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Sexual risk behavior among HIV-uninfected men who have sex with men (MSM) participating in a tenofovir pre-exposure prophylaxis (PrEP) randomized trial in the United States

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Abstract

Objective—To evaluate for changes in sexual behaviors associated with daily pill-use among MSM participating in a PrEP trial.

Design—Randomized, double-blind, placebo-controlled trial. Participants were randomized 1:1:1:1 to receive tenofovir disoproxil fumarate or placebo at enrollment or after a 9-month delay and followed for 24 months.

Methods—400 HIV-negative MSM reporting anal sex with a man in the past 12 months and meeting other eligibility criteria enrolled in San Francisco, Atlanta, and Boston. Sexual risk was assessed at baseline and quarterly visits using Audio Computer-Assisted Self-Interview. The association of pill-taking with sexual behavior was evaluated using logistic and negative-binomial regression for repeated measures.

Results—Overall indices of behavioral risk declined or remained stable during follow-up. Mean numbers of partners and proportion reporting unprotected anal sex (UAS) declined during follow-

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Conflicts of Interest
For the remaining authors, no conflicts of interest were declared.

Disclaimers:
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. In addition, the views expressed herein do not necessarily reflect the official policies of the City and County of San Francisco; nor does mention of the San Francisco Department of Public Health imply its endorsement.

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up ($p<0.05$), and mean UAS episodes remained stable. During the initial 9 months, changes in risk practices were similar in the group that began pills immediately vs. those in the delayed arm. These indices of risk did not differ significantly after initiation of pill-use in the delayed arm or continuation of study medication in the immediate arm. Use of poppers, amphetamines, and sexual performance-enhancing drugs were independently associated with one or more indices of sexual risk.

Conclusions—There was no evidence of risk compensation among HIV-uninfected MSM in this clinical trial. Monitoring for risk compensation should continue now that PrEP has been shown to be efficacious in MSM and other populations and will be provided in open-label trials and other contexts.

Keywords

risk compensation; behavioral disinhibition; sexual risk behavior; PrEP; MSM

INTRODUCTION

Pre-exposure prophylaxis (PrEP), or the use of antiretroviral medicines by HIV-uninfected individuals, is a rapidly emerging prevention strategy that could help reduce HIV incidence globally. In 2010, the iPrEx trial demonstrated a 44% reduction in HIV infections among men who have sex with men (MSM) who received daily oral emtricitabine/tenofovir (FTC/TDF) vs. a placebo pill [1]. More recently, data on PrEP in heterosexual populations have been reported [2]. While the FEM-PrEP trial evaluating daily oral FTC/TDF and the oral/topical tenofovir arms of the VOICE study, both in African women, were terminated early because of futility [3–5], the Partners PrEP study [6] in Kenya and Uganda and the CDC Botswana PrEP trial [7] found PrEP to be over 60% efficacious in heterosexual men and women at risk for HIV infection. Based on these results, the Centers for Disease Control and Prevention (CDC) issued interim guidance on PrEP use among MSM and heterosexually active adults in the United States (US) [8, 9], and the Food and Drug Administration approved FTC/TDF as PrEP in July 2012 [10]. In all trials to date, participants have been provided a comprehensive package of prevention services including risk-reduction counseling, regular HIV testing, and management of sexually transmitted infections.

While there is enthusiasm for PrEP as a novel HIV prevention approach, some have expressed concerns that the availability of a pill or gel for prevention could increase risk behavior, leading to increased HIV infections and undermine PrEP's protective benefits [11–13]. Conversely, daily PrEP could promote safer-sex behaviors by reminding people of their vulnerability to HIV and/or fostering a "preventionist" identity (e.g., one who cares about reducing one's HIV risk) [13]. Several mathematical models show that the beneficial impact of PrEP may be offset by small increases in risk behavior and could lead to an increase in new infections, particularly in scenarios of low effectiveness and coverage [14–16], while decreases in risk behavior associated with a biomedical prevention intervention could lead to synergistic reductions on population-level HIV incidence [14],[17].

The evidence for risk compensation in previous trials of HIV prevention interventions is mixed. Chesney et al. demonstrated an increase in unprotected anal sex among HIV vaccine trial recipients, and in two male circumcision trials, mean sexual contacts [18] and rates of unprotected sex [19] were higher in the circumcised vs. uncircumcised group. Conversely, Bartholow et al. observed a decrease in unprotected anal sex among MSM in the Vax004 trial [20], and Guest and colleagues found a decrease in number of sexual partners and rates of unprotected sex in a PrEP trial among high-risk women in West Africa [21]. Reported risk behaviors also declined in CAPRISA 004 [22], iPrEx [1], and Partners PrEP [6].

