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Changes in Glomerular Kidney Function Among HIV-1–Uninfected Men and Women Receiving Emtricitabine–Tenofovir Disoproxil Fumarate Preexposure Prophylaxis
A Randomized Clinical Trial

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IMPORTANCE Tenofovir disoproxil fumarate (TDF) use has been associated with declines in the estimated glomerular filtration rate (eGFR) when used as part of antiretroviral treatment by persons with human immunodeficiency virus (HIV) type 1, but limited data are available for risk when used as preexposure prophylaxis (PrEP) for HIV-1 prevention.

OBJECTIVE To determine whether TDF-based PrEP causes eGFR decline in HIV-1–uninfected adults.

DESIGN, SETTING, AND PARTICIPANTS A per-protocol safety analysis of changes in eGFR in the Partners PrEP Study, a randomized, placebo-controlled trial of daily oral TDF and emtricitabine (FTC)-TDF PrEP among heterosexual HIV-1–uninfected members of serodiscordant couples in Kenya and Uganda. The trial was conducted from 2008 to 2012.

MAIN OUTCOMES AND MEASURES Predefined outcomes of this analysis were mean eGFR change and a 25% or greater eGFR decline from baseline. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

RESULTS Of 4640 participants in the once-daily TDF (n = 1548), FTC-TDF (n = 1545), or placebo (n = 1547) groups, 63% were men. At enrollment, median age was 35 years (range, 18-64 years), and mean eGFR was 130 mL/min/1.73 m^2. During a median follow-up of 18 months (interquartile range 12-27 months), mean within-group eGFR change from baseline was +0.14 mL/min/1.73 m^2 for TDF, −0.22 mL/min/1.73 m^2 for FTC-TDF, and +1.37 mL/min/1.73 m^2 for placebo, translating into average declines in eGFR attributable to PrEP vs placebo of −1.23 mL/min/1.73 m^2 (95% CI, −2.06 to −0.40; P = .004) for TDF and −1.59 mL/min/1.73 m^2 (95% CI, −2.44 to −0.74; P < .001) for FTC-TDF. The difference in mean eGFR between PrEP and placebo appeared by 1 month after randomization, was stable through 12 months, and then appeared to wane thereafter. The respective proportions of persons who developed a confirmed 25% or greater eGFR decline from baseline by 12 and 24 months was 1.3% and 1.8% for TDF and 1.2% and 2.5% for FTC-TDF, and these frequencies were not statistically different from the confirmed decline in the placebo group (0.9% and 1.3% by 12 and 24 months, respectively).

CONCLUSIONS AND RELEVANCE In this large randomized, placebo-controlled trial among heterosexual persons, with median follow-up of 18 months and maximum follow-up of 36 months, daily oral TDF-based PrEP resulted in a small but nonprogressive decline in eGFR that was not accompanied by a substantial increase in the risk of clinically relevant (≥25%) eGFR decline.

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Invited Commentary

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Antiretroviral preexposure prophylaxis (PrEP) with tenofovir disoproxil fumarate (TDF) alone or in combination with emtricitabine (FTC) has demonstrated protection against HIV-1 acquisition in diverse geographical and at-risk populations,[1-4] showing effectiveness of 44% to 75% in randomized, placebo-controlled comparisons and about 90% in subset analyses of adherent participants.

Among HIV-1 infected individuals receiving antiretroviral therapy, studies have consistently demonstrated a significantly higher frequency of kidney dysfunction, including decline in estimated glomerular filtration rate (eGFR), in patients receiving TDF-containing regimens compared with those receiving regimens not containing TDF.[5-9] Extrapolating results from these studies to the PrEP context, however, is potentially confounded by human immunodeficiency virus (HIV) type 1 infection and concomitant use of other antiretroviral medications. In PrEP clinical trials,[1-4,10] PrEP exposure was not associated with overt kidney toxic effects. However, whether TDF exposure among HIV-1–uninfected adults causes more subtle but still clinically relevant declines in eGFR requires exploration. Use of PrEP with FTC-TDF is now recommended by the US Centers for Disease Control and Prevention and the World Health Organization,[11,12] lending greater importance to profiling the safety signals of FTC-TDF in HIV-1–uninfected persons.

We investigated the effect of daily oral TDF-based PrEP on eGFR in HIV-1–uninfected adults in a placebo-controlled trial of PrEP in which PrEP adherence was high.

Methods

Study Design and Participants

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.

