Title
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Journal
New England Journal of Medicine, 367(5)

ISSN
0028-4793

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Publication Date
2012-08-02

DOI
10.1056/nejmoa1108524

Peer reviewed

Published in final edited form as:
N Engl J Med. 2012 August 2; 367(5): 399–410. doi:10.1056/NEJMoa1108524.

Antiretroviral Prophylaxis for HIV-1 Prevention among Heterosexual Men and Women

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Abstract

Introduction—Antiretroviral pre-exposure prophylaxis (PrEP) reduces the incidence of acquisition of human immunodeficiency virus type 1 (HIV-1) in men who have sex with men and is a promising approach for preventing HIV-1 in heterosexual populations.

Methods—We conducted a randomized, three-arm trial of oral antiretroviral PrEP among heterosexual couples from Kenya and Uganda in which one member was HIV-1 seronegative and the other HIV-1 seropositive. Seronegative partners were randomly assigned to once-daily tenofovir (TDF), combination emtricitabine/tenofovir (FTC/TDF), or matching placebo and followed monthly for up to 36 months. At enrollment, HIV-1 seropositive partners were not eligible for antiretroviral therapy under national guidelines. All couples received standard HIV-1 treatment and prevention services, including individual and couples risk-reduction counseling and condoms.

Results—4758 couples were enrolled; for 62%, the HIV-1 seronegative partner was male. For HIV-1 seropositive participants, the median CD4 count was 495 cells/μL (interquartile range 375–662). Of 82 post-randomization HIV-1 infections, 17 were among those assigned TDF (incidence 0.65 per 100 person-years), 13 among those assigned FTC/TDF (incidence 0.50 per 100 person-years), and 52 among those assigned placebo (incidence 1.99 per 100 person-years), indicating a 67% relative reduction in HIV-1 incidence for TDF (95% CI 44 to 81, $p<0.001$) and 75% for FTC/TDF (95% CI 55 to 87, $p<0.001$). HIV-1 protective effects of FTC/TDF and TDF were not significantly different ($p=0.23$), and both study medications significantly reduced HIV-1 incidence in both men and women. The rate of serious medical events was similar across the study arms.

Conclusions—Oral TDF and FTC/TDF provided substantial protection against HIV-1 acquisition in heterosexual men and women, with comparable efficacy of TDF and FTC/TDF. (Funded by the Bill and Melinda Gates Foundation; ClinicalTrials.gov number NCT00557245)

Keywords

HIV-1 serodiscordant couples; pre-exposure prophylaxis; HIV-1 prevention; randomized clinical trial; Africa

Introduction

Use of antiretroviral medications for the prevention of HIV-1 transmission is a highly promising strategy for reducing HIV-1 spread.[1–4] Antiretroviral treatment for HIV-1 infected persons provides important clinical benefits and substantially reduces their infectiousness.[5–7] For HIV-1 uninfected persons, post-exposure antiretroviral prophylaxis after high-risk, recognized occupational or non-occupational exposures and pre-exposure prophylaxis (PrEP) for those with ongoing HIV-1 exposures are potential HIV-1 prevention strategies.[8,9] The rationale for PrEP is based on efficacy of antiretroviral prophylaxis for infants exposed to HIV-1 during birth and breastfeeding,[10] and from non-human primate studies showing partial or full protection against mucosal simian HIV challenge.[11] In perinatal transmission studies and animal models, protection benefits were maximized when the antiretroviral medication was administered both before and after virus exposure.[12]

Human efficacy trials of PrEP for HIV-1 protection have evaluated the antiretroviral medication tenofovir, either as a vaginal gel or as oral tenofovir disoproxil fumarate (TDF) or oral TDF co-formulated with emtricitabine (FTC/TDF). Animal model studies suggest that FTC/TDF provides greater HIV-1 protection than TDF alone.[11] The potential for differential efficacy, safety, and cost for TDF versus FTC/TDF argues for evaluating both as potential PrEP agents. HIV-1 susceptible individuals within HIV-1 serodiscordant partnerships (in which one of the partners is infected with HIV-1 and the other is uninfected)

are at ongoing risk for HIV-1 acquisition.[13,14] We conducted the Partners PrEP Study, a multi-site, phase III, randomized, double-blind, three-arm, placebo-controlled trial of daily oral TDF or FTC/TDF PrEP for the prevention of HIV-1 acquisition among East African heterosexual men and women in HIV-1 serodiscordant partnerships.

Methods

Study population

Between July 2008 and November 2010, we enrolled heterosexual HIV-1 serodiscordant couples from 9 sites in Kenya and Uganda (Tables S1 and S2).[15] HIV-1 seronegative partners had normal renal function, were not infected with hepatitis B virus (HBV), and were not pregnant or breastfeeding. HIV-1 seropositive partners were not using antiretroviral therapy and did not meet Kenyan or Ugandan guidelines for initiation of antiretroviral therapy.