One limitation of these trials is that both the control and intervention arm participants receive a pill, gel, or vaccine. Without a comparison group receiving no product, it is difficult to assess the direct effect of the intervention on risk behavior, since risk often declines as individuals enroll in a prevention trial and are provided frequent risk-reduction counseling and HIV testing. Therefore, in designing the US CDC Safety Study of daily TDF among MSM, we incorporated a wait-list control design in which half of the study cohort initiated pill use at enrollment, and the other half after a 9-month delay. This study design allowed for a more direct evaluation of the effect of pill-taking on sexual practices. We evaluate the effect of daily pill-taking on risk practices through a comparison of risk behavior in the immediate vs. delayed arms during the first 9 months of the study and describe how risk patterns changed within arms over the remainder of this 24 month study. We also evaluate correlates of reported risk behavior in this cohort, including substance use which has been associated with increased HIV risk among HIV-uninfected MSM in other studies. [23–25]

METHODS

Clinical trial

The US CDC Safety Study was a phase-2 randomized, double-blind, placebo-controlled extended safety trial of TDF in MSM in the US. The trial was conducted at sites in Atlanta (n=121 enrolled), Boston (n=79), and San Francisco (n=200). Participants were randomized 1:1:1:1 to one of 4 arms: 1) daily TDF beginning at enrollment; 2) daily placebo beginning at enrollment; 3) daily TDF beginning 9 months after enrollment; 4) daily placebo beginning 9 months after enrollment (figure 1). The sample size was chosen to provide >80% power to detect ≥12% differences in outcomes between groups assuming ≥28% reported this behavior in the delayed arm.

MSM at risk for HIV infection were enrolled from February 2005 to July 2007. Eligibility criteria included being male at birth, 18–60 years old, HIV-1 negative, healthy (no serious or life-threatening diseases or conditions and adequate hematologic, biochemical, hepatic, and pancreatic function by laboratory testing), able to understand English and provide written informed consent at screening, and reporting any anal sex with or without a condom with a man in the last 12 months (including main or casual partners). Men in a mutually monogamous relationship for ≥ 1 year with a known HIV-negative partner were excluded. Transgender women who met eligibility criteria were included in the study.

Volunteers were tested for HIV antibody at screening using a rapid HIV test kit; HIV seropositive men were not enrolled and were referred to medical care. Enrolled participants attended study visits every 3 months over a 2-year period and received HIV testing, risk-reduction counseling, free condoms and lubricants, and assessments of biomedical and behavioral safety, adherence, and acceptability. Study staff regularly counseled men that the efficacy of TDF for prevention was unknown, reminded participants they might be receiving a placebo, and reinforced the importance of maintaining safer-sex practices.

Structured Interview

All participants were administered a structured questionnaire using Audio-Computer Assisted Self-Interview (ACASI) at enrollment and each quarterly follow-up visit.

Sexual behavior and substance use—At baseline and every 3 months, participants were asked about their number of male sexual partners (including oral or anal sex) in the past 3 months for each of 3 partner types: known HIV-positive and HIV–negative partners and partners of unknown HIV serostatus. Study participants were also asked about the

number of times they engaged in insertive and receptive anal sex with and without using condoms during the prior 3 months, grouped by HIV serostatus of the partner. At baseline and quarterly follow-up visits, participants were also asked about their substance use in the past 3 months, including alcohol, poppers, cocaine, amphetamines, sedatives, and Ecstasy.

Perceived Treatment assignment—At semi-annual visits beginning at the 6-month visit for the immediate arms and the 12-month visit for the delayed arms, participants were asked which treatment group they believed they were in using the following worded choices: "I strongly think I am in the TDF (or placebo) group"; "I somewhat think I am in the TDF (or placebo) group"; and "don't know." The two TDF and two placebo categories (strongly/somewhat think) were grouped together for analysis. Consistency of responses was assessed by constructing a single variable indicating that participants consistently thought they had received TDF or placebo; consistently reported they didn't know their treatment assignment; or inconsistently perceived treatment assignment across all visits when treatment assignment was assessed and data were non-missing.

Perceived PrEP efficacy—At baseline and every 6 months, perception of PrEP efficacy was evaluated by the question, "How good do you think tenofovir is in preventing HIV infection?" Responses were based on a 0–10 scale where 10 means it prevents HIV infection all the time, 0 means it doesn't prevent HIV infection at all, and 5 means it prevents HIV half of the time. For multivariable analyses, this variable was collapsed into 4 a priori categories: 0–3 (low), 4–6 (moderate), 7–10 (high), and "didn't know." Data on perceived PrEP efficacy were collected before the release of efficacy data from other PrEP trials (e.g. iPrEx, Partners PrEP, CDC Botswana Study) and were not influenced by those results.

Data Analyses

To take advantage of our study design with pill use initiation deferred in the delayed arm, we analyzed risk practices reported at baseline, during months 3–9, when delayed arm participants were off study drug, and during months 12–24, when all subjects were given study drug. Finding no evidence in preliminary analysis of unblinding (see results section), we pooled data for the subgroups assigned to TDF and placebo within the immediate and delayed arms.