Data were from the Partners PrEP Study,[1,13] a phase III, randomized, placebo-controlled trial of daily oral TDF and FTC-TDF PrEP among heterosexual HIV-1–uninfected members of HIV-1–serodiscordant couples (clinicaltrials.gov number NCT00557245). Between July 2008 and November 2010, 4747 HIV-1–serodiscordant heterosexual couples were enrolled at 9 research sites in Kenya and Uganda. Eligible HIV-1–uninfected participants were at least 18 years old, did not have active hepatitis B infection, were sexually active, were not pregnant or breastfeeding, had normal renal function (defined as a serum creatinine level ≤1.3 mg/dL for men and ≤1.1 mg/dL for women, and Cockcroft-Gault–calculated creatinine clearance of ≥60 mL/min). Enrollees were also not receiving ongoing therapy with agents of known significant nephrotoxic potential and did not have diabetes requiring hypoglycemic medication or active and clinically significant cardiac disease. The HIV-1–uninfected partners were randomly assigned in a 1 to 1 to 1 ratio to 1 of the 3 study groups: TDF, FTC-TDF, or inert placebo. The doses of TDF and FTC were 300 mg/d and 200 mg/d, respectively; these doses are also the standard for treatment of HIV-1.[14]

The HIV-1–uninfected partners were followed up monthly for as long as 36 months with HIV-1 testing, study medication refill for 30 days, collection of the prior month's unused medication, and adherence counseling. Adherence to the study regimen was assessed by pill counts of returned bottles at each monthly visit. Laboratory safety, including serum creatinine levels, was evaluated at baseline, month 1, and quarterly thereafter. Grading of adverse events was based on the 2009 National Institute of Allergy and Infectious Diseases, Division of AIDS grading systems adapted to local laboratory reference ranges.[15] Treatment with the study medication was permanently discontinued in subjects who experienced HIV-1 acquisition and was withheld in women who became pregnant for the duration of pregnancy and breastfeeding. In addition, study medication was temporarily withheld if a participant had a confirmed creatinine abnormality (ie, confirmed with repeated testing, ideally completed within 7 days), defined as serum creatinine level increase 1.1 times the upper limit of normal and/or a greater than 1.5-fold change from baseline. Study drug treatment could be restarted if serum creatinine levels returned to normal or to within 1.3-fold of the baseline value. Study drug administration was permanently discontinued with a confirmed finding of grade 2 or higher creatinine abnormality (defined as ≥1.4 times the upper limit of normal or a Cockcroft-Gault calculated creatinine clearance <50 mL/min).

Study progress was reviewed by an independent data and safety monitoring board (DSMB), and in July 2011, the DSMB recommended that the placebo arm be discontinued owing to definitive demonstration of PrEP efficacy against HIV-1 acquisition. In addition, the DSMB recommended continued blinded follow-up of the active arms to garner additional data on safety and efficacy of FTC-TDF vs TDF.[16]

Assessment of GFR

The eGFR was calculated from serum creatinine levels using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[17] The CKD-EPI equation has recently been validated in African populations and provides more accurate estimates for eGFR values in the normal range than both the Modification of Diet in Renal Disease Study and Cockoft-Gault equations compared with a direct measure of GFR by iohexol clearance.[18,19] Serum creatinine was measured at baseline, month 1, and quarterly thereafter. For this analysis, predefined study outcomes were mean eGFR change from baseline and a decline in eGFR of 25% or more compared with baseline, as confirmed by a second measurement obtained prior to study drug discontinuation. The cutoff of 25% decline or greater in eGFR was adapted from established criteria for the diagnosis of acute kidney injury[20]; eGFR decline of this magnitude has been associated with increased morbidity and mortality.[21-23] eGFR values higher than 200 mL/min/1.73 m^2 were imputed to 200 mL/min/1.73 m^2 consistent with the range of GFR values found in the CKD-EPI study.[17] All site laboratories participated in regular proficiency testing.

Statistical Analysis

The primary analysis was a per-protocol safety analysis, censoring participants' visits occurring after 4 consecutive weeks with-

out study drug for any reason (including protocol-required safety hold, missed visits, and HIV-1 seroconversion). Our aim was to estimate the effect of continuous PrEP use on eGFR; recognizing that full adherence is naturally impractical in clinical settings, the per-protocol analysis is a robust approach to address drug safety.[24] The primary analyses were conducted using data collected from November 2008 through July 2011, when the placebo arm of the trial was discontinued.

To assess the study end points (absolute mean eGFR difference from baseline and time to first confirmed 25% or greater eGFR decline from baseline), we used standard regression methods as the primary approach and marginal structural models weighted with inverse probability of censoring weights in sensitivity analyses.[25,26] Marginal structural models have been proposed as a method to address potential selection bias or confounding that can result from postrandomization nonadherence and censoring.[25,26] We also evaluated treatment effects among sex and age subgroups. For all analyses, each active PrEP arm (TDF and FTC-TDF) was compared separately with placebo. The net mean eGFR difference associated with PrEP was computed as the difference in mean eGFR change from baseline between the TDF or FTC-TDF groups and the placebo group. Outcome and person-time were evaluated at 1 month and then quarterly.

