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Differentiating Nonoccupational Postexposure Prophylaxis Seroconverters and Non-Seroconverters in a Community-Based Clinic in Los Angeles, California

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**Background.** Nonoccupational postexposure prophylaxis (nPEP) is a 28-day regimen of antiretroviral medications taken within 72 hours of human immunodeficiency virus (HIV) exposure to prevent HIV acquisition. Although nPEP has been recommended since 1998, few studies have analyzed the characteristics that distinguish nPEP failures (seroconverters) and successes (non-seroconverters).

**Methods.** This retrospective study analyzed all nPEP courses prompted by sexual exposure that were prescribed at the Los Angeles LGBT Center between March 2010 and July 2014. Fisher exact tests and logistic regressions were used to determine characteristics that distinguished nPEP seroconverters from non-seroconverters.

**Results.** Of the nPEP courses administered, 1744 had a follow-up visit for HIV testing within 24 weeks of exposure and 17 individuals seroconverted. Seven reported a known re-exposure, 8 self-reported only condom-protected sex subsequent to the initial exposure, and 2 reported abstinence since the exposure. In multivariable analyses, seroconverters were more likely than non-seroconverters to report methamphetamine use, incomplete medication adherence, and nPEP initiation later in the 72-hour window.

**Conclusions.** Nonoccupational postexposure prophylaxis is an important emergency tool for HIV prevention. Our findings corroborate that timing of the initial nPEP dose is an important predictor of seroconversion. Although the current study did not offer the initial nPEP dose at the beginning of the visit, use of this fast-track dosing schedule will ensure that the first dose is taken as early as possible postexposure and may lower the likelihood for seroconversion. Furthermore, we recommend systematic screening for substance use because these individuals may be well suited for pre-exposure prophylaxis given their sustained risk.

**Keywords.** HIV prevention; men who have sex with men; postexposure prophylaxis; seroconversion.

Nonoccupational postexposure prophylaxis (nPEP) is a 28-day course of human immunodeficiency virus (HIV) medication taken as soon as possible up to 72 hours after known or suspected sexual or injection-drug use exposure to HIV-infected body fluids [1]. Although nPEP guidelines have been available since 1998 [2], uptake of nPEP has been slow due to low awareness among potential consumers [3–6] and a lack of definitive efficacy data from randomized trials among humans.

The Los Angeles LGBT Center (the Center) has the largest publicly funded nPEP program in Los Angeles County and has provided nPEP as part of an open-label demonstration study from March 2010 to May 2011. After the completion of this research study, a service delivery program was implemented in May 2011 at the same site and continues to the present day.

The use of chemoprophylaxis for HIV prevention more generally has been expanding given the increasing body of evidence from large efficacy studies of pre-exposure prophylaxis (PrEP) [7–9] as well as heightened public awareness due to social marketing efforts and provider education [10–12]. Although PrEP has received significant media attention, nPEP may be more appropriate for individuals who have less frequent and/or unplanned exposures, or for those who have not initiated PrEP yet find themselves unexpectedly exposed. Furthermore, studying factors associated with nPEP success or failure (ie, HIV seroconversion) may better inform PrEP delivery efforts.

Roland et al [13] evaluated HIV seroconversions after nPEP administration and found an HIV seroconversion rate of 1% at 12 weeks after nPEP initiation. Four of the reported 7 seroconverters had a clear subsequent exposure. In a study among men who have sex with men (MSM) in the Netherlands between 2000 and 2009,
Heuker et al [14] compared individuals receiving nPEP (n = 395) to individuals in the Amsterdam Cohort Study (n = 782). The HIV incidence in the nPEP cohort was 6.4 infections per 100 person-years (11 seroconversions) compared with 1.6 infections per 100 person-years (67 seroconversions) in the Amsterdam Cohort Study. A third study by Thomas et al [15] analyzed nPEP data from a Montreal clinic between October 2000 and July 2014. Of the 2731 complete courses of nPEP, 10 individuals seroconverted during follow up (12, 16, or 24 weeks depending on the year) for an overall seroconversion rate of 0.37%. However, the authors concluded that only 1 of the 10 seroconversions was a likely nPEP failure due to the continuation of high-risk behavior by the remaining 9, highlighting the challenge in these studies of distinguishing a “true” nPEP failure from a re-exposure. Although these studies suggest that nPEP is indeed effective in real-world settings, previous studies have not comprehensively analyzed how individual and regimen characteristics may differ between successful nPEP courses and nPEP failures.

The objectives of this study were 3-fold: (1) determine whether there are any demographic differences in individuals initiating nPEP who returned for follow-up HIV testing versus those who did not return for follow-up HIV testing; (2) determine the demographic, behavioral, and nPEP regimen characteristics of individuals who seroconvert after nPEP use (seroconverters) compared with individuals who take nPEP and do not seroconvert (non-seroconverters); (3) use follow-up data to distinguish between true nPEP failures and individuals who became HIV positive during the 24-week follow-up period likely due to re-exposure.

METHODS

The Postexposure Prophylaxis Pilot Program (P-QUAD) provided nPEP courses at the Center as part of a research study from March 2010 to May 2011. The PEP Los Angeles (PEP-LA) service delivery program was implemented at the Center in May 2011. The methods for nPEP administration through the PEP-LA program have been described previously [16].

