An HIV Preexposure Prophylaxis Demonstration Project and Safety Study for Young MSM

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Background: Young men who have sex with men (YMSM) are a key population for implementation of preexposure prophylaxis (PrEP) interventions. This open-label study examined adherence to PrEP and assessed sexual behavior among a diverse sample of YMSM in 12 US cities.

Methods: Eligible participants were 18- to 22-year-old HIV-uninfected MSM who reported HIV transmission risk behavior in the previous 6 months. Participants were provided daily tenofovir disoproxil fumarate/emtricitabine (Truvada). Study visits occurred at baseline, monthly through week 12, and then quarterly through week 48. Dried blood spots were serially collected for the quantification of tenofovir diphosphate (TFV-DP).

Results: Between March and September 2013, 2186 individuals were approached and 400 were found to be preliminarily eligible. Of those 400, 277 were scheduled for an in-person screening visit and 200 were enrolled (mean age = 20.2; 54.5% black, 26.5% Latino). Diagnosis of sexually transmitted infections, including urethral and rectal chlamydial/gonococcal infection and syphilis, at baseline was 22% and remained high across visits. At week 4, 56% of participants had TFV-DP levels consistent with ≥4 pills per week. By week 48, 34% of participants had TFV-DP levels consistent with ≥4 pills per week, with a noticeable drop-off occurring at week 24. Four HIV seroconversions occurred on study (3.29/100 person-years). Condomless sex was reported by >80% of participants, and condomless anal sex with last partner was associated with higher TFV-DP levels.

Conclusions: Acceptability of PrEP was high, and most participants achieved protective drug levels during monthly visits. As visit frequency decreased, so did adherence. YMSM in the United States may need PrEP access in youth-friendly settings with tailored adherence support and potentially augmented visit schedules.

Key Words: preexposure prophylaxis, youth, men who have sex with men

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INTRODUCTION

Young men who have sex with men (YMSM), particularly black and Latino YMSM, are the group most affected by HIV in the United States,[1] making them a key domestic population for implementation of HIV preexposure prophylaxis (PrEP) interventions. Based on evidence from multiple clinical trials of PrEP,[2–4] the US Food and Drug Administration approved daily use of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for the prevention of sexually acquired HIV in July 2012. In anticipation of this new drug indication, several open-label demonstration projects were launched to evaluate PrEP safety and adherence outside of a placebo-controlled trial setting; effective PrEP implementation strategies for specific at-risk populations are also being evaluated.

Although not placebo controlled, the more recent PROUD study used an open-label randomized controlled design of either immediate or delayed PrEP to pilot test the implementation of PrEP in the public health system of the

United Kingdom through measurement of enrollment and retention and also safety, adherence, and behavioral disinhibition.[5] The trial, which enrolled 544 MSM, was stopped early because of strong evidence of PrEP effectiveness leading the data safety monitoring board to recommend that all participants be offered immediate PrEP.

In addition to randomized trials, the iPrEx Open-Label Extension (OLE)[6] study enrolled MSM and transgender women who were previously enrolled in the iPrEx randomized trial and eligible participants from 2 other previously completed randomized PrEP trials: Adolescent Trials Network (ATN) 082[7] and the Centers for Disease Control and Prevention (CDC) Safety Study.[8] In total, 1603 participants enrolled in the study, of whom 76% decided to take PrEP. HIV incidence was strongly inversely correlated with PrEP adherence as measured by drug concentrations in dried blood spots (DBS), and there were no HIV infections among participants whose DBS drug levels were consistent with taking 4 or more pills per week. Additionally, drug concentrations were higher among older more educated participants and those who reported condomless receptive anal intercourse, had more sexual partners, or had a history of syphilis or herpes.[6]

Most recently, the US PrEP Demonstration (DEMO) Project investigators reported outcome results from their trial of PrEP implementation for MSM and transgender women at municipal sexually transmitted infection (STI)/community health clinics in 3 US cities (San Francisco, Miami, and Washington, DC).[9] Among the 557 participants enrolled, PrEP adherence was high with greater than 80% of those with drug levels testing via DBS demonstrating concentrations consistent with taking ≥4 doses per week at all visits. Incidence of STIs was high (90 per 100 person-years) but did not increase over time. Retention was higher among those who had previous knowledge of PrEP and self-reported condomless anal sex at baseline. Rates of adherence and engagement were significantly lower among African American participants.[10]

Young men, particularly racial and ethnic minority youth, who are increasingly disproportionately affected by HIV in the United States[1] were underrepresented in each of the aforementioned studies. Young people aged 25 years or lesser made up only approximately 20% of both the iPrEx OLE and DEMO Project samples, and the median age of participants in both the DEMO Project and PROUD was 35 years. With evidence that medication adherence is known to be a significant challenge for adolescents and young adults,[11–14] including adherence to PrEP,[6,7,15] PrEP trials specifically focused on youth aged 25 years or lesser are critical for the development of successful PrEP implementation strategies.

