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Pre-exposure Prophylaxis With Tenofovir Disoproxil Fumarate/ Emtricitabine and Kidney Tubular Dysfunction in HIV-Uninfected Individuals

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Abstract

Background—Pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) is becoming increasingly adopted for HIV prevention. Tenofovir can cause proximal tubular damage and chronic kidney disease in HIV-infected persons, but little is known regarding its nephrotoxic potential among HIV-uninfected persons. In this study, we evaluated the effects of PrEP on urine levels of the following: α1-microglobulin (α1m), a marker of impaired tubular reabsorption; albuminuria, a measure of glomerular injury; and total proteinuria.

Setting—The Iniciativa Profilaxis Pre-Exposicion (iPrEx) study randomized HIV-seronegative men and transgender women who have sex with men to oral TDF/FTC or placebo. The iPrEx open-label extension (iPrEx-OLE) study enrolled former PrEP trial participants to receive open-label TDF/FTC.

Methods—A cross-sectional analysis compared urine biomarker levels by study arm in iPrEx (N = 100 treatment arm, N = 100 placebo arm). Then, urine biomarker levels were compared before and after PrEP initiation in 109 participants of iPrEx-OLE.

Results—In iPrEx, there were no significant differences in urine α1m, albuminuria, or proteinuria by treatment arm. In iPrEx-OLE, after 24 weeks on PrEP, urine α1m and proteinuria increased by 21% [95% confidence interval (CI): 10 to 33] and 18% (95% CI: 8 to 28), respectively. The prevalence of detectable α1m increased from 44% to 65% ($P < 0.001$) and estimated glomerular filtration rate declined by 4 mL/min/1.73 m^2 ($P < 0.001$). There was no significant change in albuminuria (6%; 95% CI: −7% to 20%).

Conclusion—PrEP with TDF/FTC was associated with a statistically significant rise in urine α1m and proteinuria after 6 months, suggesting that PrEP may result in subclinical tubule dysfunction.

Keywords

HIV prevention; pre-exposure prophylaxis (PrEP); nephrotoxicity; tubular dysfunction; kidney injury; urine biomarkers; alpha-1 microglobulin

INTRODUCTION

Pre-exposure prophylaxis (PrEP) with once-daily oral tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) was approved by the United States Food and Drug Administration in 2012 for prevention of HIV acquisition.[1–3] Subsequently, the United States Centers for Disease Control and the World Health Organization issued guidelines in support of PrEP as a global strategy for HIV prevention.[4,5] With an expanding population of HIV-uninfected PrEP users, careful evaluation of adverse effects is essential for maximizing benefits while minimizing risks. The active metabolite of TDF, tenofovir (TFV), is secreted by the proximal tubule of the kidney, where it can lead to toxicity through mitochondrial injury.[6–8] Among HIV-infected persons, TDF has been associated with higher risks of chronic kidney disease, proteinuria, and acute kidney injury.[9–13] In clinical trials of PrEP, the use of TDF by

HIV-uninfected persons has also been associated with a small but statistically significant rise in serum creatinine, which seems to be reversible when the medication is discontinued.[14–17] Based on these findings, the Centers for Disease Control clinical practice guideline recommends avoidance of TDF/FTC in persons with reduced creatinine clearance (<60 mL/min) and advises clinicians to monitor serum creatinine at 6-month intervals.[4]

However, because the proximal tubule is the primary site of nephrotoxicity from TDF, tubular dysfunction may occur before an appreciable reduction in glomerular filtration rate (GFR) detected by biannual creatinine monitoring.[18] The full Fanconi syndrome of proximal tubular dysfunction (characterized by low molecular weight proteinuria, glucosuria, phosphaturia, and uricosuria) is rare among TDF users,[19–21] but subclinical tubular dysfunction has been observed in the absence of creatinine elevation.[22–27] Urine α1-microglobulin (α1m) is a low molecular weight protein that is filtered at the glomerulus and reabsorbed at the proximal tubule.[28,29] We previously reported that cumulative TDF exposure is associated with higher urine α1m levels in persons infected with HIV,[30] and that urine α1m levels are prognostic of subsequent kidney function decline.[31,32] A recent subgroup analysis of the Partners PrEP Study reported higher rates of proteinuria, tubular proteinuria (defined as urine protein/creatinine ratio >.200 mg/g with urine albumin/protein ratio, 0.4), and uricosuria among HIV-uninfected men and women randomized to TDF/FTC versus placebo.[21] To the best of our knowledge, no previous study has examined the effects of TDF-based PrEP on concentrations of α1m or other low molecular weight proteins in urine.

