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Single-Agent Tenofovir versus Combination Emtricitabine/Tenofovir for Pre-Exposure Prophylaxis against HIV-1 Acquisition: A Randomized Trial

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Declaration of Interests

We declare that we have no conflicts of interest.

Contributors

JMB and CC designed and led the study, and JMB wrote the first draft of the report. DD oversaw the analyses, and DD, KKT and LK analyzed the data. NRM, PN, JDC, JW, JWT, EAB, CC, EK, AR, ET, EW, KHF, JK, CF, and GJ-S contributed to the design of the study and oversaw the study sites. RWC, CH, MAM, and LF conducted laboratory testing as part of the study. JEH and DB led adherence measurement and interpretation work. All authors contributed to the execution of the work and all critically reviewed and approved the report.

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SUMMARY

Background—Antiretroviral pre-exposure prophylaxis (PrEP), using daily oral tenofovir disoproxil fumarate (TDF) or TDF in combination with emtricitabine (FTC/TDF), has been demonstrated to be efficacious for HIV-1 prevention. While the use of multiple antiretroviral agents is essential for effective HIV-1 treatment, multiple agents may not be required for effective prophylaxis. The relative efficacy of single-agent TDF versus combination FTC/TDF PrEP has not been directly assessed.

Methods—We conducted a randomized, double-blind, placebo-controlled three-arm trial of daily oral TDF and FTC/TDF PrEP among HIV-1 uninfected members of heterosexual HIV-1 serodiscordant couples from Kenya and Uganda. After an interim review, the trial's placebo arm was discontinued due to demonstration of PrEP efficacy, and the results of each active PrEP agent compared to placebo were reported (TDF 67%, FTC/TDF 75%). Thereafter, the active arms were continued, and participants initially randomized to placebo were offered re-randomization to TDF or FTC/TDF PrEP.

Findings—4410 couples received TDF or FTC/TDF PrEP and were followed for HIV-1 acquisition. Of 52 incident HIV-1 infections, 31 were among those assigned TDF (incidence 0.71 per 100 person-years) and 21 were among those assigned FTC/TDF (incidence 0.48 per 100 person-years); for comparison, HIV-1 incidence in the placebo arm prior to its discontinuation was 2.00 per 100 person-years. HIV-1 prevention efficacy for FTC/TDF compared to TDF alone was not statistically significantly different: HR 0.67, 95% 0.39–1.17, p=0.16. Detection of tenofovir in plasma samples, compared to no detection and as measured in seroconverters and a subset of non-seroconverters, was associated with an 85% relative risk reduction in HIV-1 acquisition for the TDF arm and 93% for the FTC/TDF arm (both p<0.0001).

Interpretation—These results do not rule out the potential for a modest difference in HIV-1 protection for TDF compared to FTC/TDF, but they demonstrate that once-daily oral TDF or FTC/TDF both provide high protection against HIV-1 acquisition among heterosexual men and women.

Keywords

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

Introduction

Combination antiretroviral treatment is central to the survival of HIV-1 infected persons and use of antiretroviral medications is the cornerstone of strategies to prevent mother-to-child HIV-1 transmission. Recent evidence has demonstrated that antiretroviral medications can also be used for the prevention of HIV-1 transmission between adults, when used as antiretroviral treatment to reduce the infectiousness of HIV-1 infected persons and as oral or

topical pre-exposure prophylaxis (PrEP) for HIV-1 uninfected persons at high risk for HIV-1 acquisition.[1–7]

Four randomized trials, conducted among diverse geographic and at-risk populations, have demonstrated that oral antiretroviral PrEP is efficacious in protecting against HIV-1 acquisition.[3–5, 7] To date, efficacy trials of oral PrEP for HIV-1 protection have evaluated the antiretroviral medication tenofovir disoproxil fumarate (TDF), either alone or co-formulated with emtricitabine (FTC/TDF). Animal data, from rectal viral challenge models, have suggested that FTC/TDF might provide greater HIV-1 protection than TDF alone.[8] However, the potential for differential efficacy, safety, and cost for TDF versus FTC/TDF argued for evaluating both TDF and FTC/TDF as potential PrEP agents.

We conducted 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 African heterosexual men and women who were at high risk for HIV-1 acquisition because they had a known HIV-1 infected sexual partner (the Partners PrEP Study).[3] An interim review found PrEP protected from HIV-1, based on pre-specified efficacy thresholds. The trial's placebo arm was discontinued and the results were reported publicly: compared to placebo, HIV-1 prevention efficacy of TDF was 67% and FTC/TDF was 75%, and the TDF and FTC/TDF efficacies were compared and did not differ significantly ($p=0.23$).[3] The trial's active TDF and FTC/TDF arms were continued thereafter and the participants initially randomized to placebo were offered re-randomization to TDF or FTC/TDF PrEP, in order to gather additional comparative safety and efficacy data related to single- versus dual-agent PrEP.

Methods

Study population

Between July 2008 and November 2010, heterosexual HIV-1 serodiscordant couples (i.e., in which one member was HIV-1 infected and the other uninfected)were enrolled from nine sites in Kenya and Uganda, as described previously (ClinicalTrials.gov number NCT00557245).[3, 9] Eligible couples were sexually active and intending to remain as a couple. HIV-1 seronegative partners had normal renal function, were not infected with hepatitis B virus, and were not pregnant or breastfeeding.