For the absolute mean change in eGFR, linear regression and marginal structural linear models were fit using generalized estimating equations, with time since enrollment fitted using 3-knot restricted cubic spline (details provided in eTable 1 in the Supplement). Models were adjusted for site, sex, and age with an independent correlation structure and robust standard errors to correct for the within-person correlations.[27] Treatment effects by visit-month since randomization were generated in a separate model fitted with treatment by categorical time interaction.

For the analysis of time to the first confirmed decline in eGFR of 25% or more, we used right-censored Kaplan-Meier methods to estimate the cumulative probability, standard Cox proportional hazards models to estimate relative hazard rates,[28] and marginal structural Cox proportional hazards models with time-dependent inverse probability-of-censoring weights[25,26] with robust standards errors derived by the Lin and Wei variance estimator[29] to control for within-person correlation (see eTable 2 in the Supplement for details of weight estimation). Cox proportional hazard models were adjusted for baseline eGFR as 3-knot restricted cubic spline and stratified by site, age groups, and sex. Ties were handled using the Efron approximation method.[30,31]

Three additional sensitivity analyses were conducted: (1) a time-to-event analysis of the repeated events of a 25% or greater eGFR decline using the Andersen-Gill counting process approach in Cox regression models under the per-protocol approach[32]; (2) an intention-to-treat analysis including all randomized persons with at least 1 postrandomization creatinine measurement regardless of time without study medication using data collected through July 2011; and (3) an intention-to-treat approach including the additional follow-up of the 2 active PrEP arms after the suspension of the placebo arm in July 2011.

Finally, in exploratory analysis, we evaluated baseline factors associated with a 25% or greater decline in eGFR from baseline. In addition, we evaluated the frequency of a 1.5-fold increase or greater in serum creatinine level above baseline and study treatment discontinuation related to creatinine abnormalities. Analyses were conducted using SAS software, version 9.3 (SAS Institute Inc).

Results

Of the 4747 HIV-1–uninfected individuals enrolled in the Partners PrEP Study,[1,13] 4640 (98%) were included in the primary per-protocol safety analysis: 1548 in the TDF group, 1545 in the FTC-TDF group, and 1547 in the placebo group (**Figure 1**). Of 107 excluded, 51 did not have any postrandomization serum creatinine measurements, and 56 were without study medication for more than 4 consecutive weeks by their first creatinine measurement, generally owing to treatment refusal, missed visits, or pregnancy. Of the 4640 participants included in the primary analysis, 63% were men, and mean age at enrollment was 35 years (range, 18-64 years). Baseline characteristics were comparable across the 3 treatment groups (**Table**).

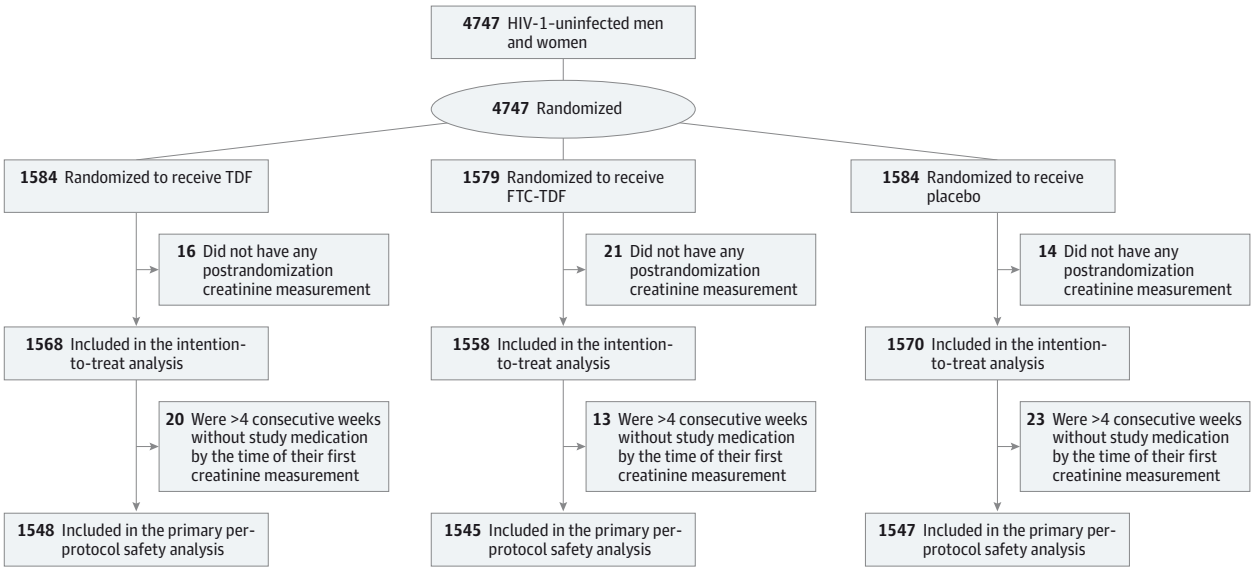
Overall, 6548.8 person-years were accrued during median follow-up of 18 months (interquartile range [IQR], 12-27 months) for this per-protocol safety analysis, representing approximately 88% of the total person-years collected in the study (ie, 12% of person-years were excluded from this per-protocol analysis by postrandomization censoring, mostly due to missed visits [5%], pregnancy [2.5%], and treatment refusal [1.4%]). The distribution of triggers for censored person-time were no more frequent in the active PrEP arms than in the placebo group, including the trigger of creatinine abnormality–related study treatment hold (0.7% overall: 0.6% TDF, 0.8% FTC-TDF, and 0.6% placebo; $P > .05$ for both TDF and FTC-TDF vs placebo).

