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Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women

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ABSTRACT

BACKGROUND

Antiretroviral preexposure prophylaxis is a promising approach for preventing human immunodeficiency virus type 1 (HIV-1) infection in heterosexual populations.

METHODS

We conducted a randomized trial of oral antiretroviral therapy for use as preexposure prophylaxis among HIV-1–serodiscordant heterosexual couples from Kenya and Uganda. The HIV-1–seronegative partner in each couple was randomly assigned to one of three study regimens — once-daily tenofovir (TDF), combination tenofovir–emtricitabine (TDF–FTC), or matching placebo — and followed monthly for up to 36 months. At enrollment, the HIV-1–seropositive partners were not eligible for antiretroviral therapy, according to national guidelines. All couples received standard HIV-1 treatment and prevention services.

RESULTS

We enrolled 4758 couples, of whom 4747 were followed: 1584 randomly assigned to TDF, 1579 to TDF–FTC, and 1584 to placebo. For 62% of the couples followed, the HIV-1–seronegative partner was male. Among HIV-1–seropositive participants, the median CD4 count was 495 cells per cubic millimeter (interquartile range, 375 to 662). A total of 82 HIV-1 infections occurred in seronegative participants during the study, 17 in the TDF group (incidence, 0.65 per 100 person-years), 13 in the TDF–FTC group (incidence, 0.50 per 100 person-years), and 52 in the placebo group (incidence, 1.99 per 100 person-years), indicating a relative reduction of 67% in the incidence of HIV-1 with TDF (95% confidence interval [CI], 44 to 81; P<0.001) and of 75% with TDF–FTC (95% CI, 55 to 87; P<0.001). Protective effects of TDF–FTC and TDF alone against HIV-1 were not significantly different (P=0.23), and both study medications significantly reduced the HIV-1 incidence among both men and women. The rate of serious adverse events was similar across the study groups. Eight participants receiving active treatment were found to have been infected with HIV-1 at baseline, and among these eight, antiretroviral resistance developed in two during the study.

CONCLUSIONS

Oral TDF and TDF–FTC both protect against HIV-1 infection in heterosexual men and women. (Funded by the Bill and Melinda Gates Foundation; Partners PrEP ClinicalTrials.gov number, NCT00557245.)

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The use of antiretroviral medications for the prevention of HIV type 1 (HIV-1) transmission is a promising strategy for reducing the spread of HIV-1.[1-4] Antiretroviral treatment for persons infected with HIV-1 provides important clinical benefits and substantially reduces infectiousness.[5-7] Antiretroviral prophylaxis is a potential HIV-1–prevention strategy for those not yet infected with HIV-1, administered either as postexposure prophylaxis after high-risk occupational or nonoccupational exposure or as preexposure prophylaxis in those with ongoing HIV-1 exposure.[8,9] The rationale for antiretroviral prophylaxis in persons with ongoing exposure is based on its efficacy in infants exposed to HIV-1 during birth and breast-feeding[10] and the partial or full protection it confers against mucosal simian HIV challenge in primates.[11] In perinatal-transmission studies and animal models, the protective benefits of antiretroviral prophylaxis were maximized when the antiretroviral medication was administered both before and after HIV exposure.[12]

The efficacy of preexposure prophylaxis for HIV-1 protection in humans has been evaluated for tenofovir, in the form of a vaginal gel or as oral tenofovir disoproxil fumarate (TDF) or oral TDF coformulated with emtricitabine (TDF–FTC). Studies in animal models suggest that TDF–FTC provides greater protection against HIV-1 than TDF alone.[11] The possibility of differential efficacy, safety, and cost suggests that TDF and TDF–FTC could be compared as potential preexposure prophylaxis agents. Persons at ongoing risk for HIV-1 acquisition in whom preexposure prophylaxis could be studied include persons who are HIV-1–seronegative but are in a partnership with a person already infected with HIV-1 (an HIV-1–serodiscordant partnership).[13,14] We conducted the Partners Preexposure Prophylaxis (PrEP) Study, a multisite, phase 3, randomized, double-blind, three-group, placebo-controlled trial of daily oral TDF or TDF–FTC given as preexposure prophylaxis against HIV-1 acquisition among East African heterosexual men and women in HIV-1–serodiscordant partnerships.

Methods

Study Oversight

The Bill and Melinda Gates Foundation funded the study but did not oversee the protocol. Gilead Sciences donated the study medication but had no role in data collection, data analysis, or manuscript preparation. All authors vouch for the completeness and accuracy of the data presented.

Study Population

From July 2008 through November 2010, we enrolled heterosexual couples in which one partner was infected with HIV-1 and the other partner was not infected (HIV-1–serodiscordant couples) from nine sites in Kenya and Uganda (see Tables S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[15] The HIV-1–seronegative partners had normal renal function, were not infected with hepatitis B virus, and were not pregnant or breast-feeding. The HIV-1–seropositive partners were not receiving antiretroviral therapy and did not meet Kenyan or Ugandan guidelines for initiation of antiretroviral therapy.

The full study protocol and statistical analysis plan are available at NEJM.org. The study protocol was approved by the University of Washington Human Subjects Review Committee and ethics review committees at each of the study sites (see Table S3 in the Supplementary Appendix). All participants provided written informed consent in English or their local language.

