Randomized Trial of Clinical Safety of Daily Oral Tenofovir Disoproxil Fumarate Among HIV-Uninfected Men Who Have Sex With Men in the United States

Lisa A. Grohskopf, MD, MPH,* Kata L. Chillag, PhD,* Roman Gvetadze, MD, MSPH,† Albert Y. Liu, MD, MPH,‡ Melanie Thompson, MD,§ Kenneth H. Mayer, MD,ǁ Brandi M. Collins, MPH,¶ Sonal R. Pathak, MPH,¶ Brandon O’Hara, MSPH,¶ Marta L. Ackers, MD, MPH,* Charles E. Rose, PhD,† Robert M. Grant, MD, MPH,# Lynn A. Paxton, MD, MPH,* and Susan P. Buchbinder, MD‡

Objectives: To evaluate the clinical safety of daily tenofovir disoproxil fumarate (TDF) among HIV-negative men who have sex with men.

Design: Randomized, double-blind, placebo-controlled trial. Participants were randomized 1:1:1:1 to immediate or delayed study drug (TDF, 300 mg orally per day, or placebo).

Methods: Four hundred healthy HIV-uninfected men who have sex with men reporting anal sex with another man within the previous 12 months enrolled in Atlanta, Boston, and San Francisco. HIV serostatus, clinical and laboratory adverse events (AEs), adherence (pill count, Medication Event Monitoring System, and self-report), and sexual and other sociobehavioral data were assessed at 3-month intervals for 24 months. Primary outcomes were clinical safety, assessed by incidence of AEs and laboratory abnormalities.

Results: Study drug was initiated by 373 (93%) participants, 2366 (97%) were mild or moderate in severity. Frequencies of commonly reported AEs did not differ significantly between TDF and placebo arms. In multivariable analyses, back pain was more likely among TDF recipients (P = 0.04); these reports were not associated with documented fractures or other objective findings. There were no grade ≥3 creatinine elevations; grades 1 and 2 creatinine increases were not associated with TDF receipt. Estimated percentage of study drug doses taken was 92% by pill count and 77% by Medication Event Monitoring System. Seven seroconversions occurred: 4 on placebo and 3 among delayed arm participants not yet on study drug.

Conclusions: Daily oral TDF was well tolerated, with reasonable adherence. No significant renal concerns were identified.

Key Words: PrEP, preexposure prophylaxis, prevention and control, HIV, antiretroviral agents, tenofovir, clinical trial, phase 2

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INTRODUCTION
Thirty years after the first published HIV/AIDS case,1 biomedical and behavioral interventions have not adequately controlled the pandemic. Globally, more than 33 million are estimated to be infected. Although estimated new infections have declined annually since the late 1990s, incidence remains unacceptably high, with certain geographical areas and risk groups disproportionately affected.2 In the United States, an estimated 48,600 new infections occur annually, over half among men who have sex with men (MSM).3 A troubling increase in incidence has been noted among MSM, particularly young MSM of color.4 HIV antiretroviral preexposure prophylaxis (PrEP) may become an important prevention option for some at-risk MSM. Human PrEP trials were undertaken based on considerations of biological plausibility, experiences with antiretroviral use for prevention of perinatal transmission and PrEP, availability of well-tolerated antiretrovirals, and indications of efficacy from animal models.5–8 Most trials have evaluated tenofovir disoproxil fumarate (TDF, Viread) or the fixed-dose combination of TDF and emtricitabine (TDF/FTC, Truvada). The US Food and Drug Administration (FDA) recently approved the use of TDF/FTC as PrEP in July 2012.9 Efficacy of oral TDF/FTC PrEP was demonstrated among MSM in several Latin American countries,6 among African women in Botswana11 and heterosexual serodiscordant couples in Kenya and Uganda.12 However, 2 studies conducted among heterosexually active women in several African countries (the Pre-exposure Prophylaxis Trial for HIV Prevention Among African Women (FEM-PrEP) trial of daily oral TDF/FTC and the Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial of daily oral TDF or TDF/FTC and daily topical 1% TDF gel) have stopped one or more arms for futility after interim data reviews.13,14 TDF use in persons with HIV infection has been associated with potentially serious adverse effects, including nephrotoxicity (proximal tubule dysfunction and Fanconi syndrome), hypophosphatemia secondary to renal wasting, and reduced bone mineral density (BMD).15–26 Less serious effects, such as nausea, flatulence, and diarrhea, may adversely affect adherence to daily TDF. We describe here clinical outcomes of the first safety study among US MSM to evaluate potential use of TDF as PrEP in this population. Effects on BMD observed in this investigation have been published previously.27 This study represents the largest safety database of US participants on oral daily PrEP to date.

