Original Investigation

Preexposure Prophylaxis for HIV Infection Integrated With Municipal- and Community-Based Sexual Health Services

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IMPORTANCE Several randomized clinical trials have demonstrated the efficacy of preexposure prophylaxis (PrEP) in preventing human immunodeficiency virus (HIV) acquisition. Little is known about adherence to the regimen, sexual practices, and overall effectiveness when PrEP is implemented in clinics that treat sexually transmitted infections (STIs) and community-based clinics serving men who have sex with men (MSM).

OBJECTIVE To assess PrEP adherence, sexual behaviors, and the incidence of STIs and HIV infection in a cohort of MSM and transgender women initiating PrEP in the United States.

DESIGN, SETTING, AND PARTICIPANTS Demonstration project conducted from October 1, 2012, through February 10, 2015 (last date of follow-up), among 557 MSM and transgender women in 2 STI clinics in San Francisco, California, and Miami, Florida, and a community health center in Washington, DC. Data were analyzed from December 18, 2014, through August 8, 2015.

INTERVENTIONS A combination of daily, oral tenofovir disoproxil fumarate and emtricitabine was provided free of charge for 48 weeks. All participants received HIV testing, brief client-centered counseling, and clinical monitoring.

MAIN OUTCOMES AND MEASURES Concentrations of tenofovir diphosphate in dried blood spot samples, self-reported numbers of anal sex partners and episodes of condomless receptive anal sex, and incidence of STI and HIV acquisition.

RESULTS Overall, 557 participants initiated PrEP, and 437 of these (78.5%) were retained through 48 weeks. Based on the findings from the 294 participants who underwent measurement of tenofovir diphosphate levels, 80.0% to 85.6% had protective levels (consistent with ≥4 doses/wk) at follow-up visits. African American participants (56.8% of visits; $P = .003$) and those from the Miami site (65.1% of visits; $P < .001$) were less likely to have protective levels, whereas those with stable housing (86.8%; $P = .02$) and those reporting at least 2 condomless anal sex partners in the past 3 months (88.6%; $P = .01$) were more likely to have protective levels. The mean number of anal sex partners declined during follow-up from 10.9 to 9.3, whereas the proportion engaging in condomless receptive anal sex remained stable at 65.5% to 65.6%. Overall STI incidence was high (90 per 100 person-years) but did not increase over time. Two individuals became HIV infected during follow-up (HIV incidence, 0.43 [95% CI, 0.05-1.54] infections per 100 person-years); both had tenofovir diphosphate levels consistent with fewer than 2 doses/wk at seroconversion.

CONCLUSIONS AND RELEVANCE The incidence of HIV acquisition was extremely low despite a high incidence of STIs in a large US PrEP demonstration project. Adherence was higher among those participants who reported more risk behaviors. Interventions that address racial and geographic disparities and housing instability may increase the impact of PrEP.

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In 2010, the Pre-exposure Prophylaxis Initiative (iPrEx) trial of preexposure prophylaxis (PrEP) for human immunodeficiency virus (HIV) infection used a combination of daily oral tenofovir disoproxil fumarate and emtricitabine to demonstrate an overall 44% reduction in HIV acquisition among men who have sex with men (MSM) and transgender women receiving PrEP and greater than 90% efficacy among those with detectable drug levels in blood samples.[1] After 2 additional randomized clinical trials demonstrated safety and efficacy,[2,3] this PrEP formulation was approved in the United States for the prevention of sexually acquired HIV infection in 2012.[4] Two recent studies of daily or intermittent PrEP among MSM[5,6] confirmed high PrEP efficacy.

Men who have sex with men account for more than two-thirds of new HIV infections in the United States and are the only risk group in whom infection rates are rising.[7] Clinics that treat sexually transmitted infections (STIs) and community-based clinics serving MSM are promising clinical sites for PrEP delivery,[8] yet little is known about PrEP use in these settings. Concerns have been raised regarding PrEP implementation, including risk compensation,[9,10] poor adherence,[11] drug resistance,[12] and safety and toxic effects.[13] We herein report results of the Demo Project, a prospective, open-label demonstration project assessing PrEP adherence, sexual practices, safety, and incidence of HIV and STI acquisition among MSM and transgender women in 3 US metropolitan areas heavily affected by HIV.

Methods

Study Design and Participants

The Demo Project enrolled participants from municipal STI clinics in San Francisco and Miami and a community health center in Washington, DC, from October 1, 2012, through January 23, 2014. The final follow-up occurred on February 10, 2015. These clinics have access to large populations of at-risk MSM, with annual HIV seroconversion rates of 2% or greater.[14] Participants were eligible if they were male at birth, were 18 years or older, were fluent in English or Spanish, had a negative rapid HIV antibody test result at screening and enrollment and a negative fourth-generation antibody-antigen test result at screening, and had a creatinine clearance rate of at least 60 mL/min (to convert to milliliters per second, multiply by 0.0167) and a urine dipstick test with negative or trace findings of protein. In addition, eligible participants reported any of the following in the preceding 12 months: condomless anal sex with at least 2 male or transgender female partners, at least 2 episodes of anal sex with at least 1 HIV-infected partner, or sex with a male or transgender female partner and having a diagnosis of syphilis, rectal gonorrhea, or chlamydia. We excluded individuals with serious active medical conditions, a history of pathologic fracture, or a positive finding for hepatitis B surface antigen or who used nephrotoxic medications. Race and ethnicity and sex assigned at birth and current gender identity were self-reported and each assessed using a 2-part question. We obtained written informed consent at screening, and eligible individuals returned for enrollment and were dispensed 1 month of tenofovir-emtricitabine. The sample size allowed us to estimate proportions within margins of sampling error of 4.4% and to detect adjusted odds ratios of 1.7 to 2.3 depending on the predictor and outcome prevalence.