Randomization and Study Procedures

At enrollment, partners seronegative for HIV-1 were assigned, in a 1:1:1 ratio, to one of the three study groups: once-daily TDF, TDF–FTC, or placebo. Randomization was achieved by means of fixed-size block randomization, with stratification by site. TDF was given at a dose of 300 mg, and FTC was given at a dose of 200 mg; these doses are also the standard for treatment of HIV-1. The study regimens were indistinguishable in appearance, and investigators, except for statistical staff at the central coordinating center, were unaware of the study-group assignments.

All participants received a comprehensive package of HIV-1 prevention services: HIV-1 testing with counseling before and after testing, individual and couples risk-reduction counseling, screening and treatment for sexually transmitted infections, free condoms with training and counseling, and referral for male circumcision and postexposure prophylaxis according to national policies. Vaccination against hepatitis B virus was also offered.

Participants seronegative for HIV-1 had monthly visits that involved HIV-1 testing, dispensation

of 30 days of study medication, collection of the prior month's unused medication, individualized adherence counseling, and standardized assessment of sexual behavior and side effects (see Table S4 in the Supplementary Appendix). Serum chemical and hematologic analyses were performed at 1 month and quarterly thereafter. Women were tested monthly for pregnancy; study medication was withheld in women who became pregnant, and they were referred for antenatal care and allowed to resume study medication when no longer pregnant or lactating.

Partners seropositive for HIV-1 were followed quarterly (see Table S5 in the Supplementary Appendix), with HIV-1 primary care services administered and with CD4 counts obtained every 6 months. Those who became eligible for the initiation of antiretroviral therapy according to national guidelines were actively counseled to initiate treatment and referred to local clinics.

END POINTS

The primary end point was seropositivity in partners previously seronegative for HIV-1. Monthly HIV-1 serologic testing involved two rapid HIV-1 antibody tests in parallel. Study medication was temporarily withheld if either test revealed seroreactivity and was permanently discontinued if enzyme-immunoassay testing confirmed HIV-1 acquisition (see Table S6 in the Supplementary Appendix). For persons with enzyme immunoassay–confirmed acquisition of HIV-1, samples were then tested by HIV-1 Western blotting and RNA polymerase-chain-reaction (PCR) assay at the University of Washington and were adjudicated by an HIV-1 end points committee. Because the study medication was taken by the seronegative partner, HIV-1 sequence analysis to assess transmission within the study partnership was not required for end-point determination and was not performed. For all participants in whom seroconversion occurred, archived plasma samples from visits before seroconversion were tested by means of the HIV-1 RNA PCR assay; those who had detectable HIV-1 RNA in samples from the time of enrollment were excluded with respect to analysis of the primary end point because HIV-1 infection had occurred before randomization.

STATISTICAL ANALYSIS

The study was end-point–driven. We calculated that 147 HIV-1 seroconversion events for each comparison (TDF vs. placebo and TDF–FTC vs. placebo) would provide 80% power, with a one-sided alpha level of 0.025, to detect a 60% relative decrease in the incidence of HIV-1 infection, with a lower bound of the 95% confidence interval excluding a 30% relative decrease in incidence (the null hypothesis).[15] We further calculated that a sample size of 4700 couples would achieve the target number of study end points, with 24 to 36 months of follow-up per couple and an expected incidence of HIV-1 infection of 2.75 per 100 person-years in the placebo group.[16]

The primary analysis was a modified intention-to-treat analysis, excluding only data from participants with HIV-1 RNA detected in plasma by means of PCR assay at enrollment. We used Cox regression, stratified according to site, to estimate the relative rates of time to first positive HIV-1 serologic test and the Kaplan–Meier method to estimate the cumulative probability of HIV-1 infection.

The study data were reviewed every 6 months by an independent data and safety monitoring board. For statistical monitoring, the Lan–DeMets spending approach was used to adjust the O'Brien–Fleming sequential-monitoring boundaries[17,18]; interim monitoring boundaries were computed by means of S+SeqTrial software (version 2.0, TIBCO). During its closed March 2011 session, the board noted a strong trend toward HIV-1 protection in the active preexposure prophylaxis groups and called an ad hoc meeting for July 10, 2011. At the July meeting, after reviewing data through May 31, 2011, the board recommended that the results of the study be publicly reported and the placebo treatment discontinued, because predetermined stopping rules were met with the demonstration of HIV-1 protection from preexposure prophylaxis. The present analysis includes updated data collected through July 10, 2011. Analyses were conducted using SAS software (version 9.2, SAS Institute).

RESULTS

STUDY PARTICIPANTS

We screened 7856 couples with discordant HIV-1 serostatus. We enrolled 4758 couples and followed 4747: 1584 randomly assigned to TDF, 1579 to TDF–FTC, and 1584 to placebo (Fig. 1). For 62% of the couples followed, the HIV-1–seronegative partner was male (Tables 1 and 2). Among participants seropositive for HIV-1, the median CD4 count was 495 cells per cubic millimeter (inter-

quartile range, 375 to 662), 80% had a CD4 count of 350 cells or more per cubic millimeter, and the median plasma HIV-1 RNA level was 3.9 $\log_{10}$ copies per milliliter (interquartile range, 3.2 to 4.5). Overall, baseline characteristics were similar across the three study groups.