Primary outcome measures included numbers of partners and unprotected anal sex (UAS) with either a primary or casual partner in the past 3 months, both overall and by partner serostatus. We first estimated overall trends across groups (immediate vs. delayed arms) for each of these risk practices during months 3–9 and months 12–24 of follow-up. We then evaluated group-specific trends as well as baseline differences between the immediate and delayed arms using a model adjusting for period (months 3–9 vs. 12–24) and interaction between period and study arm (immediate vs. delayed). To assess risk compensation due to initiation of study drug, we compared changes in risk behavior from baseline to months 3–9 in the immediate vs. delayed arms using this model. We also assessed within-group changes in risk practices between months 3–9 and months 12–24 to assess the effects of initiating pill use in the delayed arm at the 9 month visit, and of continuing pill use (months 9–24) in the immediate arm. All these analyses were by intention-to-treat, without regard to study drug adherence during periods of assigned use.

We used negative binomials models for numbers of partners and UAS episodes and logistic regression for any UAS. To account for within-subject correlation as well as over-dispersion of the count outcomes, these models were fitted using generalized estimating equations (GEE) with exchangeable working correlation matrix and robust standard errors.

Finally, we identified independent risk factors for risky behavior using multivariable negative binomial and logistic GEE models. In these analyses, potential risk factors were first screened using models controlling for treatment group and period, keeping variables with $p<0.1$; final models were then selected using backward deletion with a retention criterion of $p<0.2$. All analyses were conducted using Stata Version 12.

RESULTS

Participant haracteristics

Four hundred sexually active MSM enrolled. Over a quarter of participants were non-white (African-American, Asian/Pacific-Islander, or other race) and 9% Hispanic/Latino (table 1). Almost half (45%) reported moderate or heavy alcohol use, over a quarter reported use of poppers (27%) or sexual enhancing drugs (28%), and 11% reported amphetamine use in the past 3 months. Demographics and the proportion of men reporting alcohol/drug use were similar between the immediate vs. delayed arms. Overall study retention was high, with 16% (16.5% in the immediate and 15.5% in the delayed arm) lost to follow-up; rates of early study discontinuation were similar between arms.

Perceived Treatment Assignment and PrEP Efficacy

Perceptions of treatment assignment by study visit are shown in Figure 2a. At the 6-month visit (immediate arm only), a quarter (25%) of men believed they were assigned to TDF, about a quarter (23%) believed they were assigned to placebo, and approximately half (52%) reported that they did not know their treatment assignment. At the 12-month visit (including both immediate/delayed arms), 26% perceived they were assigned to TDF, 26% placebo, and 46% didn't know. Overall, about a quarter (24%) of study participants consistently stated that they did not know their treatment assignment, 12% consistently thought they had been assigned to TDF, and 11% consistently believed they had been assigned to placebo. Perceptions were not consistent for the remaining 53% participants. Participants assigned to TDF were equally or more likely to predict they were assigned to placebo than to TDF; the opposite was true for placebo participants, suggesting that there was no substantial degree of unblinding.

Perceptions of PrEP efficacy increased over time (Figure 2b). At baseline, 11% believed TDF had high efficacy, 19% believed TDF had moderate efficacy, 31% believed that TDF had low efficacy, and 39% reported they didn't know the efficacy of PrEP. At the 24-month visit, 31% believed that TDF had high efficacy, 33% moderate efficacy, 23% low efficacy, and 13% reporting they didn't know (p-value for trend < 0.00005).

Numbers of male sex partners

At baseline, there were no significant differences in self-reported numbers of male sex partners in the past 3 months between the immediate vs. delayed arms ($p=0.68$). Overall, mean numbers of sex partners (per subject, in the past 3 months) decreased significantly from 7.25 at baseline to 6.02 during months 3–9 and 5.71 during months 12–24 ($p<0.001$). These declines were similar between the immediate vs. delayed arms during months 3–9 (p for interaction=0.67) (see figure 3a). Furthermore, the mean number of partners did not differ in months 12–24 vs. months 3–9 with initiation of study drug in the delayed arm (IRR 0.93, $p=0.22$) or continuation of drug in the immediate arm (IRR 0.96, $p=0.56$).

When analyzed separately by partner HIV serostatus, the mean number of partners reported in the last 3 months also decreased from baseline or remained stable. Mean numbers of positive or unknown HIV-status partners declined from 4.17 at baseline to 3.51 during months 3–9 ($p=0.04$) and 3.37 during months 12–24 ($p=0.01$). The mean number of HIV-

negative partners decreased significantly from baseline (3.11) to months 3–9 (2.52, p=0.03) and months 12–24 (2.32, p=0.002). Furthermore, the proportion of participants reporting an HIV-positive sex partner decreased during follow-up (30% at baseline vs. 25% during months 3–9 (p=0.006) and 27% during months 12–24, p<0.03). There was a greater decrease in mean HIV-negative partners in the immediate vs. delayed arms during months 3–9 (IRR 0.64, p for interaction=0.01); changes from baseline to months 3–9 did not differ significantly by immediate vs. delayed arms for positive/unknown status partners (p=0.14) or proportion reporting an HIV-positive partner (p=0.73).

Correlates of number of partners in the past 3 months are shown in table 2 (left side of table). Use of poppers and sexual-enhancing drugs such as sildenafil and higher perception of PrEP efficacy were associated with higher number of partners after controlling for study period, being assigned to take pills, site, age, race/ethnicity, education, and perception of treatment assignment; amphetamine use was marginally associated with a greater number of partners (p=0.07).