Participants returned for clinic visits at 4, 12, 24, 36, and 48 weeks for HIV and STI testing, clinical monitoring, and PrEP dispensing. Participants were encouraged to return 4 weeks after stopping PrEP for a final evaluation and HIV test. Brief client-centered counseling was provided at all visits (eMethods 1 in the Supplement). Retention procedures were limited, with up to 3 contact attempts after a missed visit. Participants received $25 for each scheduled visit. Preexposure prophylaxis was discontinued in participants who underwent seroconversion, who received counseling, partner services, and linkage to HIV primary care. The tenofovir-emtricitabine PrEP, testing for HIV and STIs, and safety monitoring were provided free to participants. Among the 3 study sites, only the Washington, DC, site offered PrEP outside the Demo Project. The protocol was approved by the institutional review boards of the San Francisco City Clinic, Miami-Dade County Downtown STD Clinic, and Whitman-Walker Health.

Measures

PrEP Adherence and Engagement

Preexposure prophylaxis adherence was measured several ways. At each visit, scores on a self-reported adherence rating scale[15] were collected using an interviewer-administered questionnaire, pill counts were performed, and the medication possession ratio, defined as the number of dispensed pills divided by the number of days between visits,[16] was calculated. Dried blood spot (DBS) samples intended for measurement of tenofovir diphosphate (TFV-DP) concentrations (eMethods 2 in the Supplement) were collected at all scheduled follow-up visits and at any visit where PrEP treatment was stopped. Concentrations of TFV-DP were measured in approximately 100 randomly selected participants per site; in addition, a decision was made after completion of enrollment to perform TFV-DP DBS testing in all African American and transgender participants, who were underrepresented in the overall sample.

Engagement with PrEP at each visit was assessed using a 5-level ordinal measure in which the lowest level of engagement was missing the visit, and increasing levels of engagement were identified for those attending the visit based on the following TFV-DP concentration levels: below the limits of quantitation and less than 2 (<350 fmol/punch), 2 to 3 (350-699 fmol/punch), or at least 4 (≥700 fmol/punch) doses/wk. This categorization of TFV-DP concentrations was used in the iPrEx Open-Label Extension[17] and derived from previous pharmacokinetic modeling studies.[18]

Sexual and Drug-Use Behaviors and Depression

Sexual behaviors during the prior 3 months were assessed at screening and every 12 weeks using an interviewer-administered questionnaire, including the total number of anal sex partners and number of episodes of insertive and receptive anal sex (RAS) with and without condoms. Participants were also asked about the use of alcohol, marijuana, amyl nitrite or butyl nitrite (poppers), cocaine, amphetamines, heroin, seda-

tives, methylenedioxy-methamphetamine (MDMA, or ecstasy), and drugs used to treat erectile dysfunction in the past 3 months. *Polysubstance use* was defined as using 3 or more of the following: amyl nitrate or butyl nitrite, cocaine, amphetamines, club drugs (ketamine, MDMA, or sodium oxybate), and erectile dysfunction drugs.[19] Depressive symptoms were assessed using the Patient Health Questionnaire-2.[20]

HIV and STI Testing

Testing for HIV acquisition was performed at all visits using a rapid HIV antibody test (Clearview Stat-Pak/Complete; Chembio Diagnostics Systems, Inc) and a fourth-generation HIV antibody-antigen test (Architect; Abbott Diagnostics). In addition, participants at the San Francisco site underwent acute HIV screening with pooled HIV RNA (10 samples/pool) as standard practice in that clinic.[21] In the Miami and Washington, DC, sites, an individual HIV RNA screen (APTIMA [GenProbe Diagnositics] or TaqMan, version 2.0 [COBAS]) was performed at enrollment to screen for acute HIV infection. Those participants who demonstrated HIV seroconversion underwent HIV RNA viral load and resistance testing by genotyping and minor variant assays[22] (eMethods 3 in the Supplement). Urine specimens and rectal and pharyngeal swabs were tested quarterly for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* using a nucleic acid amplification test (APTIMA Combo-2; GenProbe Diagnostics). Serologic testing for syphilis was performed quarterly with a VDRL or rapid plasma reagin test and confirmed with a fluorescent treponemal antibody absorption test.