The objective of this study is to evaluate the effects of PrEP with TDF/FTC on urine levels of the following: α1m, a marker of impaired tubular reabsorption; albuminuria, a measure of glomerular injury; and total proteinuria. First, we perform a nested cross-sectional analysis of urine biomarker levels among participants of the Iniciativa Profilaxis Pre-Exposicion (iPrEx) study, a randomized placebo-controlled trial of TDF/FTC for PrEP among HIV-seronegative men and transgender women who have sex with men. Next, we compare urine biomarker levels before and after PrEP initiation in participants of the iPrEx open-label extension (iPrEx-OLE) study, a cohort of former participants of PrEP trials who subsequently enrolled in a study providing TDF/FTC-based PrEP to all participants. Finally, we evaluate the cross-sectional association of hair TDF/FTC levels with urine biomarker levels in iPrEx-OLE to explore a possible relationship between drug exposure and tubular toxicity.

METHODS

Study Design and Participants

The iPrEx study randomly assigned HIV-seronegative men who have sex with men (MSM) and transgender women to receive once-daily oral TDF/FTC or placebo.[1] A total of 2499 participants were enrolled from Brazil, Ecuador, Peru, South Africa, Thailand, and the United States. Inclusion criteria included a creatinine clearance (estimated by the Cockcroft–Gault equation) of ≥60 mL/min and a urine dipstick negative for proteinuria and glucosuria within the 28 days before enrollment. For our cross-sectional substudy, 100 treatment arm participants with available urine specimens between 12 and 18 months of follow-up and

ever-detectable TFV concentrations in plasma were selected randomly for inclusion. An additional 100 participants from the placebo arm were matched by age and site to the treatment arm participants. The median duration on TDF/FTC and placebo at the time of urine collection was 68 weeks [interquartile range (IQR): 56–72] and 64 weeks (IQR: 48–92), respectively.

iPrEx-OLE provided PrEP free of charge to former participants of 3 placebo-controlled PrEP trials without restriction on renal function at the time of enrollment and assessed PrEP uptake, adherence, and persistence in this cohort over 72 weeks.[33] A total of 1225 HIV-seronegative MSM and transgender women from Brazil, Ecuador, Peru, South Africa, Thailand, and the United States received PrEP during follow-up. A subset of 220 participants underwent hair collection to evaluate TFV and FTC hair concentrations as a measure of drug exposure.[34,35] The current study included all 109 iPrEx-OLE participants with: (1) urine specimens available before initiating PrEP ("baseline"); (2) urine specimens available approximately 24 weeks after initiation of PrEP ("on PrEP"); and (3) previously measured hair concentrations of TFV on the same date as "on PrEP" urine collection. Among the 109 OLE participants in our substudy, 51 received TDF/FTC previously during their participation in PrEP trials and 42 participants received placebo; previous treatment assignment was unknown for 16 participants.

The iPrEx and iPrEx-OLE study protocols were approved by institutional review boards of all participating sites, and all participants provided written informed consent in their preferred language. This study was also approved by the University of California, San Francisco and San Francisco Veterans Affairs Medical Center committees on human research.