The study protocol was approved by the University of Washington Human Subjects Review Committee and ethics review committees at each of the study sites (Table S3). All participants provided written informed consent in English or their local language.

Randomization and study procedures

At enrollment, HIV-1 seronegative partners were assigned in a 1:1:1 ratio to one of three study arms: once-daily TDF, FTC/TDF, or placebo, using a fixed-size block randomization, stratified by site. TDF (300 mg) and FTC/TDF (200 mg/300 mg) were used at the dosages approved for treatment of HIV-1. The study regimens were indistinguishable and investigators, except for statistical staff at the central Coordinating Center, remained unaware of the randomization assignments.

HIV-1 seronegative participants had monthly visits, including 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 (Table S4). Serum chemistry and hematology analyses were performed at month 1 and quarterly thereafter. Women were tested monthly for pregnancy and study medication was withheld from women who became pregnant; they were referred for antenatal care and allowed to resume study medication when no longer pregnant or lactating.

HIV-1 seropositive partners were followed quarterly (Table S5), with HIV-1 primary care services and 6-monthly CD4 counts. Those who became eligible for initiation of antiretroviral therapy according to national guidelines were actively counseled to initiate treatment, referred, and linked to care at local clinics.

HIV-1 endpoints

Monthly HIV-1 serologic testing used two rapid HIV-1 antibody tests in parallel. Study medication was temporarily held if either test was reactive and was permanently discontinued if enzyme immunoassay testing confirmed HIV-1 acquisition (Table S6). Samples from all seroconversion events were tested by HIV-1 Western blot and RNA PCR at the University of Washington and were adjudicated by an HIV-1 endpoints 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 endpoint determination and was not performed. For all seroconverters, archived plasma samples from visits prior to seroconversion were tested by HIV-1 RNA PCR; participants with detectable HIV-1 RNA from enrollment were excluded as primary study endpoints because HIV-1 infection occurred prior to randomization.

Standard HIV-1 prevention services

All participants received a comprehensive package of HIV-1 prevention services: HIV-1 testing with pre- and post-test counseling, 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 post-exposure prophylaxis according to national policies. HBV vaccination was offered.

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 or analysis. The University of Washington Coordinating Center assumed sponsor responsibilities for the study, including an Investigational New Drug application to the US Food and Drug Administration. The authors designed the study, wrote the protocol, had full access to the raw data, performed all analyses, prepared the manuscript, and were responsible for the decision to submit for publication. All authors vouch for the completeness and accuracy of the data.

Statistical analysis

The design of the study was end-point driven: 191 HIV-1 seroconversion events (147 per each comparison of TDF or FTC/TDF versus placebo) was determined necessary to provide 80% power, with a one-sided alpha of 0.025, to detect a 60% decrease in incident HIV-1, with the lower bound of the 95% confidence interval excluding a 30% decrease in rates (the null hypothesis).[15] A sample size of 4700 couples was defined to achieve the target number of study endpoints, with 24–36 months of follow-up per couple and anticipating HIV-1 incidence of 2.75 per 100 person-years in the placebo arm.[16]

The primary analysis was a modified intention-to-treat (mITT) analysis, excluding only individuals with HIV-1 RNA detected in their plasma by PCR at enrollment. We used Cox regression, stratified by site, to estimate 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 was reviewed every 6 months by an independent Data and Safety Monitoring Board (DSMB). Statistical monitoring used the Lan-Demets spending approach to adjust the O'Brien-Fleming sequential monitoring boundaries;[17,18] interim monitoring boundaries were computed using S+SeqTrial version 2.0 (TIBCO). During its closed March 2011 session, the DSMB noted a strong trend for HIV-1 protection in the active PrEP arms and called an ad hoc meeting for July 10, 2011. At the July meeting, after reviewing data through May 31, 2011. the DSMB recommended that the results of the study be publicly reported and the placebo arm discontinued, because pre-determined stopping rules were met with clear demonstration of HIV-1 protection from PrEP. The present analysis includes updated data collected through July 10, 2011.

Data were entered onto DataFax case report forms. Analyses were conducted using SAS version 9.2 (SAS Institute).

Results

Study participants

Of 7856 HIV-1 serodiscordant couples screened, 4758 were enrolled and 4747 eligible couples were followed: 1584 randomized to TDF, 1579 to FTC/TDF, and 1584 to placebo (Figure 1). For 62% of enrolled couples, the HIV-1 seronegative partner was male (Table 1).

