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Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for HIV pre-exposure prophylaxis

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Objective: Tenofovir disoproxil fumarate (TDF) pre-exposure prophylaxis decreases sexual acquisition of HIV infection. We sought to evaluate the renal safety of TDF in HIV-uninfected persons.

Design and methods: The Iniciativa Profilaxis Pre-Exposición (iPrEx) study randomly assigned 2499 HIV-seronegative men and transgender women who have sex with men (MSM) to receive oral daily TDF coformulated with emtricitabine (FTC/TDF) or placebo. Serum creatinine and phosphorus during randomized treatment and after discontinuation were measured, and creatinine clearance (CrCl) was estimated by the Cockcroft–Gault equation. Indicators of proximal renal tubulopathy (fractional excretion of phosphorus and uric acid, urine protein, and glucose) were measured in a substudy.

Results: There was a small but statistically significant decrease in CrCl from baseline in the active arm, compared to placebo, which was first observed at week 4 (mean change: -2.4 vs. -1.1 ml/min; $P = 0.02$), persisted through the last on-treatment visit (mean change: $+0.3$ vs. $+1.8$ ml/min; $P = 0.02$), and resolved after stopping pre-exposure prophylaxis (mean change: -0.1 vs. 0.0 ml/min; $P = 0.83$). The effect was confirmed when stratifying by drug detection. The effect of FTC/TDF on CrCl did not vary by race, age, or history of hypertension. There was no difference in serum phosphate trends between the treatment arms. In the substudy, two participants receiving placebo had indicators of tubulopathy.

Conclusions: In HIV-seronegative MSM, randomization to FTC/TDF was associated with a very mild nonprogressive decrease in CrCl that was reversible and managed with routine serum creatinine monitoring.

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Introduction

Pre-exposure prophylaxis (PrEP) with once-daily oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) prevents acquisition of HIV infection [1−4]. In July 2012, the US Food and Drug Administration approved oral FTC/TDF HIV PrEP and the US Centers for Disease Control and Prevention and WHO issued guidance for its use. Although well tolerated with an excellent safety profile when used in HIV-infected individuals [5,6], FTC/TDF has been associated with nephrotoxicity [7−23], resolving in most [7,22,24−26], but not all [15,19,23,27], after drug discontinuation. When present, TDF's nephrotoxicity often involves proximal tubular dysfunction [7−13,16,17,19−22,24,26,28], occasionally presenting as Fanconi syndrome [16,24,25], although declines in glomerular filtration rate (GFR) as estimated by creatinine clearance (CrCl) may also occur [7,10,11,14,15,21−23,26,27].

Most studies evaluating the role of TDF in renal dysfunction have been conducted in participants living with HIV [5−7,9−12,15−17,19,20,22,24,28], hepatitis B [29−31], and other chronic diseases that may be independently associated with kidney disease [18]. The Iniciativa Profilaxis Pre-Exposición (iPrEx) study offers an opportunity to assess the unique effects of TDF on renal function in HIV-seronegative individuals.

Methods

Participants and specimens

The iPrEx study enrolled 2499 HIV-seronegative men and transgender women who have sex with men (MSM) to evaluate the safety and efficacy of once-daily oral FTC/TDF vs. placebo for HIV prevention [1]. The study showed an FTC/TDF efficacy for decreased HIV acquisition of 44% [95% confidence interval (CI) 15−63%, $P = 0.004$) in the modified intention-to-treat analysis [1].

Study visits were scheduled every 4 weeks after enrollment. Serum creatinine was measured locally at screening; enrollment; at weeks 4, 8, 12, 16, 24; and every 12 weeks thereafter until discontinuation of study drug, and at 4 and 8 weeks after stopping the drug. CrCl was estimated by the Cockcroft−Gault equation [32] using ideal body weight. In a subset of participants, plasma was tested for the presence of FTC and TDF, and peripheral blood mononuclear cells were tested for FTC triphosphate (FTC-TP) and TFV diphosphate (TFV-DP) as described elsewhere [33]. Urine dipstick testing for protein and glucose was conducted at screening and during follow-up in participants with grade 2 [34] hypophosphatemia who wanted to remain on randomized treatment. Some sites also recorded dipstick glucosuria and proteinuria at 24-week visits in conjunction with leukocyte esterase testing.