Safety Monitoring

A clinical assessment for adverse events was performed at all follow-up visits (eMethods 4 in the Supplement). Serum creatinine levels were measured at screening and quarterly, and the creatinine clearance rate was estimated using the Cockroft-Gault equation.[23]

Statistical Analysis

Data were analyzed from December 18, 2014, through August 8, 2015. All statistical analyses were performed using STATA software (version 13.1; StataCorp). Logistic models were used to assess baseline correlates of retention at 48 weeks. Our primary adherence outcome was having protective TFV-DP levels consistent with at least 4 doses/wk (eMethods 5 in the Supplement). We used a generalized estimating equation logistic model to evaluate baseline and time-dependent correlates of having protective TFV-DP levels at each follow-up visit. The factors associated with the outcome ($P < .10$) after adjustment for site and visit were retained in the final model. For analyses of adherence and PrEP engagement, participants with TFV-DP results were weighted to be representative of all those attending each visit. We assessed the association of PrEP engagement at week 4 with engagement at week 48 using a proportional odds model.[24] Trends in sexual behavior and drug use were evaluated using generalized estimating equation logistic and Poisson distribution models. Follow-up for the incidence of HIV and STI acquisition started at enrollment and ended at the last visit with an HIV or an STI test.

Results

Uptake for PrEP and baseline characteristics of the 557 participants in the Demo Project were described previously.[25] Overall, 132 participants (23.7%) had an HIV-seropositive primary partner at baseline, including 122 participants (92.4%) who had a partner receiving antiretroviral therapy and 107 (81.1%) who had a partner who was virally suppressed. However, 72 of 107 participants (67.3%) with a primary partner with viral suppression reported more than 1 anal sex partner in the past 3 months. At baseline, any recreational drug use was reported by 413 participants (74.1%); polysubstance use, by 112 participants (20.1%); amphetamine use, by 83 participants (14.9%); and injected drug use, by 9 participants (1.6%). Testosterone or anabolic steroid use was rare (14 participants [2.5%]).

Among the 557 enrolled participants, 25 (4.5%) had no follow-up visits, whereas 383 (68.8%) completed all 5 visits. Retention at week 48 included 437 participants (78.5%) overall and 232 (78.9%) among the 294 selected for TFV-DP testing; total follow-up was 481 person-years. Baseline correlates of retention at week 48 are shown in **Table 1**. After adjusting for site, prior PrEP knowledge and reporting of condomless RAS (ncRAS) at baseline were associated with being retained in the study.

PrEP Adherence and Engagement

Mean PrEP adherence was 81.6% by pill counts and 85.9% by the medication ratio, assessed in 533 participants. Self-rated adherence was very good or excellent at 1959 of 2242 visits (87.4%). Based on 1201 DBS samples provided by 294 participants who attended follow-up visits, TFV-DP concentrations were in the protective range among an estimated 86%, 85%, 82%, 85%, and 80% of participants at weeks 4, 12, 24, 36, and 48, respectively. In multivariable analyses, African American participants and those from Miami were less likely to have protective TFV-DP levels, whereas those who had stable housing and reported at least 2 condomless anal sex partners in the past 3 months were more likely to have protective levels (**Table 2**). Trajectories of drug concentrations over time are shown graphically (eFigure in the Supplement). Among 272 participants with at least 2 DBS samples tested, 170 (62.5%) had TFV-DP levels of at least 4 doses/wk at all visits tested and 8 (2.9%) had TFV-DP levels of less than 2 doses/wk at all visits tested.

Preexposure prophylaxis engagement (including visit attendance and PrEP adherence) varied by site and by race or ethnicity (both, $P < .001$) (**Figure 1**). Furthermore, engagement at week 4 strongly correlated with engagement at week 48 ($P < .001$, **Figure 2**). Preexposure prophylaxis was interrupted 86 times among 84 participants (15.1%) for reasons other than unavailability for or unwillingness to attend follow-up, HIV seroconversion, or study completion, for a mean of 65 days that accounted for 24% of their follow-up; PrEP was restarted in 15 of those 84 participants (17.9%). Interruptions were mostly owing to participant preference, including adverse effects (25 times), concern about long-term adverse effects (16 times), and low self-perceived risk for HIV acquisition (21 times). Among participants who stopped PrEP owing to low perceived risk, 10 of 16 participants with available data (62.5%) reported ncRAS at that visit.

Table 1. Baseline Characteristics of Participants Retained Through the End of Study