METHODS

Study Design
In this randomized, double-blind, placebo-controlled trial, participants were randomized 1:1:1:1 to receive TDF, 300 mg orally per day, or matching placebo, immediately or after a 9-month delay. The delayed arms were intended to assess changes in risk behavior associated with taking study drug (results reported separately). Randomization was performed in blocks of 8, stratified by site. It was determined that a sample size of 400 would provide 73%–85% power to detect 5%–6% difference in risk of developing an adverse event (AE) between treatment groups, assuming AE risk in placebo groups as low as 1%.

Participants
From January 2005 through July 2007, participants were recruited from 3 sites: the San Francisco Department of Public Health (SFDPH), San Francisco, CA; the AIDS Research Consortium of Atlanta, Atlanta, GA; and Fenway Health, Boston, MA. Eligible participants were healthy biological males, 18–60 years of age, who reported anal sex with another man in the preceding 12 months, were HIV-1 negative by whole blood rapid enzyme immunoassay, had a calculated Cockcroft–Gault creatinine clearance ≥70 mL/min, were hepatitis B surface antigen negative, and had normal hematologic, biochemical, and urinalysis profiles. Exclusion criteria included active untreated syphilis; uncontrolled hypertension; mutual monogamy for ≥1 year with an HIV-uninfected partner; chronic renal disease; osteoporosis, osteomalacia, or osteopenia; BMD Z score less than −2.5 at the total spine, total hip, or femoral neck on screening [dual-energy x-ray absorptiometry scans done at SFDPH only]; current treatment for secondary causes of low BMD; participation in other longitudinal HIV studies; current antiretroviral use, current/planned therapy with potentially nephrotoxic agents; previous/expected requirements for immunosuppressive/immunomodulatory therapy; gastrointestinal malabsorption syndrome or chronic nausea/vomiting; or medical or social conditions that would interfere with study participation. Ethical approvals were obtained through the Institutional Review Boards of Centers for Disease Control and Prevention and all study sites. Each site maintained a community advisory board representative of the study population to provide input on acceptability and feasibility of study design, implementation, and recruitment issues. Participant follow-up was completed in July 2009.

Procedures
Study visits occurred at 1, 3, 6, 9, 12, 15, 18, 21, and 24 months postenrollment. Delayed arm recipients had an additional visit at 10 months. Visits included AE assessment, symptom-directed physical examination, blood and urine collection, sexually transmitted infection testing, behavioral assessment via audio computer-assisted self-interview, and risk reduction and adherence counseling. Participants were followed for 24 months, even if the study drug was discontinued. Persons who became HIV infected were seen at 3, 6, 9, and 12 months after diagnosis. Visits included assessment of HIV-1 RNA, CD4 cell count, and genotypic/phenotypic resistance.

Laboratory Safety Assessments
HIV testing with an FDA-approved rapid test was performed at each visit; preliminary positives were followed by both a second FDA-approved enzyme immunoassay and either a Western blot or an immunofluorescence assay. Participants with positive rapid and confirmatory tests were further evaluated as described below. Laboratory studies included complete blood count, white blood cell differential,
comprehensive metabolic panel, including creatinine, phosphorus, and liver enzymes, and urinalysis.