For HIV-1 seropositive participants, the median CD4 count was 495 cells/mm^3 (IQR 375–662), 80% had CD4 counts ≥350 cells/mm^3, and median plasma HIV-1 RNA level was 3.9 log_{10} copies/mL (IQR 3.2–4.5). Overall, baseline characteristics were similar across the three study arms.

Follow-up and adherence

Retention was ≥96% (Figure 1), with 4722 participants (99.5%) completing at least one post-randomization HIV-1 test and 7830 total person-years of follow-up for assessment of HIV-1 incidence accrued (median 23 months, IQR 16–28, range 1–36). Study medication was dispensed at 96% of attended visits. The most common reason for not dispensing study medication was pregnancy (incidence 11.9, 8.8, and 10.0 per 100 woman-years in the TDF, FTC/TDF, and placebo arms, which did not differ significantly); time off study medication due to pregnancy and breastfeeding accounted for 5.3% of follow-up time among women (2.0% overall). Study medication interruptions due to safety-related reasons accounted for <1% of study follow-up time: 0.6% TDF, 0.7% FTC/TDF, 0.6% placebo.

The primary study measure of adherence was monthly pill counts of returned study tablets: 98% of dispensed study bottles were returned and pill counts indicated that 97% of dispensed study tablets were taken (Table S7). Factoring in missed visits, other reasons for non-dispensation of study medication, and non-adherence to dispensed study pills, 92.1% of follow-up time was covered by study medication.

Effect of TDF and FTC/TDF on HIV-1 acquisition

HIV-1 seroconversion was observed in 96 persons, of whom 14 had plasma HIV-1 RNA retrospectively detected in enrollment specimens (5 TDF, 3 FTC/TDF, 6 placebo; Figure S1). Of 82 post-randomization HIV-1 infections, 17 were among those assigned TDF, 13 FTC/TDF, and 52 placebo, indicating a 67% reduction in HIV-1 acquisition due to TDF (95% CI 44–81%, p<0.001) and 75% due to FTC/TDF (95% CI 55–87%, p<0.001), each relative to placebo (Figure 2). The HIV-1 protective effects of FTC/TDF and TDF were not significantly different (p=0.23). Both TDF (p=0.003) and FTC/TDF (p<0.001) ruled out efficacy of less than 30% in the primary modified intention-to-treat analysis. An intention-to-treat analysis, including subjects who were HIV-1 infected at randomization, found similar results (Figure 3).

Among women, TDF efficacy was 71% (p=0.002) and FTC/TDF 66% (p=0.005); among men, TDF efficacy was 63% (p=0.01) and FTC/TDF 84% (p<0.001). The HIV-1 protective effects of TDF and FTC/TDF were not statistically different by sex. HIV-1 protection was generally similar between groups for other pre-specified subgroups analyses (Figure 3). During follow-up, 21% of HIV-1 seropositive partners (22% in the TDF arm, 20% FTC/TDF, 21% placebo) initiated combination antiretroviral therapy; results were similar if follow-up time was censored at the time the HIV-1 seropositive partner initiated antiretroviral therapy (Table S8).

Antiretroviral resistance

Of the 96 persons who seroconverted to HIV-1, HIV-1 RNA was amplified for resistance assessment from 92 (95.8%, Table S9). Among the eight subjects in the TDF and FTC/TDF arms who were infected at randomization, two developed HIV-1 with resistance to the study medications: one with TDF-resistant virus (K65R mutation) who was randomized to TDF and one with FTC-resistant virus (M184V mutation) randomized to FTC/TDF. No subjects who acquired HIV-1 after randomization developed HIV-1 with the K65R or M184V mutations; one on the TDF arm developed virus with a rare TDF resistance mutation (K65N).

Detection of tenofovir in plasma and HIV-1 prophylactic effect

Among 29 subjects on the TDF and FTC/TDF arms who acquired HIV-1, 31% had tenofovir detected in a plasma sample at the seroconversion visit compared with 82% of 902 samples from a randomly-selected subset of 198 subjects who did not acquire HIV-1 (Table S10). Having detectable tenofovir, as compared to an undetectable level, was associated with an estimated relative risk reduction for acquiring HIV-1 of 86% (TDF) and 90% (FTC/TDF).

Sexual behavior

At enrollment, 27% of HIV-1 seronegative partners reported sex without condoms with their HIV-1 seropositive partner during the prior month. This percentage decreased during follow-up (to 13% and 9% at 12 and 24 months) and was similar across the study arms (Figure S2). The proportion reporting outside partnerships and who acquired sexually transmitted infections during follow-up did not differ across the study arms (Table S11).