FOLLOW-UP AND ADHERENCE

Retention was 96% or greater during the study period (Fig. 1), with 4722 of the 4747 followed participants (99.5%) completing at least one post-randomization HIV-1 test, for a total of 7830 person-years of follow-up for the assessment of

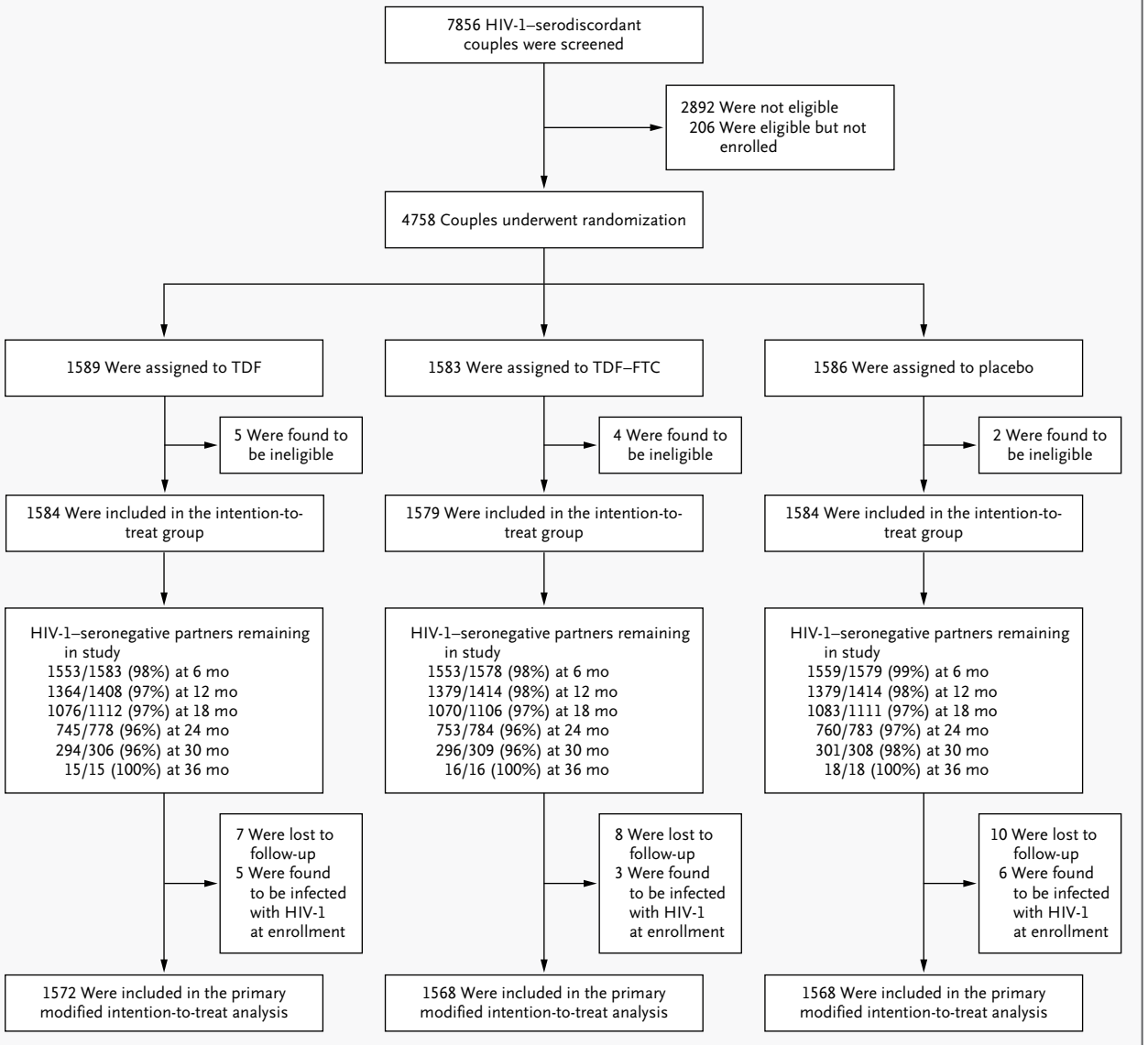


Figure 1. Enrollment and Follow-up of the Study Participants.

The most common reasons for ineligibility were HIV-1–seropositive partners' meeting national criteria for antiretroviral therapy initiation or already taking antiretroviral therapy (59%) and HIV-1–seronegative partners' being pregnant (2%), breast-feeding (0.4%), or having chronic active hepatitis B infection (10%). Less than 3% of ineligible couples met one of the exclusion criteria of creatinine elevation, glycosuria, or proteinuria in the HIV-1–seronegative partner, which were designed to minimize potential renal toxic effects from tenofovir (TDF) exposure. A total of 11 couples were enrolled and randomly assigned to one of the study groups but were later found not to meet all the eligibility criteria; they were discontinued from the study at the time their ineligibility was discovered, and their data were not included in analyses. At least 96% of HIV-1–seropositive partners remained in the study at any point during the follow-up period, and this percentage was similar across the three study groups. FTC denotes emtricitabine.