Measurements

Urine specimens from both iPrEx and iPrEx-OLE were in continuous storage at −80°C until biomarker measurement without previous freeze-thaw. Urine biomarker concentrations were measured at the Cincinnati Children's Hospital Medical Center Biomarker Laboratory. Urine α1m was measured using a commercially available assay (Siemens BNII nephelometer; Siemens, Munich, Germany). The detectable limit of the α1m assay is 0.53 mg/dL. Urine albumin, total protein, and creatinine were measured using a Siemens Dimension Xpand plus HM clinical analyzer (Siemens). Laboratory personnel performing the biomarker assays were blinded to participants' clinical information. Serum creatinine was measured in local laboratories for each study; estimated GFR (eGFR) was estimated by the Chronic Kidney Disease Epidemiology Collaboration equation using serum creatinine.[36]

Statistical Analysis

For cross-sectional comparisons by treatment arm in iPrEx, we tested differences in urine biomarker levels and other continuous variables using the Mann–Whitney U test and χ^2 tests for categorical variables. For the longitudinal iPrEx-OLE study, we analyzed within-participant changes in urine biomarkers over time using Wilcoxon signed-rank tests for continuous measures and McNemar test for dichotomous measures. Urine albumin/creatinine and protein/creatinine ratios were calculated as in clinical practice. The

distribution of α1m included a high percentage of values below the detectable limit. As in our previous work,[30] we analyzed urine α1m concentration both as a continuous variable, without standardizing to urine creatinine, and as a dichotomous variable (detectable vs undetectable). To correct for urine tonicity and to enable comparison across measures, we then used robust linear regression models to estimate relative 24-week changes in urine α1m, albumin, and protein, while controlling for urine creatinine. Because of their right-skewed distributions, the urine measures were log-transformed to normalize their distributions, and results were back-transformed to produce relative changes from baseline. Spearman coefficients evaluated correlations between TFV concentrations in hair and urine biomarker levels. Sensitivity analyses stratified OLE participants by previous exposure to TDF. In a separate analysis, we excluded persons with undetectable TFV concentrations in hair.

RESULTS

Characteristics of iPrEx and iPrEx-OLE Urine Biomarker Study Participants

Among the 200 participants included in the cross-sectional iPrEx substudy, the median age was 23 years and 18% of participants were transgender (Table 1). Persons of black race comprised 11% of participants, whereas Asians and Latinos comprised 27% and 54% of participants, respectively. There were no statistically significant differences in race, ethnicity, or blood pressure across treatment arms. At the time of urine collection, the median serum creatinine and eGFR were 0.9 mg/dL and 124 mL/min/1.73 m^2, respectively, and these values did not differ by treatment arm.

Among the 109 participants included in the longitudinal iPrEx-OLE substudy, the median age was 30 years and 6% of participants were transgender. One-tenth of the participants were of black race, 13% were Asian, and 45% were Latino. At baseline, the median serum creatinine was 0.9 mg/dL and the median eGFR was 114 mL/min/1.73 m^2.

Urine Biomarker Levels in iPrEx and iPrEx-OLE

In the cross-sectional analysis of iPrEx participants, there were no statistically significant differences in urine α1m, albuminuria, or proteinuria by treatment arm (Table 2). In the longitudinal substudy of iPrEx-OLE participants, we observed statistically significant increases in urine α1m and proteinuria over a median of 24 weeks of exposure to TDF/FTC (IQR: 23.5–24.5), but there was little change in albuminuria over time (Table 3). The mean urine α1m concentration increased from 0.78 mg/dL to 1.11 mg/dL ($P < 0.001$) and the prevalence of detectable α1m increased from 44% at baseline to 65% on PrEP ($P < 0.001$), translating to a nearly 1.5-fold increase in prevalence of detectable α1m after 6 months of therapy. The mean proteinuria level also increased from 84.4 mg/g to 95.5 mg/g ($P < 0.001$). By contrast, there was no significant change in albuminuria after 6 months on PrEP (7.6 mg/g at baseline vs 7.8 mg/g on PrEP; $P = 0.87$). In parallel with the rise in urine α1m and proteinuria, there was also a statistically significant decline in eGFR by 4 mL/min/1.73 m^2 ($P < 0.001$) after 6 months of PrEP exposure. When OLE participants were stratified by previous exposure to TDF (n = 51) vs placebo (n = 42) during their participation in PrEP trials, there were no statistically significant differences in urine biomarker levels or eGFR at

baseline or at 24 weeks (Supplemental Digital Content Table 1, http://links.lww.com/QAI/B125).