To detect proximal tubulopathy, we conducted an optional substudy. Eligible participants were on randomized treatment at the time of substudy enrollment. Urine and serum samples were collected at semi-annual visits, on the day study drug was discontinued, and again 8 weeks later. For participants who had both serum and urine specimens at drug discontinuation and at a subsequent visit, we measured urine phosphorus, calcium, creatinine, uric acid, protein, and glucose, as well as serum uric acid and phosphorus. Urine testing for indicators of tubulopathy was performed at Quest Diagnostics. All urine dipstick testing was performed in local laboratories.

The iPrEx study and substudy were approved by all applicable international agencies, and by the ethics committee at each site. Written informed consent was obtained prior to participation.

A renal toxicity management protocol was established for serum creatinine and phosphorus adverse events using the Division of AIDS (DAIDS) Adverse Event Grading Table [34] and has been described previously [1].

Definitions

Baseline serum creatinine was defined as the mean of the measurements during screening and enrollment. For creatinine adverse events of any grade, a serum creatinine measurement was repeated, usually within 7 days, and either confirmed or not for ongoing toxicity. For the substudy, we calculated fractional excretion of uric acid: [(urine uric acid × serum creatinine)/(serum uric acid × urine creatinine) × 100], and fractional excretion of phosphorus as: [(urine phosphorus × serum creatinine)/(serum phosphorus × urine creatinine) × 100]. Abnormal values were defined as a fractional excretion of phosphorus greater than 18% [20], fractional excretion of uric acid greater than 15% [20], urine glucose above 30 mg/dl with normal serum glucose (<100 mg/dl) [11], and urine protein above 30 mg/dl [11]. Urine dipstick protein and glucose with results 'trace to 4+' were considered positive for proteinuria and glucosuria, respectively.

The prespecified definition of proximal tubulopathy was an abnormal value of two of the above four indicators at the same time point [17,19,20]. The prevalence of indicators of proximal tubulopathy was determined at drug discontinuation.

Statistical methods

Baseline characteristics were compared by an unequal-variance *t*-test for continuous variables and the Fisher's exact test for categorical variables. The Fisher's exact test was also used to compare categorical variables during

follow-up. Changes in phosphorus, creatinine, and CrCl in randomized groups both during treatment and after discontinuation are reported as mean ± standard error (SE). Mean net treatment differences (absolute change in FTC/TDF minus absolute change in placebo) are reported as a mean (95% CI). Interaction hypotheses were prespecified and tested for age, black race, hypertension, NSAID use (at each visit), and BMI. All *P*-values were two-sided. Phosphorus and creatinine specimens were grouped by study visit windows, whereby collected specimens were assigned to the nearest study visit week. If there was more than one value in a visit window, the results were averaged. The average change by week and treatment was fit using generalized estimating equations with a robust SE [35]. Results by week were later stratified by detected drug when at least 100 observations were available. Results in seroconverters were censored beginning at the first visit with laboratory evidence of HIV infection. Poststop analysis compared the difference between randomized groups from baseline and the 'stop' specimen vs. baseline and the 'poststop' specimen, using a *t*-test with unequal variances.

Role of the funding source

Sponsored through a cooperative agreement, DAIDS/ National Institutes of Health had input into the study protocol on matters of study design, collection, and analysis of data. The Bill and Melinda Gates Foundation provided funding, but did not assume responsibility as a sponsor. Gilead donated study drug, but did not play a role in data collection or analysis.

Results

Iniciativa Profilaxis Pre-Exposición cohort serum creatinine, creatinine clearance and phosphate

The baseline characteristics of the active and placebo arms including CrCl, serum creatinine, phosphorous, prevalence of hypertension (SBP ≥140 or DBP ≥90), and NSAID use were similar, regardless of whether participants contributed data to the substudy (Table 1). The mean number of weeks on randomized treatment was 81 for both groups. A drift in serum creatinine measurements was noted in the placebo group over time: the magnitude of the drift from baseline to drug discontinuation was 3−5%.