**Grading of Clinical and Laboratory Events**

Clinical AEs and laboratory abnormalities (except serum creatinine) were graded using the National Institutes of Health Division of AIDS toxicity tables (January 2004). Laboratory abnormalities were AEs if they (1) were grade 3 or 4, confirmed upon repeat testing, (2) were associated with symptoms, (3) led to discontinuation of the study drug, (4) required treatment, or (5) were otherwise judged clinically significant. Serious AEs (SAEs) were defined as events (1) that were fatal or life threatening, (2) that required or prolonged hospitalization, (3) that resulted in permanent or significant disability or incapacity, or (4) that in the judgment of the investigator might jeopardize the participant and require intervention to prevent one of the outcomes above.

Serum creatinine was graded according to the Gilead Sciences Modified National Institute of Allergy and Infectious Diseases (NIAID) Common Toxicity Grading Scale, with the additional modification that grade 1 was defined as $\geq 0.5$ mg/dL above baseline. All graded elevations were repeated for confirmation. For confirmed grade 1 or 2 creatinine elevations (2.1–3.0 mg/dL), the study drug was withheld and restarted with return of the serum creatinine to within 0.3 mg/dL above baseline. Confirmed recurrence of grade 1 or 2 elevations led to permanent discontinuation of the study product. For confirmed grade 3 (3.1–6.0 mg/dL) or grade 4 ($>6.0$ mg/dL) elevations, the study drug was permanently discontinued.

**HIV-1 Seroconversions**

Participants with positive rapid tests were immediately discontinued from study drug; those with positive confirmatory tests remained off drug. HIV-1 RNA, CD4 cell count, and HIV-1 genotype studies were obtained. Seroconverting participants were followed for an additional year and referred for appropriate clinical care.

**Exposure to Drug and Adherence Measures**

Three measures were collected: pill counts at each visit, bottle openings recorded by Medication Event Monitoring System (MEMS) caps, and self-report via audio computer–assisted self-interview (participants estimated the percentage of days they took drug over the preceding month on a visual analog scale). For clinical and laboratory safety analyses, pill count or MEMS data were used to estimate exposure to study drug (ESD). Pill count ESD was calculated as a ratio of number of pills taken within study visit interval over number of days in that interval. MEMS ESD was calculated as a ratio of number of recorded cap openings in a given study visit interval over number of days in that interval (including only one opening per day). Pill count and MEMS adherence estimates were similarly defined except temporary drug interruptions were excluded from the time denominator.

**Statistical Methods**

All participants were included in baseline analyses. For clinical and laboratory safety, ESD, and adherence analyses, a treatment emergent (TE) cohort was defined, including all participants who were dispensed study drug. Participants entered the TE cohort with first dispense and exited with the first occurrence of the following: (1) completion of follow-up (24 months), (2) 30 days after permanent drug interruption, or (3) 30 days after last recorded study visit. For delayed arm participants, time before initiation of study drug was excluded from analyses.

Fifteen AEs, defined by MedDRA preferred terms, were chosen for analyses based on clinical importance, known association with TDF, and frequency of occurrence in the study: any grade 3 or 4 event, or any grade upper abdominal pain, back pain, nausea, depression, diarrhea, dizziness, fatigue, flatulence, fracture (any site), headache, increased creatinine, decreased bone density, hypophosphatemia, and proteinuria. Analyses considered each individual AE regardless of relatedness to study drug and considered both time to first reported AE and occurrence of recurrent AEs. In univariate analyses, association of AEs with treatment assignment was studied by modeling time to first reported AE using Cox proportional hazards regression. Incidence of recurrent AEs was compared between groups by modeling AE count using the generalized estimating equation formulation of Poisson regression with total follow-up time as an offset variable. Multivariable analysis included treatment assignment as the main predictor and the following covariates: site, immediate/delayed arm assignment, age, race, ethnicity, and ESD. Multivariable comparison of time to first AE was performed using the extended Cox model that accommodated time-dependent covariate ESD. To avoid underestimating risk, time to first event analysis was performed by selecting the lowest value of ESD between MEMS and pill count estimates calculated for each visit interval, dichotomized at 80% and 50%. The choice of thresholds was exploratory, given that minimal necessary adherence to PrEP for effectiveness is unknown. For analyses of recurrent events, a summary measure of ESD was obtained by taking the mean value of all available visit-specific estimates for each participant, and the lower MEMS and pill count summary estimates were also dichotomized at 80% and 50% level. Potential interactions between treatment assignment and each covariate were assessed. All statistical tests were 2 sided and interpreted at alpha = 0.05 level of significance. To minimize likelihood of missing safety signals, statistical test results were not adjusted for multiplicity. Analyses were performed using SAS/STAT Version 9.2, SAS System for Windows (SAS Institute Inc., Cary, NC).