Additionally, despite the absence of evidence of behavioral disinhibition in adult PrEP trials, concerns about young people using PrEP continue to be raised.[16] The potential for decreased adherence and increased sexual risk highlights the need for integrated behavioral interventions with PrEP programming as part of a comprehensive HIV prevention package in vulnerable populations of youth. Given the absence of any youth-specific PrEP demonstration projects, we built on the information learned from our previous PrEP pilot with YMSM[7] and designed Project PrEPare 2, an open-label demonstration project and phase II safety study of PrEP among YMSM aged 18–22 years (ATN 110). The primary objectives of this study were to (1) provide additional safety data regarding TDF/FTC use among HIV-uninfected YMSM, (2) examine acceptability, patterns of use, rates of adherence, and measured levels of drug exposure when YMSM are provided open-label TDF/FTC (Truvada), and (3) examine patterns of risk behavior when YMSM are provided with an evidence-based risk reduction behavioral intervention before starting PrEP.

METHODS

Overview

This open-label PrEP demonstration project and safety study provided PrEP along with evidenced-based behavioral HIV prevention interventions (Many Men, Many Voices[17] and Personalized Cognitive Counseling[18]) to YMSM at study sites for the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) across the United States. Study sites were located in 12 urban US cities (Baltimore, Boston, Chicago, Denver, Detroit, Houston, Los Angeles, Memphis, Miami, New Orleans, Philadelphia, and Tampa) with substantial prevalence of HIV infection among young people.[19] All study procedures were approved by the Institutional Review Boards of each participating study site.

Participants

Multiple recruitment methods were used across sites, including street and venue-based outreach, community and school presentations, and online advertising on social media Web sites and social networking applications (apps). Eligibility data were collected through screening tools programmed on mobile devices (ie, Apple iPod Touch) and web-based forms and documented on recruitment logs.

HIV-uninfected YMSM, who were born male and were 18 through 22 years of age at the time of signed informed consent, were eligible to enroll in the study. Participants had to report HIV transmission risk behavior (eg, condomless anal intercourse, multiple sexual partners, recent STI), test HIV negative at the time of screening, be willing to provide contact information, take TDF/FTC as PrEP, and participate in 1 of the 2 behavioral interventions. Potential participants were ineligible if they had a history of unexplained bone fractures, had the presence of hepatitis B surface antigen, had creatinine clearance (CrCl) <75 mL/min calculated based on the Cockroft–Gault equation, had confirmed ≥grade 2 serum phosphate, hematologic, or hepatobiliary chemistry abnormality, confirmed proteinuria or normoglycemic glucosuria, confirmed grade ≥3 toxicity on any screening evaluations, known allergy/sensitivity to the study agent or its components, or concurrent participation in an HIV vaccine study or other investigational drug study, including oral or topical PrEP (microbicide) studies.

Procedures

After participants completed the informed consent process, were confirmed to be eligible, and completed their baseline study visit, they were scheduled to attend the behavioral intervention assigned to their site. These

interventions were chosen because they are identified as effective HIV risk reduction interventions in the CDC's Diffusion of Effective Behavioral Interventions program[20] and CDC-trained professionals were locally available in each city. Once participants completed the behavioral intervention, they were scheduled for the week 0 visit at which they received additional PrEP education and were dispensed a 30-day supply of the study drug with instructions to take one tablet daily. TDF/FTC tablets were supplied by Gilead Sciences, Inc., Foster City, CA.

Study visits occurred monthly for the first quarter (weeks 4, 8 and 12) and then quarterly thereafter through 48 weeks. At each visit, behavioral and biomedical data were collected. A medical history, including review of signs and symptoms, and a symptom-directed physical examination were conducted at each visit. Laboratory evaluations included Food and Drug Administration–approved HIV antibody testing, urine nucleic acid amplification testing for gonorrhea (GC) and *Chlamydia trachomitis* (CT), self-administered rectal swabs for GC/CT nucleic acid amplification testing, rapid plasma regain, hepatitis B surface antigen, renal, liver, and pancreatic function chemistry tests, and urine dipstick testing for protein and glucose. Blood collected as DBS at each visit was shipped to the University of Colorado for quantification of tenofovir diphosphate (TFV-DP) levels. Participants also completed spine, hip, and whole-body dual-energy x-ray absorptiometry scans at baseline, week 24, and week 48.