In robust regression models that adjusted for urine creatinine (Table 4), urine α1m and protein increased by 21% ($P < 0.001$) and 18% ($P < 0.001$), respectively, over 6 months of PrEP use. Effect sizes were similar when we excluded iPrEx-OLE participants with undetectable TFV concentrations in hair (N = 29). There were no statistically significant correlations between hair TFV concentrations and urine levels of α1m (r = 0.074; $P = 0.45$), albuminuria (r = 0.010; $P = 0.92$), or proteinuria (r =0.111; $P = 0.25$).

DISCUSSION

With worldwide dissemination of TDF/FTC for PrEP of HIV, surveillance strategies for nephrotoxicity warrant close investigation. The goal of this study was to evaluate the associations of PrEP use with urine levels of α1m, albuminuria, and proteinuria as early indicators of potential toxicity. In a nested cross-sectional analysis of participants in a placebo-controlled PrEP trial (iPrEx), there were no statistically significant differences by treatment arm in urine levels of α1m, albuminuria, or proteinuria. However, in a longitudinal substudy of participants on open-label PrEP (iPrEx-OLE), urine α1m and proteinuria increased by approximately 20% over 6 months, with a 1.5-fold increase in prevalence of detectable α1m in urine. Although our findings must be validated in larger studies, these data suggest that PrEP with TDF/FTC may lead to subclinical changes in kidney tubular function, which warrant closer investigation and may indicate nephrotoxicity.

Our observation that PrEP with TDF/FTC is associated with a rise in urine α1m and total proteinuria, but not with albuminuria, is consistent with TFV's site of toxicity in the proximal tubule.[6,37,38] α1m is a 26-kDa protein that is freely filtered at the glomerulus and reabsorbed by the proximal tubule.[39,40] Impaired tubular reabsorption leads to elevated urine levels of α1m and other low molecular weight proteins, including retinol-binding protein and β2-microglobulin.[29,41] Albuminuria, by contrast, is primarily a marker of glomerular injury. Because the routine dipstick urinalysis predominantly detects albumin, it is also less likely to capture tubular toxicity from TDF. In a recent cohort study of HIV-infected men, each year of cumulative TDF exposure was associated with 7.6% higher urine α1m levels [95% confidence interval (CI): 5.4 to 9.9] and 3.2% higher proteinuria (95% CI: 1.7 to 4.7), but showed little association with albuminuria.[30] This pattern of tubular dysfunction was also observed in the Partners PrEP study, which reported higher rate of tubular proteinuria among participants in the TDF/FTC arm, as compared with participants on placebo.[21] Our data are consistent with these studies and extend the association of TDF exposure with α1m to HIV-uninfected PrEP users.

The clinical implications of renal tubular changes of the magnitudes observed among the iPrEx-OLE participants are unknown. However, recent literature suggests that minor impairments of renal tubular function are associated with adverse prognosis. In a cohort of HIV-infected women, participants who exhibited urine α1m levels in the highest tertile had an estimated 2.1-fold risk of incident chronic kidney disease (95% CI: 1.3 to 3.4) and 1.6-fold mortality risk over 8 years (95% CI: 1.0 to 2.6), compared with participants who had

undetectable α1m in urine.[31] Among HIV-uninfected participants of that study, those with urine α1m levels in the highest tertile also experienced faster kidney function decline during follow-up, compared with participants who had undetectable urine α1m. Furthermore, in a study of kidney transplant recipients, higher urine α1m concentrations were associated strongly with subsequent kidney allograft failure (hazard ratio per doubling 1.73; 95% CI: 1.43 to 2.08), after adjustment for traditional risk factors for kidney disease, eGFR, and albuminuria.[32] These previous studies did not evaluate the impact of changes in urine α1m on subsequent kidney outcomes, nor did they specifically examine drug-induced elevations in urine α1m, and therefore cannot be translated directly to our study. It is important to note that the effect sizes of PrEP use on urine α1m and proteinuria elevation were each approximately 20%, and that most of the participants in this small substudy had proteinuria levels in the "normal" range at follow-up. However, PrEP may be taken for substantially longer periods than the 6-month duration of this study and one-quarter of participants in iPrEx-OLE had undetectable drug levels in hair, indicating incomplete adherence to PrEP. Further longitudinal studies in a larger sample of PrEP users will be needed to determine the threshold of change in α1m or proteinuria that would be associated with clinically relevant kidney toxicity, and to evaluate the reversibility of these urinary abnormalities after cessation of PrEP.