Table 1. Baseline Characteristics of the Study Participants, According to Study Group and HIV-1 Serostatus.*

Characteristic	TDF (N=1584 couples)		TDF–FTC (N=1579 couples)		Placebo (N=1584 couples)	
	Seronegative Partner	Seropositive Partner	Seronegative Partner	Seropositive Partner	Seronegative Partner	Seropositive Partner
Male sex — no. (%)	986 (62)	598 (38)	1013 (64)	566 (36)	963 (61)	621 (39)
Age — no. (%)						
18–24 yr	184 (12)	268 (17)	177 (11)	287 (18)	172 (11)	273 (17)
25–34 yr	721 (46)	657 (41)	690 (44)	636 (40)	688 (43)	629 (40)
35–44 yr	480 (30)	474 (30)	498 (32)	460 (29)	513 (32)	509 (32)
≥45 yr	199 (13)	185 (12)	214 (14)	196 (12)	211 (13)	173 (11)
Education — yr						
Median	7	7	7	7	7	7
Range	4–10	4–9	4–10	4–9	4–10	4–9
Any monthly income — no. (%)	1275 (80)	1069 (67)	1236 (78)	1052 (67)	1259 (79)	1079 (68)
Any sex with outside partner in prior month — no. (%)	150 (9)	84 (5)	134 (8)	106 (7)	122 (8)	103 (7)
CD4 cell count — cells/mm^3						
Median	NA	491	NA	497	NA	499
Range	NA	370–661	NA	380–664	NA	375–663
HIV-1 plasma RNA — $\log_{10}$ copies/ml†						
Median	NA	3.9	NA	3.9	NA	3.9
Range	NA	3.2–4.5	NA	3.1–4.5	NA	3.2–4.5
Circumcised (men only) — no./total no. (%)	533/986 (54)	198/598 (33)	540/1013 (53)	177/566 (31)	509/963 (53)	202/621 (33)
Using contraception (women only) — no./total no. (%)‡	263/598 (44)	290/986 (29)	275/566 (49)	324/1013 (32)	299/621 (48)	321/963 (33)
Pregnant — no./total no. (%)	0/598	152/986 (15)§	0/566	135/1013 (13)	0/621	118/963 (12)
Infection with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Trichomonas vaginalis* — no./ total no. (%)¶‖	86/1551 (6)§	117/1520 (8)	93/1557 (6)§	122/1525 (8)	126/1550 (8)	137/1534 (9)
Syphilis seropositivity — no./total no. (%)¶**	59/1569 (4)	73/1576 (5)	60/1572 (4)	52/1573 (3)	62/1569 (4)	73/1571 (5)
HSV-2 seropositivity — no./total no. (%)¶††	835/1506 (55)	NA	814/1507 (54)§	NA	875/1512 (58)	NA

* FTC denotes emtricitabine, HIV-1 HIV type 1, NA not applicable, and TDF tenofovir.

† Plasma HIV-1 RNA concentrations were quantified in enrollment samples by means of batch testing at the University of Washington with the use of the Real-Time HIV-1 RNA assay (Abbott) at a limit of quantification of 80 copies per milliliter.

‡ Contraception includes hormonal oral, injectable, or implantable contraceptive agents; intrauterine devices; and hysterectomy or bilateral tubal ligation. A total of 83% of the HIV-1–seronegative women and 85% of the HIV-1–seropositive women using contraception used a hormonal agent.

§ Results of only four comparisons with the placebo group were significant: prevalence of *Neisseria gonorrhoeae, Chlamydia trachomatis,* or *Trichomonas vaginalis* infection among HIV-1–seronegative partners receiving TDF (6%, vs. 8% receiving placebo; P=0.04) and receiving TDF–FTC (6%, vs. 8% receiving placebo; P=0.02), prevalence of HSV-2 seropositivity among HIV-1–seronegative partners receiving TDF–FTC (54%, vs. 58% receiving placebo; P=0.03); and prevalence of pregnancy among HIV-1–seropositive women receiving TDF (15%, vs. 12% receiving placebo; P=0.04).

¶ Data on sexually transmitted infections were available for more than 95% of participants.

‖ Participants were treated for symptomatic sexually transmitted infections that were found. *T. vaginalis* was the most common infection, accounting for 75% of all the infections detected. *N. gonorrhoeae* and *C. trachomatis* were tested for by different means (APTIMA Combo 2 [Gen-Probe] or COBAS Amplicor [Roche Diagnostics]) than was *T. vaginalis* (APTIMA Trichomonas vaginalis [Gen-Probe] or InPouch TV [BioMed Diagnostics]).

** Syphilis serologic testing was by means of rapid plasma reagin, confirmed with the use of a treponema-specific assay.[15] Seropositivity could indicate current or past infection.

†† Herpes simplex virus type 2 (HSV-2) testing was done by means of the HerpeSelect 2 enzyme immunoassay (Focus Technologies) at enrollment only; an index value of 3.5 or greater was considered a positive result.[19]

Table 2. Baseline Characteristics of the Study Couples, According to Study Group.*

Characteristic	TDF (N=1584)	TDF–FTC (N=1579)	Placebo (N=1584)
Married — no. (%)	1543 (97)	1540 (98)	1552 (98)
Years living together			
Median	7.0	7.1	7.3
Range	3.0–13.5	3.0–14.0	3.0–14.0
Number of children in partnership			
Median	2	2	2
Range	1–4	1–4	1–4
No children — no. (%)	343 (22)	368 (23)	342 (22)
Years aware of HIV-1–serodiscordant status			
Median	0.5	0.4	0.4
Range	0.1–2.0	0.1–2.0	0.1–2.0
Number of sex acts in prior month			
Median	4	4	4
Range	2–8	3–8	2–8
Any unprotected sex acts in prior month — no. (%)	442 (28)	416 (26)	409 (26)

* Characteristics of the couple were reported by the HIV-1–seronegative partner. No comparisons between either treatment group and the placebo group were significant.