Randomization and study procedures

At enrollment, HIV-1 seronegative partners were assigned in a 1:1:1 ratio to one of three blinded study arms: once-daily TDF, FTC/TDF, or placebo, using a block randomization with a fixed size of 30 subjects, stratified by site. TDF (300 mg) and FTC/TDF (200 mg/300 mg) were used at the dosages approved for treatment of HIV-1. HIV-1 seronegative participants had monthly visits for up to 36 months, including HIV-1 testing, dispensation of 30 days of study medication, collection of the prior month's unused medication, and individualized adherence counseling. Assessment of adverse events occurred throughout study follow-up; serum chemistry and hematology analyses were performed at month 1 and quarterly thereafter. Women were tested monthly for pregnancy and study medication was

with held from women who became pregnant; they were referred for antenatal care and allowed to resume study medication when no longer pregnant or lactating. Individuals who seroconverted to HIV-1 were permanently discontinued from study medication; they continued in follow-up, including HIV-1 care and 6-monthly CD4 counts.

HIV-1 seropositive partners were followed quarterly, with HIV-1 primary care services and 6-monthly CD4 counts. At the time of enrollment, HIV-1 seropositive partners were not using antiretroviral therapy; 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.

Interim review

An independent Data and Safety Monitoring Board (DSMB) met every six months to review the conduct of the trial, including interim reviews of HIV-1 protection efficacy. In July 2011, the DSMB recommended that the placebo arm of the study be discontinued, due to definitive demonstration of PrEP protection against HIV-1 acquisition, based on pre-specific stopping rules, and the study results be made public, including immediate dissemination of the findings to study participants. Additionally, the DSMB recommended that follow-up of subjects assigned to the active PrEP arms be continued, without changes to study procedures for HIV-1 testing and study medication provision, to gain additional blinded information on the relative efficacy and safety of PrEP using TDF versus FTC/TDF. Finally, the DSMB recommended that those originally assigned to the placebo arm be offered re-randomization (in a 1:1 ratio) to the active PrEP arms. Provision of active PrEP to the placebo arm was done to increase the amount of comparative information for TDF versus FTC/TDF PrEP while also fulfilling a commitment to provide PrEP to participants for 12 months should it prove efficacious for HIV-1 prevention, in accordance with international guidance to ensure access for trial participants to effective biomedical prevention interventions against HIV-1.[10–12] Procedures for re-randomization have been detailed elsewhere; in brief, all participants were informed of the interim efficacy results, those who had been assigned TDF or FTC/TDF were told they were receiving active PrEP but were not informed of the specific PrEP medication, subjects assigned placebo were informed of that initial assignment and offered re-randomization to the two active PrEP arms, and the study continued in a double-blinded fashion.[12] Thus, after July 2011, all participants were receiving either TDF or FTC/TDF, in a blinded fashion, for a period for up to 12 months; follow-up concluded in December 2012.

Standard HIV-1 prevention services and ethics review

All participants received a comprehensive package of HIV-1 prevention services including HIV-1 testing with pre- and post-test counseling, individual and couples risk-reduction counseling, screening and treatment for sexually transmitted infections, free condoms, counseling on the HIV-1 prevention benefits of antiretroviral therapy, and referral for male circumcision and post-exposure prophylaxis according to national policies. The study protocol was approved by the University of Washington Human Subjects Review Committee and ethics review committees at each of the study sites. All participants provided

written informed consent in English or their local language, including, for those initially assigned placebo, consent for re-randomization.

Laboratory testing

Laboratory methods have been detailed previously.[3, 9] Monthly HIV-1 serologic testing used two rapid HIV-1 antibody tests in parallel; reactive results were confirmed by enzyme immunoassay, HIV-1 Western blot, and HIV-1 RNA PCR and were adjudicated by an HIV-1 endpoints committee, which was blinded to trial randomization arm. 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 the enrollment or re-randomization visit, signifying seronegative acute HIV-1 infection, were excluded as primary study endpoints because HIV-1 infection occurred prior to treatment assignment.

HIV-1 resistance to antiretrovirals was assessed by consensus sequencing in those who acquired HIV-1. RNA extracted from plasma was reverse transcribed and HIV-1 *pol* was PCR amplified and sequenced using the ViroSeq HIV-1 Genotyping System (Abbott Molecular, Des Plaines, IL) or an in-house assay, as previously described.[3, 13] Nucleic acid sequences were reported to GeneBank (accession #JQ625596-JQ625661, JX123571-JX123680, and KC900521-KC900816). The primary resistance mutations for the study were pre-defined as K65R and K70E (which confer resistance to TDF) and M184V and M184I (which confer resistance to FTC), due to their potential relationship to the study medications.

In subjects who acquired HIV-1 and a subset who remained HIV-1 uninfected, detection of tenofovir in plasma was measured via ultra-performance liquid chromatographic-tandem mass spectrometric (LC-MS/MS), with a limit of quantification of 0.31 ng/mL.[3] Tenofovir was antiretroviral agent tested since it was the common medication between the two active study arms.

Sample size

The trial was designed to provide 80% power, with a one-sided alpha of 0.025, to detect a 60% decrease in incident HIV-1 infection for each active PrEP arm versus placebo, with the lower bound of the 95% confidence interval excluding a 30% decrease in rates (the null hypothesis), as previously detailed.[3, 9] After discontinuation of the trial's placebo arm in July 2011, it was estimated that the trial would accrue a total of approximately 50 HIV-1 seroconversion endpoints between the two active PrEP arms, summed across those observed before and after July 2011, which would provide 87% power to demonstrate a 60% difference in HIV-1 incidence between TDF and FTC/TDF and 67% power for a 50% difference.

Statistical analysis

The primary analysis presented here was a modified intention-to-treat (mITT), comparing HIV-1 incidence for those assigned TDF versus FTC/TDF, and excluding only individuals with HIV-1 RNA detected in their plasma by PCR at randomization (or for those initially assigned placebo, re-randomization), as individuals with HIV-1 RNA detected at the time of

randomization were already HIV-1 infected and could not have benefitted from HIV-1 acquisition by PrEP. Participants in the re-randomized cohort were entered into the risk set at the study duration corresponding to the time of re-randomization. ITT results were also calculated. Cox regression, stratified by site, was used to estimate relative hazard rates for time to first positive HIV-1 serologic test; efficacy was calculated for pre-specified subgroups.