In brief, individuals desiring nPEP were instructed to come to the Center as soon as possible within 72-hours after exposure. Individuals who needed to initiate nPEP when the Center was closed were advised to obtain a 3-day starter pack from another facility and then come to the Center to receive the remainder of the 28-day course. Human immunodeficiency virus testing was performed at baseline to ensure the patient was HIV negative, and a baseline risk assessment was used to assess exposure and other sexual risk factors. After a negative HIV-antibody test, the first dose of a course of nPEP was given by the provider. A course is defined as an antiretroviral medication provided for daily administration up to 28 days after the exposure. Medication adherence was assessed at a 2-week telephone call as well as an in-person follow-up visit between 4 and 6 weeks after baseline. Follow-up HIV testing also occurred at the 4- to 6-week visit as well as at 12 weeks and 24 weeks. All in-person visits administered both a HIV-antibody test as well as an HIV nucleic acid amplification test (NAAT) to test for acute HIV infection.

There were important differences in data collection methods between PQUAD and PEP-LA: medication adherence was assessed in PQUAD by self-report over a 14-day horizon; PEP-LA used a 4-day self-report horizon (Supplementary Figure A and B). Furthermore, the majority of nPEP courses in the PQUAD study were 3 drug regimens, whereas the majority of nPEP courses in the PEP-LA study were 2 drug regimens. Otherwise, criteria for enrollment and laboratory testing were identical between programs.

Study Population

We performed analyses at the level of the nPEP course. Incidence rates were calculated as number of seroconversions over entire observation periods for an individual participant. The same individual could contribute multiple independent nPEP sequences provided there was HIV testing with a negative result on a follow-up visit before the subsequent round of nPEP.

The nPEP courses were included in the analysis if (1) administered as part of the PQUAD study or the PEP-LA program at the Los Angeles LGBT Center between March 2010 and July 2014, (2) at least 1 follow-up HIV test was recorded post-nPEP-intake, (3) the exposure prompting PEP was sexual (ie, not exposed from occupational means or injection drugs), and (4) self-reported completion of the 28-day nPEP course.

Outcome

The primary outcome was HIV serostatus at the 24-week follow-up visit or the last recorded visit during the 24-week follow-up period. Seroconversions that occurred after the 24-week follow-up time point were not included.

The nPEP courses that had at least 1 follow-up HIV testing visit postintake were separated into 2 groups based on HIV serostatus at last contact: (1) individuals who tested HIV positive by either NAAT (antibody negative, NAAT positive) or enzyme immunoassay (EIA) testing (antibody positive) after their completed course of nPEP at any point in the 24 weeks of follow up were classified as seroconverters; and (2) individuals who tested HIV negative at each follow-up visit up to 24 weeks were classified as non-seroconverters. As previously reported, the Center’s HIV testing algorithm reflex tests all negative EIA assays with NAAT testing [16].

Covariates

Demographics were collected either via a series of assessments of each Center patient while registering for clinic services (PEP-LA) or via specific demographic case report forms (CRFs) (PQUAD). These included gender, age, race/ethnicity, sexual orientation, partner type, and education level. Risk behavior was assessed as part of an 82-item intake assessment administered to Center patients at service registration (PEP-LA) or
via specific risk behavior CRFs (PQUAD). Risk assessment included substance use, partner characteristics, and number of partners in the 30 days preceding the nPEP regimen. Although these risk behaviors may not directly apply to events that initiated the nPEP course, we analyzed these predictors because they have been shown to be related to HIV seroconversion outside of the nPEP context. In both the PEP-LA and PQUAD datasets, data on type of initial exposure that prompted nPEP services, HIV status of the source of exposure, time from initial exposure to first nPEP dose, and nPEP regimen prescribed were collected.

Statistical Methodology

Bivariate analyses to determine predictors of seroconversion used Fisher exact tests for categorical predictors and logistic regressions for continuous predictors in the PQUAD study, PEP-LA program, and PQUAD and PEP-LA combined. Multivariable logistic regression models were used to test demographic, behavioral, and nPEP predictors for HIV seroconversion within the pooled PQUAD and PEP-LA population. In the multivariable logistic regression, we used a penalized likelihood in the model to adjust for the small sample bias caused by the low number of seroconverters in the study [17]. All χ² and logistic regression statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Ethical Review

This study and the PQUAD study were approved by the University of California, Los Angeles (Institutional Review Board No. 14-000555). All participants in the PQUAD study provided written informed consent before study participation.

RESULTS

Follow-up for Postexposure Prophylaxis

There were no differences between nPEP courses that returned for a follow-up HIV testing visit (n = 1744) and those who did not return for a follow-up HIV testing visit (n = 492) by race/ethnicity (P = .41), sexual orientation (P = .26), partner type