All participants received a comprehensive package of HIV prevention services at each visit (ie, risk reduction counseling, condoms, symptomatic STI screening, and treatment) and met with a study counselor to complete an Integrated Next Step Counseling session.[21] The Integrated Next Step Counseling approach includes exploration, problem solving, and skills building around nonbiomedical strategies to prevent HIV and for those receiving PrEP assesses participant's desire to remain on PrEP and strategies to improve or maintain adherence.[6,22] At each study visit, participants completed behavioral assessments via audio computer-assisted self-interview, received condoms, and were dispensed study drug. Participants were provided compensation for each study visit as determined by each local Institutional Review Board.

Measures

PrEP Acceptability

Assessments of acceptability were conducted at the week 12 and 48 study visits. This instrument, which has been used in a previous PrEP study with youth, assesses (1) the usability of PrEP; (2) the user-friendliness of the medication regimen, including an assessment of side effects and dosing frequency; and (3) the acceptability of behavioral intervention sessions.[7] Beliefs about PrEP were assessed using 9 questions adapted from the iPrEx OLE[6] study to explore the potential ways that PrEP may influence subjects' health, condom use, sexual behavior, and reasons that subjects would choose not to take PrEP.

Adherence

The AIDS Clinical Trial Group Adherence Follow-up Questionnaire[12] was adapted to examine the possible reasons for missing PrEP doses. The questionnaire presents a number of possible reasons for missed doses and asks subjects to rate how often they have missed taking their medications over the previous month because of these reasons. PrEP medication levels were assessed via DBS collected at each visit to quantify intracellular TFV-DP and FTC-triphosphate concentrations.[23] DBS results were translated into dosing categories previously used in PrEP trials with adult MSM.[6] Dosing categories included below lower limit of quantitation, lower limit of quantitation to 349 fmol per punch (fewer than 2 tablets per week), 350–699 fmol per punch (2–3 tablets per week), ≥700 fmol per punch (4 or more tablets per week).

Sexual Behavior

A self-report questionnaire was used to assess each participant's overall sexual behavior history and in-depth analysis of the sexual behavior that occurred with the last sexual partner. Participants were also routinely tested for syphilis at baseline and week 48 and as clinically indicated at other visits. Rectal swabs for GC and chlamydia were routinely collected at baseline, 24 weeks, and 48 weeks and as clinically indicated at other visits. Urine-based testing for GC and chlamydia occurred at every visit. Participants were defined as STI positive if they tested positive for urethral or rectal GC or CT and if they had evidence of acute syphilis (defined as positive rapid plasma regain with titers along with review of previous diagnoses/treatment).

Data and Safety Monitoring

The protocol team monitored the study for clinical adverse events (AE) and abnormal laboratory values using the ATN Table for Grading Severity of Adolescent AE (October 2006—Clarification March 2011). Expedited AE reporting followed standard reporting requirements as defined in the Manual for Expedited Reporting of AE to ATN/NICHD, version 2.0, March 2011. Social harms were recorded on case report forms at the site and entered into the database electronically. An external data safety monitoring board reviewed study safety data 6 times at 6-month intervals during trial implementation and recommended that the study continue to completion.

Statistical Analyses

Baseline demographics, number of AE, rates of toxicity, rates of acceptability, patterns of use, rates of adherence, measured levels of drug exposure, and patterns of risk behavior were summarized using frequencies, means, medians, standard deviations, and ranges as appropriate. Bone mineral density (BMD) Z scores were generated by the dual-energy x-ray absorptiometry software using population norms. Risk behaviors were compared between youth who were adherent to PrEP (≥4 pills per week) and those

who were nonadherent (<4 pills per week) over time by generalized estimating equations, to adjust for multiple measurements within subjects, with a logit link and binomial distribution. Generalized estimating equations were also used to test for trend in STI diagnoses over time and whether the TFV-DP levels over time differed by status of engaging in recent condomless sex or self-reported condomless receptive anal sex with their last partner. Incidence was calculated as the number of seroconversions divided by the total number of person-years on PrEP. Statistical analyses were carried out using SAS,[24] and $P < 0.05$ was used to determine statistical significance.