**RESULTS**

**Trial Profile**

Overall, 679 persons were screened (Fig. 1). Among 279 participants who were screened but did not enroll, the most common reasons for ineligibility were laboratory abnormalities [58 (20.7%)], passive refusals [persons who did not return after screening, 50 (17.9%)], and active refusals [persons who actively declined enrollment, 37 (13.2%)].

Four hundred participants were enrolled (200 in San Francisco, 121 in Atlanta, and 79 in Boston). Two hundred were randomized to each of the delayed and immediate arms; 201 were randomized to TDF and 199 to placebo. Among all...
enrolled participants, 331 (83%) completed the final study visit; those who did not complete this visit were similarly distributed among the study arms (P = 0.71). A higher proportion of participants completed the final study visit in San Francisco (180/200, 90%) as compared with Atlanta (91/121, 75%) and Boston (60/79, 76%) (P = 0.0006).

A total of 373 (93%) participants were dispensed study drug at least once and thus entered the TE cohort. All 200 participants in the immediate arms initiated study drug, compared with 173 (87%) of 200 delayed arm participants (P < 0.001). Among those participants who initiated study drug, 325 (87%) completed the final study visit.

Baseline Demographic and Other Characteristics

Participants were distributed similarly among the study arms in terms of age, ethnicity, education, number of male partners in previous 3 months, and number of unprotected anal sexual contacts within the previous 3 months (Table 1). Race distribution differed, with higher proportions of participants reporting African American race in the placebo arms.

Estimates of ESD and Adherence

A total of 178 temporary drug interruptions were documented among the 373 participants: 84 on TDF and 94 on placebo. The median length of temporary drug interruptions for TDF was 37 days (range 2–428 days) and for placebo was 47 days (range 1–533 days, P = 0.055).

Sixty-six permanent drug interruptions were documented (17.6% of participants). Among these, 2 were for persistent elevation of serum creatinine ≥0.5 mg/dL over baseline (both participants were assigned to placebo) and one was for confirmed grade 4 hypophosphatemia (participant was assigned to placebo). As reported previously, among participants from San Francisco who received baseline and at least one follow-up dual-energy x-ray absorptiometry evaluation, 11 were permanently discontinued from study drug because of decrease in BMD of less than 5% relative to baseline (8 on TDF, 3 on placebo; P = 0.13).

Overall, median ESD estimated from pill count was 92% (range 79%–98%). Estimated exposure on drug based on MEMS data was lower, at 77% (range 57%–92%). When periods of directed drug interruption were removed from this calculation to estimate adherence, results did not substantially change: overall adherence was estimated to be 93% (range 81%–98%) by pill count and 79% (range 60%–92%) by MEMS.

Adverse Events

Overall, 2428 TE clinical and laboratory AEs were recorded to have occurred among 334 (90%) participants. Most
Hypophosphatemia

Mild to moderate hypophosphatemia was relatively common among study participants and occurred with similar rates on TDF and placebo. Grade 1 hypophosphatemia occurred in 12 (6.5%) participants on TDF vs. 12 (6.4%) on placebo ($P = 0.85$), grade 2 hypophosphatemia occurred in 31 (17%) participants on TDF vs. 25 (13%) on placebo ($P = 0.45$), and grade 3 hypophosphatemia occurred in 1 participant on TDF vs. 4 on placebo ($P = 0.20$). Only one grade 4 hypophosphatemia was reported; this participant received placebo.