Additional sensitivity analyses were performed: first, a per-protocol analysis excluding time periods when subjects were known to be off study medication (for example, as a result of a protocol-defined medication hold due to pregnancy), and second, a high-adherer analysis, limited to periods when study medication was dispensed and when medication adherence, as measured by pill counts of returned, unused medication, was ≥80%.[14] The latter analysis was adjusted for a number of pre-specified covariates potentially associated with HIV-1 infection, adherence, or randomization arm in the cohort: gender, age, male circumcision status, presence of a sexually transmitted infection at baseline, CD4 count and plasma HIV-1 RNA concentration in the HIV-1 infected partner, and sexual behavior.

Finally, a case-cohort design was used to assess the relationship between tenofovir detection in plasma (an objective marker of adherence) and HIV-1 protection. Cases were all subjects who acquired HIV-1 after randomization/re-randomization; the cohort comparison included 100 subjects from the TDF arm and 104 subjects from the FTC/TDF arm who were randomly selected from the entire study population (thus, in an approximately 1:4 ratio compared to cases; cohort subjects were chosen equally from the TDF and FTC/TDF arms). The case-cohort design was chosen because it required testing a subset of subjects and was thus efficient; by design, cases and cohort members were not comparable, as cases acquired HIV-1 while the cohort was a sample of the entire population, although random selection of cohort was designed to select a representative sample of the study population as a whole. All available plasma samples from Months 1, 3, 6, 12, 18, 24, 30, and 36 after randomization/re-randomization were tested; in addition, for case subjects, the sample from the visit at which HIV-1 seroconversion was detected was also tested. In total, 281 samples from case subjects and 1373 samples from cohort subjects were tested.

Analyses were conducted using SAS version 9.2 (SAS Institute) and, for the case-cohort comparison, in R version 2.12.2 using the Lumley survey package (version 3.26 http://faculty.washington.edu/tlumley/survey/).[15]

Role of the funding source—The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Study participants and follow-up

At the time of initial randomization, a total of 4747 couples were enrolled: 1584 assigned TDF, 1579 FTC/TDF, and 1584 placebo. Of the 1584 HIV-1 uninfected subjects initially

randomized to placebo, 1264 (89.1% of 1418 who were still eligible to receive PrEP) consented to re-randomization, of whom 631 were assigned TDF and 633 FTC/TDF. Thus, a total of 4427 subjects were assigned active PrEP during the trial (2215 TDF and 2212 FTC/TDF)(Figure 1) and are the population described in this analysis. Subject characteristics were similar across the study arms (Table 1).

Of the 4427 assigned TDF or FTC/TDF PrEP during the trial, 4410(99.6%; 2208 TDF and 2202 FTC/TDF) completed at least one post-randomization test for assessment of HIV-1 acquisition. For assessment of HIV-1 incidence in those assigned to TDF or FTC/TDF, 8791 person-years of follow-up were accrued, with a median follow-up of 35.9 months (interquartile range [IQR] 30–36) for those assigned active PrEP at the initial randomization and 12 months (IQR 12-12) for those re-randomized from placebo. During follow-up, antiretroviral therapy was initiated by 706 HIV-1 infected partners of those assigned TDF (32.6%) and 676 partners of those assigned FTC/TDF (31.2%).

Interruptions in study medication due to protocol-defined safety-related reasons, including pregnancy and breastfeeding, accounted for 3.7% of study follow-up time: 4.2% TDF and 3.2% FTC/TDF. When factoring in protocol-defined study medication interruptions, missed visits, and non-adherence to dispensed study pills, as measured by monthly pill counts of returned study tablets, it was estimated that study medication was taken by participants on 90.0% of days during follow-up time.

Incident HIV-1 infection and comparative effect of TDF and FTC/TDF on HIV-1 acquisition

A total of 64 HIV-1 seroconversions were observed during the study for individuals assigned active PrEP: 39 TDF and 25 FTC/TDF (Table 2). Of these, 38 (22 TDF and 16 FTC/TDF) occurred prior to July 2011 and 26 (17 TDF and 9 FTC/TDF) occurred after July 2011. A total of 12 subjects (8 TDF and 4 FTC/TDF) who acquired HIV-1 were subsequently determined by HIV-1 RNA PCR testing of archived plasma to have been infected at the time of initial randomization or re-randomization (5 and 3, respectively, for TDF and 3 and 1 for FTC/TDF). Thus, 52 post-randomization infections occurred and were included in the primary modified intention-to-treat analysis: 31 among those randomized to TDF (incidence 0.71 per 100 person-years) and 21 among those randomized to FTC/TDF (incidence 0.48 per 100 person-years), a difference that was not statistically significant (hazard ratio [HR] 0.67, 95% confidence interval [CI] 0.39–1.17, p=0.16). HIV-1 incidence for those receiving active PrEP was similar during the placebo-controlled phase of the study compared to post-July 2011 when the study included only the active arms: for TDF 0.78 (95% CI 0.43–1.31) versus 0.65 (95% CI 0.38–1.05) per 100 person-years and for FTC/TDF 0.45 (95% CI 0.19–0.88) versus 0.50 (95% CI 0.27–0.85) per 100 person-years. For comparison, HIV-1 incidence in placebo arm participants prior to July 2011 was 2.00 per 100 person-years.[3] An intention-to-treat analysis, including subjects who were HIV-1 infected at randomization and re-randomization, found similar results to the primary mITT analysis comparing TDF to FTC/TDF as PrEP, as did subgroup analyses defined by sex, age, sexual behavior at baseline, country of residence, circumcision status of HIV-1 uninfected male subjects, and enrollment markers of HIV-1 disease of HIV-1 infected partners.

