Delivery of TDF/FTC for Pre-exposure Prophylaxis to Prevent HIV-1 Acquisition in Young Adult Men Who Have Sex With Men and Transgender Women of Color Using a Urine Adherence Assay

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Background: Pre-exposure prophylaxis (PrEP) for HIV prevention with daily tenofovir and emtricitabine is effective when taken consistently. Currently, there is no objective way to monitor PrEP adherence. Urine has been shown to be highly correlated with plasma tenofovir levels, with urine tenofovir levels >1000 ng/mL demonstrating recent (1–2 days) adherence to PrEP.

Setting: This study was conducted at an urban community health center in Philadelphia, Pennsylvania.

Methods: PrEP was administered to 50 young men who have sex with men and transgender women of color using weekly, biweekly, and/or monthly dispensation schedules. Primary objectives were retention at 48 weeks (in care at week 48 and completing ≥50% of medication pickups) and adherence assessed by urine tenofovir levels. Risk behaviors and sexually transmitted infection diagnoses were also collected.

Results: Seventy percent of participants were retained in care at 48 weeks. The proportion of subjects with urine tenofovir consistent with recent adherence was 80, 74.4, 82.4, 82.4, and 69.7% at weeks 4, 12, 24, 36, and 48, respectively. Sixty-one sexually transmitted infections were diagnosed over 231 screenings throughout 48 weeks, with no significant change between the first and second 24-week periods ($P = 0.43$; 0 seroconversions). At week 48, more than half of subjects reported an increase or no change in condom use, an increase in their ability to discuss HIV with partners, and no change in number of sexual partners from baseline.

Conclusions: These data demonstrate PrEP can be successfully delivered to a high-risk population with high program retention and medication adherence measured by urine tenofovir levels.

Key Words: PrEP, HIV PrEP, adherence, urine

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INTRODUCTION

Once daily, oral tenofovir and emtricitabine (TDF/FTC) for pre-exposure prophylaxis (PrEP) reduces HIV transmission in populations at risk of infection.[1–6] Young men of color who have sex with men (yMSMc) and transgender women who have sex with men (TGW) are at the highest risk for new infection[1] with blacks/African Americans accounting for 45% of new HIV diagnoses in 2015.[7] Between 2005 and 2014, new HIV diagnoses rose 87% in black and Hispanic/Latino MSM, with current models predicting that around 40% of young, black MSM will acquire HIV by age 30.[7] In addition, in 2012, between 44% and 60% of HIV-positive adolescents and young adults were unware of their HIV status at the time of diagnosis, and in 2014, adolescents and young adults accounted for 22% of new HIV-1 infections.[7] These trends extend and are further amplified in TGW, in whom the risk of HIV is 49 times higher than in the general population.[8]

PrEP is an effective HIV-prevention strategy for high-risk populations and can be integrated with other effective HIV-prevention tools such as sexual health counseling and condoms.[9] However, the public health effect of PrEP depends largely on uptake[10] and adherence.[1] Studies in MSM indicate a willingness to take PrEP given its efficacy,[11,12] but young people have historically been known to struggle with medication adherence[13] both in and outside the realm of PrEP.[14] Results from recent trials and demonstration projects suggest that self-reported adherence correlates fairly well with true adherence in some populations[4,15] but poorly in others, such as youth/young adults[16,17] and women.[18,19] In the Fem-PrEP trial for, less than 40% of women taking PrEP,[18,19] had detectable

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drug in plasma, in contrast to the 95% of women reporting that they "always" or "usually" used the product during the trial period, and despite pill counts suggesting study drug was taken on 88% of days.[18] Similarly, in the VOICE trial, tenofovir was detected in an average of 29% of samples, starting at approximately 40% in the first quarter of the study and falling to nearly 20% in the final quarter of the study. Fifty percent of women did not have detectable drug in any sample throughout the study, despite 95% retention and high self-reported rates of medication adherence (92% as measured by study drug return, and 91% by self-report).[20] Another study from the Adolescent Trials Network (ATN), ATN 110,[16] looked at PrEP adherence among 200 high-risk MSM ages 18–22 years, including black, Latino, mixed race, white, and Asian participants, wherein the black participants, on average, did not achieve protective drug concentrations at any point in the study despite high-reported self-adherence.[16] Poor adherence patterns such as these limit the public health impact of PrEP in at-risk populations.