During treatment, there was a small but statistically significant decrease in CrCl (reflecting an increase in serum creatinine) from baseline in the FTC/TDF group as compared to placebo (Fig. 1). This finding was of a similar magnitude when calculated using measured body weight, the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration equations (data not shown) [36,37]. The effect was apparent as early as week 4 (mean change in CrCl, FTC/TDF: −2.4 ml/min vs. placebo:

−1.1 ml/min; $P = 0.02$). The between-group change from baseline ranged from −2.7 to 0.038 ml/min over the 144 study weeks. Stratifying by presence of detectable drug corroborated the treatment effect except at week 24 (at week 8, the difference in mean change from baseline in CrCl between detected FTC/TDF and placebo groups: FTC/TDF detected vs. placebo: mean −4.61 vs. −1.57 ml/min, difference: −3.04 ml/min; $P < 0.001$) (Fig. 1). The mean net difference in CrCl between treatment arms resolved once study drug was discontinued (at stop, mean, FTC/TDF: +0.3 ml/min vs. placebo: +1.8 ml/min; $P = 0.02$; poststop, mean, FTC/ TDF: −0.1 ml/min vs. placebo: 0.0 ml/min; $P = 0.83$). There was a significantly greater net increase in CrCl with FTC/TDF compared to placebo, from stop to poststop ($P = 0.04$). The between-group differences (FTC/TDF with detected drug vs. placebo) in change from baseline persisted and were of varying magnitude compared to the overall FTC/TDF arm (at week 8: −3.04 ml/min; $P < 0.001$; at week 12: −2.90 ml/min; $P = 0.002$; at week 24: −0.49 ml/min; $P = 0.57$; at week 48: −2.09 ml/min; $P = 0.076$) (Fig. 1).

The difference in mean CrCl between groups reflects a small difference in a large portion of the cohort (Fig. 2). The interquartile range for change in mean CrCl at week 4 was −9.5 to +4.5 ml/min for FTC/TDF and −8.5 to +6.0 ml/min for placebo. At week 12, a majority of participants in both groups had a less than 10% decrease (or an increase) in CrCl (78% in FTC/TDF vs. 82% in placebo; $P = 0.009$), 19 vs. 15% had a decrease in CrCl of 10−20%, and 3 vs. 2% had a decrease of more than 20% (Fig. 2).

In none of the confirmed creatinine elevations (creatinine values above the normal range as well as those with ≥50% increase from baseline) were there coincident elevations in blood-urea nitrogen (BUN) or decreases in serum bicarbonate. The effect of FTC/TDF on CrCl did not vary according to the presence of hypertension, race, age over 40, or BMI, except at one time point (week 120) for participants with a BMI over 30 kg/m². The decrease in CrCl in the active arm (relative to placebo) was not greater among those using NSAIDS considering all visits, although there was a difference at week 60 (between-group difference in mean absolute change in CrCl from baseline was −3.4 ml/min on NSAID vs. −0.3 ml/min no NSAID; $P = 0.039$).

There was no significant difference in serum phosphorus levels over time, but there was a trend towards a greater decrease at week 4 in the FTC/TDF group (mean change from baseline FTC/TDF: −0.06 mg/dl vs. placebo: mean −0.01 mg/dl; $P = 0.06$) (Fig. 1).

Adverse events

Overall, there were 62 creatinine elevations (37 FTC/ TDF, 25 placebo; $P = 0.28$) (Table 2) including those

reported previously [1]. Over half (56%) of the 54 grade 1 events involved a creatinine elevation at least 1.5 times above baseline, but did not meet other grade 1 criteria ($\geq$1.1 times the upper limit of normal or CrCl <50 ml/min). Only eight (13%) creatinine elevations were confirmed on repeat testing (seven FTC/TDF group, one placebo; $P = 0.03$). Among confirmed creatinine elevations before 1 May 2010 (the visit cut-off for primary analysis) [1], all five occurred in the active arm, all resolved 4–20 weeks after stopping the study drug, and four were re-challenged with active drug but without recurrence in creatinine elevations. Subsequent creatinine elevations occurred near the end-of-study observation, so none were re-challenged. One resolved after the end of the study; another returned for an unblinding visit without evidence for renal disease, and subsequently died of cocaine intoxication. Of eight confirmed creatinine elevations, five had dipstick measurements obtained of which four revealed 'trace to 4+' protein. The frequency of confirmed phosphorus-related adverse events did not differ by study arm ($P = 0.56$) (Table 2). No grade 4 creatinine or phosphorus events occurred.