Safety and tolerability

There were no statistically significant differences in the frequency of deaths, serious adverse events, or serum creatinine and phosphorus abnormalities across the study arms (Tables 2 and S12). Neutropenia was seen more commonly in the FTC/TDF arm (15% with a grade 1 or 2 event, 4% with grade 3 or 4 event, Table S13), but not the TDF arm (12% with grade 1/2, 2% grade 3/4), compared to placebo (12% with grade 1/2, 2% grade 3/4). The study medication was well-tolerated, with modest increased reporting of gastrointestinal side effects and fatigue in the two active arms compared to the placebo arm, primarily during the first month of administration (Table S14).

Discussion

In this study of heterosexual men and women who had a known HIV-1 infected partner, once-daily oral TDF and FTC/TDF provided 67% and 75% protection against HIV-1, respectively, when provided in the context of other HIV-1 prevention services. Both TDF and FTC/TDF demonstrated significant, and comparable, HIV-1 protection for both women and men. TDF and FTC/TDF PrEP were safe and well-tolerated in this healthy African population.

Clinical trials of tenofovir-based PrEP have had conflicting results. Once-daily oral FTC/TDF reduced HIV-1 acquisition by 44% in a multi-country study among men who have sex with men and by 63% among young heterosexuals from Botswana,[19,20] and use of 1% tenofovir vaginal gel decreased HIV-1 incidence among South African women by 39%.[21] Biologic and behavioral hypotheses have been proposed to explain the failure of two trials of oral PrEP among African women to demonstrate HIV-1 protection benefits,[22,23] including vaginal drug concentrations achieved with oral TDF that may be highly sensitive to non-adherence,[24] sexually transmitted infections and other cofactors for HIV-1 acquisition in young women, acute infection with high HIV-1 concentrations in source partners, and innate or acquired immunologic factors that may provide adjunctive protection in long-term HIV-1 serodiscordant couples. Further study is needed to understand which, if any, of these factors influence PrEP efficacy. Although our study was conducted among established partnerships, known to be HIV-1 serodiscordant, all HIV-1 transmissions ultimately occur within HIV-1 discordant relationships. Our findings provide proof-of-concept that PrEP can reduce HIV-1 acquisition in heterosexual populations.

High adherence is essential to achieve clinical benefits from antiretrovirals for HIV-1 treatment,[25] and emerging evidence suggests adherence to PrEP is also important for HIV-1 prevention benefits. In the iPrEx trial among men who have sex with men, overall HIV-1

protection due to FTC/TDF PrEP was 44% but was higher in those with ≥90% pill count adherence (73%) and with detectable tenofovir in blood (92%); however, only half of participants had tenofovir detected.[19] In our study, retention and pill count adherence were high, tenofovir was detected in 82% of samples from randomly-selected participants, and detectable tenofovir was associated with a >85% protection from HIV-1. The high proportion of samples with detectable tenofovir is consistent with the 92% study drug coverage we calculated based on missed visits, drug holds, and non-adherence, with the difference between these numbers likely reflecting that pill counts can overestimate adherence if pills are not returned. Analyses of objective adherence measures across PrEP trials will be informative for understanding the relationship between adherence and HIV-1 protection. Among a subset of our cohort, intensive adherence monitoring using medication electronic measurement caps and monthly unannounced home visits for pill counts support high adherence,[26] and in-depth interviews have emphasized that trust and relationship support within serodiscordant partnerships reinforce high adherence.[27] Strategies to promote and reach high adherence outside of clinical trial settings will be necessary to achieve maximum public health benefits of PrEP.

We found similar degrees of HIV-1 protection for TDF and FTC/TDF, in contrast to animal model studies.[11] Dual-agent therapy will likely be more expensive than single-agent PrEP and the potential for differential tolerability and antiretroviral resistance in breakthrough HIV-1 seroconverters requires consideration for public health policies regarding PrEP. We are continuing the TDF and FTC/TDF arms of our study, including offering randomization to TDF versus FTC/TDF to placebo arm participants, to gather additional information on the relative safety, efficacy, and HIV-1 resistance of TDF versus FTC/TDF.

In our study, 25% (2/8) of subjects who had acute HIV-1 infection at the time of PrEP initiation developed resistant virus (one M184V, one K65R); initiation of PrEP or post-exposure prophylaxis in acute HIV-1 infection can select for resistance and strategies to improve recognition of acute infection are needed.[19,28,29] Resistance was rare in seroconverters acquiring HIV-1 after randomization, of whom a minority had tenofovir detected. PrEP adherence, HIV-1 protection, and antiretroviral resistance appear to be tightly interwoven: with low adherence providing little HIV-1 protection but little risk of resistance if infection is acquired, whereas high adherence potentially blocks most transmissions, leaving few breakthrough cases at risk for resistance. Notably, 4 HIV-1 seroconverters acquired HIV-1 resistant to non-nucleoside reverse transcriptase inhibitors, which would not be selected by the study medication and instead likely reflects circulating resistance, which is increasingly being detected in Africa.[30]