| Table 1. Bivariate Fisher Exact Tests of Demographics by Serostatus for PQUAD, PEP-LA, and Both Programs, March 2010–July 2014 (n = 1744) |
| Demographics | PQUAD Study | | PEP-LA Program | | Total (PQUAD and PEP-LA) |
| --- | --- | --- | --- | --- | --- |
| | HIV Negative (n = 218) | HIV Positive (n = 7) | Row% | HIV Negative (n = 1509) | HIV Positive (n = 10) | Row% | HIV Negative (n = 1727) | HIV Positive (n = 17) | Row% |
| Gender | | | | | | | | | |
| Male | 204 | 7 | 3.3% | 1424 | 10 | 0.7% | 1628 | 17 | 1.0% |
| Female | 11 | 0 | 0.0% | 47 | 0 | 0.0% | 58 | 0 | 0.0% |
| Trans Male to Female | 3 | 0 | 0.0% | 38 | 0 | 0.0% | 41 | 0 | 0.0% |
| Age Group | | | | | | | | | |
| <30 | 98 | 1 | 1.0% | 642 | 5 | 0.8% | 740 | 6 | 0.8% |
| 30–39 | 63 | 3 | 4.5% | 543 | 3 | 0.5% | 606 | 6 | 1.0% |
| 40–49 | 48 | 2 | 4.0% | 247 | 0 | 0.0% | 295 | 2 | 0.7% |
| 50+ | 9 | 1 | 10.0% | 77 | 2 | 2.5% | 86 | 3 | 3.4% |
| Race/Ethnicity | | | | | | | | | |
| White | 109 | 2 | 1.8% | 671 | 6 | 0.9% | 780 | 8 | 1.0% |
| Black | 13 | 0 | 0.0% | 127 | 2 | 1.6% | 140 | 2 | 1.4% |
| Hispanic | 71 | 5 | 6.6% | 494 | 2 | 0.4% | 565 | 7 | 1.2% |
| Other | 25 | 0 | 0.0% | 213 | 0 | 0.0% | 238 | 0 | 0.0% |
| Unknown | 0 | 0 | 0.0% | 4 | 0 | 0.0% | 4 | 0 | 0.0% |
| Sexual Orientation | | | | | | | | | |
| Gay/homosexual | 168 | 7 | 4.0% | 1193 | 6 | 0.5% | 1361 | 13 | 0.9% |
| Bisexual | 27 | 0 | 0.0% | 151 | 4 | 2.6% | 178 | 4 | 2.2% |
| Heterosexual | 12 | 0 | 0.0% | 130 | 0 | 0.0% | 142 | 0 | 0.0% |
| Other | 7 | 0 | 0.0% | 32 | 0 | 0.0% | 39 | 0 | 0.0% |
| Unknown | 4 | 0 | 0.0% | 3 | 0 | 0.0% | 7 | 0 | 0.0% |
| Partner Type | | | | | | | | | |
| MSM | 191 | 7 | 3.5% | 1182 | 6 | 0.5% | 1373 | 13 | 0.9% |
| MSMW | 11 | 0 | 0.0% | 193 | 4 | 2.0% | 204 | 4 | 1.9% |
| Non-MSM | 16 | 0 | 0.0% | 134 | 0 | 0.0% | 150 | 0 | 0.0% |
| Education Level | | | | | | | | | |
| College or higher | 182 | 6 | 3.2% | 1201 | 6 | 0.5% | 1383 | 12 | 0.9% |
| HS graduate or below | 35 | 1 | 2.8% | 187 | 3 | 1.6% | 222 | 4 | 1.8% |
| Missing | 1 | 0 | 0.0% | 121 | 1 | 0.8% | 122 | 1 | 0.8% |
| Total | 218 | 7 | 100.0% | 1509 | 10 | 100.0% | 1727 | 17 | 100.0% |

Abbreviations: HIV, human immunodeficiency virus; HS, high school; MSM, men whom have sex with men; MSMW, men whom have sex with men and women; P-QUAD, Postexposure Prophylaxis Pilot Program; PEP-LA, postexposure prophylaxis Los Angeles; Trans, transition.
(\(P = .14\)), or number of sex partners in the last 30 days (\(P = .45\)). However, individuals who identified as male (\(P = .001\)), were older at nPEP initiation (\(P = .01\)), reported a college education or higher (\(P = .001\)), and/or reported not using methamphetamine in the last year (\(P = .0005\)) were more likely to return for follow-up HIV testing.

The PQUAD research study provided 259 nPEP courses to 242 unique individuals at the Center from March 2010 to May 2011. PQUAD was also conducted at The OASIS Clinic in South Los Angeles (n = 23); those data are not included in the current analysis. Of the 259 nPEP courses that were initiated, 225 (87%) returned for at least 1 follow-up visit within the 6-month follow-up period.

From May 2011 until July 2014, the PEP-LA program provided 1979 nPEP courses to 1580 unique individuals. Of the 1979 nPEP courses, 1519 (77%) returned for at least 1 follow-up HIV testing visit or initiated another course of nPEP within the 6-month follow-up period. Therefore, a total of 2238 courses of nPEP were dispensed at the Center through the PQUAD or PEP-LA programs and at least 1 follow-up HIV test was performed for 1744 nPEP courses within 6 months of nPEP initiation (78%). Approximately 2% of individuals received nPEP services from both the PQUAD study and PEP-LA programs, and 25% received nPEP services 2 or more times from the PEP-LA program.

### Demographics

A majority of nPEP courses were dispensed to males (94%), 3% were dispensed to females, and 2% were dispensed to transgender women (Table 1). Approximately 45% of nPEP courses were provided to individuals who identified as white, 8% as African-American, 33% as Hispanic, and 14% that identified as another race. The nPEP courses were provided to 1594 individuals who were MSM or men who have sex with men and women (MSMW) (91%) and 150 individuals who were neither MSM nor MSMW (9%). For individuals who reported an education status, 80% of nPEP courses were provided to individuals with a college education or higher and 13% reported a high school education or lower (7% missing).