Urine dipstick results

Urine dipstick results at follow-up included data from 1589 participants at 5081 visits; routine testing (764 participants and 2748 visits) was performed at five clinical sites. Of 5081 dipsticks, 613 were positive for proteinuria (12%) and 62 (1%) were positive for glucosuria. Of those positive for proteinuria, four were associated with a confirmed creatinine elevation [positive predictive value (PPV) for confirmed creatinine elevation 0.7%]. Of the 62 dipsticks positive for glucosuria, none were associated with a confirmed creatinine elevation (PPV for confirmed creatinine elevation 0%).

There was no between-group difference in the proportion of participants ever positive for proteinuria (20% placebo, 21% FTC/TDF; $P = 0.62$, Fisher's exact test) or

Table 1. Baseline characteristics of all participants.

	Contributed data to the renal substudy			All others		
	FTC/TDF	Placebo	P	FTC/TDF	Placebo	P
Study site	N (%)	N (%)	0.69	N (%)	N (%)	0.85
Lima, Peru	260 (46)	249 (43)		210 (31)	221 (33)	
Iquitos, Peru	169 (30)	182 (32)		61 (9)	48 (7)	
Guayaquil, Ecuador	0 (0)	0 (0)		150 (22)	150 (22)	
Rio de Janeiro, Brazil	68 (12)	73 (13)		79 (11)	74 (11)	
Sao Paulo, Brazil	0 (0)	0 (0)		39 (6)	37 (5)	
San Francisco, USA	20 (4)	29 (5)		50 (7)	41 (6)	
Boston, USA	1 (0.2)	1 (0.2)		42 (6)	43 (6)	
Chiang Mai, Thailand	45 (8)	39 (7)		12 (2)	18 (3)	
Cape Town, RSA	0 (0)	1 (0.2)		45 (7)	42 (6)	
Age (years)			0.38			0.11
18–24	267 (47)	300 (52)		325 (47)	362 (54)	
25–29	123 (22)	107 (19)		150 (22)	134 (20)	
30–39	116 (21)	110 (19)		133 (19)	114 (17)	
>40	57 (10)	57 (10)		80 (12)	64 (9)	
Race			0.98			0.17
Black/African-American	25 (4)	26 (5)		92 (13)	71 (11)	
White	68 (12)	71 (12)		155 (23)	137 (20)	
Mixed/other	424 (75)	434 (76)		425 (62)	444 (66)	
Asian	46 (8)	43 (7)		16 (2)	22 (3)	
Ethnicity			0.71			0.99
Hispanic/Latino	451 (80)	465 (81)		449 (65)	440 (65)	
Non-Hispanic/Latino	112 (20)	109 (19)		239 (35)	234 (35)	
Hypertension			0.57			0.34
No	535 (95)	550 (96)		622 (90)	620 (92)	
Yes	28 (5)	24 (4)		66 (10)	54 (8)	
Weight (kg) (mean, std)	66 (12.6)	66.3 (12.9)	0.10	70.4 (15.1)	69.1 (14.2)	0.71
Height (cm) (mean, std)	167 (8)	168 (8)	0.18	170 (8)	170 (8)	0.21
NSAID use			0.31			0.31
No	265 (47)	288 (50)		436 (63)	445 (66)	
Yes	298 (53)	286 (50)		252 (37)	229 (34)	
Creatinine (mg/dl) (mean, std)	0.9 (0.1)	0.9 (0.1)	0.42	0.9 (0.1)	0.9 (0.1)	0.84
Creatinine clearance (ml/min) (mean, std)	118.4 (21.7)	119.5 (20.4)	0.39	116.4 (21.4)	116.8 (22.5)	0.73
Phosphorus (mg/dl) (mean, std)	3.7 (0.5)	3.7 (0.5)	0.42	3.7 (0.5)	3.7 (0.5)	0.25
BMI (kg/m^2)			0.96			0.52
<18.5	30 (5)	31 (5)		23 (3)	26 (4)	
18.5–24.9	362 (65)	375 (65)		414 (60)	422 (63)	
25.0–29.9	139 (25)	139 (24)		203 (30)	175 (26)	
>30	32 (5)	29 (5)		48 (7)	51 (8)	

FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

glucosuria (3% for both groups; $P=0.55$). Proteinuria showed a sensitivity of 80% (4/5) and a specificity of 89% for confirmed creatinine elevations. The one confirmed creatinine elevation that did not show dipstick positivity for urine protein occurred in a participant whose creatinine had increased by 50% but was still within
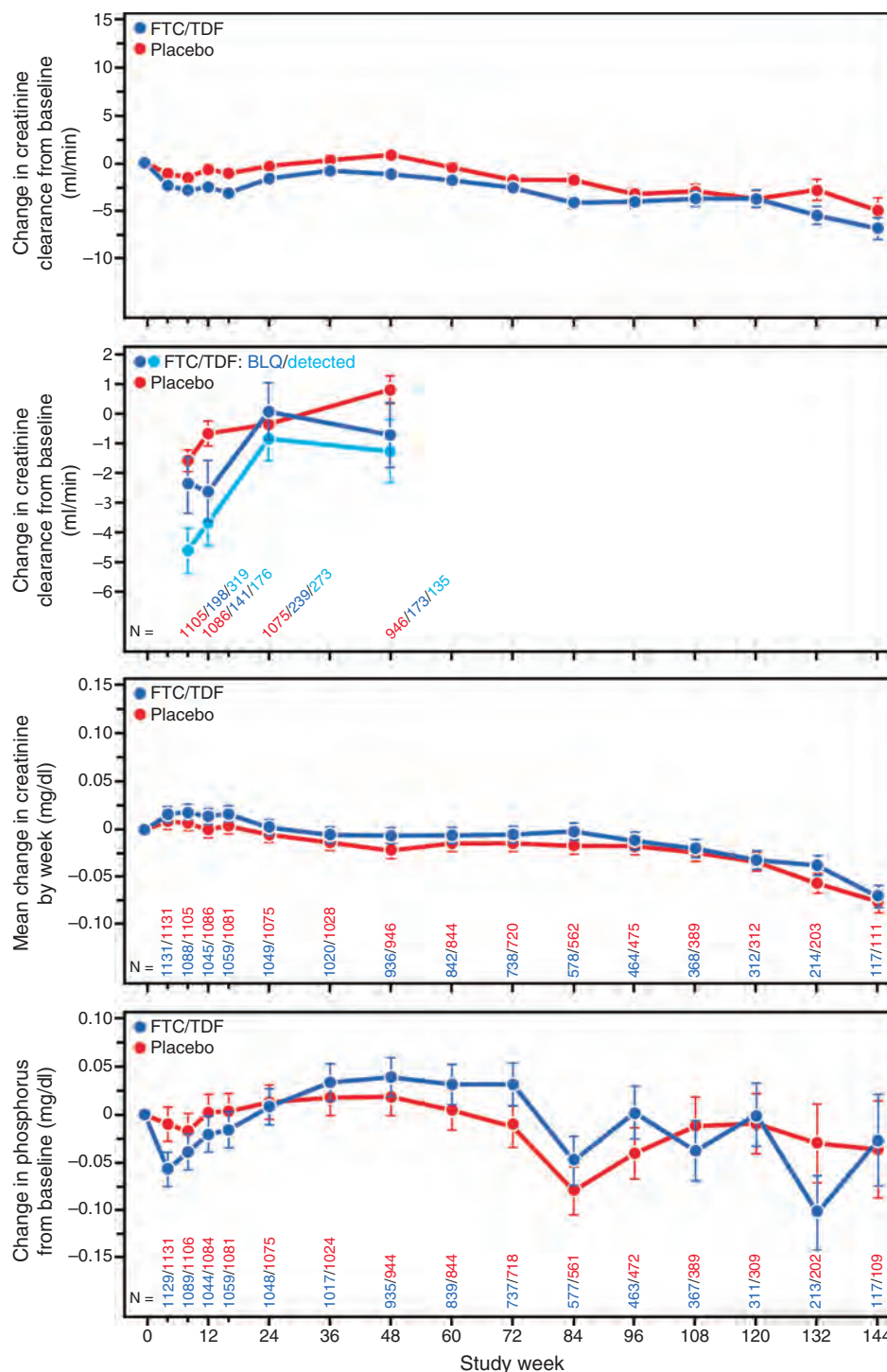