Characteristic	No. (%) of Participants[a]		*P* Value	
	Retained (n = 437)[b]	Not Retained (n = 120)	Unadjusted	Adjusted[c]
Site				
San Francisco, California	253 (84.3)	47 (15.7)	<.001	NA
Miami, Florida	98 (62.4)	59 (37.6)		
Washington, DC	86 (86.0)	14 (14.0)		
Age, y				
18-25	77 (68.8)	35 (31.3)	.009	.12
26-35	161 (77.0)	48 (23.0)		
36-45	115 (85.8)	19 (14.2)		
>45	84 (82.4)	18 (17.6)		
Race and/or ethnicity				
White	226 (85.0)	40 (15.0)	.002	.53
Latino	139 (72.4)	53 (27.6)		
African American	25 (62.5)	15 (37.5)		
Asian	21 (80.8)	5 (19.2)		
Other	26 (81.3)	6 (18.8)		
Sex				
Male	430 (78.5)	118 (21.5)	.65	.49
Transgender woman	5 (71.4)	2 (28.6)		
Other	2 (100)	0		
Educational level				
High school or less	55 (67.1)	27 (32.9)	.04	.41
Some college	119 (78.8)	32 (21.2)		
College graduate	156 (79.6)	40 (20.4)		
Any postgraduate	107 (83.6)	21 (16.4)		
Income, $				
<20 000	128 (69.6)	56 (30.4)	<.001	.07
20 000-59 999	158 (81.0)	37 (19.0)		
≥60 000	139 (87.4)	20 (12.6)		
Health insurance				
No	149 (71.6)	59 (28.4)	.002	.28
Yes	288 (82.8)	60 (17.2)		
Living situation				
Rent or own housing	362 (81.2)	84 (18.8)	.002	.07
Other (live with friends or family, live in public housing, or homeless)	75 (67.6)	36 (32.4)		
Referral status				
Self-referral	252 (84.6)	46 (15.4)	<.001	.08
Clinic referral	185 (71.4)	74 (28.6)		
Prior PrEP knowledge				
No	91 (64.1)	51 (35.9)	<.001	.01
Yes	346 (83.4)	69 (16.6)		
ncRAS in past 3 mo at baseline				
No	125 (68.3)	58 (31.7)	<.001	.002
Yes	312 (83.4)	62 (16.6)		
Postexposure prophylaxis use at baseline visit				
No	422 (78.4)	116 (21.6)	.96	.63
Yes	15 (78.9)	4 (21.1)		
Consumption of ≥5 alcoholic drinks/d when drinking in past 3 mo				
No	390 (79.1)	103 (20.9)	.30	.59
Yes	47 (73.4)	17 (26.6)		
Any recreational drug use in past 3 mo				
No	111 (77.6)	32 (22.4)	.78	.56
Yes	326 (78.7)	88 (21.3)		
Amphetamine use in past 3 mo				
No	366 (77.2)	108 (22.8)	.09	.35
Yes	71 (85.5)	12 (14.5)		
Polysubstance use in past 3 mo[d]				
No	343 (77.1)	102 (22.9)	.12	.36
Yes	94 (83.9)	18 (16.1)		
Injected drug use in past 3 mo				
No	430 (78.5)	118 (21.5)	.96	.55
Yes	7 (77.8)	2 (22.2)		
Use of testosterone or anabolic steroids in past 3 mo				
No	425 (78.3)	118 (21.7)	.51	.48
Yes	12 (85.7)	2 (14.3)		

Abbreviations: NA, not applicable; ncRAS, condomless receptive anal sex; PrEP, preexposure prophylaxis.

[a] Data for race and/or ethnicity were missing for 1 participant; for income, 19 participants; and for health insurance, 1 participant.

[b] Retained participants include those who completed their 48-week visit regardless of prior missed visits.

[c] Indicates adjusted for study site.

[d] Defined as use of 3 or more of the following substances in the past 3 months: amyl nitrite or butyl nitrite (poppers), club drugs (ketamine, methylenedioxy-methamphetamine [ecstasy], or sodium oxybate), cocaine, methamphetamine, or erectile dysfunction drugs.

Sexual and Drug Use Behaviors and STIs

The mean number of anal sex partners in the past 3 months declined from baseline to week 48 (10.9 to 9.3; *P* = .04). Three hundred sixty-five of 557 participants (65.5%) reported ncRAS at baseline, which remained stable during follow-up (*P* = .99) (**Figure 3**A). Overall numbers of RAS episodes in the past 3 months decreased (*P* = .007), driven by a decline in episodes with a condom (*P* < .001), whereas episodes without a condom remained stable (*P* = .73). Site differences in sexual risk trajectories were observed, with increases in ncRAS (214 of 300 [71.3%] to 187 of 247 [75.7%]) and mean number of ncRAS episodes (8.4 to 11) seen only in San Francisco (*P* < .05 for interaction for both). Use of any recreational drugs (*P* = .42) and amphetamines (*P* = .41), heavy use of alcohol (≥5 drinks/d; *P* = .81), and use of amyl nitrite or butyl nitrite (*P* = .59) were stable, whereas the use of powder cocaine (109 of 557 [19.6%] to 60 of 424 [14.2%]; *P* = .006) and club drugs (129 of 557 [23.2%] to 77 of 424 [18.2%]; *P* = .02) decreased.

Table 2. Correlates of TFV-DP Levels Consistent With Protection in Dried Blood Spot Samples[a]