Because of the truncated follow-up of the placebo group, few participants (n = 718) contributed more than 30 months of follow-up in the primary per-protocol analysis. An additional 2638 person-years were accrued in the active PrEP arms after July 2011 and contribute to the sensitivity analyses in the intent-to-treat approach. Overall, including the additional follow-up of the active PrEP arms beyond July 2011 in the sensitivity analysis, participants were followed up for a median of 30 months (IQR, 24-36); with the TDF and FTC-TDF arms observed for a median of 36 months (IQR, 27-36).

Effect of TDF and FTC-TDF PrEP on Absolute Mean eGFR Change From Baseline

Overall, mean eGFR at baseline was 130 mL/min/173 m^2 for the TDF group, 129 mL/min/173 m^2 for the FTC-TDF group, and 129 mL/min/173 m^2 for placebo group. During randomized treatment, PrEP was associated with a small but statistically significant decline in eGFR. During a median 18 months of PrEP treatment, the mean within-group eGFR change from baseline was +0.14 mL/min/1.73 m^2 for the TDF group, −0.22 mL/min/1.73 m^2 for the FTC-TDF group, and +1.37 mL/min/1.73 m^2 for placebo, representing absolute mean eGFR change associ-

Figure 1. Sequence of Randomization and Subsequent Exclusion or Study Completion of Study Participants



FTC indicates emtricitabine; TDF, tenofovir disoproxil fumarate.

Table. Enrollment Characteristics by Treatment Group[a]

Characteristic	FTC-TDF (n = 1545)	TDF (n = 1548)	Placebo (n = 1547)
Age, y			
≤24	11	12	11
25-34	44	45	43
35-44	32	30	33
≥45	13	13	13
Mean (range)	35 (18-64)	34 (18-64)	35 (18-64)
Men	64	62	61
Creatinine, mg/dL	0.78 (0.15)	0.78 (0.15)	0.78 (0.15)
eGFR, mL/min/173 m^2	129 (17)	130 (17)	129 (17)
≥90	98	97	98
Patient weight, kg	61 (10)	61 (10)	61 (11)
>50 kg	87	86	87
Systolic BP ≥140 mm Hg	5	5	6
Diastolic BP ≥90 mm Hg	3	3	5