Unprotected anal sex (UAS)

At baseline, over half (57%) of men reported engaging in any UAS in the past 3 months (table 1). These proportions were similar between the immediate vs. delayed arm (p = 0.29). Overall, the proportion of men engaging in UAS decreased from baseline (57%) to months 3–9 (48%, p=0.001) and months 12–24 (52%, p=0.03). The change in proportion of men reporting UAS from baseline to months 3–9 was similar between the immediate vs. delayed arms (p for interaction = 0.15)(see figure 3b). The proportion of men reporting UAS did not change significantly after initiation of study drug in the delayed arm (p=0.41) but may have increased slightly with continuation of drug in the immediate arm (IRR 1.17, 95% CI 0.98–1.39, p=0.09).

The proportions reporting any unprotected anal sex with an HIV-positive or unknown HIV-status partner (UASPU) also declined during study follow-up (29% at baseline, vs. 21% during months 3–9 and 22% during months 12–24, p<0.001). Declines in UASPU from baseline did not differ by immediate vs. delayed arms during follow-up (overall p for interaction=0.43). The proportion of men reporting UASPU did not significantly change after initiation of study medication in the delayed arm (p=0.55) or continuation of study medication in the immediate arm (p=0.60).

In the multivariable analysis (table 2, middle columns), correlates of reporting any UAS included younger age and use of poppers, amphetamines, or sexual performance enhancing drugs, after adjusting for being on pills, site, race/ethnicity, education, and perception of treatment assignment and PrEP efficacy. UAS significantly declined during the first 3–9 months after adjustment for these factors.

Episodes of unprotected anal sex

At baseline, the mean number of episodes of UAS (per subject, in the past 3 months) reported at baseline was 4.78, with a marginally significantly greater number of episodes in the immediate vs. delayed arms (5.79 vs. 3.78 episodes respectively, p=0.08). Overall, mean episodes of UAS did not change significantly from baseline during months 3–9 (p=0.98) and months 12–24 (p=0.28). Furthermore, UAS episodes did not differ significantly between immediate vs. delayed arms during months 3–9 (p=0.10) and did not change significantly after initiation of study drug in the delayed group (p=0.42) or with continuation of drug in the immediate arm (p=0.22).

Mean UAS episodes with a positive or unknown HIV status partner (UASPU episodes) remained stable or decreased during follow-up (2.02 at baseline vs. 1.51 during months 3–9

(p=0.22) and 1.37 during months 12–24 (p=0.05)). Overall, UASPU episodes were similar in the immediate vs. delayed arms during months 3–9 (p value for interaction=0.29). In contrast, numbers of UAS episodes with HIV-negative partners increased during follow-up, especially during months 12–24 (2.75 episodes at baseline vs. 4.00 at 12–24 months, p=0.01), but the patterns were similar in the immediate vs. delayed arms (p for interaction=0.42).

In multivariable analyses, greater mean numbers of UAS episodes was associated with use of sexual-enhancing drugs. Fewer UAS episodes were reported in African American men, at the Boston site, and among those who believed they were taking TDF.

DISCUSSION

We found no evidence of risk compensation among at-risk MSM initiating PrEP in this trial. In particular, mean numbers of partners and proportion of men reporting UAS decreased significantly from baseline during 24 months of follow-up, and declines were similar in the immediate vs. delayed arms. Episodes of UAS remained stable over time. Furthermore, there was little or no increase in these risk indices after initiation of study drug. These findings are consistent with other studies showing a similar reduction of risk practices with initiation of a biomedical prevention strategy within a clinical trial [1],[22],[21]. As in previous trials, men in this study received risk-reduction counseling, condoms and lubricants, regular HIV/STI testing, and linkage to prevention services (including substance use treatment) which may explain the observed risk declines and could mitigate any potential for risk compensation.

We also analyzed changes in risk practices by HIV serostatus of the participants' partners. For positive and unknown HIV-status partners, all risk indices decreased during follow-up. These declines were similar in the immediate vs. delayed arms during months 3–9 and did not increase in the delayed arm with drug initiation. For HIV-negative partners, mean numbers of partners declined significantly during follow-up. Episodes of UAS with HIV-negative partners increased during follow-up, especially during months 12–24, in both immediate and delayed arms. Given that episodes of UAS with HIV-negative partners began increasing in the delayed arm prior to pill initiation and increased in both arms during months 12–24, these findings most likely represent secular behavioral trends in this cohort, rather than risk compensation due to pill initiation; these changes may reflect a possible increase in seroadaptive practices, in which men preferentially have more episodes of UAS with assumed HIV-negative partners.