Fig. 1. Changes in renal parameters. The figure depicts mean change from baseline in estimated creatinine clearance (first and second panels), serum creatinine (third panel), and serum phosphorous (fourth panel) by study week and treatment arm. The second panel stratifies the active arm into whether drug was detected at the study visit. See online supplemental materials for a table of mean changes in estimated creatinine clearance from baseline by study arm and study visit (Table S3 http://links.lww.com/QAD/A486). N's represent the number of valid test results by color-coded group. Error bars are SEM. BLQ, below limit of quantitation.
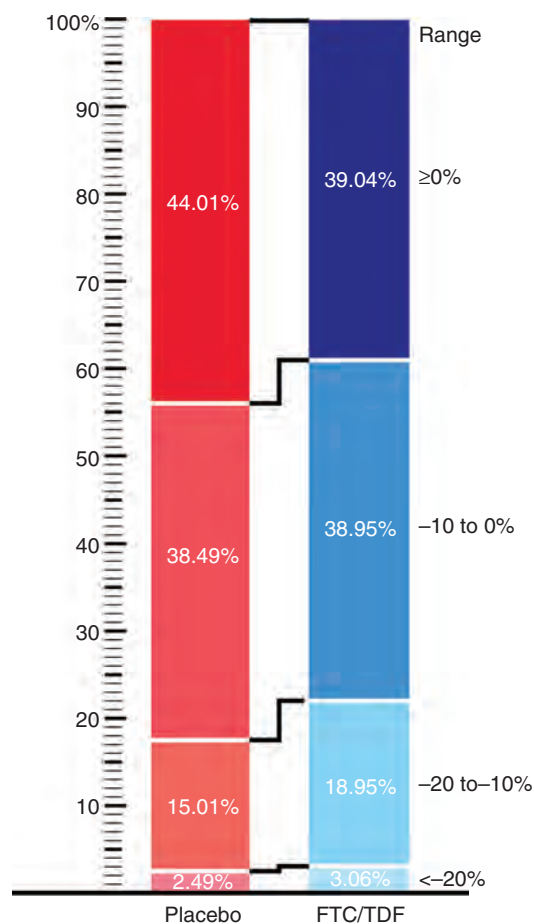
Fig. 2. Distribution of creatinine clearance changes. The figure depicts the distribution of change in estimated creatinine clearance from baseline to week 12 by treatment arm. The *y*-axis and the percentages depicted inside the bars are the proportion in each treatment arm falling within the range of change in estimated creatinine clearance depicted to the right of the bars. CrCl, estimated creatinine clearance.

the normal range. All confirmed creatinine elevations with dipstick testing were negative for glucosuria.

Of the nine participants with confirmed grade 2 hypophosphatemia with dipstick results (remained on

Table 2. Creatinine and phosphorus adverse events by treatment arm designated as total or confirmed on repeat testing.

	Number of participants with maximum grade (total/confirmed)				Number of participants with elevation		
	1	2	3	4	N	Events	P
Creatinine							0.28/0.03
FTC/TDF	27/5	5/2	0/0	0/0	32/7	37/7	
Placebo	21/1	2/0	1/0	0/0	24/1	25/1	
Phosphorus							0.78/0.56
FTC/TDF	81/8	110/17	13/5	0/0	204/30	300/37	
Placebo	110/9	91/11	10/6	0/0	211/26	292/32	

FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

randomized treatment with grade 2 hypophosphatemia), five had trace to 1+ proteinuria and two had trace to 1+ glucosuria. All five of nine continued to have trace or 1+ proteinuria and one of nine had 1+ glucose at the end of the study. Of those with hypophosphatemia and proteinuria or glucosuria, only one stopped drug (due to persistent glucosuria). All cases of hypophosphatemia resolved.

Proximal renal tubule substudy

One thousand, one hundred and thirty-seven individuals contributed data to the substudy and were followed for a mean of 1.9 years. Baseline characteristics of the two study groups were similar (Table 1) and did not differ significantly from the remainder of the iPrEx cohort.

At drug discontinuation, 94% of participants showed no indication of proximal tubulopathy. Fifty-nine had one indicator [34 (6%) FTC/TDF, 25 (5%) placebo]. Two participants had two indicators (one had proteinuria and glucosuria; the other had increased fractional excretion of phosphorus and uric acid), and thus met study criteria for proximal tubulopathy; both had been randomized to placebo. Additionally, one placebo-arm participant had evidence for tubulopathy after drug discontinuation without subsequent follow-up.