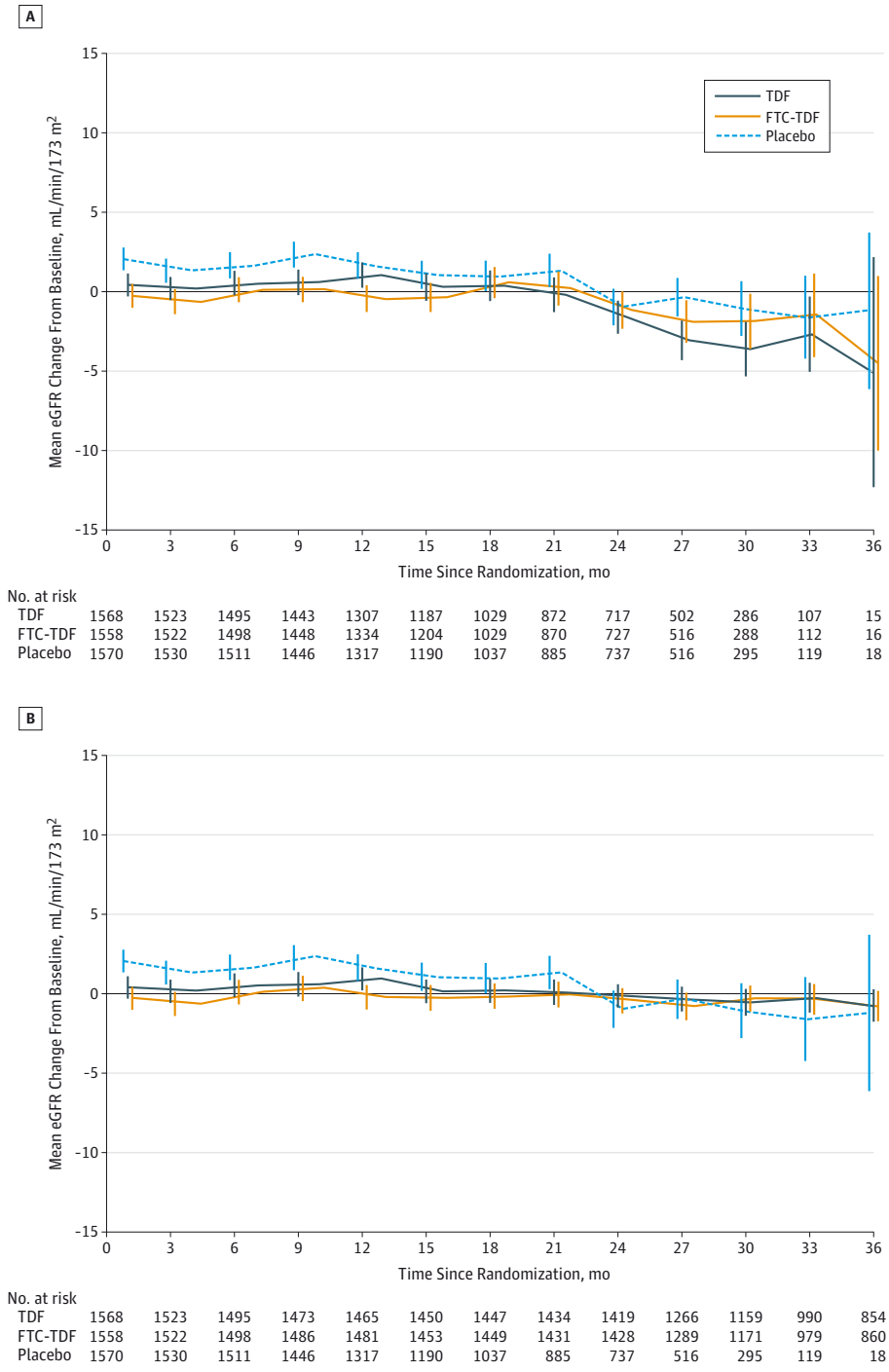
Abbreviations: BP, blood pressure; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

[a] Unless otherwise stated, data are reported as percentages for categorical covariates and mean (SD) values for continuous covariates.

ated with PrEP of −1.23 mL/min/1.73 m^2 (95% CI, −2.06 to −0.40; P = .004) for TDF and −1.59 mL/min/1.73 m^2 (95% CI, −2.44 to −0.74; P < .001) for FTC-TDF (eTable 3 in the Supplement). Compared with baseline eGFR, the estimated differences in mean eGFR change from baseline between PrEP and placebo translated into a 0.9% and 1.2% decline in eGFR that was associated with TDF and FTC-TDF, respectively. The difference between PrEP and placebo in eGFR changes from baseline appeared by 4 weeks after randomization (−1.70 mL/min/1.73 m^2, P = .001 for TDF vs placebo and −2.42 mL/min/1.73 m^2, P < .001 for FTC-TDF vs placebo), was stable to 12 months, and then appeared to gradually wane thereafter (at 24 months, −0.81 mL/min/1.73 m^2, P = .31 for TDF vs placebo and −0.42 mL/min/1.73 m^2, P = .63 for FTC-TDF vs placebo). The pattern of change over time in crude mean eGFR difference from baseline had upper limits of the 95% CIs under 3 mL/min/1.73 m^2 through 36 months postrandomization with the additional follow-up of the 2 active PrEP arms (**Figure 2**). Overall, PrEP effects were consistent among age and sex subgroups and in all sensitivity analyses including marginal structural models.