### Bivariate Differences Between Seroconverters and Non-Seroconverters

Of those 1744 initiated nPEP courses that had follow-up HIV testing, 17 individuals seroconverted over the course of 746.2 person-years of follow-up, an incidence rate of 2.3 HIV infections per 100 person-years. By comparison, individuals who did not access nPEP service at the Center, but met the criteria for nPEP as indicated by a risky sexual exposure and HIV screening within 3 days of the exposure, had an HIV incidence rate of 6.92 HIV infections per 100 person-years during the same period. Other demographic and behavioral differences between sexually high-risk individuals who access nPEP and those who did not access nPEP have been described previously [16].

For those who accessed nPEP, there were no significant differences between the nPEP seroconverters and non-seroconverters by gender (\(P = \text{NS}\)), categorical age group (\(P = .17\)), race/ethnicity (\(P = .3\)), sexual orientation (\(P = .25\)), partner type (\(P = .21\)), or education level (\(P = .26\)). All seroconversions were among either MSM (n = 13) or MSMW (n = 4).

### Table 2. Bivariate Fisher Exact Tests of Risk Behaviors by Serostatus for PQUAD, PEP-LA, and Both Programs, March 2010–July 2014 (n = 1744)

| Risk Behaviors                  | PQUAD Study | PEP-LA Program | Total (PQUAD and PEP-LA) |
|---------------------------------|-------------|----------------|-------------------------|
|                                 | HIV Negative | HIV Positive   | HIV Negative | HIV Positive | HIV Negative | HIV Positive |
|                                 | (n = 218)    | (n = 7)        | (n = 1509)    | (n = 10)      | (n = 1727)    | (n = 17)      |
| Methamphetamine Use            |             |                | P = .03       | P = .33       | P = .02       |                |
| Not within the past year        | 193 4 2.0%   | 1210 7 0.6%    | 1403 11 0.8%  |                |                |                |
| Past year                       | 21 3 12.5%   | 178 2 1.1%     | 199 5 2.5%    |                |                |                |
| Missing                         | 4 0 0.0%     | 121 1 0.8%     | 125 1 0.8%    |                |                |                |
| Nitrates Use                    | P = 1.00     | P = .7         | P = .99       |                |                |                |
| Not within the past year        | 165 6 3.5%   | 1032 6 0.6%    | 1197 12 1.0%  |                |                |                |
| Past year                       | 49 1 2.0%    | 352 3 0.8%     | 401 4 1.0%    |                |                |                |
| Missing                         | 4 0 0.0%     | 125 1 0.8%     | 129 1 0.8%    |                |                |                |
| Sex Partners in the Last 30 Days| P = .47      | P = .58        | P = .87       |                |                |                |
| 1 partner                       | 69 2 2.8%    | 391 2 0.5%     | 460 4 0.9%    |                |                |                |
| 2 partners                      | 47 1 2.1%    | 415 4 1.0%     | 462 5 1.1%    |                |                |                |
| 3 partners                      | 41 1 2.4%    | 208 0 0.0%     | 249 1 0.4%    |                |                |                |
| 4 partners                      | 15 1 6.3%    | 124 2 1.6%     | 139 3 2.1%    |                |                |                |
| 5 or more partners              | 37 2 5.1%    | 246 1 0.4%     | 283 3 1.0%    |                |                |                |
| Missing                         | 9 0 0.0%     | 125 1 0.8%     | 134 1 0.7%    |                |                |                |
| Total                           | 218 7 100.0% | 1509 10 100.0% | 1727 17 10.0% |                |                |                |

Abbreviations: HIV, human immunodeficiency virus; P-QUAD, Postexposure Prophylaxis Pilot Program; PEP-LA, postexposure prophylaxis Los Angeles.
Table 3. Bivariate Fisher Exact Tests of PEP Regimen Characteristics by Serostatus for PQUAD, PEP-LA, and Both Programs, March 2010–July 2014 (n = 1744)