Characteristic	No. of Participants Undergoing Testing[b]	Level Indicative of ≥4 Doses/wk, % of Visits[c,d]	OR (95% CI)[e]	*P* Value	AOR (95% CI)[f]	*P* Value
Site						
San Francisco, California	103	89.6	1 [Reference]	NA	1 [Reference]	NA
Miami, Florida	95	65.1	0.21 (0.12-0.37)	<.001	0.32 (0.17-0.60)	<.001
Washington, DC	96	88.5	0.89 (0.47-1.70)	.73	1.08 (0.54-2.19)	.82
Age, y						
18-25	62	77.5	1 [Reference]	NA	NA	NA
26-35	109	85.4	1.41 (0.78-2.56)	.25	NA	NA
36-45	70	82.6	1.28 (0.64-2.55)	.49	NA	NA
>45	53	87.4	1.97 (0.91-4.28)	.09	NA	NA
Race/ethnicity						
White	130	91.1	1 [Reference]	NA	1 [Reference]	NA
Latino	98	77.0	0.68 (0.35-1.30)	.24	0.81 (0.41-1.61)	.55
African American	33	56.8	0.22 (0.10-0.47)	<.001	0.28 (0.12-0.64)	.003
Asian	16	83.6	0.48 (0.13-1.80)	.28	0.72 (0.17-3.03)	.65
Other	17	82.4	0.43 (0.13-1.35)	.15	0.42 (0.13-1.38)	.15
Educational level						
High school or less	37	71.7	1 [Reference]	NA	NA	NA
Some college	79	79.9	1.08 (0.57-2.07)	.81	NA	NA
College graduate	178	87.7	1.76 (0.94-3.31)	.08	NA	NA
Income, $						
<20 000	99	77.2	1 [Reference]	NA	NA	NA
20 000-59 999	96	87.3	1.72 (0.97-3.06)	.06	NA	NA
≥60 000	88	87.0	1.12 (0.55-2.29)	.75	NA	NA
Health insurance						
No	108	74.0	1 [Reference]	.04	NA	NA
Yes	185	88.4	1.71 (1.03-2.85)			
Living situation						
Rent or own housing	68	86.8	2.32 (1.39-3.88)	.001	2.02 (1.14-3.55)	.02
Other (live with friends or family, live in public housing, or homeless)	226	69.7	1 [Reference]		1 [Reference]	
Referral status						
Clinic referral	150	77.3	1 [Reference]	.07	NA	NA
Self-referral	144	89.2	1.65 (0.97-2.83)			
Prior PrEP knowledge						
No	88	75.6	1 [Reference]	.95	NA	NA
Yes	206	86.1	0.98 (0.57-1.68)			
Depression						
PHQ-2 score <2[g]	261	83.4	1 [Reference]	.89	NA	NA
PHQ-2 score ≥2	33	85.0	0.96 (0.57-1.63)			
ncRAS in past 3 mo						
No	107	79.2	1 [Reference]	.37	NA	NA
Yes	187	86.0	1.22 (0.79-1.89)			
No. of ncRAS partners in past 3 mo						
0-1	105	75.1	1 [Reference]	.003	1 [Reference]	.01
≥2	189	88.6	1.95 (1.26-3.01)		1.82 (1.14-2.89)	
Consumption of ≥5 alcoholic drinks/d when drinking in past 3 mo						
No	265	83.9	1 [Reference]	.95	NA	NA
Yes	29	81.4	1.02 (0.54-1.92)			
Recreational drug use in past 3 mo						
No	89	78.8	1 [Reference]	.26	NA	NA
Yes	205	85.7	1.29 (0.83-2.00)			
Amphetamine use in past 3 mo						
No	253	82.8	1 [Reference]	.12	NA	NA
Yes	41	90.6	1.88 (0.85-4.18)			

Abbreviations: AOR, adjusted odds ratio; NA, not applicable; ncRAS, condomless receptive anal sex; OR, odds ratio; PHQ-2, Patient Health Questionnaire-2; PrEP, preexposure prophylaxis; TFV-DP, tenofovir diphosphate.

[a] Analysis includes all 294 participants who underwent measurement of TFV-DP levels at a given visit.

[b] For time-dependent covariates, distribution of participants reflects the first visit where TFV-DP levels were measured.

[c] Defined as protective level of TFV-DP.

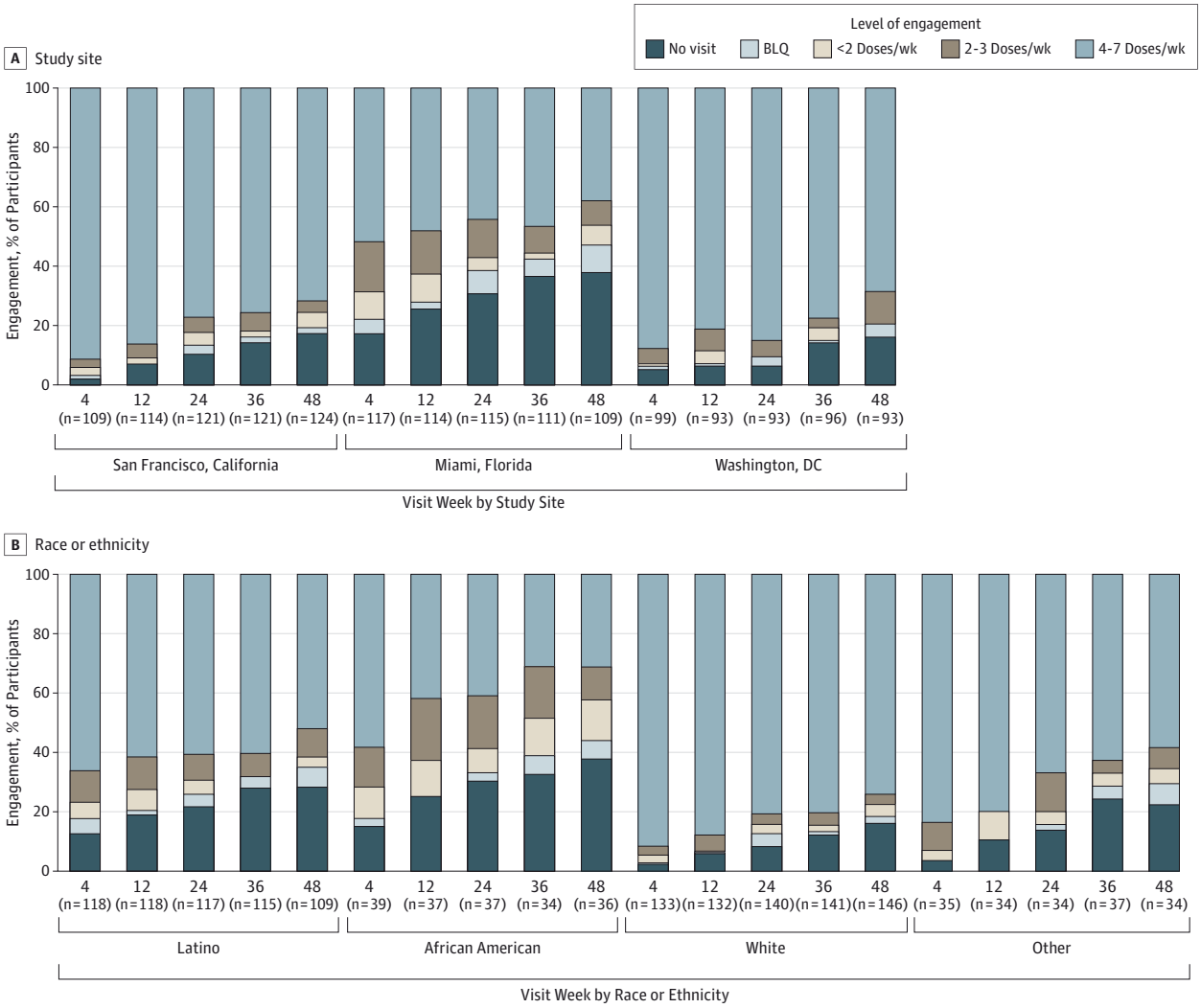
[d] Unadjusted prevalence of having TFV-DP levels consistent with at least 4 doses/wk, weighted by site to reflect the full cohort and calculated as the mean across weeks.