In a per-protocol sensitivity analysis limited to periods when study medication was dispensed, 33 HIV-1 infections occurred, 20 among those receiving TDF (incidence 0.52 per 100 person-years) and 13 among those receiving FTC/TDF (incidence 0.33 per 100 person-years), resulting in an efficacy estimate not substantively different from the primary mITT analysis (HR 0.63, 95% CI 0.31–1.27, p=0.20). Results were similar when comparing HIV-1 incidence between the two study arms restricted to periods with product adherence ≥80%: TDF incidence 0.53 per 100 person-years (20 infections) versus FTC/TDF incidence 0.31 per 100 person-years (12 infections) (adjusted HR 0.60, 95% CI 0.29–1.22, p=0.16).

Among subjects who acquired HIV-1, the minority (14/51, 27.5%) had tenofovir detected in a plasma sample at the visit at which HIV-1 seroconversion was detected, compared with the majority (1047/1334, 78.5%) of samples from a randomly selected subset of subjects who did not acquire HIV-1 (Table 3). Having detectable tenofovir, as compared to an undetectable level, was associated with an estimated relative risk reduction for acquiring HIV-1 of 85% for TDF and 93% FTC/TDF (both p<0.0001), results that were not statistically different from each other ($p_{interaction}$=0.34). The majority of subjects had consistent PrEP use during follow-up, with a modest decrease in use over time; intermittent use (i.e., stopping and restarting PrEP) was uncommon (Figure 2A). For those who acquired HIV-1, HIV-1 seroconversion generally occurred during periods of PrEP non-use (Figure 2B).

Antiretroviral resistance

Of the 64 persons assigned TDF or FTC/TDF PrEP who acquired HIV-1, HIV-1 RNA was amplified for assessment of antiretroviral resistance from 60 (93.8%); for the remainder, HIV-1 RNA could not be amplified. As previously reported,[3] in the eight subjects who were retrospectively found to be already HIV-1 infected at initial 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. Of four subjects who were retrospectively found to be HIV-1 infected at re-randomization from placebo to active PrEP, none had evidence for resistance to the study medications. Finally, of the 52 subjects who acquired HIV-1 after randomization/re-randomization, 48 had resistance data; K65R, K70E, M184V, or M184I mutations were not detected. Thus, there were no new cases of antiretroviral resistance measured among HIV-1 infections observed after July 2011.

Safety and tolerability

There were no statistically significant differences in the frequency of deaths, serious adverse events, or serum creatinine and phosphorus abnormalities between those assigned TDF and those assigned FTC/TDF (Tables 4). The frequency of adverse events overall was comparable to that seen in the placebo arm prior to July 2011.[3]

Discussion

In this randomized trial of PrEP conducted among heterosexual men and women who were at high risk for HIV-1 infection as a result of having a known HIV-1 infected sexual partner,

we evaluated the relative efficacy of single-agent TDF compared with dual-agent FTC/TDF PrEP for HIV-1 prevention. As previously reported, both TDF and FTC/TDF had significant HIV-1 protection compared to placebo and were safe and well-tolerated in this population.[3] The updated findings presented here include an additional 3569 person-years of follow-up, re-randomization of the placebo arm to TDF or FTC/TDF, and 26 additional HIV-1 infection endpoints. The results suggest comparable HIV-1 protective efficacy and safety for once-daily oral TDF and FTC/TDF.

Four randomized, placebo-controlled trials have demonstrated that daily oral TDF-based PrEP is efficacious against HIV-1 acquisition.[3–5, 7] Two trials (among heterosexual men and women in Botswana and men who have sex with men from four continents) evaluated only combination FTC/TDF,[4, 5] one trial (among injection drug users in Thailand) evaluated only single-agent TDF, and our study assessed both TDF and FTC/TDF.HIV-1 protective efficacy in intention-to-treat analyses compared with placebo in these studies ranged from 44% to 75%, with no clear differentiation in efficacy estimates for TDF compared with FTC/TDF. Notably, in each of these studies, the HIV-1 protection effects of TDF and FTC/TDF were estimated to be higher (≥85%) in secondary analyses limited to subjects with objective evidence of adherence to the medication (i.e., detectable medication in blood samples).[3, 4, 7] Two clinical trials of PrEP – one which evaluated FTC/TDF[16] and one which evaluated both TDF and FTC/TDF, as well as vaginal tenofovir gel[17] – failed to demonstrate efficacy for HIV-1 protection; in both trials, objective measures of study medication use found very low (<30%) adherence. Our results add to this body of data by providing a direct comparison of single-agent TDF and dual-agent FTC/TDF. Due to the high efficacy of both PrEP medications in our study, our ability to detect small differences between them was limited, but in as-randomized analyses, our data rule out an approximately 60% or greater reduction in risk from FTC/TDF versus TDF alone, and the observed reduction (33%) was not statistically significant. Similarly, no significant difference was found in subgroups or in sensitivity analyses restricting to time periods with evidence of protocol compliance; case-cohort analyses assessing HIV-1 protection associated with objective evidence of study medication use, both TDF and FTC/TDF had high (≥85%) efficacy for HIV-1 protection, which were both highly statistically significant.

Animal model studies provided early evidence that antiretroviral PrEP might be an efficacious HIV-1 prevention intervention,[18] and subsequent animal experiments have assessed various antiretroviral agents, delivery approaches, and dosing strategies for PrEP.[8, 19, 20] Both TDF and FTC/TDF were included in our trial to provide a direct comparison of these two PrEP approaches, with the rationale that dual-agent versus single-agent therapy may differ in efficacy, tolerability, antiretroviral resistance in breakthrough HIV-1 seroconverters, and costs. Antiretroviral resistance related to PrEP medications was rare in clinical trials of PrEP, hypothesized to be a result of low medication adherence (and thus absence of drug pressure) in persons who acquired HIV-1, and has been generally limited to persons who had seronegative acute HIV-1 infection at the time of PrEP initiation. Across PrEP trials, more resistance to FTC has been observed than resistance to TDF, consistent with a higher genetic barrier to resistance to TDF compared to FTC, although resistance was detected only in a small minority of seroconverters in our trial and in other trials, in the context of monthly HIV-1 testing within the clinical trials. Given that resistance

is rare and the marginal additional risk of resistance with FTC/TDF versus TDF PrEP is small, this consideration may not be a deciding factor in choosing a PrEP agent.