RESULTS

Recruitment and Participant Retention

From January to September 2013, 2186 individuals were screened for eligibility in the field and 400 were found to be preliminarily eligible. Of those, 277 were interested in study participation and were scheduled for the clinic-based screening visit. Eleven individuals (4%) were found ineligible at the screening visit because of undiagnosed HIV infection, 27 failed to attend the screening visit, and 39 were ineligible for other reasons (Fig. 1).

Two hundred youth (n = 200) with a median age of 20 years were enrolled into the study. Twenty-six percent of the participants (n = 53) self-identified as Latino. Of non-Latinos, most of the participants identified their race as black/African American (66%), with an additional 29% identifying as white, 3% as mixed race, and 2% Asian/Pacific Islander or American Indian. Most participants identified as either gay (77.8%) or bisexual (13.7%). Almost half (45.5%) of the young men had completed some college education, and 30.1% were currently unemployed. Just over 15% of participants reported that they had been homeless in their lifetime, and 28.6% reported experience with exchanging sex for money (Table 1).

Fifty-eight participants were prematurely discontinued from the study. The most common reason was loss to follow-up (n = 34) followed by withdrawal of consent (n = 9) and moving out of the area (n = 7). In addition, 2 participants were prematurely discontinued because of diagnosis with acute HIV infection identified by HIV RNA assay at the baseline visit. Overall study retention was 71%, including premature discontinuations and those who were lost to follow-up. For those who remained on study, visit retention was very high at 91.8% of all expected visits.

Safety

There were 3 grade 3 AE (nausea, weight loss, and headache) among 3 participants that were deemed to be related to the study drug, all of which fully resolved when

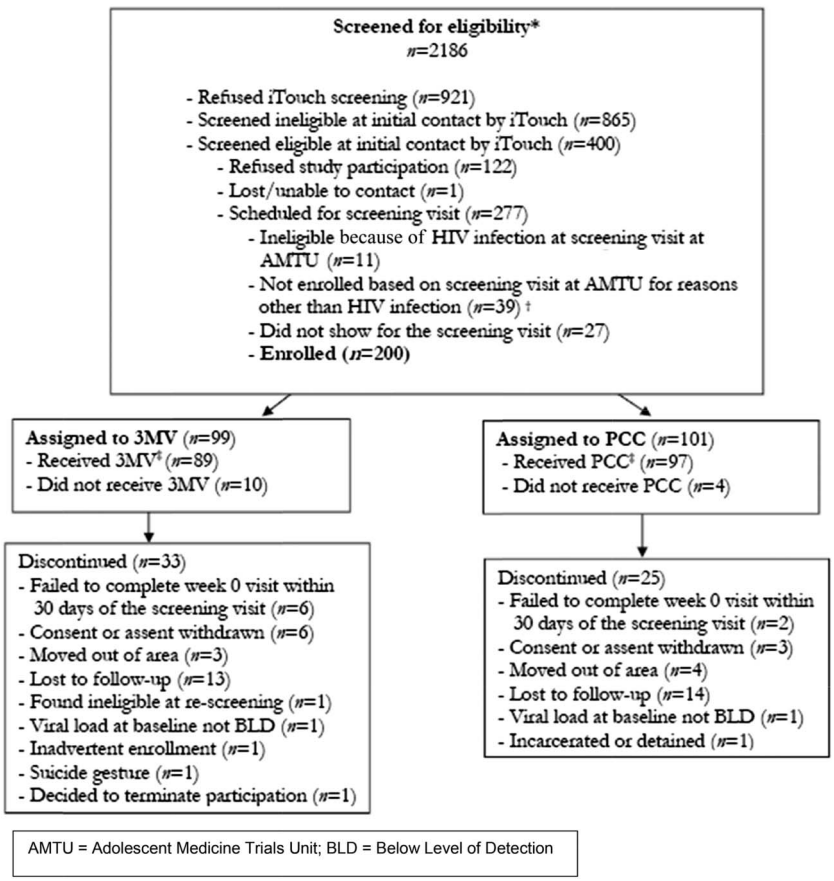

FIGURE 1. Consort diagram. *Some screening data was lost at one site and is not included here. †Please see text for complete listing of reasons. ‡The "Received 3MV" and "Received PCC" categories represent the number of subjects who received the 3MV/PCC intervention.