Both cases of proximal tubulopathy had no indicators of tubulopathy 56 and 75 days, respectively, after withdrawal of placebo. Of those with one indicator of tubulopathy at drug discontinuation, 15 (68%) on placebo and 25 (83%) on FTC/TDF had their marker of proximal tubulopathy resolve at the poststop visit ($P = 0.32$). After stratifying for detected drug level, there were no significant between-group differences at drug discontinuation in fractional excretion of phosphorus (FTC/TDF detected vs. FTC/TDF below the level of quantitation (BLQ) vs. placebo, mean 6.89 vs. 7.25 vs. 7.08%; $P = 0.26$), urine glucose (FTC/TDF detected vs. FTC/TDF BLQ vs. placebo, mean 6.12 vs. 4.84 vs. 5.47 mg/dl; $P = 0.85$), urine protein (FTC/TDF detected vs. FTC/TDF BLQ vs. placebo, mean 12.67 vs. 10.45 vs. 10.71 mg/dl; $P = 0.22$), or fractional excretion of uric acid (FTC/TDF detected vs. FTC/TDF BLQ vs. placebo, mean 5.51 vs. 5.87 vs. 5.90%; $P = 0.52$; Fig. 3).

Discussion

In this large randomized, double-blinded, placebo-controlled clinical trial of PrEP, FTC/TDF was associated with a small yet statistically significant decrease in CrCl. This effect first appeared at week 4, persisted until drug discontinuation, and then resolved. These mean differences represented a subclinical effect broadly distributed across the treatment group. We did not find a statistically significant effect of FTC/TDF on serum phosphorus

levels or indicators of proximal tubulopathy after stratifying by the presence of detectable drug affirming the association. Proteinuria by dipstick when tested
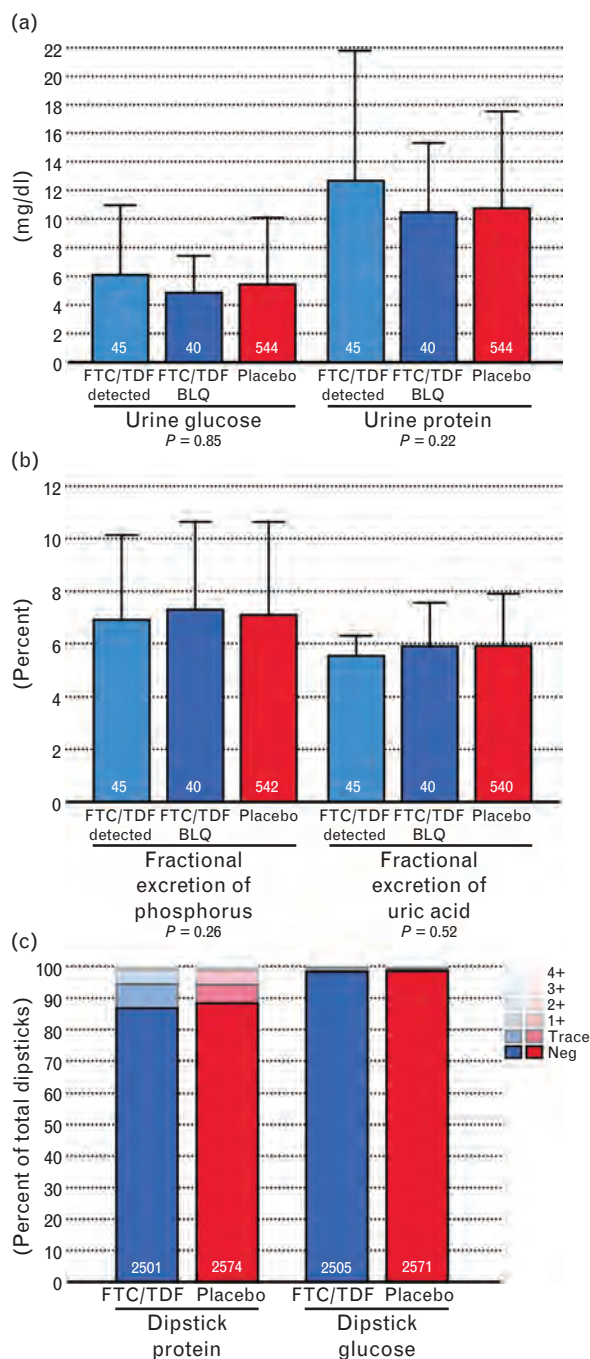
(a)

(b)

(c)