TDF is known to cause mild decreases in glomerular filtration, of uncertain clinical significance, when used for HIV-1 treatment.[31] In our population of HIV-1 seronegative persons without pre-existing 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 PrEP, as well as safety in pregnant, breastfeeding, and adolescent women, among whom HIV-1 rates are high.[32,33]

For known serodiscordant couples, antiretroviral treatment of the HIV-1 infected partner provides substantial, although not complete, HIV-1 transmission protection, as 25–30% of HIV-1 acquisitions in serodiscordant couples are from outside partners.[5,7] Mathematical modeling may help guide policy decisions regarding optimal targeting and timing of treatment and PrEP for reducing HIV-1 incidence in couples.[34] Antiretroviral-based HIV-1 prevention strategies may be particularly important for couples seeking to conceive and bear children.[35–37] In addition, PrEP offers an HIV-1 prevention strategy for uninfected persons

with partners who do not know their HIV-1 status or who are HIV-1 infected but have not initiated antiretroviral therapy.

Successful HIV-1 prevention on a population scale will need to incorporate multiple, evidence-based biomedical and behavioral strategies to achieve maximum benefits. HIV-1 incidence in this study was less than that seen in previous studies of serodiscordant African couples,[14,38] emphasizing the important and synergistic HIV-1 prevention benefits of couples HIV-1 testing, ongoing counseling, and other prevention services, combined with PrEP, for reducing risk in heterosexual populations. Potential implementation of PrEP as a public health measure will require clinical monitoring, support for adherence, and ensuring 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; national and international guidelines should consider how and whether to incorporate PrEP for HIV-1 serodiscordant couples into combination HIV-1 prevention policies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: The Partners PrEP Study was funded through a research grant from the Bill & Melinda Gates Foundation (grant ID #47674).

We thank the couples who participated in this study for their motivation and dedication and the referral partners, community advisory groups, institutions, and communities that supported this work. We are grateful to Drs. Stephen Becker and Renee Ridzon, Robyn Eakle, and the HIV team at the Bill and Melinda Gates Foundation for careful oversight and support, and to Dr. James Rooney and others at Gilead Sciences for donation of study drug. We thank the members of the independent Data and Safety Monitoring Board for their expertise and guidance: Drs. Richard Whitley (co-chair), James Neaton (co-chair), Ann Arvin, Scott Hammer, Ruth Nduati, David Serwadda, and Catherine Wilfert.