To better address the concerns of reliance on self-report adherence data in patients taking PrEP,[21] we have developed and validated a urine assay with high sensitivity and specificity for tenofovir (TFV), using liquid chromatography–tandem mass spectrometry (LC-MS/MS) This assay determines TFV concentrations in log categories from 0 ng/mL to >10,000 ng/mL. We determined that urine TFV concentration predicted when the last dose of TDF/FTC was taken within the previous 7–10 days, with a direct correlation of concentration to time since last dose in this period. In fact, we showed that urine TFV concentration >1000 ng/mL was highly predictive of presence of TFV in plasma (>10 ng/mL) (PPV 0.95, 95% CI: 0.82 to 0.99; NPV 0.79, 95% CI: 0.49 to 0.95), suggesting recent dosing in the previous 1–2 days (high adherence), compared with urine levels that were detectable but under 1000 ng/mL suggesting a dose intake within the last week but not the last 1–2 days (low adherence), and undetectable urine levels (0 ng/mL)[21] suggesting that the last dose was taken more than 1 week ago (nonadherence). These data were derived from 10 HIV-negative subjects receiving daily PrEP for a 24-week study.[21]

Given these data, our primary objectives were to assess program retention and medication adherence of yMSMc and TGWc taking oral PrEP. Both outcome measures were deemed important to measure separately because adherence has been shown to be correlated with but not always predictive of retention in HIV care.[22]

We hypothesized that our program could retain at least 70% of participants, with retention measured by the proportion of patients who pick up at least 50% of their medication at their scheduled weekly, biweekly, or monthly medication pickup visits throughout the 48 weeks of the study. The 50% rate of pickups was chosen as the cutoff based on observational pharmacokinetic data that suggest that taking TDF/FTC as PrEP 4 or more days per week (slightly above half of the time), conveyed similar HIV-prevention efficacy as taking TDF/FTC 7 days per week (96% vs. 99% risk reduction).[23] The level of adherence to PrEP was assessed through the proportion of medication pickup visits attended at Y-HEP as well as by urine and plasma drug concentrations.

Our secondary objective evaluated risk-taking behavior during the course of the study. The change in reported number of risk behaviors between the beginning and the end of the study was assessed using an adapted risk assessment battery (RAB).[24] The incidence of sexually transmitted infections (STIs) was captured as well, with a 30% change in the incidence of STIs in the second half of the study period compared with the first half considered as clinically significant.

METHODOLOGY

Study Setting

Recruitment, enrollment, and study visits were conducted at Philadelphia FIGHT, a community-based organization that provides comprehensive care to patients living with and at risk for HIV infection (http://fight.org/). All participants received standard HIV-prevention services including condom provision, risk reduction counseling, HIV testing, and STI screening and treatment in addition to basic medical care. In accordance with CDC guidelines, participants were screened for HIV, STIs, and renal function at baseline and every 3 months during the study protocol period. Participants were also offered rapid tests for HIV on a monthly basis. Treatment was provided for STIs diagnosed during this study, and nonimmune subjects were offered vaccines against hepatitis A and B.

The current study offered the traditional components of successful PrEP initiatives in conjunction with several unique components hypothesized to increase program retention and medication adherence including (1) the provision of youth, minority, and Lesbian/Gay/Bisexual/Transgender/Queer/Intersex/Asexual (LGBTQIA)-specific educational, counseling, and support interventions, (2) PrEP provided in the context of a wellness program, rather than an HIV prevention, and (3) a need-based adherence support system wherein TDF/FTC was dispensed in a directly observed manner on a weekly, biweekly, or monthly basis.

Study Design and Participants

Study Design

This study used a 48-week prospective observational design to test the hypothesis that a program in which PrEP is administered to yMSMc and TGWc who have sex with men in a community drop-in center in conjunction with a multifaceted behavioral intervention and augmented adherence monitoring using urine TFV levels can achieve at least 70% retention, as well as a medication adherence rate significantly better than that previously reported in the literature.[16,17]Subjects consisted of HIV-negative, English-speaking persons assigned male sex at birth between the ages of 18 and 30 years. Patients with evidence of acute or chronic hepatitis B infection at the time of screening, severe infections requiring treatment such as tuberculosis, renal dysfunction (creatinine clearance <50 mL/minute by Cockroft–Gault equation), history of bone fractures not explained by trauma, grade 3 laboratory abnormality at screening tests/assessments as

defined by the DAIDS grading system, concurrent participation in an HIV vaccine study, known allergy/sensitivity to the study TDF/FTC or its components, or concurrent use of any antiretroviral agent other than TDF/FTC for any reason were excluded from participation. Subjects were recruited through word of mouth and advertising on social media sites. Written informed consent was obtained from all subjects with the use of approved consent forms. This study was approved by the Institutional Review Board at Philadelphia FIGHT.