HIV-1 incidence accrued (median, 23 months; interquartile range, 16 to 28; range, 1 to 36). Study medication was dispensed at 96% of the attended visits. The most common reason for not dispensing study medication was pregnancy (with an incidence of 11.9, 8.8, and 10.0 pregnancies per 100 woman-years in the TDF, TDF–FTC, and placebo groups, respectively; P>0.05). Time off the study medication due to pregnancy and breastfeeding accounted for 5.3% of the follow-up time among women (2.0% among all participants). Study-medication interruptions for safety-related reasons accounted for less than 1% of the overall follow-up time: 0.6% in the TDF group, 0.7% in the TDF–FTC group, and 0.6% in the placebo group.

The primary study measure of adherence was monthly counts of the returned study bottles and tablets: 98% of the dispensed study bottles were returned, and 97% of dispensed study tablets were taken (see Table S7 in the Supplementary Appendix). Factoring in missed visits, all reasons for nondispensation of study medication, and nonadherence to dispensed study pills, we calculated that study medication was in use during 92.1% of the total follow-up time.

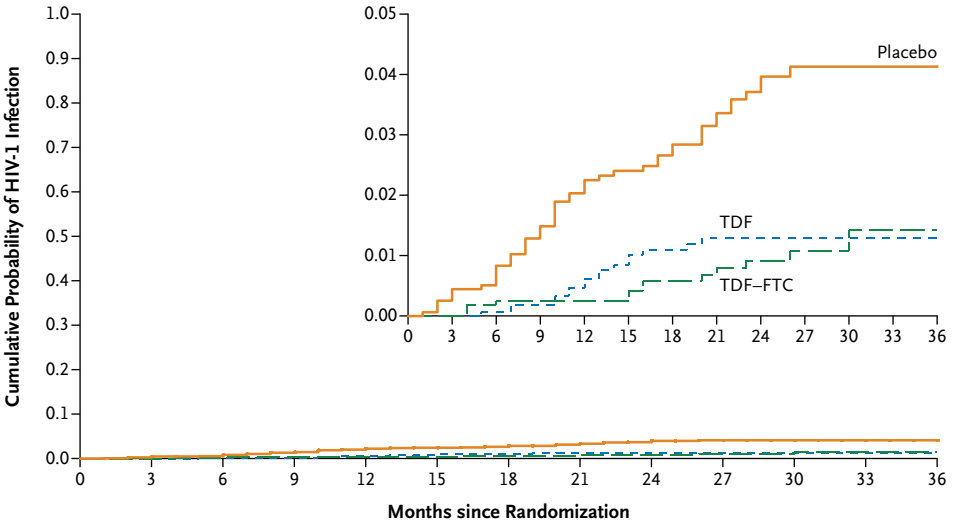
EFFECT OF TDF AND TDF–FTC ON HIV-1 ACQUISITION

HIV-1 seroconversion was observed in 96 participants, of whom 14 had plasma HIV-1 RNA retrospectively detected in specimens obtained at enrollment (5 receiving TDF, 3 receiving TDF–FTC, and 6 receiving placebo) (Fig. 1, and Fig. S1 in the Supplementary Appendix). Of 82 HIV-1 infections developing after randomization, 17 were in the TDF group, 13 were in the TDF–FTC group, and 52 were in the placebo group, indicating relative reductions in the rates of HIV-1 acquisition of 67% due to TDF (95% confidence interval [CI], 44 to 81; P<0.001) and 75% due to TDF–FTC (95% CI, 55 to 87; P<0.001), each relative to placebo (Fig. 2). The HIV-1–protective effects of TDF–FTC and TDF were not significantly different (P=0.23). With both TDF (P=0.003) and TDF–FTC (P<0.001), efficacy of less than 30% was ruled out in the primary modified intention-to-treat analysis. The intention-to-treat analysis including data for participants who were infected with HIV-1 at randomization yielded similar results (Fig. 3).

As compared with placebo, among women, the efficacy of TDF was 71% (P=0.002) and of TDF–FTC 66% (P=0.005); among men, the efficacies were 63% (P=0.01) and 84% (P<0.001), respectively. The HIV-1–protective effects of TDF and TDF–FTC were not statistically different according to sex. Protection against HIV-1 was generally similar between subgroup categories for other prespecified subgroups analyses (Fig. 3). During the follow-up period, 21% of the partners seropositive for HIV-1 (22% in the TDF group, 20% in the TDF–FTC group, and 21% in the placebo group) started combination antiretroviral therapy; the HIV-1–protective effects of TDF and TDF–FTC were similar to those observed in the primary modified intention-to-treat analysis if follow-up time after the HIV-1–seropositive partner started antiretroviral therapy was excluded (see Table S8 in the Supplementary Appendix).

ANTIRETROVIRAL RESISTANCE

Of the 96 persons who had seroconversion to HIV-1 positivity, 92 (96%) had plasma samples available for amplification of the HIV-1 RNA to assess for resistance (Table S9 in the Supplementary Appendix). Among the 8 participants in the TDF and TDF–FTC groups who were found to have been infected at randomization, HIV-1 with resistance to the study medications developed in 2 participants: 1 in the TDF group had a TDF-



No. at Risk													
TDF	1572	1559	1547	1498	1350	1223	1062	902	735	510	287	108	15
TDF–FTC	1568	1557	1546	1493	1371	1248	1059	901	743	525	291	114	16
Placebo	1568	1557	1544	1487	1347	1224	1061	902	744	523	295	120	18

Figure 2. Kaplan–Meier Estimates of the Primary End Point in the Modified Intention-to-Treat Analysis, According to Study Treatment.

resistant virus (K65R mutation), and 1 in the TDF–FTC group had an FTC-resistant virus (M184V mutation). No participants who acquired HIV-1 after randomization were infected with an HIV-1 strain with the K65R or M184V mutation.