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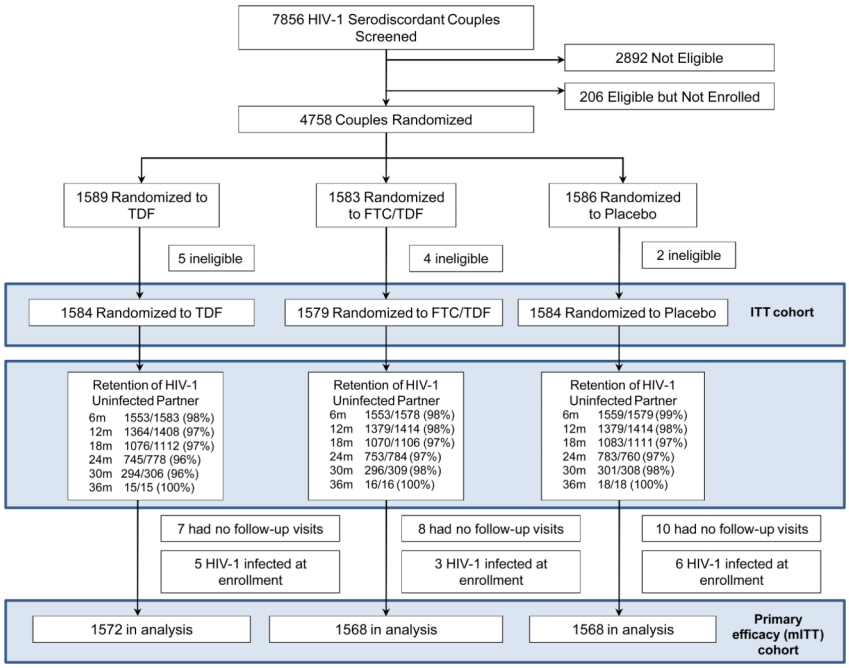
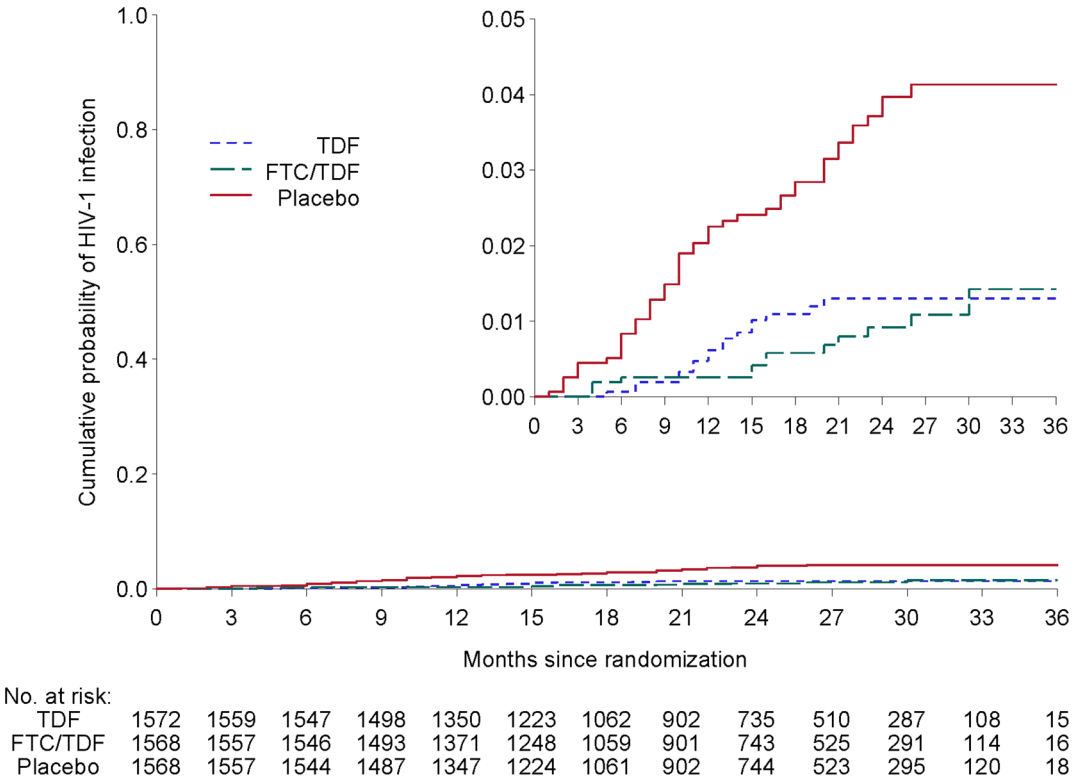


Figure 1. Enrollment and outcomes

For couples found to be ineligible for the study, 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 pregnancy (2%), breastfeeding (0.4%), or chronic active hepatitis B infection (10%) among HIV-1 seronegative partners. Less than 3% of couples screened out for creatinine elevation, glycosuria or proteinuria in the HIV-1 seronegative partner, which were exclusion criteria to minimize potential renal toxicity from tenofovir exposure.

A total of 11 couples were enrolled and randomly allocated to one of the study arms but were later found to not meet all eligibility criteria; they were exited from the study at the time their ineligibility was discovered and their data were not included in the analysis. Retention of HIV-1 seropositive partners was ≥96% throughout the study follow-up period and was similar across randomization arms (data not shown).

ITT, intention-to-treat; mITT modified intention-to-treat



No. at risk:

TDF	1572	1559	1547	1498	1350	1223	1062	902	735	510	287	108	15
FTC/TDF	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 curve for the primary modified intention-to-treat analysis

The cumulative probability of HIV-1 acquisition by study arm is presented.

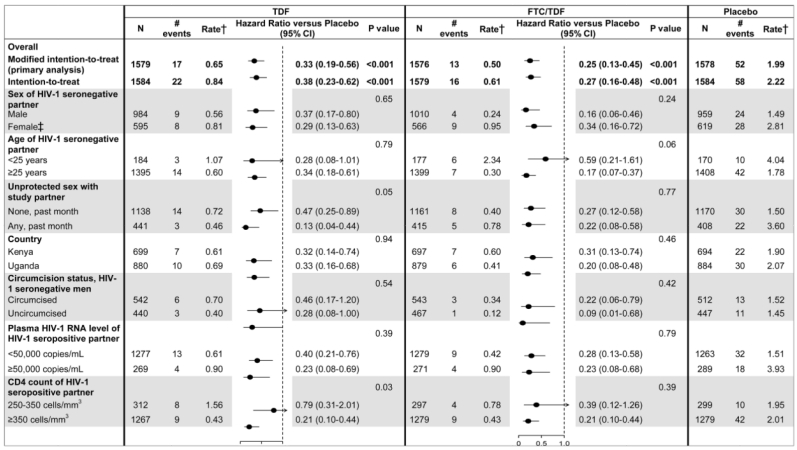


Figure 3. HIV-1 incidence by study arm, overall and among subgroups.*

P values for the modified intention-to-treat and the intention-to-treat analyses apply to 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.