TABLE 1. Baseline Demographic Data

	Overall
n	200
Age at baseline, yrs	
Mean	20.2
SD	1.3
Median	20.0
Race (%)	
Black/African American	93 (46.5)
Asian/Pacific Islander	2 (1.0)
White/non-Hispanic	42 (21.0)
White/Hispanic	21 (10.5)
Other/Mixed race	42 (21.0)
Ethnicity (%)	
Hispanic or Latino	53 (26.5)
Non-Hispanic or Latino	145 (72.5)
Condomless sex previous month, %	80.79
Condomless receptive anal intercourse with last partner, %	57.98
Any positive STI test, %	22
Ever kicked out of house because of sexual orientation, %	17.2
Ever spent at least one night in homeless shelter, %	15.5
Ever exchanged sex for money, %	28.6

medication was discontinued. Only a single renal event, a grade 1 elevation of serum creatinine, was noted at the last study visit and resolved by the subsequent safety follow-up visit. An additional 21 grade 3 or higher AE that were deemed unrelated to study drug occurred among 15 participants. Twenty-two participants decided to discontinue study drug (median time on PrEP was 0.35 years), but stay on the study, primarily because of personal choice or self-reported side effects, including gastrointestinal discomfort.

At baseline, median BMD Z scores among participants were below zero (spine −0.50, hip −0.45, whole body −0.40), suggesting lower bone mass than would be expected in healthy young men. Between baseline and week 24, BMD decreased modestly but significantly in the hip (median −0.44%, $P < 0.001$) and whole body (−0.61%, $P < 0.001$) and tended to decrease in the spine (−0.23%, $P = 0.11$). Decreases in all Z scores were statistically significant (median absolute changes in Z score in spine −0.10, $P < 0.001$; hip −0.02, $P = 0.017$; whole body −0.10, $P < 0.001$). Between weeks 24 and 48, hip BMD and Z score continued to decline significantly but no further significant losses were seen in the spine or whole body.

Two social harms reported were deemed related to participation in the study. In one case, a participant was coerced to have condomless sex with his HIV-positive partner because he was on PrEP. The second social harm involved a parent threatening to evict the participant from the home if he did not stop taking PrEP. In both cases, participants were linked directly to appropriate counseling.

Acceptability

When asked at week 48 about acceptability of the study procedures, including HIV/STI testing, physical examinations, and behavioral counseling, over 90% of participants "liked" or "liked them a lot." Regarding the acceptability of the TDF/FTC pill, one-third of participants did not like the size of the pill and over half (52.2%) did not like the taste of the pill. Nevertheless, most (60.3%) found taking a pill every day to be acceptable. There were no significant changes from week 12 to week 48.

Medication Adherence

DBS TFV-DP demonstrated that most of the participants had detectable drug over the course of the study, with over 90% of participants having detectable drug through the first 12 weeks, 81% at week 24 and 69% at week 48 (Fig. 2). Quantitative analysis of TFV-DP levels demonstrated a similar pattern of decline over time: most of the participants had TFV-DP levels consistent with ≥4 pills per week over the first 12 weeks of the study, a noticeable drop-off occurred at week 24, and by week 48, only 34% of participants had this level of drug detected (Fig. 3). Median levels for African American participants were below the protective threshold of ≥4 pills per week at all time points.

The most common overall reasons reported by participants for missing study pills were that they "often" or "sometimes" simply forgot (28.5%), were away from home (27.3%), or too busy with other things (26.7%). A few participants reported that they missed medication because they wanted to avoid side effects (4.48%), did not want others to see them taking the medication (2.47%), or they believed the pill was harmful (1.9%).

There were several statistically significant differences in beliefs about PrEP by whether participants were categorized as adherent (≥4 pills or week) or nonadherent (<4 pills or week). Adherent participants worried less about getting HIV ($P = 0.01$), felt more comfortable having sex with an HIV-positive partner ($P = 0.01$), and feared developing medication resistance if they contracted HIV ($P = 0.004$) compared with nonadherent participants. Significantly more nonadherent participants reported not liking taking pills than adherent participants ($P = 0.02$).

Sexual Risk Behavior and Risk Compensation

At enrollment, 81% of participants reported condomless sex with a partner in the previous month and 58% reported condomless receptive anal sex with their last partner. Participants reported an average of 5 sexual partners in the previous month, and 22% of participants were diagnosed with an STI at baseline. The overall STI incidence rate on study was 66.44 (95% confidence interval: 50.53 to 82.35), with greater STI incidence in the first 24 weeks of study (76.48/100 person-years) than the latter half of the study (60.99/100 person-years). An additional indicator of HIV exposure—postexposure prophylaxis prescriptions—also remained stable with one or zero participants requesting postexposure prophylaxis at each study visit week.