DETECTION OF TENOFOVIR AND PROPHYLACTIC EFFECT

Among 29 participants in the TDF and TDF–FTC groups who became infected with HIV-1, 31% had a detectable tenofovir level in a plasma sample obtained at the seroconversion visit, as compared with 82% of 902 samples from a random subgroup of 198 participants who did not acquire HIV-1 (Table S10 in the Supplementary Appendix). A detectable level of tenofovir, as compared with an undetectable level of the drug, was associated with estimated reductions in the relative risk of acquiring HIV-1 of 86% (with TDF) and 90% (with TDF–FTC).

SEXUAL BEHAVIOR

At enrollment, 27% of partners seronegative for HIV-1 reported having sex without a condom with their HIV-1–seropositive partner during the prior month. This percentage decreased during the follow-up period (to 13% and 9% at 12 and 24 months, respectively) and was similar across the study groups (see Fig. S2 in the Supplementary Appendix). The proportions of participants reporting outside partnerships and acquiring sexually transmitted infections during the follow-up period did not differ significantly across the study groups (see Table S11 in the Supplementary Appendix).

SAFETY AND ADVERSE EVENT PROFILES

There were no significant differences in the frequency of deaths, serious adverse events, or serum creatinine or phosphorus abnormalities across the study groups (Table 3, and Table S12 in the Supplementary Appendix). Neutropenia was seen more commonly in the TDF–FTC group (17% of participants with a grade 1 or 2 event and 1% with a grade 3 or 4 event) (see Table S13 in the Supplementary Appendix) than in the TDF group (15% of participants with a grade 1 or 2 event and 1% with a grade 3 or 4 event) or the placebo group (12% of participants with a grade 1 or 2 event and 1% with a grade 3 or 4 event). The active study medications were associated with modestly increased reports of gastrointestinal side effects

Subgroup	TDF	TDF–FTC	Placebo	Hazard Ratio (95% CI), TDF vs. Placebo	P Value	Hazard Ratio (95% CI), TDF–FTC vs. Placebo	P Value
	no. of events/total no. (rate per 100 person-yr)						
Overall							
Modified intention-to-treat population	17/1579 (0.65)	13/1576 (0.50)	52/1578 (1.99)	0.33 (0.19–0.56)	<0.001	0.25 (0.13–0.45)	<0.001
Intention-to-treat population	22/1584 (0.84)	16/1579 (0.61)	58/1584 (2.22)	0.38 (0.23–0.62)	<0.001	0.27 (0.16–0.48)	<0.001
Sex of HIV-1–seronegative partner					0.65		0.24
Male	9/984 (0.56)	4/1010 (0.24)	24/959 (1.49)	0.37 (0.17–0.80)		0.16 (0.06–0.46)	
Female	8/595 (0.81)	9/566 (0.95)	28/619 (2.81)	0.29 (0.13–0.63)		0.34 (0.16–0.72)	
Age of HIV-1–seronegative partner					0.79		0.06
<25 yr	3/184 (1.07)	6/177 (2.34)	10/170 (4.04)	0.28 (0.08–1.01)		0.59 (0.21–1.61)	
≥25 yr	14/1395 (0.60)	7/1399 (0.30)	42/1408 (1.78)	0.34 (0.18–0.61)		0.17 (0.07–0.37)	
Unprotected sex with study partner during past mo					0.05		0.77
No	14/1138 (0.72)	8/1161 (0.40)	30/1170 (1.50)	0.47 (0.25–0.89)		0.27 (0.12–0.58)	
Yes	3/441 (0.46)	5/415 (0.78)	22/408 (3.60)	0.13 (0.04–0.44)		0.22 (0.08–0.58)	
Country					0.94		0.46
Kenya	7/699 (0.61)	7/697 (0.60)	22/694 (1.90)	0.32 (0.14–0.74)		0.31 (0.13–0.74)	
Uganda	10/880 (0.69)	6/879 (0.41)	30/884 (2.07)	0.33 (0.16–0.68)		0.20 (0.08–0.48)	
Circumcision status of HIV-1–seronegative men					0.54		0.42
Circumcised	6/542 (0.70)	3/543 (0.34)	13/512 (1.52)	0.46 (0.17–1.20)		0.22 (0.06–0.79)	
Uncircumcised	3/440 (0.40)	1/467 (0.12)	11/447 (1.45)	0.28 (0.08–1.00)		0.09 (0.01–0.68)	
Plasma HIV-1 RNA level of HIV-1–seropositive partner					0.39		0.79
<50,000 copies/ml	13/1277 (0.61)	9/1279 (0.42)	32/1263 (1.51)	0.40 (0.21–0.76)		0.28 (0.13–0.58)	
≥50,000 copies/ml	4/269 (0.90)	4/271 (0.90)	18/289 (3.93)	0.23 (0.08–0.69)		0.23 (0.08–0.68)	
CD4 count of HIV-1–seropositive partner					0.03		0.39
250–349 cells/mm^3	8/312 (1.56)	4/297 (0.78)	10/299 (1.95)	0.79 (0.31–2.01)		0.39 (0.12–1.26)	
≥350 cells/mm^3	9/1267 (0.43)	9/1279 (0.43)	42/1279 (2.01)	0.21 (0.10–0.44)		0.21 (0.10–0.44)	

Figure 3. Hazard Ratios for HIV-1 Infection Overall and among Subgroups, According to Study Group.