In our multivariable analyses, we found that substance use (including poppers, amphetamines, and sexual-enhancing drugs) was associated with increased reported risk. Drug use remained stable throughout the study (data not shown) and therefore did not explain overall decreases in overall partner number and UAS in this cohort. Services to link substance-using MSM into counseling and treatment should be considered in future PrEP programs. Future trials focusing on substance-using MSM should be conducted to provide additional clinical and behavioral safety data on PrEP use in this group. We also found younger men were more likely to engage in UAS. Young MSM, particularly African American MSM, have recently experienced significant increases in HIV incidence [26] and may be a target population for PrEP; counseling and other strategies to help reduce risk and support PrEP adherence will be important in this population. Our finding that African-American MSM reported fewer UAS episodes compared with white MSM in our cohort is consistent with reports from other studies finding lower reported risk behaviors among African-American MSM [27, 28] and suggests other factors, including social/sexual networks [29] and undiagnosed HIV infection [30, 31], may place this population at elevated

risk for HIV infection. While a higher perception of PrEP efficacy was associated with a small increase in total partners, this was not associated with increases in UAS or UAS episodes; perception of treatment assignment to TDF was associated with fewer UAS episodes.

Our findings are subject to several limitations. Participants were counseled that they may be receiving a placebo, and that there was no known efficacy of PrEP. Therefore, risk behavior changes in this trial may not reflect changes that may occur with open-label PrEP administration in the setting of known efficacy. Also, our sexual behavior measures recorded participants' self-report of risk practices over the prior 3 months, which may be subject to social desirability (although likely mitigated with ACASI) and recall difficulties over this period. Our risk behavior analysis included multiple comparisons of various sexual behaviors, so any significant associations should be interpreted with appropriate caution. Finally, this trial was conducted in 3 large metropolitan US cities (San Francisco, Boston, and Atlanta) and just over one-quarter of participants were men of color; results may not generalize to other populations of MSM who may use PrEP.

Despite these limitations, our data provide important information on changes in risk practices among MSM in the US initiating PrEP in a clinical trial setting. A major strength is the unique study design incorporating randomization of a comparison group in which participants did not receive study pills during the first 9 months, allowing for a direct comparison of the magnitude of behavior change in the immediate vs. delayed arms. Other strengths of this study include the intention-to-treat analysis, thus minimizing confounding factors, and good retention rates.

Now that PrEP has been shown to be efficacious in MSM [1], it will be important for future studies and programs to monitor for changes in sexual practices as PrEP is provided in an open-label context. Behavioral measures in open-label extension phases of successful PrEP trials as well as upcoming PrEP demonstration projects will provide important information on changes in sexual practices in more real-world settings. Data from these programs will also help inform the development of optimal behavioral interventions that can be coupled with PrEP delivery as part of a comprehensive prevention package. Our findings suggest the importance of addressing substance use issues and providing counseling about the relative benefits and harms of seroadaptive practices as part of PrEP support interventions [32]; this combination of prevention strategies will likely have the largest public health impact.

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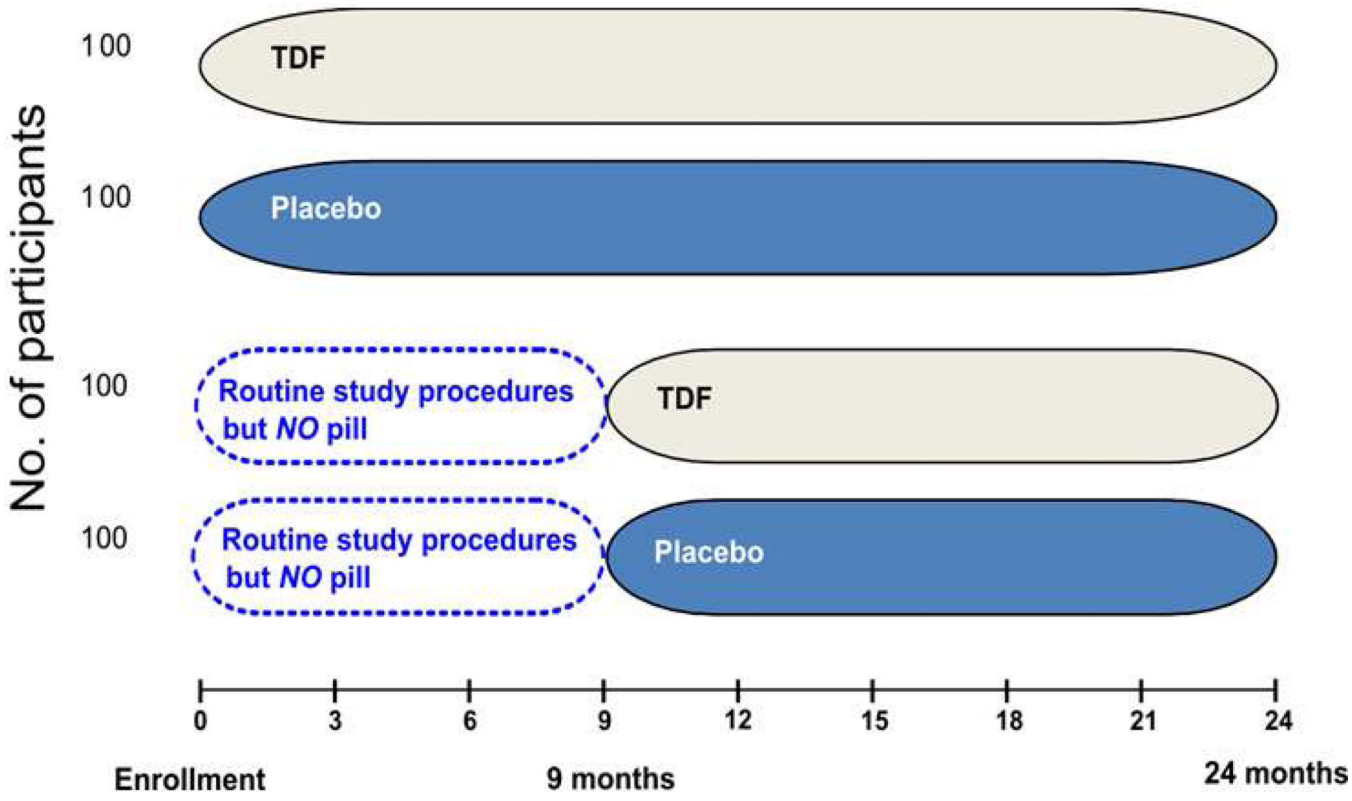