*Subgroups defined by baseline characteristics. In the forest plots, dashed line indicates HR of 1.0 (0% efficacy for HIV-1 protection).

†Per 100 person-years

‡Of 45 HIV-1 infections in women, 5 (2 TDF, 0 FTC/TDF, 3 placebo) occurred in subjects who were not receiving study medication for >3 months due to pregnancy or breastfeeding.

Table 1

Baseline characteristics of the study subjects

	Median (interquartile range) or N (%)					
	TDF n=1584		**FTC/TDF n=1579**		**Placebo n=1584**	
	HIV-1 seronegative partner	**HIV-1 seropositive partner**	**HIV-1 seronegative partner**	**HIV-1 seropositive partner**	**HIV-1 seronegative partner**	**HIV-1 seropositive partner**
Demographic Characteristics						
Male sex	986 (62%)	598 (38%)	1013 (64%)	566 (36%)	963 (61%)	621 (39%)
Age, years						
18–24	184 (12%)	268 (17%)	177 (11%)	287 (18%)	172 (11%)	273 (17%)
25–34	721 (46%)	657 (41%)	690 (44%)	636 (40%)	688 (43%)	629 (40%)
35–44	480 (30%)	474 (30%)	498 (32%)	460 (29%)	513 (32%)	509 (32%)
≥45	199 (13%)	185 (12%)	214 (14%)	196 (12%)	211 (13%)	173 (11%)
Education, years	7 (4,10)	7 (4,9)	7 (4,10)	7 (4,9)	7 (4,10)	7 (4,9)
Monthly income, any	1275 (80%)	1069 (67%)	1236 (78%)	1052 (67%)	1259 (79%)	1079 (68%)
Couple Characteristics *						
Married to study partner	1543 (97%)		1540 (98%)		1552 (98%)	
Years living with study partner	7.0 (3.0,13.5)		7.1 (3.0,14.0)		7.1 (3.0,14.0)	
Number of children in partnership	2 (1,4)		2 (1,4)		2 (1,4)	
Proportion of couples without children	343 (22%)		368 (23%)		342 (22%)	
Years aware of HIV-1 serodiscordant status	0.5 (0.1,2.0)		0.4 (0.1,2.0)		0.4 (0.1,2.0)	
Sexual Risk Behavior *						
Number of sex acts in prior month	4 (3,8)		4 (3,8)		4 (3,8)	
Any unprotected sex acts in prior month	442 (28%)		416 (26%)		409 (26%)	
Any sex with outside partner in prior month	150 (9%)	84 (5%)	134 (8%)	106 (7%)	122 (8%)	103 (7%)
Clinical Characteristics						
CD4 cell count/mm^3	N/A	491 (370,661)	N/A	497 (380,664)	N/A	499 (375,663)
HIV-1 plasma RNA, log_{10} copies/mL †	N/A	3.9 (3.2, 4.5)	N/A	3.9 (3.1, 4.5)	N/A	3.9 (3.2, 4.5)
Circumcised (men only)	533 (54%)	198 (33%)	540 (53%)	177 (31%)	509 (53%)	202 (33%)

	Median (interquartile range) or N (%)					
	TDF n=1584		**FTC/TDF n=1579**		**Placebo n=1584**	
	HIV-1 seronegative partner	**HIV-1 seropositive partner**	**HIV-1 seronegative partner**	**HIV-1 seropositive partner**	**HIV-1 seronegative partner**	**HIV-1 seropositive partner**
Using contraception[‡] (women only)	263 (44%)	290 (29%)	275 (49%)	324 (32%)	299 (48%)	321 (33%)
Pregnant (women only)	0 (0%)	152 (15%)[†††]	0 (0%)	135 (13%)	0 (0%)	118 (12%)
Neisseria gonorrhoeae, *Chlamydia trachomatis*, or *Trichomonas vaginalis* [**††]	86 (6%)[†††]	117 (8%)	93 (6%)[†††]	122 (8%)	126 (8%)	137 (9%)
Syphilis seropositivity[††‡‡]	59 (4%)	73 (5%)	60 (4%)	52 (3%)	62 (4%)	73 (5%)
Herpes simplex virus type 2 seropositive[***]	835 (55%)	N/A	814 (54%)[†††]	N/A	875 (58%)	N/A

[*] Couple characteristics and sexual risk behavior within the study partnership were as reported by the HIV-1 seronegative partner.

[†] Plasma HIV-1 RNA concentrations from enrollment samples were quantified in batch testing at the University of Washington using the Abbott Real-Time HIV-1 RNA assay (Abbott) at a limit of quantification of 80 copies/mL.

