and bisexual men reside. Based on this experience, about 8-10 male individuals monthly could be expected to seek PEP treatment using publicly funded resources.

Findings also demonstrate that the advertisement and outreach strategy used for this project successfully reached individuals at extremely high risk for HIV infection. The methods and procedures used to mount this intervention bypassed the "worried well," and effectively rationed the care to those who, indeed, encountered HIV as a result of their sexual behaviors. A total of two of the participants who believed they were HIV negative at study entry, were found to be HIV positive upon having their first HIV test in the project. This corresponds with a prevalence rate of 2.0 infections per 100 person years for similar others who might seek post-exposure prophylaxis. Clearly and in contrast to several reports of PEP for non-occupational exposure in major U.S. cities, the materials and procedures we used in Los Angeles for positioning this study of PEP successfully reached individuals who experienced high risk for HIV transmission.

A number of observations arise from the examination of the project findings. Foremost is the difficulty in retaining participants for the full length of the study and the corresponding low follow-up rate. This was a sample of individuals in crisis who made decisions quickly about their participation in this research project. Upon making the initial telephone call to the study hotline, these individuals were within 72 hours of an event, whether sexual or drug-related, and that they believed placed them at risk for a chronic, perhaps fatal, infectious disease. The distress experienced by the individuals was clearly discernable in the tone of the initial phone call. Sometimes in close to a state of panic, these participants were eager, even desperate, to receive help and in that state were agreeable to most any study requirements.

Another striking observation is the relatively low occurrence of reported illicit drug use accompanying the risk events. The majority of events (55%) occurred in the absence of substance use. The anticipated role of cocaine and methamphetamine in the risk events was surprisingly minor, with most participants who reported any substance use at the time of the risk event mentioning alcohol use. These characteristics combine to indicate the majority of risk events occurred to relatively sober-minded adults who found themselves vulnerable to HIV infection, to an atypical series of events.

In addition to anecdotal evidence from study staff members who took the initial calls, the distressed thinking states for participants are demonstrated in the data showing a significant decrease in the degree to which participants felt certain they would never have unsafe sex again from baseline to follow-up visits. At baseline, participants rated themselves as quite certain they would never again engage in unsafe sex. By follow-up visits and long after the initial crisis had subsided, however, participants were much less certain in the likelihood they would never engage in unsafe sex. We believe that this change in distress levels and corresponding re-evaluations about the probability of engaging in future risk behaviors likely contributed greatly to our problems in retaining participants through the active phase of the study, as well as to distal follow-up evaluations. This observation also raises questions as to whether relatively infrequent sexual risk events that occasionally happen to individuals warrant PEP intervention. In a catchment area the size of Los Angeles County this rate of exposure is consistent, though low and the demand for such an intervention is consistent and low. Cost-benefit analyses using these parameters and costs of potential infections prevented might advise policy makers on the relative value of PEP instituted in infectious disease clinics in relevant areas of the City or County, especially in light of current strained health-care budgets.

It remains that PEP is an expensive prevention intervention. Even leveraging existing resources in the most efficient manner, costs for providing the medications, medical staff time, laboratory costs, and behavioral counseling likely exceed $2,000 per case. These costs, however, should be compared against the type of intervention it represents. Primary HIV prevention efforts reach large numbers of individuals, the vast majority of whom experience minimal to no potential contact with HIV. The size of the demand for PEP could be important in influencing the cost-effectiveness of PEP. Its importance is a function of the fixed costs of having a program and the qualified health personnel in place. If it costs a minimum of $150,000 per year to maintain a PEP program, then that minimum cost will remain, even with just one patient. As the number of patients increases, the cost per case decreases (assuming the marginal cost of treating each additional patient is less than the fixed cost), and the cost effectiveness of the program would increase. An overall conclusion about PEP is that it can be conceptualized as a method that targets few individuals in the population, but they are those who experience the highest probabilities for contact with HIV. Therefore, when implemented in a population the size of Los Angeles county, arguments about its cost effectiveness become more defensible.

An easily defined index for the benefit of PEP is the number of seroconversions prevented among those whose exposure to HIV would have led to seroconversion in the absence of PEP. One way of estimating this is to use a measure of the number of people found to be HIV positive at treatment entry divided by the total number of months of exposure. Using this concept, the aggregate risk experienced by the participants in this study is based on the average interval since previous HIV testing for all participants, which was 10.8 months (SD=18.6). The risk estimate using this indicator would average 2.2 seroconversions per 100 person years, with an upper limit of 0.5 seroconversions per 100 person years (using +2 standard deviations).

Providing PEP may also provide other benefits. For those who were exposed to the risk of HIV but not to the virus, and who would not therefore have seroconverted without PEP, a course of PEP may be an intervention that reduces their level of risk behavior for some period of

time, which may or may not also translate into future seroconversions prevented. The size of such a benefit depends on the extent of behavior change, its duration, and the magnitude of the risk avoided (a function of the likelihood that partners are infected, etc.), all of which are difficult to estimate.

A low follow-up rate severely limits evaluation of the efficacy of PEP within L.A. County. The primary factor this low rate involved a lack of funding for the follow-up evaluations. In contrast to ample resources for recruitment, outreach, study medications, and medically-related costs, very modest resources were available for following the participants after the initial treatment phase. Findings are also limited by the fact that this is a single-site trial of PEP following non-occupational exposures to HIV. The epidemic in Los Angeles is different than in East Coast cities or in local rural areas. The sample who received these services appeared to be well educated as to where to call following their non-occupational exposure and were very efficient in finding themselves in care quickly thereafter, which is likely non-representative of other groups. Although the design used makes it impossible to draw conclusions on the efficacy of AZT and 3TC for preventing seroconversion following non-occupational HIV exposure, results carry some promise. The method used demonstrates ways multiple funding sources can be blended to provide this service. Costs for such PEP can likely be minimized by integrating it into the context of primary care, infectious disease or emergency care settings. Finally, though intent to avoid risk was dampened over time, reported numbers of sexual partners and frequencies of receptive oral sex from baseline through final follow-up were reduced. While the low follow-up rate limits the generalizability of these results, they still provide an encouraging suggestion that during the "window of opportunity" when patients are in crisis, long-term behavior may be changed in the context of a biomedical HIV prevention intervention.

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Appendix A: Recruitment Materials