Figure 1. Study design diagram with 4 arms

Participants were randomly assigned to one of four arms. Participants in the 2 immediate arms (TDF vs. placebo) initiated study drug at enrollment; those in the 2 delayed arms (TDF vs. placebo) initiated study drug at the 9 month visit.

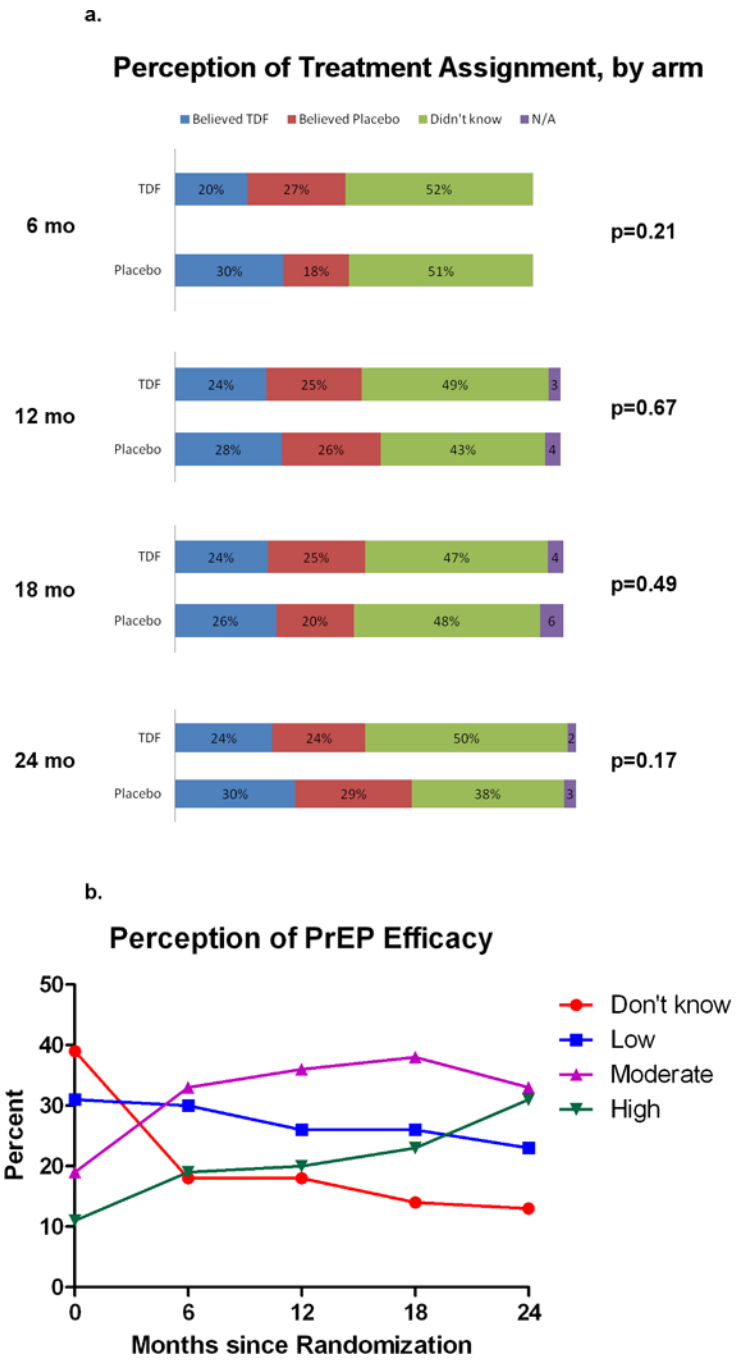

Figure 2. a and 2b. Perception of Treatment Assignment and PrEP efficacy, by treatment arm

Bar graphs in Figure 2a show the proportion of participants who believed they were taking either TDF, placebo, or didn't know, by the participant's actual treatment assignment. At 6 months, only data from the immediate arm are included; other time points include data from both immediate and delayed arms. P value represents Fisher's exact test for differences in perception of treatment assignment by actual treatment arm.