All subjects were dispensed TDF/FTC as PrEP on an either weekly, biweekly, or monthly basis depending on an initial assessment of need for adherence support with TDF/FTC dispensed at the clinic rather than a commercial pharmacy. Subjects used private, federal, or family insurance to secure TDF/FTC for PrEP, and patients without insurance obtained PrEP through the manufacturer's Patient Assistance program. Study subjects were considered to have picked up their medications if they presented at any time during the week designated as a medication pickup week. Adherence was assessed by the percentage of medication pickup visits attended, as well as urine tenofovir levels collected every 2 or 4 weeks (depending on each subject's PrEP pickup schedule), and plasma tenofovir levels at study weeks 24 and 48.

The purpose of urine and plasma collections were detailed within the informed consent forms, and patients were routinely made aware of what laboratory analyses (urine TFV, gonorrhea/chlamydia, syphilis, etc.) were being conducted, including when urine would be collected for TFV assessment. Subjects received feedback on urine TFV results as samples were analyzed. It is important to note that the samples collected over the course of the study were delivered for LC-MS/MS TFV testing per laboratory requirements in batches of 35 or more; as such, real-time results were not available to patients. Samples were sent for LC-MS/MS every 4–12 weeks, and results were reported back to the clinical site within 6–14 business days of delivery. Participants were made aware of their TFV levels from each collection analyzed in person at their next appointment, or by phone or email as requested by the participant. Participants were able to discuss their adherence over time if multiple samples from an individual participant were analyzed in the previous sample batch (ie, urine collected at weeks 4 and 8 from a single participant sent for LC-MS/MS before week 12 would be discussed at the week 12 visit if returned). Study staff provided standard of care adherence counseling to all participants at each visit. Risk behaviors were assessed by STI rates, and the adapted RAB questionnaire presented at baseline, week 24, and week 48.

RESULTS

Between February and July of 2015, 50 healthy participants assigned male sex at birth gave consent to participate in the trial. Patient demographic characteristics are summarized in Table 1. Participant mean age was 22.1 years (range 18–29 years, SD = 2.97 years), 10% were TGW, 64% were African American, and participants' mean time on PrEP before study initiation was 35.2 weeks with 18 participants (36%) taking FTC/TDF for PrEP before enrollment. Common risk factors for HIV were inconsistent condom use (80%), a history of STIs (58%), self-reported drug and/or alcohol use (74%), and sexual partners of unknown HIV status (54%).

Over the 48-week trial, 70% (35) of the participants were retained in the program with 90% retention at 12 weeks, 74% retention at 24 weeks, and 70% retention at 36 and 48 weeks when retention was adjusted for out-of-window medication pickups. Ten participants withdrew consent over the course of 48 weeks; reasons for withdrawal included relocation out of state (n = 4), lifestyle changes to remain HIV− such as abstinence and increased condom use (n = 4), schedule conflicts (n = 1), and new onset stomach cramping (n = 1). In addition, 1 participant was incarcerated and 4 participants were lost to follow-up. Table 2 depicts retention patterns over the course of the trial, both adjusted and not adjusted for out-of-window medication pickups. The proportion of subjects with urine TFV concentrations consistent with recent adherence to PrEP (>1000 ng/mL) was 80, 74.4, 82.4, and 69.7% at weeks 4, 12, 24, and 36, and at week 48, respectively. The proportion of subjects with evidence of inconsistent adherence (>10 to >100 ng/mL) was 15.6% at week 4, 11.6% at week 12, 11.8% at weeks 24 and 36, and 15.2% at week 48. The proportion of subjects who demonstrated nonadherence to TDF/FTC for PrEP over the preceding 7 days (<10 ng/mL) was 4.4% at week 4, 14% at week 12, 5.9% at weeks 24 and 36, and 15% at week 48 (Fig. 1). When medication pickup frequency (7, 14, or 28 days) was examined for a correlational relationship with urine TFV concentrations, no statistically significant relationship was observed. Similarly, presenting for visits outside of the ascribed study window, period was not correlated with urine TFV concentrations at a statistically significant level. All 50 participants received STI testing at screening, and subsequent testing was based on practice guidelines and patient request. Of 231 individual tests performed, 61 STIs were diagnosed. Six participants tested positive for rectal gonorrhea and or chlamydia at screening; 9 additional participants tested