We also examined the relationship between HIV sexual risk behavior and pill adherence. For participants who reported engaging in recent condomless sex, TFV-DP levels

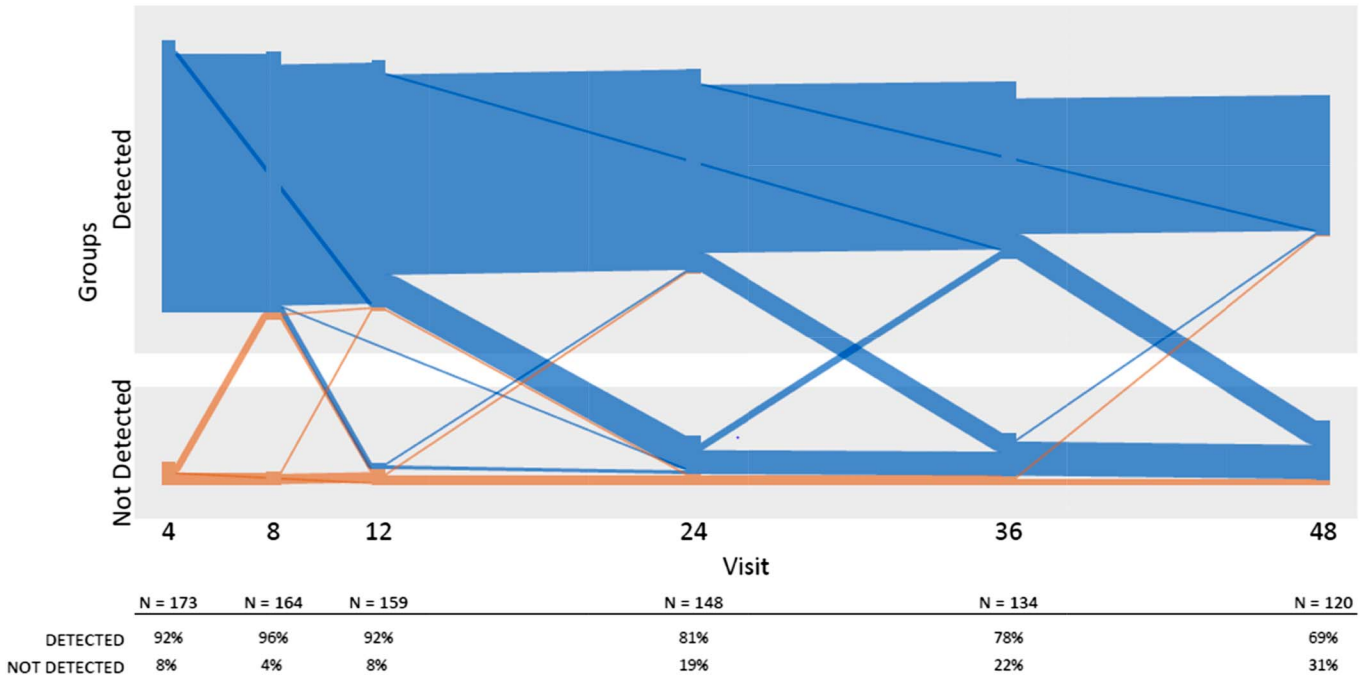

FIGURE 2. Longitudinal drug detection in plasma in the ATN 110 cohort by individual participant and visit week. Lines in blue and orange represent participants who had drug detected and not detected, respectively, at the earliest follow-up visit with drug-level testing. Plasma was tested every 4 weeks up to week 12 and every 12 weeks up to week 48. Overall declining numbers reflect fewer individuals with longer duration of follow-up because of enrolling on a later date and loss to follow-up (approximately 29% of participants had an early termination visit). AMTU, Adolescent Medicine Trials Unit; BLD, below level of detection.

were consistently higher ($P = 0.01$) and remained higher over the course of the study. A similar, yet not statistically significant, trend for higher TFV-DP was seen among participants who reported condomless receptive anal sex with their last partner.

Four HIV seroconversions occurred during the study (one each at weeks 4, 32, 40, and 48) for an HIV incidence rate of 3.29 per 100 person-years (95% confidence interval: 0.07 to 6.52). None of the participants who seroconverted had detectable levels of TFV-DP in the sample that was drawn closest to the seroconversion date (Fig. 4). All participants who seroconverted were immediately linked to medical care, and no antiretroviral drug resistance was detected.