Previous clinical trials have demonstrated a small but statistically significant rise in serum creatinine in association with TDF-based PrEP.[14–16] Two randomized controlled trials, iPrEx and Partners PrEP, reported a low risk of the Fanconi syndrome, or proximal tubulopathy. In the iPrEx renal substudy, there was no significant difference in the incidence of proximal tubulopathy by treatment arm; however, adherence to PrEP was not universal and tubulopathy was defined stringently as ≥2 of the following: dipstick proteinuria, glucosuria, phosphaturia, and uricosuria.[14] The generally low adherence rates to PrEP in the treatment arm of iPrEx may have contributed to the similarity in urine biomarker levels across arms in our nested cross-sectional analysis. By comparison, the Partners PrEP study reported a higher risk of tubular proteinuria (7.3% vs 4.0%, $P < 0.01$), urine protein/creatinine ratio . 200 mg/g (8.0% vs 4.4%; $P < 0.01$), and uricosuria (3.5% vs 1.3%; $P = 0.001$) among participants in the TDF/FTC arm, as compared with participants on placebo.[21] Our findings build on this previous work by using a urinary marker that is specific for impaired tubular reabsorption, α1m, and by performing measurements longitudinally before and after PrEP initiation. Real-world studies of PrEP users who receive PrEP for longer periods will be needed to evaluate the cumulative renal effects of daily TDF among HIV-seronegative individuals.

Limitations of this study include the small sample size, relatively short period of follow-up, and low adherence rates to PrEP in the iPrEx trial and in iPrEx-OLE. We addressed the issue of low adherence in a sensitivity analysis restricted to iPrEx-OLE participants with detectable hair TFV concentrations. However, we had limited power to evaluate measures of drug exposure as predictors of tubular toxicity.[35,42] Additional studies are needed to examine the relationship between drug exposure and renal tubular changes over time, and to determine whether the surveillance of PrEP users should include urinary measures, particularly among persons with additional risk factors for kidney disease.

In summary, in an open-label study of PrEP among MSM and transgender women, TDF/FTC initiation was associated with a statistically significant rise in urine α1m, a marker of impaired kidney tubular function, and proteinuria, but not with albuminuria. Future work should investigate the utility of α1m and other biomarkers of tubule dysfunction as indicators of nephrotoxicity among PrEP users in the real-world setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Characteristics of iPrEx* and iPrEx-OLE† Participants in the Urine Biomarker Substudy

	iPrEx (N = 200)			iPrEx-OLE (N = 109)
	Active Arm (N = 100)	Placebo (N = 100)	*P*	
Age (y)	23 (20, 26)	22 (20, 26)	0.65	30 (24, 43)
Transgender	17 (17%)	18 (18%)	0.85	6 (6%)
Race				
Black	12 (12%)	9 (9%)	0.79	11 (10%)
White	14 (14%)	11 (11%)		29 (27%)
Mixed/other	48 (48%)	53 (53%)		55 (50%)
Asian	26 (26%)	27 (27%)		14 (13%)
Ethnicity				
Non-Latino	48 (48%)	44 (44%)	0.57	60 (55%)
Latino	52 (52%)	56 (56%)		49 (45%)
Body mass index (kg/m^2)	23 (20, 26)	23 (20, 26)	0.74	26 (23, 30)
Systolic blood pressure (mm Hg)	110 (100, 121)	116 (108, 125)	0.99	118 (110, 128)
Diastolic blood pressure (mm Hg)	70 (63, 80)	70 (69, 79)	0.53	76 (70, 81)
Serum creatinine (mg/dL)	0.9 (0.8, 0.9)	0.9 (0.8, 0.9)	0.40	0.9 (0.8, 0.9)
eGFR ($ml/min/1.73m^2$)	124 (116, 130)	124 (117, 132)	0.85	114 (100, 123)

Continuous data are summarized as median (interquartile range).