Our results indicate that one efficacious PrEP medication might be of comparable efficacy to more than one medication. This paradigm is in contrast to antiretroviral treatment, where mono- and dual-agent therapy is definitively inferior to combination therapy using at least three active agents, but is similar to post-exposure prophylaxis, where mono-agent zidovudine has been estimated to provide ~80% protection against HIV-1[21] and two antiretroviral agents are commonly used.[22] Recent guidelines for post-exposure prophylaxis, however, recommend three antiretroviral agents, with a rationale that circulating resistance in populations may make some prophylaxis agents ineffective. For PrEP, guidance from the World Health Organization and the US Centers for Disease Control and Prevention recommend FTC/TDF,[23–25] based on the totality of evidence across different at-risk populations, although both note that TDF alone is an alternative for heterosexual populations; the US Food and Drug Administration has approved a formal label indication for FTC/TDF as PrEP.[26] Our findings may be informative to decision-making for policies related to recommended PrEP medications, in which TDF versus FTC/TDF efficacy, safety, costs, and resistance need to be weighed by policymakers. For HIV-1 serodiscordant couples PrEP offers an HIV-1 prevention option under the control of the uninfected partner, particularly in couples in which the infected partner declines antiretroviral therapy; in our study population, half of HIV-1 infected partners who became eligible for treatment during study follow-up delayed initiating by at least 6 months.[27] In addition, our results should inform future development of prophylactic medications against HIV-1, many of which are being developed as single-agent products.[28]

In this clinical trial, early discontinuation of the placebo arm with continuation of the active arms and re-randomization of those initially assigned placebo to active PrEP provided an opportunity for additional evaluation of the relative efficacy of TDF compared to FTC/TDF for the prevention of HIV-1 infection.[12] Blinded follow-up of participants initially assigned to TDF and FTC/TDF was continued, and placebo arm participants were randomly re-assigned in a blinded fashion to the TDF and FTC/TDF arms, preserving the integrity of the TDF versus FTC/TDF comparison. Power calculations estimated reasonable statistical power for a 50–60% difference in HIV-1 protection between TDF and FTC/TDF in our study, but power was limited for smaller differences. Decisions, at the individual and policy level, to use TDF versus FTC/TDF PrEP will need to take into account the potential for a modest difference in HIV-1 protection, but also modest differences in cost, risk of antiretroviral resistance (primarily resistance to FTC), and side effects. Importantly, as previously reported, both TDF alone and combination FTC/TDF were highly efficacious for HIV-1 prevention in our study when compared to placebo, with efficacy estimates of 67% and 75%, respectively (both $p<0.001$), emphasizing that potential differences in HIV-1 protection between these two PrEP options is against a background where both have definitive efficacy compared to placebo.

In summary, among heterosexual men and women at risk of HIV-1 infection, once-daily oral TDF and FTC/TDF provide high and comparable risk reduction against HIV-1 acquisition, when provided in the context of other HIV-1 prevention services. Strategies to deliver PrEP

to at-risk populations, and promote high adherence, are being evaluated in demonstration projects and roll-out programs currently being conducted.[29] Successful HIV-1 prevention on a population scale will need to incorporate multiple, evidence-based biomedical and behavioral strategies, including PrEP, to achieve maximum benefits.[30]

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Panel: Research in context

Systematic review

On 14 August 2014 we searched PubMed with the terms “pre-exposure prophylaxis,” “HIV,” “tenofovir,” “emtricitabine,” “randomized trial,” and combinations thereof. The search results included primary reports of five of the six completed randomized efficacy trials of PrEP using oral TDF-based therapy[3–5, 7, 16]; one trial has been reported in abstract form.[17] In addition, secondary analyses of these trials as well as review articles and commentaries were retrieved. Three trials (among men who have sex with men from six countries and heterosexual women and men in three countries in Africa) tested combination FTC/TDF and one (among injection drug users in Thailand) tested TDF alone. Two trials, among at-risk African populations, including the prior placebo-controlled report from the present study,[3] evaluated both TDF and combination FTC/TDF. HIV-1 protective efficacy in the four trials that demonstrated HIV-1 protection ranged from 44% to 75%, with no clear differentiation across trials in the efficacy estimates for TDF compared with combination FTC/TDF. Two trials, including one testing both TDF and combination FTC/TDF, found that use of the study medication was too low to evaluate HIV-1 protection.[16, 17] The previous report from the present trial included 38 HIV-1 seroconversion endpoints among those receiving either TDF or FTC/TDF; the present report includes an additional 26 HIV-1 seroconversion events. No other studies have directly compared HIV-1 incidence among those receiving TDF versus FTC/TDF as pre-expsosure prophlyaxis against HIV-1 acquisition.

Interpretation

Our results indicate that, for HIV-1 prevention, one efficacious PrEP medication maybe of comparable efficacy to two. Due to high protective efficacy of PrEP in the study population, we had limited statistical power to demonstrate a modest difference in HIV-1 protection for TDF compared to combination FTC/TDF. However, in analyses assessing HIV-1 protection associated with objective evidence of study medication use, as measured by detection of tenofovir in plasma, both TDF and FTC/TDF were estimated to have very high (≥85%) HIV-1 protection. Decisions, at the individual and policy level, to use TDF or combination FTC/TDFPrEP in heterosexual populations will need to take into account the potential for a modest difference in HIV-1 protection, but also modest differences in cost, risk of antiretroviral resistance (primarily resistance selected by FTC), and other factors. In summary, these results demonstrate that once-daily oral FTC/TDF and combination FTC/TDF both provide high protection against HIV-1 acquisition among heterosexual men and women at risk for HIV-1 acquisition.