DISCUSSION

This study, which enrolled the youngest and most diverse cohort of YMSM of any domestic PrEP study to date, provides critical safety and adherence data for youth who are at greater risk for HIV infection in the United States. Although loss-to-follow rates did increase over time, possibly reflecting the chaotic and mobile nature of youths' lives,

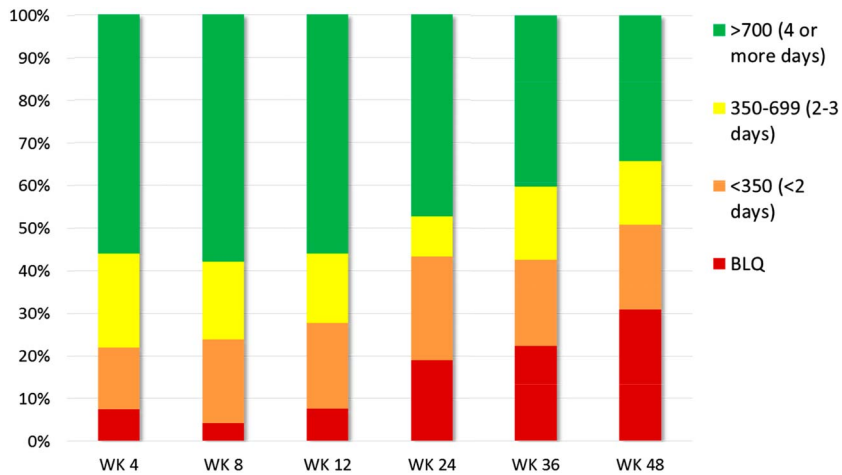

FIGURE 3. TFV-DP levels (femtomoles per punch) and PrEP dosing estimates as measured by DBS assay.