Fig. 3. Indicators of proximal tubulopathy. The figure depicts mean urine protein and urine glucose by treatment arm (a), mean fractional excretion of uric acid and fractional excretion of phosphorous by treatment arm (b), and the proportion of study visits having the depicted urine dipstick results by treatment arm (c). Fractional excretions of uric acid and phosphorous are displayed as a percent of excretion of creatinine (see methods). Error bars are SEM. Numbers inside the bars are the number of participants ((a) and (b)) or number of study visits (c) with valid test results.

occurred regularly (12%) and was present in 80% of confirmed cases of serum creatinine elevation. However, the PPV of proteinuria (<1%) and glucosuria (0%) for a confirmed creatinine elevation was poor.

A recent systematic review and meta-analysis of the renal safety in over 10 000 HIV-infected persons found a greater decrease in CrCl among TDF recipients as compared to controls [14]. However, the degree of TDF-associated renal function loss was smaller in randomized controlled trials than in observational cohorts, and the overall clinical significance was modest [14]. A large retrospective analysis in a Veterans' Affairs population found that TDF exposure among HIV-infected individuals was independently associated with increased risk for kidney disease that did not resolve with TDF discontinuation [15], similar to a few prior analyses [19,23,27]. In that observational study, pre-existing risk factors for renal disease (including HIV infection) could confound the associations and may explain the lack of resolution of renal effects after stopping TDF. In contrast, renal function returned to placebo levels after stopping oral FTC/TDF in the present study.

Our study differs from other published work because of its prospective, randomized design and inclusion criteria requiring that participants be HIV-seronegative and generally healthy. In the current study, the mean decrease in CrCl from baseline was of the order of 1−3 ml/min for the active arm when compared to placebo. Given that mean baseline CrCl was approximately 117 ml/min, this small mean change represents approximately 2% loss in estimated CrCl after taking the study drug for, on average, 81 weeks. Whereas some participants experienced greater decreases in CrCl, the mean decline in CrCl remained stable after week 4 despite continuation of FTC/TDF. Importantly, we observed a 3−5% downward drift in creatinine in both study arms, which was greater than the overall mean treatment effect.

Limitations included the lack of direct measurement of GFR, although this is a common limitation in large studies of kidney function. Mean exposure to FTC/TDF was 81 weeks, thus limiting our ability to predict the longer-term effects on the kidney, although the renal effects were stable after week 4. The low adherence to PrEP in the study is another limitation, as it would mitigate toxicities. Stratifying the analysis according to FTC/TDF drug detection in the active arm indicated evidence of a dose response that was statistically significant at some time points, although there was evidence of lower CrCl at week 12 even among those with no detectable drug in blood, suggesting that prior low level use may still have an effect in some PrEP users. Our study population was composed of MSM, although a similar low incidence of renal injury was observed in heterosexual men and women in African PrEP studies [3,4]. Finally, this trial required normal renal function at

entry. Demonstration projects may also provide additional data on frequency of monitoring required or factors that will enable clinicians to identify those at greatest risk for renal effects of TDF. The next step will be to monitor renal safety as PrEP is offered to broader populations with multiple comorbidities including pre-existing renal disease or predisposing risk factors for it (e.g. older age or diabetes) to determine whether FTC/TDF's effects on renal function are similarly modest in these populations.

Creatinine elevations confirmed at consecutive visits were more frequent in the treatment arm (7 vs. 1), but rare overall (7/1248 or 0.6%): The number needed to harm, defined as a confirmed creatinine elevation including elevations that remain in the normal range, was approximately 166. The risk of adverse renal outcomes was readily managed with every 12-week serum creatinine testing. This study indicates that TDF use in PrEP may lead to mild and subclinical decline in CrCl without proximal tubular dysfunction.

These findings support the Centers for Disease Control and Prevention interim guidance that oral FTC/TDF PrEP should include monitoring of serum creatinine [38]. Monitoring BUN, serum phosphate, and urine-derived parameters of proximal tubulopathy had no discernible value. We advise repeating the abnormal serum creatinine measurements on a separate specimen before discontinuing FTC/TDF because the majority of elevations are self-limited. The safety and optimal monitoring frequency for oral FTC/TDF PrEP users having risk factors for renal dysfunction warrants evaluation.

Acknowledgements

Conflicts of interest
There are no conflicts of interest.

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