*Characteristics at time of urine collection in iPrEx participants.

†Characteristics at baseline for OLE participants.

TABLE 2

Comparison of Urine Biomarker Levels in iPrEx by Study Arm

Urine biomarker	Active arm (N = 100)	Placebo arm (N = 100)	*P*
α1m* (mg/dL)	≤0.5 (≤0.5, 0.8)	≤0.5 (≤0.5, 0.6)	0.25
Detectable α1m	42 (42%)	35 (35%)	0.31
Albumin/creatinine ratio (mg/g)	4.1 (2.7, 7.4)	4.6 (2.6, 5.9)	0.64
Albumin/creatinine ratio .30 mg/g	2 (2.0%)	2 (2.0%)	0.99
Protein/creatinine ratio (mg/g)	78.0 (60.2, 105.2)	72.4 (56.8, 94.3)	0.27

Data are presented as median (interquartile range) or numbers (percentage).

*Detectable limit of the α1m assay was 0.5 mg/dL.

TABLE 3

Urine Biomarker Levels at Baseline and After Initiation of PrEP in iPrEx-OLE Participants

Urine Biomarker	Baseline (N = 109)	On PrEP (N = 109)	*P**
α1m (mg/dL)†			
Median (IQR)	≤0.50 (≤0.50–0.80)	0.70 (≤0.50–1.10)	<0.001
Mean ± SD	0.78 ± 0.49	1.11 ± 1.02	
Range	≤0.50–2.80	≤0.50–5.90	
Detectable α1m			
N (%)	48 (44%)	71 (65%)	<0.001
Albumin/creatinine ratio (mg/g)			
Median (IQR)	5.2 (3.4–8.6)	4.8 (3.2–7.6)	0.87
Mean ± SD	7.6 ± 8.8	7.8 ± 10.7	
Range	0.1–68	0.6–73	
Albumin/creatinine ratio >30 mg/g			
N (%)	4 (3.7%)	5 (4.6%)	0.65
Protein/creatinine ratio (mg/g)			
Median (IQR)	72 (53–98)	85 (65–111)	<0.001
Mean ± SD	84 ± 72	96 ± 52	
Range	0–740	15–327	
eGFR by CKD-EPI (ml/min/1.73m^2)			
Median (IQR)	114 (100–123)	109 (96–122)	<0.001
Mean ± SD	112 ± 19	108 ± 20	
Range	59–169	57–171	

*P values from Wilcoxon signed-rank test (continuous) or McNemar test (dichotomous) using median biomarker levels.

†Detectable limit of the α1m assay was 0.5 mg/dL.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

TABLE 4

Relative Change in Urine Biomarker Levels After PrEP Initiation in iPrEx-OLE

Urine Biomarker	All Participants (N = 109)		Participants With Detectable Tenofovir in Hair (N = 80)	
	Percent Change* (95% CI)	*P*	Percent Change* (95% CI)	*P*
α1m				
Unadjusted	19.7 (8.6 to 31.9)	<0.001	20.1 (6.1 to 35.9)	0.004
Adjusted for urine creatinine	20.9 (10.2 to 32.7)	<0.001	20.9 (8.0 to 35.4)	0.001
Albumin				
Unadjusted	10.0 (−7.6 to 31.1)	0.28	2.9 (−16.8 to 27.1)	0.79
Adjusted for urine creatinine	5.6 (−6.8 to 19.7)	0.39	0.0 (−12.1 to 13.7)	0.99
Protein				
Unadjusted	19.9 (2.4 to 40.2)	0.024	15.1 (−6.4 to 41.7)	0.18
Adjusted for urine creatinine	17.5 (7.6 to 28.3)	<0.001	15.6 (3.9 to 28.6)	0.008

*Outcome is log (post/pre) biomarker; estimates are back-transformed to produce geometric % changes from robust linear regression models.