P values for the modified intention-to-treat and the intention-to-treat analyses are for the hypothesis of any evidence of efficacy (i.e., testing against a null hypothesis of 0%); P values for the other comparisons correspond to a test for significant interaction in the site-stratified Cox proportional-hazards model. Of 45 HIV-1 infections in women, 5 occurred in women (2 in the TDF group and 3 in the placebo group) who had not received study medication for more than 3 months owing to pregnancy or breast-feeding.

Table 3. Adverse Events, According to Study Group.*

Adverse Event	TDF (N=1584)	P Value vs. Placebo	TDF–FTC (N=1579)	P Value vs. Placebo	Placebo (N=1584)
	no. (%)		*no. (%)*		*no. (%)*
Any adverse event	1350 (85)	1.00	1362 (86)	0.42	1350 (85)
Any serious adverse event	118 (7)	1.00	115 (7)	0.89	118 (7)
Death†	8 (1)	0.80	8 (1)	0.80	9 (1)
Any grade 4 event	34 (2)	0.64	44 (3)	0.58	39 (3)
Any grade 3 event	289 (18)	0.35	293 (19)	0.24	268 (17)
Confirmed laboratory events‡					
Elevated creatinine§					
Grade 1	16 (1)	0.57	18 (1)	0.28	12 (1)
Grade 2 or 3	3 (<1)	0.62	2 (<1)	0.62	1 (<1)
Decreased phosphorus¶					
Grade 2	134 (8)	0.56	128 (8)	0.79	124 (8)
Grade 3	8 (1)	0.50	12 (1)	1.00	12 (1)

* All clinical adverse events of grade 2 or higher and all confirmed laboratory adverse events that were reported in 1% or more (≥47) of study participants are listed in Table S9 in the Supplementary Appendix. P values were calculated with the use of Fisher's exact test except for those for death, which were calculated by means of the Cox proportional-hazards model of time to death.

† In the TDF group, two participants died from trauma, two from alcohol poisoning, and one each from esophageal carcinoma, lung abscess, shigella gastroenteritis, and acute abdomen. In the TDF–FTC group, three participants died from trauma and one each from poisoning, pulmonary embolism, pulmonary tuberculosis, gastroenteritis, and acute febrile illness. In the placebo group, three participants died from trauma and one each from electrocution, suicide, hematemesis, complications of diabetes, febrile illness, and hypotension.

‡ Laboratory adverse events are reported here only if they were confirmed by means of repeat testing, ideally conducted within 7 days after the event.

§ One confirmed grade 3 case of elevated creatinine was observed in the study, in a 46-year-old male participant receiving TDF who had had seroconversion to HIV-1 seropositivity and had discontinued study medication 22 days previously. The creatinine level returned to normal after hydration. No confirmed grade 4 creatinine events were observed.

¶ According to the study protocol, there was no grade 1 decrease in phosphorus level, and no confirmed grade 4 phosphorus decreases were observed. Clinically significant proteinuria (≥grade 1) was observed in association with 27 confirmed grade 2 phosphorus decreases (nine participants in each of the three study groups) and 1 confirmed grade 3 event (in the placebo group). Glycosuria of grade 1 or greater was observed in association with 7 confirmed grade 2 phosphorus decreases (two participants each in the TDF and placebo groups and three in the TDF–FTC group) and 2 confirmed grade 3 events (one each in the TDF and placebo groups).

and fatigue as compared with placebo, primarily during the first month of administration (see Table S14 in the Supplementary Appendix).

DISCUSSION

In this study of heterosexual men and women with a partner known to have HIV-1 infection, once-daily oral TDF and TDF–FTC were associated with risk reductions of 67% and 75%, respectively, against HIV-1 infection when provided in conjunction with other HIV-1 prevention services. Both TDF and TDF–FTC showed significant, and a similar magnitude of, HIV-1 protection for both women and men.

Clinical trials of tenofovir-based preexposure prophylaxis have had conflicting results. Once-daily oral TDF–FTC reduced the risk of HIV-1 acquisition by 44% in a multicountry study among men who have sex with men and by 62% among young heterosexuals from Botswana,[20,21] and the use of 1% tenofovir vaginal gel decreased the incidence of HIV-1 among South African women by 39%.[22] Biologic and behavioral hypotheses have been proposed to explain the failure of two trials of preexposure prophylaxis among African women to show protection against HIV-1 infection,[23,24] including a lack of adherence to daily doses of preexposure prophylaxis, vaginal concentrations of tenofovir achieved with oral dosing that may be particularly sensitive to nonadherence,[25] sexually transmitted infections or other cofactors

affecting infection with HIV-1 in young women, high HIV-1 concentrations in the seropositive partner during primary HIV-1 infection, and innate or acquired immunologic factors that may provide adjunctive protection in long-term couples with HIV-1 serodiscordance. Further study is needed to understand which, if any, of these factors influence the efficacy of preexposure prophylaxis.

Although we studied established couples known to be HIV-1–serodiscordant, all HIV-1 transmissions ultimately occur between serodiscordant partners. Our findings provide proof of concept that preexposure prophylaxis can reduce HIV-1 acquisition in heterosexual populations.