Graph in figure 2b shows the perception of PrEP efficacy by months of follow-up since randomization in the trial.

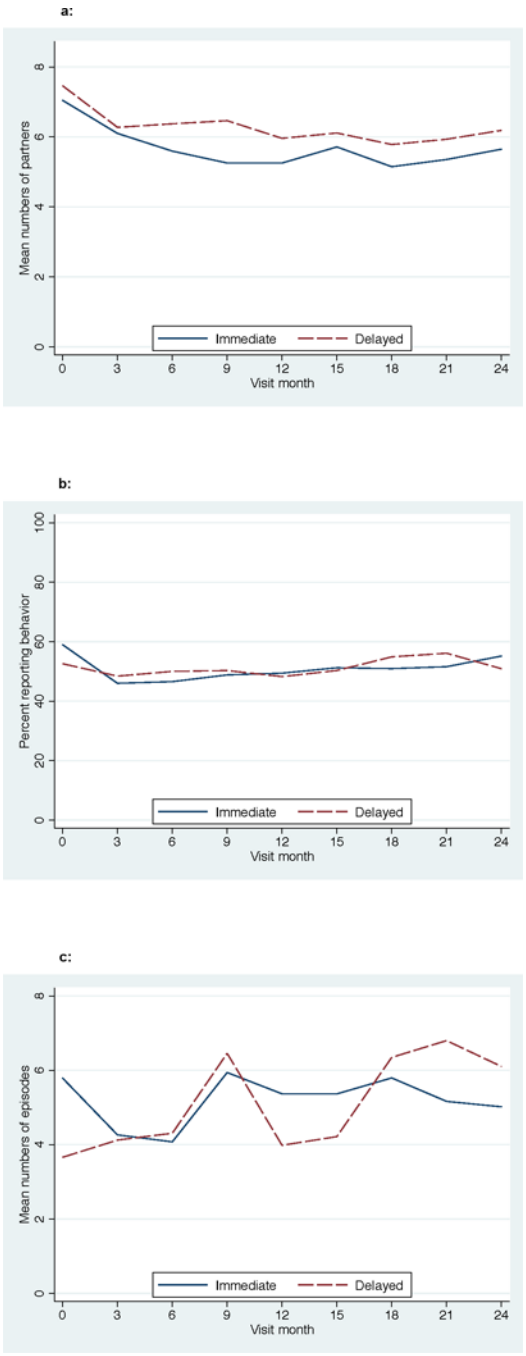

Figure 3. a–c. Mean number of sex partners, proportion reporting UAS, and mean number of UAS episodes, by immediate vs. delayed arms

Figure 3a shows mean number of male sex partners in the past 3 months, by immediate vs. delayed arms. Figure 3b shows proportion of men reporting unprotected anal sex (UAS) in the past 3 months, by immediate vs. delayed arms. Figure 3c shows mean number of UAS episodes in the past 3months, by immediate vs. delayed arms.

Table 1

Participant Demographics and Risk Characteristics at Baseline (%)

Characteristic	Immediate arm (n=200)	Delayed arm (n=200)	*P*
Age, years (median, range)	38 (18–60)	38.5 (18–59)	0.82
Race n (%)			
White	144 (72)	149 (75)	
African-American	32 (16)	28 (14)	0.63
Asian/Pacific-Islander	9 (5)	5 (3)	
Other	15 (8)	18 (9)	
Hispanic n (%)	20 (10)	16 (8)	0.60
Education n (%)			
Never graduated from high school	5 (3)	4 (2)	
High school graduate or GED	18 (9)	16 (8)	0.94
Some college	65 (33)	69 (35)	
College graduate	112 (56)	111 (56)	
Site n (%)			
San Francisco	100 (50)	100 (50)	1.00
Atlanta	61 (31)	60 (30)	
Boston	39 (20)	40 (20)	
Number of male partners in past 3 months n (%)			
0	4 (2)	6 (3)	
1	28 (14)	25 (13)	0.81
2–5	105 (53)	96 (48)	
6–9	26 (13)	28 (14)	
≥10	37 (19)	44 (22)	
Steady male partner (overall) n (%)	82 (41)	78 (39)	0.68
With an HIV-negative partner	56 (28)	54 (27)	0.82
With an HIV-positive or unknown status partner	26 (13)	24 (12)	0.77
Any unprotected anal sex (overall) n (%)	117 (59)	107 (54)	0.27
With an HIV-negative partner	80 (41)	61 (31)	0.06
With an HIV-positive or unknown status partner	52 (26)	62 (32)	0.27
Any unprotected receptive anal sex (overall) n (%)	67 (34)	58 (29)	0.33
With an HIV-negative partner	50 (25)	36 (18)	0.09
With an HIV-positive or unknown status partner	26 (13)	27 (14)	0.88
Alcohol use* in past 3 months n (%)			
None	33 (17)	30 (15)	0.78
Light	75 (38)	82 (41)	