[e] Odds ratios adjusted for site only.

[f] Multivariable model included site, race or ethnicity, educational level, health insurance, housing status, referral status, number of condomless anal sex partners, and erectile dysfunction drug use.

[g] Scores range from 0 to 6, with scores greater than 2 indicating a positive screen finding for depression.

Figure 1. Distribution of Preexposure Prophylaxis Engagement by Visit Week



Engagement is a 5-level ordinal measure, with missing the visit as the lowest level of engagement and increasing levels of engagement based on estimated dosing frequency based on tenofovir diphosphate concentrations. Numbers indicate number of participants contributing data at each time point. Engagement varied by site and by race or ethnicity ($P < .001$). BLQ indicates below the limit of quantitation.

Overall, 147 participants (26.4%) had early syphilis, *N gonorrhoeae*, or *C trachomatis* at baseline, and 256 of 503 participants who had at least 1 follow-up STI evaluation (50.9%) were diagnosed as having at least 1 STI during follow-up. The proportion of participants who had early syphilis or infection with *N gonorrhoeae* or *C trachomatis* at the urethra, rectum, or pharynx during each visit interval is shown in Figure 3B. Positive findings for rectal and pharyngeal STIs decreased from baseline to week 24, then increased ($P < .05$). The incidence (95% CI) of STIs per 100 person-years was 48 (42-55) for *C trachomatis*, 43 (37-49) for *N gonorrhoeae*, 12 (9-16) for syphilis, and 90 (81-99) for any STI; in each case, the incidence was stable across quarterly intervals (all, $P > .10$).

HIV Seroconversions and Incidence

Three participants had acute HIV infection at enrollment. All three had negative rapid and antibody-antigen HIV test results at screening and enrollment and initiated PrEP. Two had a positive pooled HIV RNA finding at enrollment, and infection was subsequently confirmed by results of individual quantitative RNA testing. The third participant had a positive qualitative RNA test result at enrollment, which was confirmed by quantitative HIV RNA findings. One participant had a mixture of emtricitabine-resistant and wild-type viruses (M184MI) 1 week after enrollment, which was not present at enrollment, suggesting acquired resistance; this participant switched to combination antiretroviral therapy (consisting of tenofovir-emtricitabine, darunavir ethanolate, ritonavir, and raltegravir potassium) and has maintained virologic suppression. Viral load was insufficient to perform resistance testing in the second participant (120 copies/mL), and he has maintained virologic suppression with antiretroviral therapy. The third participant had no evidence of HIV resistance on results of standard or ultrasensitive minor variant testing, although testing was performed 6 weeks after PrEP discontinuation.

Two participants acquired HIV infection during follow-up, yielding an HIV incidence of 0.43 infections per 100 person-years (95% CI, 0.05-1.54). The first infection was detected approximately 19 weeks after enrollment. This participant reported last taking PrEP 37 days before seroconversion and had TFV-DP levels of less than 2 doses/wk at his seroconversion and all prior visits. The second seroconversion was detected approximately 4 weeks after the 48-week visit, when study drug was no longer dispensed. This participant had TFV-DP levels consistent with daily dosing only at week 4, dropping to less than 2 doses/wk or below the limits of quantitation thereafter. Neither participant had evidence of tenofovir-emtricitabine resistance on standard or ultrasensitive minor variant genotyping assays.