| PEP Regimen Characteristics | PQUAD Study | | PQUAD Study | | PQUAD Study | | PQUAD Study |
|-----------------------------|-------------|--|-------------|--|-------------|--|-------------|
|                             | HIV Negative | HIV Positive | Row% | HIV Negative | HIV Positive | Row% | HIV Negative | HIV Positive | Row% |
| Type of Initial Exposure    | P = .05     | | P = .15     | | P = .02     | | P = .26     | | P = .02     | | P = .005 |
| Anal receptive only         | 111         | 2          | 1.8% | 797         | 8          | 1.0% | 908         | 10          | 1.1% |
| Anal insertive only         | 68          | 1          | 1.4% | 445         | 0          | 0.0% | 513         | 1           | 0.2% |
| Anal receptive and insertive| 24          | 4          | 14.3%| 141         | 2          | 1.4% | 165         | 6           | 3.5% |
| Vaginal only                | 9           | 0          | 0.0% | 74          | 0          | 0.0% | 83          | 0           | 0.0% |
| Other                       | 5           | 0          | 0.0% | 45          | 0          | 0.0% | 50          | 0           | 0.0% |
| Missing                     | 1           | 0          | 0.0% | 5           | 0          | 0.0% | 6           | 0           | 0.0% |
| Type of initial exposure (collapsed) | P = .13 | | P = .53     | | P = .05     | | P = .001 |
| Anal receptive (any)        | 135         | 6          | 4.3% | 938         | 10         | 1.1% | 1073        | 16          | 1.5% |
| Insertive only or other     | 82          | 1          | 1.2% | 566         | 0          | 0.0% | 648         | 1           | 0.2% |
| Missing                     | 1           | 0          | 0.0% | 5           | 0          | 0.0% | 6           | 0           | 0.0% |
| Reported HIV Status of Initial Exposure | P = .08 | | P = .12     | | P = .004 |
| HIV positive                | 115         | 6          | 5.0% | 688         | 6          | 0.9% | 803         | 12          | 1.5% |
| HIV status unknown          | 96          | 1          | 1.0% | 804         | 4          | 0.5% | 900         | 5           | 0.6% |
| Missing                     | 7           | 0          | 0.0% | 17          | 0          | 0.0% | 24          | 0           | 0.0% |
| PEP Regimen                 | P = .08     | | P = .12     | | P = .0001 |
| TDF + FTC only              | 2           | 0          | 0.0% | 1490        | 9          | 0.6% | 1492        | 9           | 0.6% |
| TDF + FTC and LPV/r         | 148         | 2          | 1.4% | 6           | 0          | 0.0% | 152         | 2           | 1.3% |
| TDF + FTC and RAL           | 54          | 3          | 5.3% | 0           | 0          | N/A  | 54          | 3           | 5.3% |
| AZT + 3TC and LPV/r         | 13          | 2          | 13.3%| 0           | 0          | N/A  | 13          | 2           | 13.3% |
| AZT + 3TC only              | 0           | 0          | N/A  | 12          | 1          | 7.7% | 12          | 1           | 7.7% |
| AZT + 3TC and RAL           | 1           | 0          | 0.0% | 0           | 0          | N/A  | 1           | 0           | 0.0% |
| Missing                     | 2           | 0          | 0.0% | 1           | 0          | 0.0% | 3           | 0           | 0.0% |
| PEP regimen                 | P = 1.00    | | P = 1.00     | | P = .004 |
| 3 Drugs                     | 214         | 7          | 3.2% | 6           | 0          | 0.0% | 220         | 7           | 3.1% |
| 2 Drugs                     | 2           | 0          | 0.0% | 1502        | 10         | 0.7% | 1504        | 10          | 0.7% |
| Missing                     | 2           | 0          | 0.0% | 1           | 0          | 0.0% | 3           | 0           | 0.0% |
| Self-Reported Medication Adherence* | P = .67 | | P = .11     | | P = .04 |
| Complete adherence          | 108         | 4          | 3.6% | 1005        | 8          | 0.8% | 1113        | 12          | 1.1% |
| Incomplete adherence        | 41          | 2          | 4.7% | 62          | 2          | 3.1% | 103         | 4           | 3.7% |
| Missing                     | 69          | 1          | 1.4% | 442         | 0          | 0.0% | 511         | 1           | 0.2% |
| Repeat PEP User             | P = .44     | | P = .99     | | P = .26 |
| No                          | 149         | 6          | 3.9% | 908         | 6          | 0.7% | 1057        | 12          | 1.1% |
| Yes                         | 69          | 1          | 1.4% | 601         | 3          | 0.5% | 670         | 4           | 0.6% |
| Missing                     | 0           | 0          | 0.0% | 0           | 1          | 0.0% | 0           | 1           | 0.0% |
| Time From Initial Exposure to First PEP Dose* | P = .05 | | P = .14     | | P = .02 |
| Less than 2 hours           | 0           | 0          | 0.0% | 8           | 0          | 0.0% | 8           | 0           | 0.0% |
Approximately 2.5% of all individuals who reported methamphetamine use in the past year were seroconverters compared with only 0.8% of individuals who did not report using methamphetamine in the past year (P = .02) (Table 2). No differences were seen by either nitrate use (P = NS) or number of sexual partners in the 30 days before the PEP intake visit (P = .87).

The reported HIV exposure route was significantly different between seroconverters and non-seroconverters: 1.5% of individuals reporting any receptive anal intercourse were seroconverters compared with only 0.2% of individuals who reported insertive anal intercourse only and/or vaginal intercourse (P = .005) (Table 3). Individuals who self-reported a positive HIV status of their partner were more likely to convert (1.5%) compared with individuals who reported an unknown serostatus (0.6%) (P = .05). There was no significant difference in the number of seroconversions between individuals who used nPEP once and those who used nPEP multiple times during the analysis period (P = .26). Individuals who self-reported complete adherence to nPEP medication were less likely to seroconvert than those who reported incomplete adherence (P = .04).

There was also a significant difference between seroconverters and non-seroconverters in time from initial exposure to first nPEP dose. Individuals who received their first nPEP dose in the 72-hour window were more likely to seroconvert compared with individuals who received their first nPEP dose earlier in the 72-hour window (P = .02). The average time from exposure to first nPEP dose was 49.8 hours (standard deviation [SD] = 18.2 hours; median = 58.5 hours) in the nPEP seroconverter group compared with 38.5 hours (SD = 19 hours; median = 39.5 hours) in the non-seroconverter group.

The most common adverse events reported during nPEP treatment were fatigue (n = 228), diarrhea (n = 163), nausea (n = 150), and abdominal discomfort (n = 110) (Table 4). For individuals with data available, the presence of any adverse event was significantly associated with completion of regimen (P = .007).