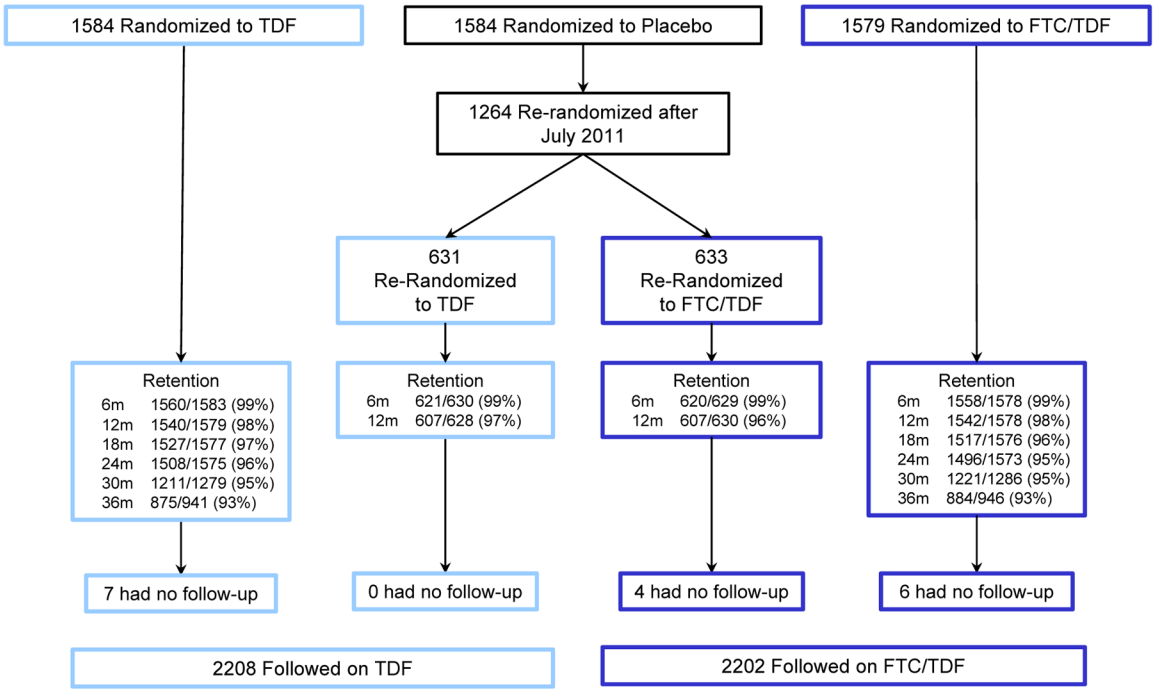


Figure 1. Initial randomization, re-randomization, and follow-up

A total of 4758 HIV-1 serodiscordant couples were initially randomized. In July 2011, the trial's Data and Safety Monitoring Board recommended discontinuation of the placebo arm and re-randomization of eligible placebo arm participants to the remaining active PrEP arms. Of 1584 participants initially randomized to placebo, 1502 were alive and had not seroconverted to HIV-1, of whom 84 (5.6%) were deemed ineligible to receive active PrEP, primarily due to pregnancy and breastfeeding (which were exclusion criteria for PrEP provision in the study protocol), with 7 (0.5%) determined to be ineligible due to clinical safety reasons or investigator decision. Thus, 1418 were clinically eligible to receive PrEP, of whom 1264 (89.1% of those considered for re-randomization) agreed to receive PrEP and continue in the study, 100 declined further study participation, and 54 had been lost to follow-up. Participants originally assigned to the active PrEP arms were eligible for up to 36 months of follow-up from the time of randomization, including up to 12 months after July 2011; those re-randomized from the placebo arm were eligible for up to 12 months of active PrEP after July 2011.