[‡] Any contraceptive use includes: hormonal oral, injectable and implantable contraceptives, intrauterine device, hysterectomy or bilateral tubal ligation. 83% of HIV-1 seronegative and 85% of HIV-1 seropositive women using contraception used a hormonal method.

[**] Data were available from 98% of HIV-1 seronegative and 96% of HIV-1 seropositive participants. *T. vaginalis* was the most common infection, accounting for 75% of total infections detected. *N. gonorrhoeae* and *C. trachomatis* testing were by APTIMA Combo 2 (Gen-Probe) or COBAS Amplicor (Roche Diagnostics), and *T. vaginalis* testing was by APTIMA TV TMA (Gen-Probe) or In Pouch TV (Biomed Diagnostics).

[††] Laboratory screening for asymptomatic curable infections was done at baseline and annually. Assessment for symptomatic sexually transmitted infections was conducted quarterly, or more frequently if clinically indicated. Participants were treated for symptomatic sexually transmitted infections and asymptomatic infections found as a result of scheduled screening.

[‡‡] Syphilis serologic testing was by rapid plasma reagin, confirmed by a treponema-specific assay.[15] Seropositive results could indicate current or past infection.

[***] Herpes simplex virus type 2 testing was done using the HerpeSelect-2 EIA (Focus Technologies) at enrollment only; an index value of ≥3.5 was used to define a positive result.[39]

[†††] Of 58 comparisons of enrollment characteristics for this table (i.e., 29 factors, including for HIV-1 seronegative and HIV-1 seropositive partners and for couples, and for TDF versus placebo and FTC/TDF versus placebo), four had p-values <0.05: prevalence of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Trichomonas vaginalis* among HIV-1 seronegative partners in the TDF arm (6% versus 8% for placebo, p<0.01) and for the FTC/TDF arm (6% versus 8% for placebo, p<0.05), the prevalence of HSV-2 among HIV-1 seronegative partners in the FTC/TDF arm (54% versus 58% for placebo, p<0.05), and the proportion of HIV-1 seropositive female participants who were pregnant in the TDF arm (15% versus 12%, p<0.05).

N/A not available/not applicable

Table 2

Adverse events

Adverse event	**TDF n=1584**			**FTC/TDF n=1579**			**Placebo n=1584**	
	# participants	***%***	***P value versus placebo***	***# participants***	***%***	***P value versus placebo***	***# participants***	***%***
Any adverse event	1350	85.2	1.00	1362	86.3	0.42	1350	85.2
Any serious adverse event	118	7.4	1.00	115	7.3	0.89	118	7.4
Death *	8	0.5	0.80	8	0.5	0.80	9	0.6
Any grade 4 event	34	2.1	0.64	44	2.8	0.58	39	2.5
Any grade 3 event	289	18.2	0.35	293	18.6	0.24	268	16.9
Confirmed laboratory events †								
Elevated creatinine ‡								
Grade 1	16	1.0	0.57	18	1.1	0.28	12	0.8
Grade 2+	3	0.2	0.62	2	0.1	0.62	1	0.1
Decreased phosphorus **								
Grade 2	134	8.5	0.56	128	8.1	0.79	124	7.8
Grade 3	8	0.5	0.50	12	0.8	1.00	12	0.8

*Deaths were due to the following causes: TDF: trauma (2), alcohol poisoning (2), esophageal carcinoma, lung abscess, *Shigella* gastroenteritis, acute abdomen; FTC/TDF: trauma (3), poisoning, pulmonary embolism, pulmonary tuberculosis, gastroenteritis, acute febrile illness; Placebo: trauma (3), electrocution, suicide, hematemesis, complications of diabetes, febrile illness, hypotension.

†Laboratory adverse events were confirmed by repeat testing, ideally conducted within 7 days. Only events that were confirmed on repeat testing are reported.

‡One confirmed grade 3 creatinine event was observed in the study, in a 46 year-old male participant in the TDF arm who had seroconverted to HIV-1 and had discontinued study medication 22 days previously. Creatinine resolved to normal after hydration. No confirmed grade 4 creatinine events were observed.

**The study protocol defined that there was no grade 1 range for decreased phosphorus; no confirmed grade 4 phosphorus events were observed. Significant proteinuria (≥2+) was observed in association with 27 confirmed grade 2 phosphorus events (9 TDF, 9 FTC/TDF, 9 placebo) and 1 confirmed grade 3 event (placebo). Glycosuria ≥1+ was observed in association with 3 grade 2 confirmed phosphorus events (1 FTC/TDF, 2 placebo).

A listing of all clinical adverse events of grade 2 or higher and confirmed laboratory adverse events that were reported in >1% (n=47 or greater) of study subjects is presented in Table S9.

P-values were calculated using the Fisher's exact test except for those comparing deaths, which are from Cox proportional hazards model of time to death.