Safety

Nineteen serious adverse events were reported, 8 of which were psychiatric (suicidal ideation and/or attempt, bipolar disorder, or anxiety); none were assessed as related to the study drug. Twenty-three elevations of creatinine levels occurred in 13 of 557 individuals (2.3%), including 22 grade 1 and 1 grade 2 events. Only 3 elevations among 3 participants were confirmed on repeated testing results, and all resolved within 2 to 20 weeks without stopping PrEP. The PrEP regimen was discontinued in 3 participants owing to elevated creatinine levels; however, these elevations were not confirmed, and therapy was restarted in all cases. Two participants had grade 1 elevations of creatinine levels continuing at the end of the study. In one participant, the elevation was attributed to underlying mild renal disease and assessed as unrelated to the study treatment. In the other participant, the elevation was assessed as related, but the participant chose to continue PrEP with his primary care clinician after study completion. Twelve bone fractures were reported during the study. All but one (tooth fracture) were explained by trauma, and none were related to the study treatment.

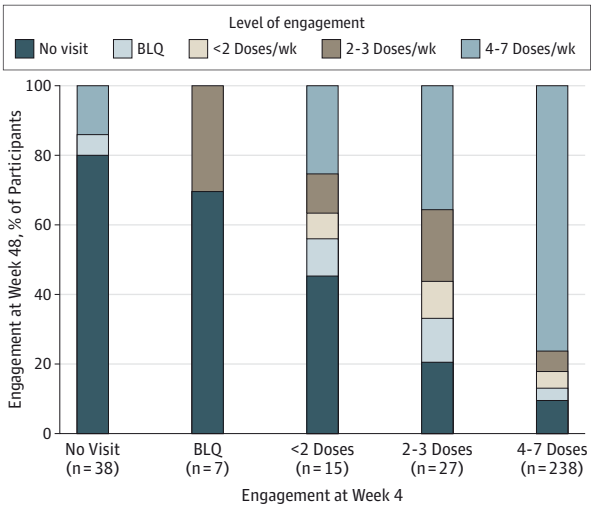
Discussion

Despite low adherence seen in some placebo-controlled PrEP trials,[26,27] we observed high adherence among MSM taking PrEP in this open-label demonstration project. The study drug was detected in nearly all participants who underwent testing, and more than three-quarters achieved levels associated with high levels of protection.[17,18] This higher adherence rate may be attributable to provision of open-label PrEP in a setting of known efficacy[28,29] and to growing community acceptance.[8] Greater adherence was observed among those reporting greater sexual risk, a finding that was also seen in the Global iPrEx Study[30] and the Partners PrEP Study[31] and is expected to increase the impact and cost-effectiveness of PrEP.[32,33] Adherence to PrEP was not diminished among people using alcohol or other recreational drugs.

Despite the achievement of most participants of protective PrEP levels, lower drug levels were observed among African American participants, those with unstable housing, and those at the Miami site. These disparities were not explained by other demographic characteristics, depression, or substance use. Racial differences in pharmacokinetics have not been fully evaluated, but small studies have not identified such differences to date.[34] Lower adherence to medication regimens has been reported among African Americans, including those with HIV infection,[35-38] diabetes mellitus,[39] hypertension,[40] and heart failure.[41] Other factors, including mistrust of health care professionals,[35] privacy concerns,[42] lower levels of health literacy,[39] and unmet medical and social structural needs,[43] may explain these disparities and warrant further exploration in future PrEP programs. African American MSM have high rates of HIV acquisition in the United States, highlighting the importance of customizing support for PrEP uptake and adherence for this population. Addressing structural barriers, including lack of insurance and access to supportive health care, will also be critical. Several studies are under way that evaluate novel PrEP delivery and support approaches in African American MSM, including a care coordination model in the ongoing HIV Prevention Trials Network 073 demonstration study (http://www.hptn.org/research_studies/hptn073.asp) and a mobile health adherence intervention in Enhancing PrEP in Communities.[44]

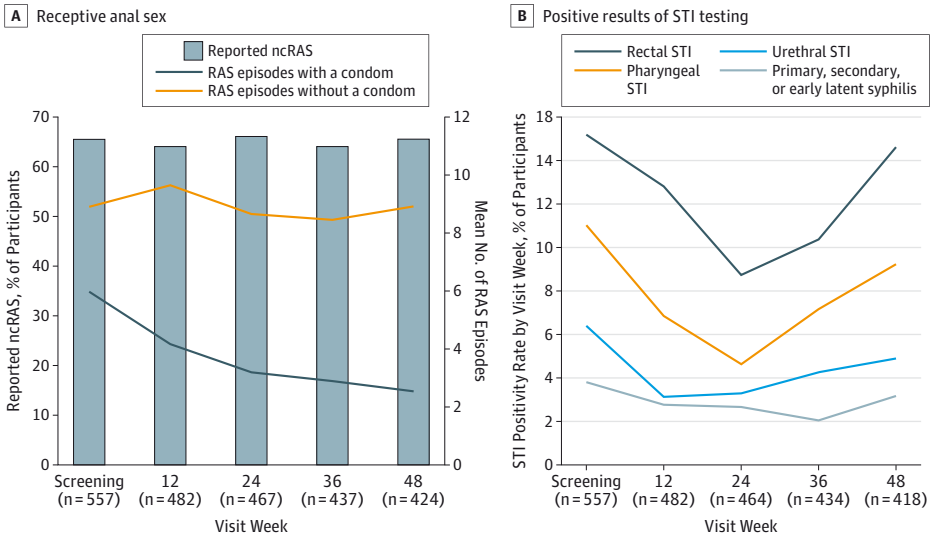
The reasons for lower retention and adherence in the Miami site are unclear. Although Miami participants were younger, were more likely to be Latino, and had lower educational levels,[25] these variables were not independently predictive in adjusted analyses; likewise, although PrEP awareness was lower in Miami, it did not predict retention there. Unmeasured factors, including transportation, social support, health literacy, acculturation, and community acceptance of PrEP, may help to explain this disparity.