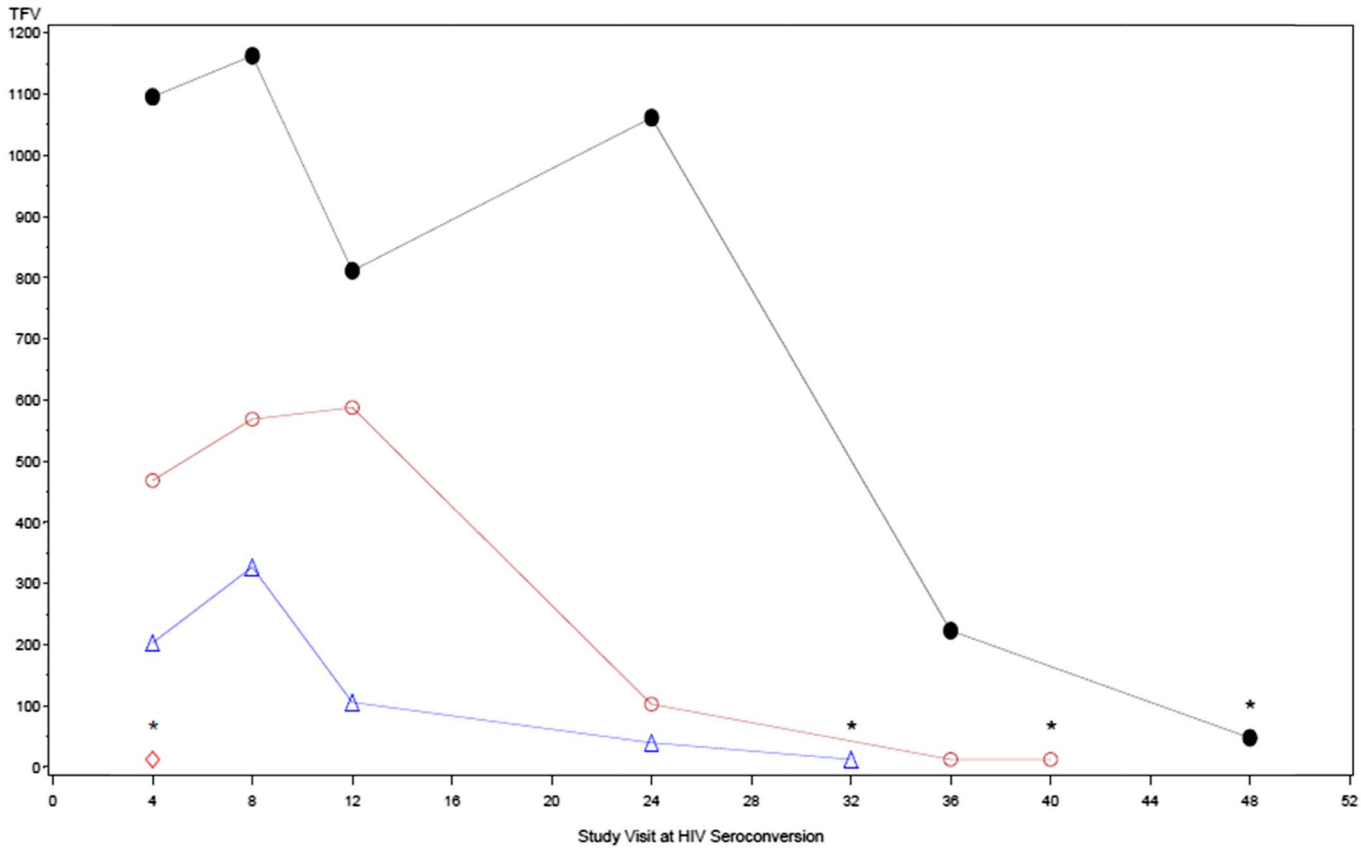

FIGURE 4. TFV-DP levels among seroconverters by study week until seroconversion (*).

participants reported high acceptability of many of the study components. Despite the loss to follow-up, the ratio of expected to actual visits was very high and likely a reflection of the culturally competent and youth-friendly sites used for this study.

Low BMD at baseline was not unexpected, particularly among YMSM from racial and ethnic minority communities. Although the causes are not yet explained, lower than expected BMD Z scores at baseline have been seen in other studies of HIV-negative at-risk men.[25–28] However, despite the absence of any significant bone events on study, loss before attainment of peak bone mass in such young men who are starting out with low BMD may raise the risk for potential fragility in adulthood and merits further investigation. An extended follow-up of such individuals who met predefined safety criteria at the end of this study is currently underway to determine the extent of how reversible these changes may be. That said, the absence of any significant renal toxicities or other clinical AE among participants was reassuring, though renal injury from TDF may require longer exposure than participants experienced in this study.

Adherence to the daily medication regimen waned over time, but most participants were able to achieve protective levels of PrEP for the first quarter of the study, and very few participants had undetectable drug levels overall. These adherence rates are an improvement to a previous youth-focused PrEP trial[7] and demonstrate that these participants tried to take PrEP as directed. However, as has consistently been shown in the literature, rates of medication adherence among youth are often far below the rates seen in adults and tend to decline over time,[29] indicating that youth-specific adherence intervention strategies are still needed. Adherence "boosters," such as text messaging or check-in calls that have been successful in improving adherence to treatment for HIV-positive youth, could potentially prove useful for PrEP.[30,31] Of further note was the decline in adherence seen as study visit intervals increased from monthly to quarterly. Other pediatric and adolescent specialties have documented the relationship between visit frequency, improved adherence, and better health outcomes.[32–34] It may also be the case that clinical schedules for PrEP care need to be flexible and a more developmentally appropriate approach could be to see young people more frequently. Studies to evaluate alternative visit schedules for PrEP implementation among youth are needed.

Consistent with other recent PrEP demonstration studies,[5,6,10] baseline rates of HIV transmission risk behavior and STIs were very high among participants enrolled in this study, and these behaviors remained largely stable over time. Although this suggests that behavioral disinhibition was uncommon, it also suggests that risk maintenance remained high and underscores the importance of PrEP and adherence counseling for HIV prevention in YMSM. The identification of previously undiagnosed prevalent cases of HIV (4%) during screening for this study and 2 acute HIV infections

and their expedient linkage to life-saving care is an important public health advantage of PrEP programs.

The most concerning finding in this study was the adherence discrepancies seen among those who identified as black/African American compared with participants of other racial/ethnic groups. Unfortunately, this finding is consistent with recent research highlighting lack of exposure to HIV prevention interventions, and PrEP in particular, by black YMSM.[35–37] In-depth analyses are needed to further our understanding of potential racial differences in DBS pharmacokinetics and the historical, societal, behavioral, and attitudinal barriers to PrEP access and adherence among those most affected in the United States—black/African American YMSM.

In conclusion, the ATN 110 study, the first entirely youth-focused open-label PrEP trial, enrolled a highly diverse sample of YMSM who demonstrated elevated vulnerability to HIV and levels of reported risk behavior remained relatively constant throughout the study. Among those youth who were eligible for the study, uptake of PrEP was very high and most of the participants achieved protective drug levels (≥4 pills per week) during monthly visits. As the study visits decreased in frequency, adherence to the daily PrEP regimen declined. The striking racial disparities in adherence indicate that much more work is needed to understand and implement PrEP in a way that is culturally competent. Finally, given the number of STI diagnoses while on study, HIV infections among this cohort would likely have been much higher in the absence of PrEP.

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