High adherence is essential to achieve clinical benefits from antiretroviral agents for HIV-1 treatment,[26] and emerging evidence suggests that adherence to preexposure prophylaxis is also important for HIV-1 prevention. In the Preexposure Prophylaxis Initiative trial involving men who have sex with men, the relative reduction in the risk of HIV-1 infection from TDF–FTC preexposure prophylaxis was 44% overall but was 73% among the participants with an adherence of 90% or more (as measured by means of pill counts) and 92% among the participants with detectable tenofovir levels in the blood — although only half the participants had detectable levels.[20]

In our study, retention and pill-count adherence were high, tenofovir was detected in 82% of samples from randomly selected participants, and detectable tenofovir levels were associated with a reduction in the relative risk of HIV-1 infection of more than 85%. The high proportion of samples with detectable tenofovir levels is consistent with the 92% study-drug coverage we calculated on the basis of missed visits, withholding of the study drug, and nonadherence, with the absolute difference of 10 percentage points most likely reflecting the fact that pill counts can overestimate adherence if pills are not returned.

Analyses of objective adherence measures across preexposure prophylaxis trials will be informative for understanding the relationship between adherence and protection against HIV-1 infection. In a subgroup of our study cohort, intensive monitoring of adherence by means of pill bottles with caps that electronically monitor bottle openings and monthly unannounced visits to the home for purposes of pill counting supported high adherence,[27] and in-depth interviews have emphasized that trust and the support of a partner reinforce high adherence.[28] Strategies to promote and achieve high adherence outside clinical-trial settings will be necessary to achieve maximum public health benefits of preexposure prophylaxis.

We found similar degrees of protection against HIV-1 with TDF and TDF–FTC, in contrast to findings in studies of animal models.[11] Dual-agent preexposure prophylaxis would most likely be more expensive than single-agent preexposure prophylaxis, and the potential for differential tolerability and antiretroviral resistance in persons with HIV-1 seroconversion despite the use of preexposure prophylaxis should be considered in decision making with regard to public health policies regarding preexposure prophylaxis. We are continuing the TDF and TDF–FTC groups of our study, including offering randomization to TDF or TDF–FTC to participants originally assigned to the placebo group, to gather additional information on the relative safety, efficacy, and HIV-1 resistance of TDF as compared with TDF–FTC.

In our study, 25% (two of eight) of participants who had acute HIV-1 infection at the time of study-drug initiation had viral resistance develop (through the M184V mutation in one and the K65R mutation in the other). The initiation of preexposure or postexposure prophylaxis in persons with acute HIV-1 infection can select for resistance; strategies to improve the recognition of acute infection are needed.[20,29,30] Resistance was rare in partners in whom seroconversion occurred after randomization, of whom a minority had detectable tenofovir levels.

Adherence to preexposure prophylaxis, protection against HIV-1 infection, and antiretroviral resistance appear to be tightly interwoven. Low adherence provides little HIV-1 protection but little risk of resistance if infection is acquired. High adherence potentially blocks most transmissions, and the few persons who acquire HIV-1 despite preexposure prophylaxis potentially have an increased risk of drug resistance. Four participants with HIV-1 seroconversion in our study became infected with HIV-1 that was resistant to nonnucleoside reverse-transcriptase inhibitors, which should not have been selected for by the study medication and instead probably reflects circulating resistance, which is increasingly being detected in Africa.[31]

When used for HIV-1 treatment, TDF is known to cause small decreases in glomerular filtration that are of uncertain clinical significance.[32] In

our population of HIV-1–seronegative participants without preexisting renal impairment, we found no evidence of clinically significant elevations in serum creatinine. Additional studies are needed of proximal renal tubular function, bone mineral density, and other aspects of long-term safety of TDF-based preexposure prophylaxis, as well as safety in pregnant, breast-feeding, or adolescent women, among whom HIV-1 rates are high.[33,34]

For couples known to have HIV-1 serodiscordance, antiretroviral treatment of the partner infected with HIV-1 provides substantial, though incomplete, protection against HIV-1 transmission; 25 to 30% of HIV-1 infection in serodiscordant couples are from infected partners outside the couple.[5,7] Mathematical modeling may help guide policy decisions regarding optimal targeting and timing of treatment and preexposure prophylaxis for reducing HIV-1 incidence in couples.[35] Antiretroviral-based HIV-1–prevention strategies may be particularly important for couples seeking to have children.[36-38] In addition, preexposure prophylaxis offers an HIV-1 prevention strategy for uninfected persons with partners who do not know their HIV-1 status or who are infected with HIV-1 but have not begun antiretroviral therapy.

Successful prevention of HIV-1 infection on a population scale will need to incorporate multiple, evidence-based biomedical and behavioral strategies to achieve maximum benefits. The HIV-1 incidence in this study was lower than that seen in previous studies of HIV-1–serodiscordant African couples,[14,39] emphasizing the importance of and synergy among HIV-1 testing in individuals and couples, risk-reduction counseling, and other prevention services, in combination with antiretroviral preexposure prophylaxis, for reducing the risk of HIV-1 infection in heterosexual populations. Potential implementation of preexposure prophylaxis as a public health measure will require clinical monitoring, methods for encouraging adherence, and ensured access to antiretroviral therapy for HIV-1–infected persons. Nonetheless, to stem the global HIV-1 epidemic, effective primary HIV-1 prevention strategies are critical.

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APPENDIX

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