Serious AEs

A total of 29 protocol-defined SAEs occurred among 18 participants (10 on TDF and 8 on placebo, $P = 0.62$). The most commonly reported SAE was depression (4 reports from participants on TDF and 2 on placebo). The following were reported for individual participants in the TDF arms: pulmonary edema, appendicitis, prostate cancer, atrial fibrillation, colon cancer, gastrointestinal ulcer hemorrhage, mania, poisoning, seroma, and spinal fracture. Only one SAE, the grade 4 hypophosphatemia on placebo noted above, was considered possibly related to study drug.

One SAE involved a participant death. The cause was determined to be combined opioid and alcohol intoxication and was judged to be unrelated to study drug. The participant had been taking TDF.

Seroconversions

Among all 400 participants, 7 seroconversions were documented. None occurred among participants taking TDF. Three occurred among participants taking placebo; 3 occurred among delayed arm participants who had not yet started drug. One occurred in a participant assigned to placebo who was HIV-1 antibody negative at screening and enrollment and then was seropositive at the 1-month visit. Confirmatory Western blot was also positive. Viral load performed on a stored specimen from the enrollment visit was 1770 copies per milliliter; thus, this participant was already infected at enrollment. No K65R mutations were noted among any seroconverting participants.

## DISCUSSION

In these analyses from a study of PrEP among MSM from 3 US cities, TDF was generally well tolerated. While most participants reported at least one AE, most ($>90\%$) were of mild/moderate severity and were not associated with TDF. Severe and SAEs were uncommon and were not associated with TDF as compared with placebo. Few creatinine and phosphorous abnormalities were detected. Creatinine elevations were mild to moderate in severity and not associated with TDF.

BMD studies among the subset of SFPDPH participants demonstrated that receipt of TDF was associated with small but statistically significant decreases in BMD at the femoral neck (1.1% decrease) and total hip (0.8% decrease). In the

### TABLE 1. Baseline Characteristics by Study Arm, Randomized Trial of Clinical Safety of Daily Oral TDF Among HIV-Uninfected MSM

<table>
<thead>
<tr>
<th>TDF (N = 201)</th>
<th>Placebo (N = 199)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years, median (range)</strong></td>
<td>38 (18–60)</td>
<td>37 (18–60)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>160 (79.6)</td>
<td>133 (66.8)</td>
</tr>
<tr>
<td>African American</td>
<td>23 (11.4)</td>
<td>37 (18.6)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>10 (5.0)</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (4.0)</td>
<td>25 (12.6)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>16 (8.0)</td>
<td>20 (10.1)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>185 (92.0)</td>
<td>179 (89.9)</td>
</tr>
<tr>
<td><strong>Education, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never graduated from high school</td>
<td>6 (3.0)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>High school graduate or equivalency</td>
<td>14 (7.0)</td>
<td>20 (10.1)</td>
</tr>
<tr>
<td>Some college</td>
<td>68 (33.8)</td>
<td>66 (33.2)</td>
</tr>
<tr>
<td>College graduate</td>
<td>113 (56.2)</td>
<td>110 (55.3)</td>
</tr>
<tr>
<td><strong>Immediate/delayed arm, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>101 (50.2)</td>
<td>99 (49.7)</td>
</tr>
<tr>
<td>Delayed</td>
<td>100 (49.8)</td>
<td>100 (50.3)</td>
</tr>
<tr>
<td><strong>Site, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atlanta</td>
<td>61 (30.3)</td>
<td>60 (30.2)</td>
</tr>
<tr>
<td>Boston</td>
<td>40 (19.9)</td>
<td>39 (19.6)</td>
</tr>
<tr>
<td>San Francisco</td>
<td>100 (49.8)</td>
<td>100 (50.3)</td>
</tr>
<tr>
<td><strong>Male partners in last 3 mo, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (2–9)</td>
<td>4 (2–7)</td>
<td>0.140†</td>
</tr>
<tr>
<td><strong>Unprotected receptive anal sex with man last 3 mo, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 (29.9)</td>
<td>65 (32.7)</td>
<td>0.544†</td>
</tr>
</tbody>
</table>

*Wilcoxon rank sum test.
†Negative binomial regression.