Significantly more individuals seroconverted in the PQUAD program (3.2%) compared with the PEP-LA service delivery program (0.7%) (P = .004). Of the seroconverters, 7 (41%) reported a known re-exposure, 8 (47%) self-reported only condom-protected sex subsequent to the initial exposure, and 2 (12%) reported abstinence since the exposure (Table 5). Of the 10 who did not report subsequent condomless anal intercourse (CAI), 3 were diagnosed with an acute HIV infection (HIV NAAT positive, HIV rapid negative) at the 12-week follow-up visit.

**Multivariable Results**

In a multivariable model analyzing demographics, risk behaviors, and nPEP regimen characteristics, methamphetamine use in the past year (P = .03), self-reported medication adherence (P = .02), and time from initial exposure to first nPEP dose (P = .02) were significant predictors of seroconversion (Table 6). Individuals who reported methamphetamine use in the past year had a 3-fold greater odds of seroconversion (odds ratio [OR] = 3.23; 95% confidence interval [CI], 1.12–9.31)
compared with those who did not report methamphetamine use. In addition, the odds of seroconversion were approximately 4-fold higher among individuals who reported incomplete medication adherence compared with individuals who reported complete medication adherence (OR = 3.73; 95% CI, 1.2–11.56). Finally, individuals who initiated nPEP 48 hours or more after exposure had a 3-fold increased odds of seroconversion compared with those who initiated nPEP within the first 48 hours after exposure.

To our knowledge, this is the first study to demonstrate that delay in nPEP initiation for sexual exposures is associated with seroconversion. Wade et al [18] previously reported a similar trend among infants who received HIV prophylactic drugs to prevent mother-to-child transmission. Specifically, the authors found that for HIV-infected women who were untreated antepartum and intrapartum, infants who were administered zidovudine within 48 hours of birth and 72 hours or later had an HIV infection rate of 9.3% and 18.4%, respectively. In addition, a meta-analysis by Irvine et al [19] found that timing was associated with seroconversion in nonhuman primates (P = .03).

Besides advising potential nPEP users to seek treatment as soon as possible after exposure, we recommend that clinics offering nPEP modify their protocol to match New York State guidelines, which recommends that the first dose of medication be given at the beginning of the visit to minimize exposure-to-dose interval [20]. This procedure would (1) ensure that the first dose is taken correctly and (2) prevent unnecessary delay of the first dose that may be caused by collecting other laboratory specimens or performing risk assessments. Other novel delivery methods, such as nPEP initiation in nontraditional and potentially even nonmedical settings, should also be studied to ensure that the first dose is taken as soon as possible among nPEP candidates.

Table 4. Adverse Events Reported by Regimen for PQUAD and PEP-LA Clients, March 2010–July 2014 (n = 1744)*

| Symptom                  | TDF + FTC Only | TDF + FTC and LPV/r | TDF + FTC and RAL | AZT + 3TC and LPV/r | AZT + 3TC Only | AZT + 3TC and RAL | Total Number of nPEP courses |
|--------------------------|----------------|---------------------|-------------------|--------------------|---------------|-------------------|--------------------------|
| Fatigue                  | 174 12%        | 30 19%              | 18 32%            | 2 13%              | 3 23%         | 1 100%            | 228                      |
| Diarrhea                 | 80 5%          | 65 42%              | 14 25%            | 2 13%              | 1 8%          | 1 100%            | 163                      |
| Nausea                   | 101 7%         | 34 22%              | 11 19%            | 2 13%              | 1 8%          | 1 100%            | 150                      |
| Abdominal discomfort     | 81 5%          | 20 13%              | 6 11%             | 0 0%               | 3 23%         | 0 0%              | 110                      |
| Headaches                | 33 2%          | 4 3%                | 6 11%             | 1 7%               | 0 0%          | 0 0%              | 44                       |
| Dizziness                | 28 2%          | 2 1%                | 0 0%              | 0 0%               | 0 0%          | 0 0%              | 30                       |
| Sore throat              | 0 0%           | 0 0%                | 0 0%              | 0 0%               | 0 0%          | 0 0%              | 0                        |
| Cough                    | 0 0%           | 0 0%                | 0 0%              | 0 0%               | 0 0%          | 0 0%              | 0                        |
| Otherb                   | 68 5%          | 28 18%              | 17 30%            | 1 7%               | 1 8%          | 0 0%              | 115                      |
| None                     | 568 38%        | 3 2%                | 0 0%              | 0 0%               | 3 23%         | 0 0%              | 574                      |
| Missingc                 | 474 32%        | 64 42%              | 32 56%            | 10 67%             | 4 31%         | 0 0%              | 584                      |
| Total number             | 1501 100%      | 154 100%            | 57 100%           | 15 100%            | 13 100%       | 1 100%            | 1742                     |

Abbreviations: AZT, zidovudine; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; nPEP, nonoccupational postexposure prophylaxis; P-QUAD, Postexposure Prophylaxis Pilot Program; PEP-LA, PEP Los Angeles; RAL, raltegravir; TDF, tenofovir; 3TC, lamivudine.

aOnly adverse events reported on 15 or more occasions are listed; listed in order of frequency reported.

bThree PEP courses were missing data on the medication regimen.

cIncludes constipation, strange dreams, and dehydration.

dFor the PQUAD study, missing adverse events are equivalent to no adverse events.