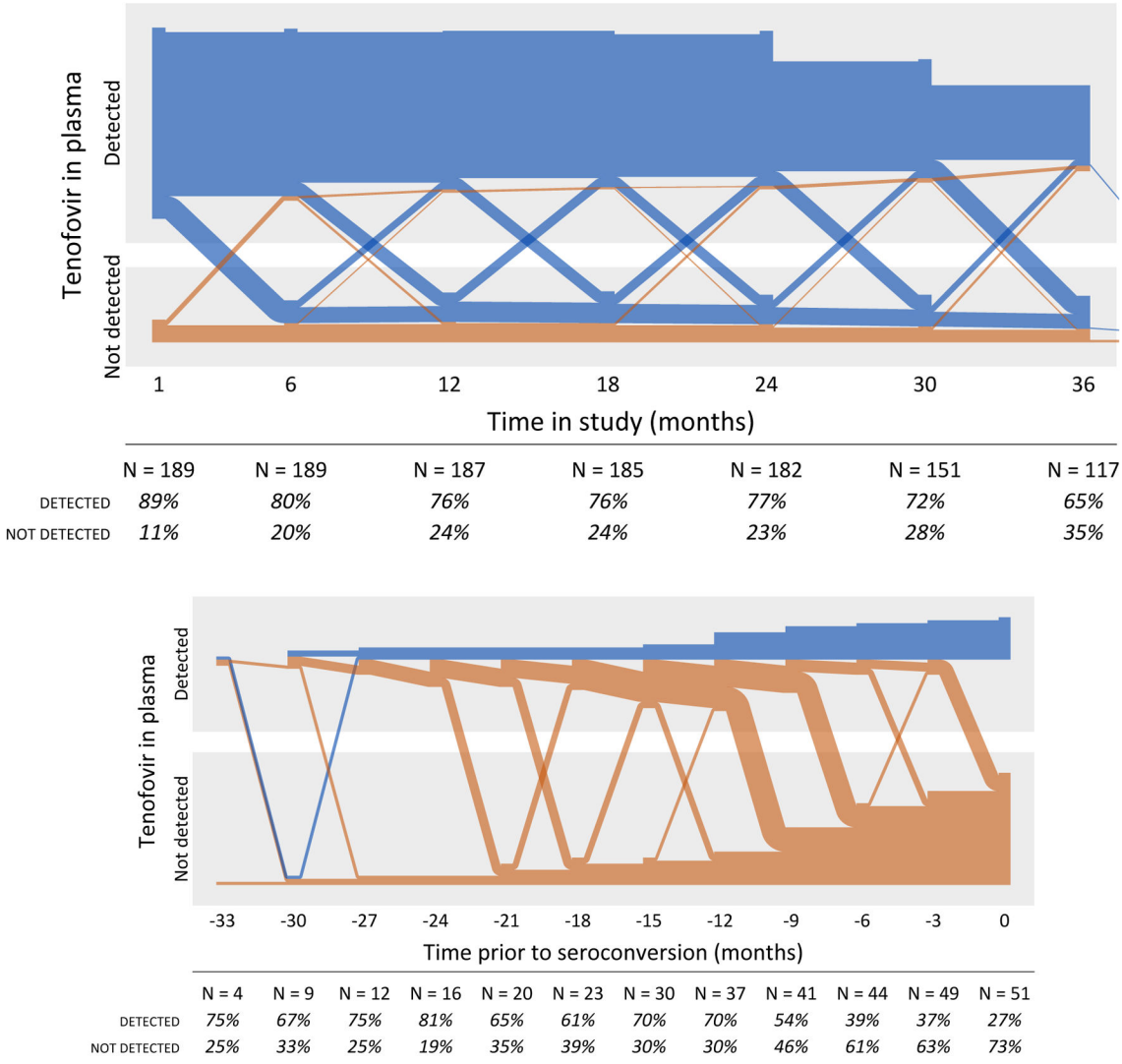


Figure 2. PrEP drug detection in blood over time

Panel A depicts the proportion of participants from the randomly-selected cohort with tenofovir detected in plasma samples collected during study follow-up. Individuals are grouped based on tenofovir detection at the first month after randomization (blue = tenofovir detected at Month 1, orange = tenofovir not detected at Month 1). Panel B depicts the proportion of subjects who acquired HIV-1 with tenofovir detected in plasma samples, with the time axis aligned to the visit at which HIV-1 seroconversion was observed. Individuals are grouped based on tenofovir detection at the HIV-1 seroconversion visit (blue = tenofovir detected at the HIV-1 seroconversion visit, orange = tenofovir not detected at the HIV-1 seroconversion visit).

Table 1

Characteristics of the study subjects at enrollment

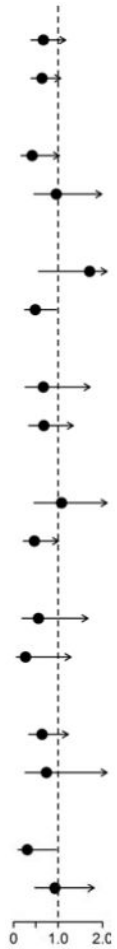
	TDF			FTC/TDF		
	Initially randomized to TDF	**Placebo later re-randomized to TDF**	**Total TDF**	**Initially randomized to FTC/TDF**	**Placebo later re-randomized to FTC/TDF**	**Total FTC/TDF**
	n=1584	**n=631**	**n=2215**	**n=1579**	**n=633**	**n=2212**
Participant Characteristics						
Male sex	986 (62%)	394 (62%)	1380 (62%)	1013 (64%)	395 (62%)	1408 (64%)
Age, years	33 (28,39)	34 (30, 40)	33 (29, 40)	33 (28, 40)	34 (29, 40)	34 (28, 40)
Education, years	7 (4,10)	7 (4, 10)	7 (4, 10)	7 (4,10)	7 (4, 10)	7 (4, 10)
Monthly income, any	1275 (80%)	511 (81%)	1786 (81%)	1236 (78%)	512 (81%)	1748 (79%)
Circumcised (men only)	533 (54%)	213 (54%)	746 (54%)	540 (53%)	195 (49%)	735 (52%)
Couple Characteristics						
Married to study partner	1543 (97%)	619 (98%)	2162 (98%)	1540 (98%)	621 (98%)	2161 (98%)
Years living with study partner	7.0 (3.0,13.5)	8.2 (3.3, 14)	7.2 (3.0, 14.0)	7.1 (3.0,14.0)	7.0 (2.7, 14.0)	7.0 (3.0, 14.0)
Proportion without children	343 (22%)	115 (18%)	458 (21%)	368 (23%)	141 (22%)	509 (23%)
Years aware of HIV-1 serodiscordant status	0.5 (0.1,2.0)	0.6 (0.1, 2)	0.5 (0.1, 2)	0.4 (0.1,2.0)	0.6 (0.1, 2)	0.4 (0.1, 2)
Sexual Risk Behavior						
Number of sex acts, prior month	4 (2,8)	4 (2, 8)	4 (2, 8)	4 (3,8)	4 (3, 8)	4 (3, 8)
Any unprotected sex acts, prior month	442 (28%)	159 (25%)	601 (27%)	416 (26%)	163 (26%)	579 (26%)
Any sex with outside partner, prior month	150 (9%)	49 (8%)	199 (9%)	134 (8%)	55 (9%)	189 (9%)
Clinical Characteristics, HIV-1 Infected Partner						
CD4 cell count/mm^3	491 (370,661)	513 (383, 684)	497 (374, 666)	497 (380,664)	493 (370, 645)	496 (377, 659)
HIV-1 plasma RNA, log_{10} copies/mL	3.9 (3.2, 4.5)	3.9 (3.2, 4.5)	3.9 (3.2, 4.5)	3.9 (3.1, 4.5)	3.9 (3.2, 4.5)	3.9 (3.1, 4.5)

Results are median (interquartile range) or N (%). Data are from the time of initial enrollment into the trial.