(2366, 97%) were of mild (grade 1) or moderate (grade 2) severity: 1845 (76%) grade 1 events and 521 (21%) grade 2 events. Sixty-two grade 3 or 4 AEs occurred among 37 (9.9%) participants. Univariate analyses of selected clinical AEs are summarized in Figure 2. None occurred significantly more frequently in the TDF as compared with the placebo arms.

Multivariable analyses of clinical AEs, adjusted for demographic parameters and drug exposure levels of ≥50% and ≥80%, are described in Table 2. In these analyses, back pain was associated with receipt of TDF. Review of study records of participants reporting back pain revealed no recorded fractures or other objective findings.

Creatinine Abnormalities

No grade 3 or 4 creatinine elevations were recorded. Grades 1 and 2 elevations were uncommon and occurred with similar frequency in the TDF and placebo groups: 1 (0.5%) grade 1 elevation on TDF vs. 4 (2.1%) on placebo ($P = 0.20$) and 1 (0.5%) grade 2 elevation on TDF vs. 2 (2.1%) on placebo ($P = 0.55$). Confirmed elevated creatinine values of ≥0.5 mg/dL over baseline occurred in 2 participants; both were discontinued from study drug. Both were assigned to placebo.

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multivariable analyses reported here (which were not corrected for multiple comparisons), only back pain was associated with receipt of TDF. Back pain was reported by participants in earlier clinical studies of TDF but did not occur at higher frequency than with placebo. No vertebral fractures were documented among those reporting back pain in this study; overall bone fractures at any anatomic site were not associated with the receipt of TDF.

TABLE 2. Multivariable Analyses of Treatment Condition on Multiple Occurrence of Selected AEs, Adjusted for Demographic Characteristics, Immediate or Delayed Arm Assignment, Study Site, and Summary ESD Dichotomized at 80% and 50% Level, Randomized Trial of Clinical Safety of Daily Oral TDF Among HIV-Uninfected MSM, January 2005–July 2009

<table>
<thead>
<tr>
<th>MedDRA Term</th>
<th>Poisson GEE Regression With Summary ESD (80%)</th>
<th>Poisson GEE Regression With Summary ESD (50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted IRR* (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Grade 3 or 4 AE</td>
<td>1.08 (0.57 to 2.03)</td>
<td>0.820</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.73 (0.49 to 1.09)</td>
<td>0.126</td>
</tr>
<tr>
<td>Back pain</td>
<td>1.97 (1.02 to 3.82)</td>
<td>0.040</td>
</tr>
<tr>
<td>Headache</td>
<td>0.85 (0.50 to 1.46)</td>
<td>0.556</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.56 (0.74 to 3.30)</td>
<td>0.233</td>
</tr>
<tr>
<td>Depression</td>
<td>0.74 (0.41 to 1.33)</td>
<td>0.311</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.39 (0.74 to 2.61)</td>
<td>0.312</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0.92 (0.49 to 1.72)</td>
<td>0.791</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.20 (0.88 to 5.49)</td>
<td>0.089</td>
</tr>
<tr>
<td>Fracture (any site)</td>
<td>1.90 (0.50 to 7.17)</td>
<td>0.329</td>
</tr>
</tbody>
</table>

*Incidence rate ratio.
CI, confidence interval; GEE, generalized estimating equation.
This study has a number of limitations. Generalizability of these findings may be limited, in that participants were required to meet relatively stringent eligibility requirements. The adherence measures used in this study to estimate time on drug—self-report, pill count, and MEMS—each have characteristic limitations. The level of adherence required for protection is unknown. There were few seroconversions, none of which occurred while the participant was on active drug. This prevents assessment of the contribution of single-drug PrEP with TDF on the development of drug resistance. Most AEs in our study population occurred with relatively low frequency, restricting power to determine association with TDF and to perform multivariable analyses. However, the MEMS data suggest that the participants in this study were reasonably adherent; so, the lack of findings of TDF-associated toxicity is reassuring. Finally, this study was neither powered nor designed for efficacy assessment. These data are reassuring in that all new infections occurred among men who were not using TDF chemoprophylaxis—3 were on placebo and 3 were delayed arm participants who had not yet started drug. Pooling participants not yet on drug with those on placebo would negate the placebo-controlled aspect of the study design and would break randomization (as not all who were in the delayed arm were randomized to start placebo).