TABLE 1. Baseline Characteristics

(n = 50)	Total (%)
African American race	32 (64)
Ethnicity Hispanic/Latino	9 (18)
Transgender (male to female)	5 (10)
Self-identified sexual orientation	
Gay/homosexual	35 (70)
Bisexual	13 (26)
Risk factors for HIV	
HIV+ partner	4 (8)
Inconsistent condom use	40 (80)
History of STI	29 (58)
Exchange of sex for commodities	9 (18)
Drug/alcohol use	37 (74)
History of incarceration	11 (22)
Partner(s) of unknown HIV status	27 (54)
4 or more partners in last 6 mo	15 (30)

TABLE 2. Retention in Care

Retention (n = 50)	%	% Adjusted for "Out-of-Window" PrEP Pickups
Week 12	84	90
Week 24	62	74
Week 36	62	70
Week 48	50	70

positive for rectal gonorrhea and or chlamydia between weeks 2–24, and 12 participants tested positive for these infections between weeks 25–48, with no significant change in STI incidence over the study period ($P = 0.43$). No participants seroconverted to HIV-positive status during the study period. In addition, 4 participants were diagnosed with syphilis over the course of 48 weeks (2 on or before week 24, and 2 between weeks 26 and 48); there were no cases of trichomonas or hepatitis C diagnosed during the study.

We evaluated the change in PrEP knowledge and reported risk behaviors between the first and second 24-week period, using the adapted RAB (Fig. 2). At week 48, compared with week 24, 76.5% of participants reported increased knowledge and understanding of the role of PrEP, 73.5% reported feeling better protected against HIV because of PrEP, and 67.6% reported a decrease in their perception of HIV risk. In addition, 73.5% of respondents reported being better able to discuss HIV with partners, and 82.4% of participants reported both no change in their number of sexual partners and either an increase or no change in condom use between the first and second 24-week duration of the study.

DISCUSSION

The current study sought to evaluate retention in care and longitudinal adherence to PrEP over 48 weeks among yMSMc and TGWc when flexible medication dispensation and intensive adherence support were offered through the use of frequent visits and urine TFV monitoring. Retention was high over the study period, with 70% of this young cohort still actively in care at 48 weeks. More importantly, adherence to PrEP also remained consistently high, with 70% of subjects demonstrating protective levels throughout 48 weeks and irrespective of whether medication was picked up at participant-determined 7-, 14-, or 28-day intervals. Overall, STI rates remained stable over 48 weeks, and participants' risk behaviors did not change.

This study succeeded in delivering PrEP safely, consistently, and effectively to a population that has historically been found to have suboptimal adherence to TDF/FTC when measured objectively and thus has remained at high risk of HIV acquisition through the use of a flexible, drop-in model of care coupled with hands-on PrEP dispensation in intervals designed to meet participants' needs. The current study also lends further support to the idea of using urine TFV measurement as an objective indicator of PrEP adherence. The role of objective adherence monitoring in patients taking PrEP is beginning to be characterized. Although, for some populations, self-report may be reliable,[15] self-report has been shown to correlate poorly for other groups, namely youth/young adults[16] (particularly yMSMc) and women.[20] An easy, noninvasive, and low-cost urine test that can provide accurate adherence information, that is acceptable to these populations, could be invaluable as we work to enhance programmatic support for groups at very high risk of HIV acquisition. In our population of yMSMc, current (previous week) adherence data as measured by urine TFV concentration may have greater value than other research measures of average/long-term adherence such as dried blood spot or hair analysis given increased vulnerability to HIV exposure,[1] as well as increased fluctuation in life circumstances among young people on a daily basis, and may create a greater number of opportunities for clinicians to reinforce PrEP adherence behaviors.[25] In addition, among yMSM, urine collection may be less intimidating or stigmatizing than blood draw or finger-prick procedures.[26]

This study has several limitations. First, the study design was a single-arm study rather than a randomized