Confirmed CKD-EPI eGFR decline to less than 60 mL/min/1.73 m^2 was recorded in 2 participants, both in the TDF group. First, a 58-year-old, 61-kg man with baseline CKD-EPI eGFR of 99 mL/min/1.73 m^2 had a CKD-EPI eGFR of 10 mL/min/1.73 m^2 (serum creatinine, 7.2 mg/dL) at 36 months with concurrent 2+ dipstick proteinuria, grade 4 liver transaminases, and clinical features suggestive of acute hepatitis. He was taking no concurrent nephrotoxic medication. Treatment with the study drug was permanently discontinued, after which the eGFR returned to greater than 60 mL/min/1.73 m^2 within 4 weeks. Sec-

Figure 2. Variation Over Time in Crude Mean eGFR Changes From Baseline by Treatment Group



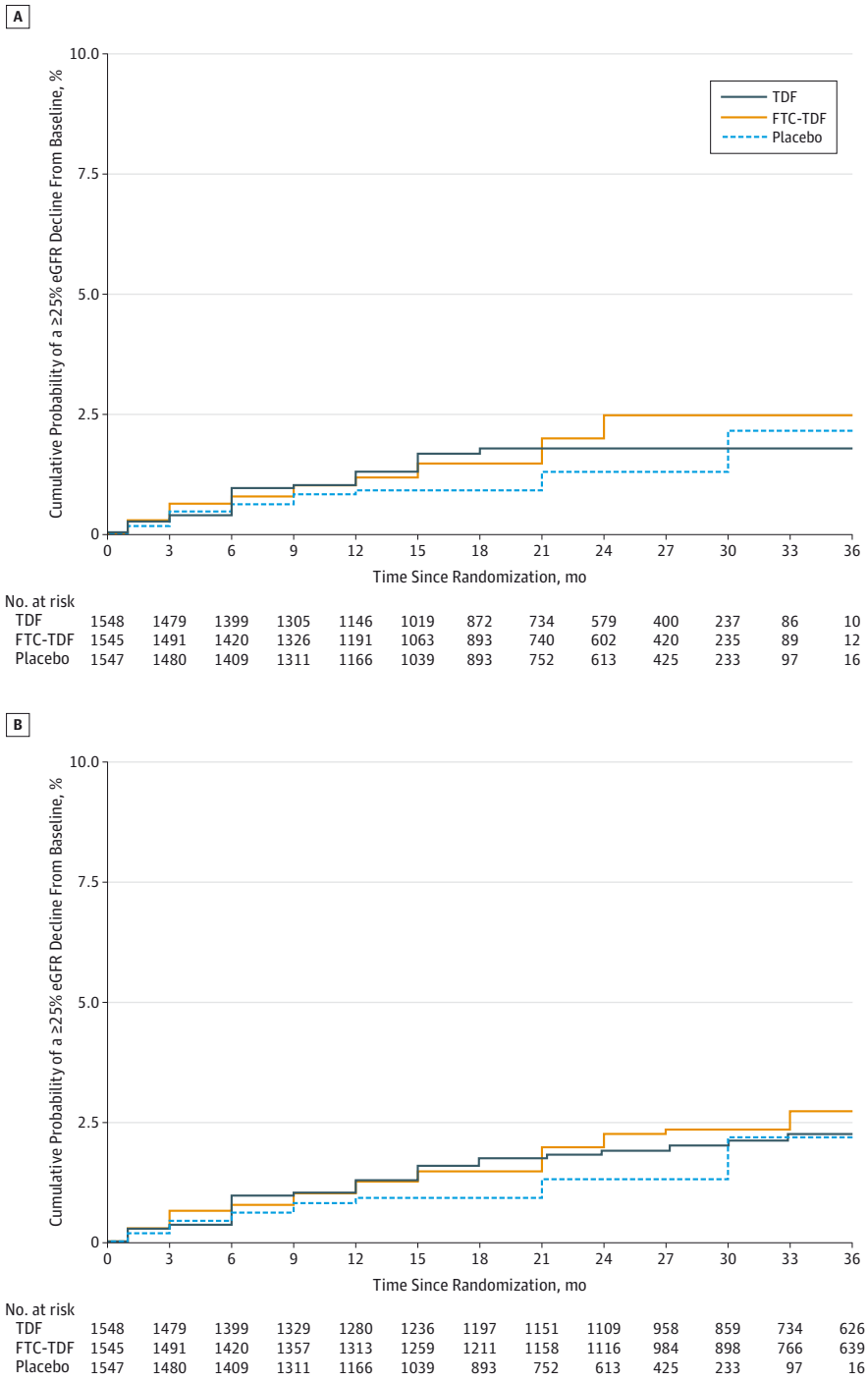
A, Graph represents all data collected through July 2011, when the trial's placebo arm was discontinued; because of truncation of follow-up time in July 2011, few participants had achieved more than 30 months of follow-up. B, Graph represents crude mean eGFR changes from baseline that includes additional follow-up of the TDF and FTC-TDF arms beyond July 2011. The placebo group contributed person-time up to only July 2011. A and B, Vertical lines indicate 95% CIs; eGFR, estimated glomerular filtration rate; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

ond, a 34-year-old, 58-kg man with baseline eGFR of 154 mL/min/1.73 m^2 had a CKD-EPI eGFR of 57 mL/min/1.73 m^2 (serum creatinine, 1.53 mg/dL) at 30 months with a history of recent relocation to a hot and dry region. Urine dipstick and liver enzyme test results were normal, and he was taking no concomitant medication. Treatment with the study drug was discontinued permanently, and eGFR returned to greater than 60 mL/min/1.73 m^2 within 2 weeks. Both events were conservatively managed.