It is interesting that significantly fewer participants randomized to the delayed arms initiated study drug. The reasons for this are not known. It is possible that risk reduction counseling provided at every visit may have resulted in some participants feeling less personal need for PrEP. Also, the long interval may have provided participants time to reflect further on the potential implications of taking a pill every day. The majority of delayed arm participants, 87%, did elect to start study drug as planned.

In contrast to other PrEP trials, which required monthly visits, this trial implemented quarterly clinical and laboratory assessments. This visit schedule was adequate to detect important safety events and may be more feasible than a monthly schedule. The current Centers for Disease Control and Prevention interim guidance for the use of PrEP recommends HIV antibody testing, risk behavior assessment, and risk reduction counseling every 2–3 months after initiation of PrEP and assessment of blood urea nitrogen and creatinine 3 months after PrEP initiation and annually thereafter. Adherence assessment and counseling are also recommended at each visit; more frequent monitoring is recommended if inconsistent adherence is identified.

This study is relatively unusual among published PrEP studies in involving a single drug rather than a 2-drug regimen. For this first safety study of PrEP in MSM, TDF alone was evaluated, as this was potentially the more toxic agent of the combination TDF/FTC regimen and permitted more straightforward assessment of drug-associated AEs. Subsequent efficacy trials evaluated TDF/FTC, although some trials included a TDF-only arm. Although efficacy was high in the TDF-only arm of PrEP in the Partners PrEP study, there are concerns that PrEP with TDF alone could select viruses that have the RT K65R mutation that confers broad cross-resistance to nucleoside and nucleotide RT inhibitors, whereas FTC/TDF PrEP more commonly selects the RT M184V/I mutations that cause resistance limited to FTC and 3TC and typically cause hypersusceptibility to TDF and zidovudine (AZT). Regardless of regimen, the risk of drug resistance has been limited in trials to those starting PrEP with preexisting infection, emphasizing that HIV testing using sensitive fourth generation antigen + antibody assays or RNA assays will reduce drug resistance risk during PrEP to very low levels. The single-pill, fixed-drug combination FTC/TDF provides a simple once-daily regimen and has demonstrated a favorable safety profile in several studies.

Efficacy of daily PrEP with oral FTC/TDF has been demonstrated among MSM and heterosexual men and women in 3 studies to date; one study was not able to demonstrate efficacy of oral FTC/TDF for heterosexual women. Oral TDF alone (without FTC) was efficacious among serodiscordant couples, a group that is thought to have high adherence, whereas an evaluation of oral TDF PrEP in individual heterosexual women was discontinued because of futility. The reasons for these conflicting results for heterosexual women are unclear but could represent differential penetration of the drugs into vaginal vs. rectal or penile tissues or differences in adherence.

Evidence for efficacy of daily oral FTC/TDF for MSM is clear on an intention to treat basis, and the reduction of HIV risk was high among those with detectable drug exposure, highlighting how the use of PrEP is a critical determinant of PrEP activity. However, important questions remain that bear on feasibility, desirability, and appropriateness of PrEP as an HIV prevention intervention. Financial cost and other barriers to access must be considered. The long-term safety of antiretroviral drugs in HIV-negative individuals is not yet known, nor is the likelihood for emergence of resistance in real-world use, with potentially less meticulous HIV monitoring than in the clinical research setting. Also uncertain is the percentage of individuals who will be able to adhere to a PrEP regimen and the necessary monitoring. The potential for behavioral risk compensation remains an open question, although risk compensation was observed neither in previous PrEP trials nor in open-label studies of postexposure prophylaxis. PrEP will require ongoing engagement with the health care system to monitor adherence, potential HIV exposure, and the appropriateness of PrEP for each individual over time.

In conclusion, these data contribute important information for the development of clinical guidelines for PrEP among US MSM. This trial augments a growing body of evidence demonstrating the safety of oral PrEP and with other published reports supports the need for thorough exploration of feasibility and acceptability of this potentially promising intervention.

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