Figure 2. Preexposure Prophylaxis Engagement at Week 48 by Engagement at Week 4



Proportion of participants with no visit attendance or with tenofovir diphosphate (TFV-DP) concentrations in dried blood spot samples in different adherence categories at week 48 are stratified by visit attendance and TFV-DP concentrations at week 4. This analysis includes 325 participants, 287 of whom underwent measurement of TFV-DP levels at week 4 and 38 of whom missed the week 4 visit. Engagement at week 4 strongly correlated with engagement at week 48 ($P < .001$). BLQ indicates below the limit of quantitation.

Figure 3. Sexual Behaviors and Sexually Transmitted Infections (STIs) in the Demo Project



A, Participants reporting condomless receptive anal sex (ncRAS) and mean number of RAS episodes with and without a condom. B, The positive STI findings by anatomic site include *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections and syphilis. The week 48 visit includes testing performed at the optional follow-up visit 4 weeks after week 48.

Early engagement, measured by clinic attendance and PrEP adherence at week 4, was highly predictive of engagement at the end of the study, highlighting the importance of early assessment and support of adherence. Specifically, early monitoring, such as testing for drug levels, could be useful in identifying those who need additional support.[45] Reductions in the cost and turnaround time of DBS testing would facilitate implementation.

A substantial minority of participants reported 1 or more interruptions in PrEP. Adverse effects were the most common reason, suggesting the need for additional education and support on the safety and tolerability of tenofovir-emtricitabine. Elevations of creatinine levels were uncommon, mostly unconfirmed, and managed with regular monitoring. Although therapy was discontinued 21 times owing to low self-perceived risk, most of these participants reported recent sexual risk. Strategies to improve risk perception, including online risk assessment tools[46] and sexual diaries,[47] may improve decisions about starting and stopping PrEP.

Despite a high incidence of STI acquisition and reported risk behaviors, we observed a very low incidence of HIV acquisition (0.43 infections per 100 person-years), with only 2 incident infections. Both participants had low or undetectable TFV-DP levels, a pattern seen in the recent Preexposure Option for Reducing HIV in the UK (PROUD)[5] and On Demand Antiretroviral Pre-exposure Prophylaxis for HIV Infection in Men Who Have Sex With Men (IPERGAY)[6] PrEP trials. These studies, with similarly high reported risk and STI prevalence and high HIV incidence in the placebo arms (8.9 and 6.8 per 100 person-years in the PROUD and IPERGAY studies, respectively), demonstrated high levels of PrEP efficacy (86%) and low numbers needed to treat (13 and 18 in the PROUD and IPERGAY studies, respectively). The low HIV incidence observed in the Demo Project likely reflects high overall adherence to PrEP and demonstrates that high levels of effectiveness can be achieved outside controlled studies. Three acute HIV infections were detected by HIV RNA at enrollment. Testing for HIV RNA at PrEP initiation would help to detect early infection and facilitate early initiation of antiretroviral therapy.

We observed high STI positivity rates at baseline and during follow-up, but the STI incidence was stable over time. The initial decline of rectal and pharyngeal STIs followed by an increase may reflect clearance of prevalent infections at screening, regression to the mean, cohort and seasonal effects, and/or risk compensation. High STI rates were also observed among MSM in the PROUD and IPERGAY studies.[5,6] Although current PrEP guidelines by the Centers for Disease Control and Prevention recommend STI testing every 6 months,[48] we recommend quarterly screening for MSM taking PrEP, including testing at extragenital sites.

This study had several limitations. First, African American and transgender persons were underrepresented in the sample, reflecting underrepresentation at the participating clinics. This underrepresentation highlights the need for additional strategies to engage these populations and to deliver PrEP in settings in which these individuals feel comfortable and safe receiving care. For example, integration of PrEP into transgender health care, including provision of cross-sex hormone treatments, may increase uptake in that population.[49] Second, although we conducted this study in 3 diverse US clinics, these results may not generalize to the broader MSM population in these cities, other parts of the United States, or international settings. Finally, although this project sought to assess PrEP use in clinical settings where medication and monitoring were provided for free, cost and lack of insurance coverage may present significant barriers to PrEP access and adherence outside of a study, particularly in states with weak safety nets.[50] Strategies to increase affordability are critical to ensuring PrEP access to all individuals at risk for HIV. Cost-effectiveness studies of different PrEP delivery models are also needed to inform PrEP implementation.

Conclusions

The incidence of HIV acquisition was extremely low despite a high incidence of STIs in the study population. Adherence was higher among those participants with more reported risk behaviors. These results provide support for expanding PrEP implementation in MSM in similar clinical settings and highlight the urgent need to increase PrEP awareness and engagement and to develop effective adherence support for highly affected African American and transgender populations.

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