Effect of TDF and FTC-TDF on a 25% or Greater eGFR Decline From Baseline

Confirmed 25% eGFR decline or greater was rare (eTable 4 in the Supplement). A total of 72 events occurred in the study, 68 during the per-protocol observation period and 4 during the censored period. Of these 68 events, 23 were in the TDF group (incidence rate, 1.08 per 100 person-years); 27 were in the FTC-TDF group (incidence rate, 1.24 per 100 person-years); and 18 were in the placebo group (incidence rate, 0.83 per 100 person-

Figure 3. Cumulative Probability of a 25% or Greater eGFR Decline From Baseline by Study Treatment



A, Estimates for the primary per-protocol safety analysis including data accrued up to July 2011, when the placebo arm was discontinued. B, Estimates for the sensitivity analysis that included additional follow-up of the TDF and FTC-TDF arms beyond July 2011, with the placebo arm data truncated at July 10, 2011. A and B, Failure function was calculated over full data and evaluated at indicated times; it is not calculated from aggregates of number of persons shown on the x-axis plots. eGFR indicates estimated glomerular filtration rate; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

years), representing attributable incidence rate differences of 0.41 per 100 person-years (95% CI, −0.19 to 1.01) for FTC-TDF and 0.25 per 100 person-years (95% CI, −0.33 to 0.83) for TDF alone, neither of which was statistically different from the placebo group. The proportions of persons who developed a 25% eGFR decline or greater from baseline were 1.3% for TDF, 1.2% FTC-TDF, and 0.9% for the placebo by 12 months; 1.8% for TDF, 2.5% FTC-TDF, and 1.3% for the placebo by 24 months; and 1.8% for TDF, 2.5% for FTC-TDF, and 2.2% for placebo by 36 months (**Figure 3**). Compared with placebo, the adjusted relative hazards for a confirmed 25% eGFR decline or greater from baseline associated with active PrEP was 1.33 (95% CI, 0.71-2.48; $P = .37$) for TDF alone and 1.45 (95% CI, 0.79-2.64; $P = .23$) for FTC-TDF (eTable 4 in the Supplement). In exploratory analysis, older age, female sex, and higher baseline eGFR appeared to be independently associated with increased likelihood for

25% eGFR decline or greater from baseline ($P < .05$ for all). Overall, PrEP effects were consistent among age and sex subgroups and in all sensitivity analyses including marginal structural models.

Frequency of a 1.5-Fold or Greater Serum Creatinine Level Increase Above Baseline

A total of 451 unconfirmed events of serum creatinine level increase of 1.5-fold or greater above baseline were recorded (n = 237 participants). Of these, 159 (35%) were confirmed on repeat measurements from 47 participants (1% of 4696 total subjects regardless of time without study medication): 63 events occurred in the TDF group, 60 in the FTC-TDF group, and 36 in the placebo group. Treatment with study medication was permanently discontinued in 5 of these participants per protocol specification (2 each in the TDF and FTC-TDF groups and 1 in the placebo group; all had borderline creatinine clearance at baseline; range, 60-72 mL/min/1.73 m^2).

Discussion

In this safety analysis from a large randomized placebo-controlled trial, daily oral TDF-based PrEP resulted in a small but statistically significant decrease in eGFR—specifically, a change of less than 1.5% from baseline that was nonprogressive for 36 months and not accompanied by a significant increase in the likelihood of a clinically relevant change in eGFR (ie, ≥25%). The observed results were consistent in different subgroups and in multiple statistical approaches to evaluate the treatment causal effects. To our knowledge, this is the largest randomized trial to quantify the magnitude of subclinical eGFR decline in the presence of high adherence to PrEP in HIV-1–uninfected men and women and across a broad range of ages.

Glomerular filtration rate is easily estimated from serum creatinine levels using prediction equations that take into account age, sex, and race or body weight, and provides a more reliable and accurate index for detection and monitoring of glomerular kidney dysfunction than serum creatinine levels alone. Age-related decline in GFR has been considered part of the normal aging process, declining by approximately 1 mL/min/1.73 m^2 per year beginning after age 40 years.[33,34] However, the clinical significance of drug-related subclinical eGFR decrease in healthy HIV-1–uninfected adults is unknown. In the current study, we observed small subclinical declines in mean eGFR with upper bounds of the 95% CIs in the range of 1 to 3 mL/min/1.73 m^2; PrEP effects were reversible after drug treatment discontinuation. Because PrEP use is a time-dependent intervention for months or years of greatest HIV-1 risk and not lifelong, the clinical significance of the observed changes in eGFR may be quite small. Early TDF-induced nephrotoxic effects appear to be reversible in both HIV-1–infected and –uninfected persons after TDF discontinuation.[35,36] In our study, an increase in the within-group eGFR over time for the placebo and TDF groups is likely a regression to the mean rather than a true biological effect,[37] and the between-group differences represent unbiased estimates of PrEP effects; analysis of covariance yielded similar between-group estimates.