*Sums may exceed the total because an individual could have experienced more than 1 adverse event; 3 individuals were missing data on regimen prescribed.
Table 5. PEP Regimen Characteristics, Type of Exposure, and Timing of Seroconversion for PEP Seroconverters, March 2010–July 2014 (n = 17)

| Seroconverter | Visit of Seroconversion | Condom Use at Exposure? | Time to PEP Initiation After Exposure (Hours) | Antiretroviral Therapya | Plasma HIV RNA Level at First-Identified Infection (Copies/mL) | Genotypeb | % Medication Adherence at 4-Week Visitc | Risk Behavior With Partners | At PEP Initiationd | After PEPe,f |
|---------------|-------------------------|-------------------------|-------------------------------------------|-------------------------|-------------------------------------------|----------------|----------------------------------------|-----------------------------|----------------|----------------|
| 1 PQUAD 12-week F/U | None used | 63.8 | TDF + FTC and LPV/r | 145000 | L10I | 100 | RAI and IAI | cRAI and cIAI (1) |
| 2 PQUAD 12-week F/U | None used | 40.8 | AZT + 3TC and LPV/r | 32500 | A71V | 100 | RAI and IAI | ncIAI and cRAI (1); cRAI (1) |
| 3 PQUAD 12-week F/U | None used | 26.1 | TDF + FTC and RAL | 1200000 | M36I, A71V | 90 | RAI | None |
| 4 PQUAD 12-week F/U | Broke/slipped off | 62 | TDF + FTC and LPV/r | 30900 | Polymorphisms only | 100 | RAI | cRAI and cIAI (1) |
| 5 PQUAD 12-week F/U | Broke/slipped off | 35.8 | TDF + FTC and RAL | 4810 | Wild type | 100 | RAI | cRAI and ncIAI (1) |
| 6 PEP-LA 12-week F/U | None used | 63.5 | TDF + FTC only | 2450000 | Polymorphisms only | Unk | RAI and IAI | cRAI (2); cRAI and cIAI (1) |
| 7 PQUAD 24-week F/U | None used | 64.5 | TDF + FTC and RAL | 56500 | PR: A71T | 100 | RAI and IAI | cRAI (1); cIAI (1) |
| 8 PQUAD 12-week F/U | None used | 67 | AZT + 3TC and LPV/r | 138000 | Wild type | 99 | RAI and IAI | cRAI (2); ncIAI (2) |
| 9 PEP-LA 12-week F/U | Broke/slipped off | 71 | TDF + FTC only | 11800 | Wild type | 100 | RAI | cRAI (1) |
| 10 PEP-LA 24-week F/U | Broke/slipped off | Unknown | TDF + FTC and LPV/r | Unknown | Polymorphisms only | 100 | RAI | cIAI (2) |
| 11 PEP-LA 24-week F/U | None used | 11.7 | TDF + FTC only | 1760000 | Not done | Unk | RAI and IAI | ncRAI (3) |
| 12 PEP-LA 12-week F/U | Broke/slipped off | 49.4 | TDF + FTC only | >10000000 | Wild type | 100 | RAI | cRAI (1) |
| 13 PEP-LA 24-week F/U | None used | 24.5 | TDF + FTC only | 93200 | Wild type | 100 | RAI | None |
| 14 PEP-LA 24-week F/U | None used | 36.5 | TDF + FTC only | 239000 | Wild type | Unk | RAI | ncIAI (3); cRAI (1) |
| 15 PEP-LA 24-week F/U | None used | 64 | AZT + 3TC only | 3680000 | Wild type | 75 | RAI | cRAI and cIAI (1) |
| 16 PEP-LA 24-week F/U | Broke/slipped off | 61.9 | TDF + FTC only | 34300 | Not done | 100 | RAI | ncRAI (1); cRAI (1) |
| 17 PEP-LA 12-week F/U | None used | 55.1 | TDF + FTC only | 125000 | Not done | 100 | RAI | ncRAI and ncIAI (1) |

Abbreviations: AZT, zidovudine; cIAI, insertive anal intercourse with a condom; cRAI, receptive anal intercourse with a condom; FTC, emtricitabine; F/U, follow up; HIV, human immunodeficiency virus; LPV/r, loprinavir/ritonavir; ncIAI, condomless insertive anal intercourse; ncRAI, condomless receptive anal intercourse; P-QUAD, Postexposure Prophylaxis Pilot Program; PEP, postexposure prophylaxis; PEP-LA, PEP Los Angeles; PR, protease; RAL, raltegravir; RNA, ribonucleic acid; TDF, tenofovir; Unk, unknown; 3TC, lamivudine.

aAntiretroviral therapy differences are mainly attributed to different drug dispensed between PQUAD and PEP-LA.

bAny mutations specified are PR mutations.

cAdherence measured differently between PQUAD (14-day recall) and PEP-LA (4-day recall).

dEvent that prompted enrollment in the PEP program.

fNumber denotes the number of acts of each type.
Furthermore, individuals who reported methamphetamine use in the past year were more likely to seroconvert, and there was a significant interaction between methamphetamine use and medication adherence. Notably, the interaction in the second model showed that individuals who reported methamphetamine use in the past year and were not adherent to medication had a 33% chance of seroconversion. This compares to a seroconversion rate of only 1% for those who either reported methamphetamine use alone or incomplete medication adherence alone. Frequency of methamphetamine use should be assessed, because more frequent or recurrent methamphetamine users may be better served for HIV prevention by sustained dosing via PrEP [21]. Although there is a paucity of data on adherence to daily PrEP among stimulant users, the pre-exposure prophylaxis initiative open label extension study did not find a significant difference in adherence between the small number of stimulant users and nonusers [22]. Triage mechanisms are needed that more accurately identify individuals at recurrent risk to determine (1) whether an nPEP or PrEP-based strategy is more appropriate for a given person or (2) for which patients an nPEP episode warrants a seamless transition from an nPEP course directly onto PrEP [23].