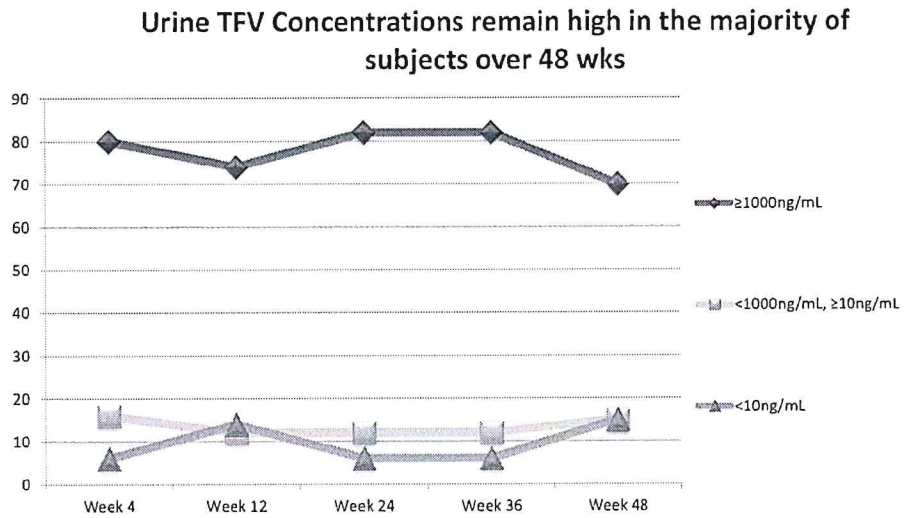

FIGURE 1. Urine TFV concentrations remain high in most subjects over 48 weeks.

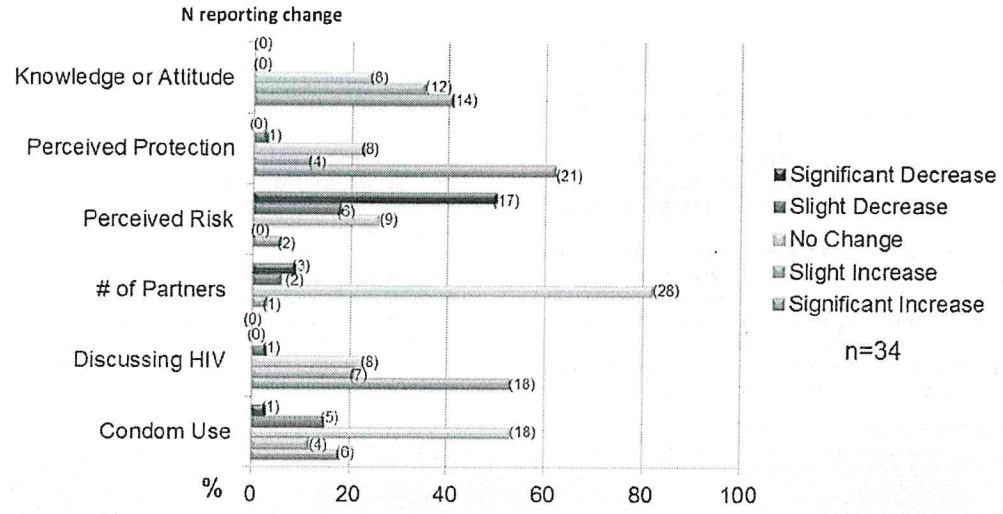

FIGURE 2. Risk and attitude change between study weeks 24 and 48 by adapted risk assessment battery.

controlled trial, and therefore, it cannot be stated that the current biomedical/behavioral programming is superior to other HIV-prevention strategies. Furthermore, the study sample size was small in comparison with other major PrEP trials, and 36% (n = 18) patients were already taking FTC/TDF for PrEP when enrolled. This study made every effort to retain patients in care, achieving levels of interaction that are often not feasible in the setting of traditional community-based or family practice medical settings. Reasons for study discontinuation were documented but were not analyzed for the purpose of this study. Finally, this study could not give real-time feedback from urine TFV analysis to patients because the urine assay was not commercially available at the time of the study. Participants were given feedback on batched test results over several collections, but the impact of a point-of-care test for TFV has yet to be studied.

A PrEP program for youth and young adults achieved high rates of program retention and adherence to PrEP when adherence was objectively monitored through the use of a urine TFV assay. Further studies need to be performed to determine whether use of urine TFV monitoring increases adherence relative to programmatic support alone, as well as to determine the role of urine TFV monitoring in other PrEP populations.

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