Mean eGFR decline appeared to be nonprogressive to a period of 36 months, as assessed with the additional follow-up of the 2 active PrEP arms beyond July 2011. The majority of creatinine elevations observed were self-limited and were not confirmed on subsequent measurement, and the occurrence of clinically relevant decline in eGFR (ie, ≥25% eGFR decline from baseline) was low. In the 2 subjects who developed eGFR of less than 60 mL/min/1.73 m^2, eGFR rebounded to greater than 60 mL/min/1.73 m^2 within 4 weeks after drug treatment discontinuation. There was no evidence of substantial increase in clinically relevant eGFR decline related to PrEP compared with placebo, although given the 95% CIs, an increase in absolute rate of a greater than 25% eGFR decline as high as 1% per year attributable to PrEP cannot be ruled out.

Drug exposure is an important determinant of both PrEP efficacy and assessment for safety. Adherence in the Partners PrEP Study was the highest of any published PrEP clinical trial[1,38]: tenofovir was detectable in plasma in 82% of a randomly selected cohort of subjects, and 17% of those samples with no detected drug were a result of protocol-defined drug holds.[39] Our findings, which enriched for drug exposure in the primary analysis by limiting to per-protocol periods, are thus encouraging because they demonstrate that clinically relevant eGFR decline was rare in the context of high exposure to PrEP.

Our study provides both new and complementary evidence to the recent analysis from the iPrEx study,[40] a PrEP trial among men who have sex with men in which FTC-TDF PrEP was associated with a small but statistically significant decrease in calculated creatinine clearance. However, an important limitation of the iPrEx analysis was that PrEP adherence, based on detection of tenofovir in plasma, was estimated to be only about 50%.

The results should be interpreted in light of the following limitations. First, creatinine-based GFR estimating equations are less accurate in persons with low creatinine generation, including those with low muscle mass, muscle wasting, or reduced meat intake, which may be more common in African individuals. The CKD-EPI equation has demonstrated high accuracy in African populations, and intraindividual changes in eGFR are less susceptible to this limitation of creatinine-based estimates.

Second, long-term treatment effects beyond the study period cannot be ascertained. However, it is reassuring that in a large observational study with long-term follow-up (median, 7.9 years) of HIV-1–infected individuals undergoing TDF-containing combination antiretroviral therapy, most of the observed eGFR loss occurred during the first year of TDF exposure and stabilized after 2 years.[7] In our study, mean eGFR decline appeared to stabilize after the first year of observation and then waned over time.

Third, postrandomization censoring has the potential to introduce selection bias and/or confounding. However, the consistency of the primary analysis estimates with marginal structural models estimates lends confidence to our findings.

Fourth, against a low background level of a 25% eGFR decline or greater (ie, 0.83% per year recorded in the placebo group), we had the ability to detect only large increases in the

risk of 25% or greater eGFR decline. However, the low absolute rates of 25% or greater eGFR decline recorded in the active arms with additional follow-up (median of 36 months in the active PrEP arms) is encouraging.

Fifth, the study required participants with normal renal function at entry, and PrEP effects among subpopulations with comorbidities or concurrent nephrotoxic medications could not be fully evaluated.

Finally, the present study did not evaluate changes in proximal tubular function, another potential consequence of TDF exposure. A recent substudy in iPrEx did not show evidence of nephrotubulopathy,[40] and we observed no significant difference in graded abnormalities in serum phosphorus levels between the PrEP and placebo.[1] Whether TDF-based PrEP causes early proximal tubular injury in HIV-1–uninfected individuals warrants additional evaluation.

Conclusions

In this large, randomized, placebo-controlled trial among HIV-1–uninfected African men and women, with median follow-up of 18 months and maximum follow-up of 36 months, daily oral TDF-based PrEP was associated with a small but nonprogressive decline in eGFR that was not accompanied by a substantial increase in the risk of clinically relevant eGFR decline. Our data support the safety of TDF-based PrEP in heterosexual populations as part of a comprehensive HIV-1 prevention package.

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Acquisition, analysis, or interpretation of data: Mugwanya, Wyatt, Celum, Donnell, Mugo, Kiarie, Baeten.
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