Characteristic	Immediate arm (n=200)	Delayed arm (n=200)	*P*
Moderate	83 (42)	82 (41)	
Heavy	9 (5)	6 (3)	
Any non-injection drug use, past 3 months n (%)			
Poppers, amyl nitrate	52 (26)	54 (27)	0.91
Crack/powder cocaine	35 (18)	30 (15)	0.59
Amphetamines	23 (12)	20 (10)	0.75
Sedatives	26 (13)	20 (10)	0.43
Ecstasy	20 (10)	18 (9)	0.74
Use of sexual enhancing drugs, past 3 months n (%)	58 (29)	53 (27)	0.58

*Alcohol use was categorized as none, light (1–2 drinks/occasion on no more than 1–2 days/week, or 3–4 drinks/occasion, no more than once a month), moderate (1–2 drinks/occasion on a daily basis or 3–4 drinks/occasion at least 2–3 times/month), or heavy (5–6 drinks/occasion on a daily basis or 6 or more drinks on any one occasion)

Table 2

Multivariable models for Total Sex Partners, UAS, and UAS episodes

Characteristic	Total Partners		Any UAS		UAS episodes	
	IRR (95% CI)	P value	OR (95% CI)	P value	IRR (95% CI)	P value
Period (relative to baseline)		**0.02***		**0.003***		0.33*
Months 3–9	**0.85 (0.76–0.95)**	**0.005**	**0.76 (0.60–0.98)**	**0.03**	1.00 (0.70–1.42)	0.98
Months 12–24	**0.82 (0.70–0.97)**	**0.02**	0.95 (0.69–1.30)	0.74	1.17 (0.76–1.81)	0.48
Assigned pills†	0.93 (0.82–1.06)	0.28	0.88 (0.69–1.11)	0.27	0.91 (0.64–1.30)	0.61
Age (per 10 year increase)¥	1.09 (0.96–1.25)	0.20	**0.81 (0.69–0.95)**	**0.01**	0.85 (0.66–1.08)	0.18
Site		0.12*		0.23*		0.08*
Atlanta	(ref)		(ref)		(ref)	
San Francisco	1.24 (0.89–1.74)	0.21	0.96 (0.67–1.39)	0.85	0.95 (0.66–1.38)	0.80
Boston	0.91 (0.67–1.24)	0.55	0.73 (0.50–1.08)	0.12	**0.66 (0.45–0.96)**	**0.03**
Race		0.13*		0.46*		0.15*
White	(ref)		(ref)		(ref)	
African-American	0.80 (0.59–1.08)	0.14	0.72 (0.47–1.11)	0.14	**0.56 (0.34–0.92)**	**0.02**
Asian/Pacific Islander	0.78 (0.38–1.62)	0.51	0.86 (0.41–1.79)	0.69	1.00 (0.50–2.00)	1.00
Other	1.49 (0.96–2.31)	0.07	0.80 (0.45–1.43)	0.46	1.08 (0.59–2.00)	0.80
Ethnicity						
Non-Hispanic	(ref)		(ref)		(ref)	
Hispanic	1.22 (0.80–1.86)	0.36	1.09 (0.67–1.78)	0.74	1.34 (0.79–2.29)	0.28
Education		0.05*		0.91*		0.53*
High school graduate or less	(ref)		(ref)		(ref)	
Some college	0.98 (0.65–1.47)	0.92	0.96 (0.57–1.62)	0.87	0.88 (0.46–1.70)	0.71
College graduate	1.30 (0.89–1.90)	0.18	0.90 (0.53–1.53)	0.71	1.07 (0.57–2.03)	0.83
Drug use (time-dependent)						
Poppers	**1.34 (1.16–1.54)**	**<0.001**	**1.27 (1.04–1.54)**	**0.02**	1.15 (0.88–1.52)	0.31

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Characteristic	Total Partners		Any UAS		UAS episodes	
	IRR (95% CI)	P value	OR (95% CI)	P value	IRR (95% CI)	P value
Amphetamines	1.18 (0.98–1.41)	0.07	**1.75 (1.31–2.35)**	**<0.001**	1.23 (0.90–1.69)	0.19
Sexual-enhancing drugs	**1.32 (1.19–1.48)**	**<0.001**	**1.74 (1.43–2.11)**	**<0.001**	**1.40 (1.14–1.72)**	**0.002**
Perception of treatment assignment						
Placebo	(ref)		(ref)		(ref)	
TDF	0.91 (0.81–1.03)	0.14	0.88 (0.70–1.09)	0.23	**0.77 (0.65–0.91)**	0.002
Perception of PrEP efficacy‡	**1.04 (1.00–1.08)**	**0.04**	0.99 (0.93–1.05)	0.79	1.03 (0.97–1.10)	0.32

UAS=unprotected anal sex; IRR=incident rate ratio (ratio of mean effects); ref=reference group

*Test for overall effects of categorical variables

†Assigned pills variable set to 1 for immediate group starting at month 3 and delayed group starting at month 12

‡Per 1-unit increase in perception of PrEP efficacy coded as a 4-level variable (0 for don't know or N/A, 1=low, 2=moderate, 3=high)

¥Interpreted as the IRR or OR for each 10 year increase in age

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