Table 2

HIV-1 incidence by study arm, overall and among subgroups

	TDF			FTC/TDF				
	N	# events	Rate†	N	# events	Rate†	Hazard Ratio FTC/TDF versus TDF (95% CI)	P-value
Overall								
Modified intention-to-treat (primary analysis)	2207	31	0.71	2208	21	0.48	0.67 (0.39–1.17)	0.16
Intention-to-treat	2215	39	0.89	2212	25	0.57	0.64 (0.39–1.06)	0.08
Sex of HIV-1 seronegative partner								0.16
Male	1375	16	0.59	1404	7	0.25	0.42 (0.17–1.03)	
Female	832	15	0.90	804	14	0.88	0.96 (0.46–1.98)	
Age of HIV-1 seronegative partner								0.43
<25 years	233	5	1.07	239	8	1.79	1.71 (0.56–5.26)	
≥25 years	1974	26	0.66	1969	13	0.33	0.49 (0.25–0.96)	
Unprotected sex with study partner								0.71
None, past month	1607	20	0.62	1631	14	0.43	0.67 (0.26–1.72)	
Any, past month	600	11	0.95	577	7	0.62	0.68 (0.34–1.34)	
Country								0.15
Kenya	961	10	0.52	967	11	0.57	1.08 (0.46–2.55)	
Uganda	1246	21	0.85	1241	10	0.40	0.47 (0.22–1.01)	
Circumcision status, HIV–1 seronegative men								0.44
Circumcised	753	9	0.61	732	5	0.34	0.56 (0.19–1.67)	
Uncircumcised	620	7	0.56	672	2	0.15	0.27 (0.06–1.29)	
Plasma HIV-1 RNA level of HIV-1 seropositive								0.80
<50,000 copies/mL	1798	23	0.64	1794	15	0.42	0.64 (0.34–1.23)	
≥50,000 copies/mL	375	8	1.06	383	6	0.79	0.74 (0.26–2.14)	
CD4 count of HIV-1 seropositive partner								0.09
250–350 cells/mm^3	425	13	1.53	424	4	0.47	0.31 (0.10–0.96)	



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	TDF			FTC/TDF				
	N	**# events**	**Rate†**	**N**	**# events**	**Rate†**	**Hazard Ratio FTC/TDF versus TDF (95% CI)**	**P-value**
≥350 cells/mm^3	1782	18	0.51	1784	17	0.48	0.93 (0.48–1.81)	

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% efficacy); P-values for the other comparisons correspond to a test for significant interaction in the site-stratified Cox proportional hazards model. Re-randomized placebo participants entered the risk set at the study time corresponding to their assignment to active PrEP.

Table 3

Detection of tenofovir in plasma and HIV-1 prophylactic effect

	Number / total samples (%) with tenofovir detected			Risk estimate for HIV-1 protection: detection versus no detection of tenofovir	
	Case at seroconversion	**Case before seroconversion**	**Cohort**	**HR (95% CI)**	**p-value**
TDF arm	11 / 31 (35.5%)	102 / 149 (68.5%)	545 / 667 (81.7%)	0.15 (0.06–0.37)	<0.0001
FTC/TDF arm	3 / 20 (15.0%)	42 / 81 (51.9%)	502 / 667 (75.3%)	0.07 (0.02–0.23)	<0.0001

Cases were subjects from each arm who acquired HIV-1 after study randomization: n=31 for TDF and n=20 for FTC/TDF (one subject from the FTC/TDF arm did not have sample available, this individual was found to have seroconverted to HIV-1 23 months after randomization, after not having attended any other post-randomization follow-up). The cohort comparison included subjects from the TDF and FTC/TDF arms who were randomly selected from the entire study population. Samples from study Months 1, 3, 6, 12, 18, 24, 30, and 36 after randomization/re-randomization (as available) were tested for all case and cohort subjects; in addition, for cases, a sample from the visit at which HIV-1 seroconversion was detected was tested.

Table 4

Adverse events, cumulative over the entire study period

Adverse event	TDF n=2215		FTC/TDF n=2212		p-value
	# participants	*%*	*# participants*	*%*	
Any adverse event	2010	90.7	2016	91.1	0.68
Any serious adverse event	209	9.4	207	9.4	0.96
Death	17	0.8	11	0.5	0.26
Any grade 4 event	56	2.5	75	3.4	0.09
Any grade 3 event	482	21.8	516	23.3	0.22
Confirmed laboratory events[*]					
Elevated creatinine[†‡]					
Grade 1	20	0.9	28	1.3	0.31
Grade 2+	6	0.3	3	0.1	0.51
Decreased phosphorus[**]					
Grade 2	201	9.1	199	9.1	0.96
Grade 3	15	0.7	19	0.9	0.50

[*] 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, as already reported.[3] One confirmed grade 4 creatinine events was also observed, in a 34 year-old male participant in the TDF arm who had concurrent grade 4 transaminitis at his Month 36 visit, assessed by an independent consulting nephrologist as potentially a result of acetaminophen or alcohol toxicity, viral hepatitis, or leptospirosis; both the creatinine elevation and transaminitis resolved to baseline within one month.

[‡] The study protocol defined that there was no grade 1 range for phosphorus; no confirmed grade 4 phosphorus events were observed. 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.