Table 6. Multivariate Logistic Regression Results for Demographic, Behavioral, and PEP Differences Between PEP Non-Seroconverters and PEP Seroconverters, March 2010–July 2014 (Complete Data Were Available on 831 nPEP Courses and 14 Seroconversions)

| Predictor                                           | Estimate | SE  | P Value | OR (95% CI) |
|-----------------------------------------------------|----------|-----|---------|-------------|
| Age Group (REF = 40–49)                             |          |     |         |             |
| <30                                                 | 0.47     | 0.90| .61     | 1.59 (0.27–9.31) |
| 30–39                                               | 0.92     | 0.86| .29     | 2.50 (0.46–13.58) |
| 50+                                                 | 2.25     | 0.99| .02     | 9.52 (1.37–66.21) |
| Race/ethnicity (REF = white)                        |          |     |         |             |
| Black                                               | 0.40     | 0.88| .65     | 1.49 (0.26–8.38) |
| Hispanic                                            | 0.36     | 0.53| .50     | 1.43 (0.51–4.01) |
| Education Level (REF = College Grad or Above)       |          |     |         |             |
| HS Grad or Below                                    | 0.55     | 0.60| .36     | 1.74 (0.54–5.61) |
| Methamphetamine Use in the Past Year (REF = No)     | 1.17     | 0.54| .03     | 3.23 (1.12–9.31) |
| Medication Adherence (REF = Complete Adherence)     |          |     |         |             |
| Incomplete Adherence                                | 1.32     | 0.58| .02     | 3.73 (1.20–11.56) |
| Reported HIV Status of Initial Exposure (REF = HIV Status Unknown) | 0.62 | 0.52 | .23 | 1.85 (0.67–5.10) |
| Time From Initial Exposure to First PEP Dose (REF = Less Than 48 Hours) | 1.12 | 0.50 | .02 | 3.08 (1.16–8.18) |
| Regimen Type (REF = Other)                          |          |     |         |             |
| TDF + FTC and RAL                                   | 0.50     | 0.36| .16     | 2.72 (0.68–10.95) |

Abbreviations: CI, confidence interval; FTC, emtricitabine; Grad, graduate; HIV, human immunodeficiency virus; HS, high school; nPEP, nonoccupational postexposure prophylaxis; OR, odds ratio; PEP, postexposure prophylaxis; RAL, raltegravir; REF, reference group; SE, standard error; TDF, tenofovir.

There were also noteworthy covariates that were not related to nPEP seroconversion such as race/ethnicity and previous nPEP use. The rate of seroconversion was marginally higher among black and Hispanic participants compared with whites, albeit not statistically significant. Coupled with our previous finding that nPEP access was lower among African Americans [16], future studies should evaluate how enhanced outreach and adherence counseling could improve both access to, and success using, nPEP in racial/ethnic minority populations. One previous study found that repeat nPEP participation was associated with eventual seroconversion [24], whereas 2 subsequent studies found no significant relationship [23, 25]. Nonoccupational postexposure prophylaxis may still be preferable as a prevention strategy to those whose risk is unplanned and infrequent.

This analysis has several limitations. First, adherence data were self-reported, and pill counts were not conducted for the PEP-LA program but were done for the PQUAD study. Second, the recall horizons for medication adherence were different between programs: 14 days for PQUAD and 4 days for PEP-LA. Therefore, we used a binary measure of complete versus incomplete instead of a continuous measure. In addition, adherence data for the PEP-LA program were not available for approximately 29% of courses due to missing data for the 2-week follow-up visit. Furthermore, recall bias and social desirability bias could have influenced data on baseline risk factors (eg, partner’s HIV status, condom use) and follow-up data on medication adherence as well as subsequent exposures for both seroconverters and non-seroconverters. Lastly, we used the Firth correction to accommodate the small number of seroconversions. However, there may be other adjustment procedures to account for the small sample size.

Finally, it is difficult to distinguish between true nPEP treatment failures and individuals who became HIV positive due to a re-exposure after nPEP initiation. Seven of the 17
seroconverters reported at least 1 subsequent instance of CAI during the 6-month follow-up period, and 3 were acute HIV infections. Given that this 2-week window is 10 weeks removed from the initial event that prompted nPEP, it is probable that these 3 individuals also had a re-exposure that may have led to seroconversion.

CONCLUSIONS
Although nPEP is a highly efficacious tool, it is often overshadowed by PrEP in discussions of biomedical HIV prevention. Although PrEP may be appropriate for individuals with consistent sexual risk, nPEP may be a more appropriate intervention for individuals with episodic or infrequent sexual risk. As the biomedical prevention era evolves, strategies that incorporate both nPEP and PrEP must be adopted to maximize the limited resources available for HIV prevention.

Supplementary Data
Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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