Research Letter

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Kidney injury biomarkers during exposure to tenofovir-based preexposure prophylaxis

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We previously reported a higher incidence of non-albumin proteinuria and a small but significant decline in estimated glomerular filtration rate (eGFR) among HIV-negative adults randomized to emtricitabine/tenofovir disoproxil fumarate preexposure prophylaxis (FTC/TDF PrEP) versus placebo. In a nested case–control study among participants randomized to FTC/TDF PrEP, established kidney injury biomarkers measured at 12 months were not significantly different between participants who subsequently experienced one of these kidney endpoints and randomly selected controls who did not.

Preexposure prophylaxis (PrEP) with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) reduces the risk of HIV acquisition in individuals at high risk [1,2]. In people with HIV (PWH), TDF is associated with proximal tubulopathy and decreased glomerular filtration rate (eGFR) [3–5]. FTC/TDF PrEP has also been shown to cause a small but significant decline in eGFR compared with placebo [6,7]. Although proximal tubulopathy was rare in clinical trials [7,8], we previously reported a higher rate of non-albumin proteinuria among participants randomized to FTC/TDF PrEP versus placebo in the Partners PrEP Study [8]. In the current nested case–control study among participants randomized to FTC/TDF PrEP, we sought to determine whether established biomarkers of subclinical kidney injury may facilitate early identification of individuals at risk for clinically evident kidney injury with TDF.

The Partners PrEP Study was a randomized, placebo-controlled trial of daily oral TDF and co-formulated FTC/TDF to reduce the risk of HIV transmission to HIV-negative partners in serodiscordant heterosexual couples (NCT00557245) [1]. Four thousand seven-hundred and fifty-eight couples were enrolled in Kenya and Uganda, and HIV-negative partners were randomly assigned to receive daily TDF, FTC/TDF, or placebo for up to 36 months. HIV-negative partners with hepatitis B virus infection, calculated creatinine clearance less than 60 ml/min, or dipstick proteinuria or glycosuria were excluded. Serum creatinine was measured quarterly, and eGFR was calculated using the Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) equation. Urine samples were archived at −80 °C.

We previously reported a small but statistically significant decline in eGFR among participants randomized to FTC/TDF versus placebo in Partners PrEP (−1.59 ml/min/1.73 m^2; 95% confidence interval (CI) −2.44 to −0.74). Clinically significant declines in eGFR of at least 25% from baseline were also more common in the FTC/TDF arm, although the difference was not statistically significant [6]. In a random sample of participants in the FTC/TDF and placebo arms, we observed no difference in incidence of proximal tubulopathy at month 24, as defined by at least two of the following: non-albumin proteinuria, euglycemic glycosuria, increased urinary phosphate excretion, or increased urinary uric acid excretion [8]. Non-albumin proteinuria was more common among participants randomized to FTC/TDF versus placebo (7.3 versus 4.0%, $P < 0.01$).

In the current analysis among participants in the FTC/TDF arm, kidney injury was defined as an eGFR decline of at least 25% from baseline at any time-point or proximal tubulopathy or non-albumin proteinuria at month 24. Kidney injury cases ($n = 73$) were compared with randomly selected controls from the FTC/TDF arm without non-albumin proteinuria or proximal tubulopathy at month 24 and in whom eGFR declined by less than 10% from baseline throughout follow-up ($n = 66$). Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1), established biomarkers of tubular injury, were measured in archived urine collected at month 12. Urine NGAL greater than 100 ng/ml and urine KIM-1 greater than 2 ng/ml were considered clinically meaningful elevations for the purposes of descriptive analyses [9].

Median urine NGAL and KIM-1 levels were compared between cases and controls using Wilcoxon rank-sum tests. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, North Carolina, USA). All participants provided written informed consent. The Partners PrEP Study protocol was approved by the University of Washington Institutional Review Board and by the ethics review committees at enrolling sites.

Demographics of the study sample reflected the demographics of the Partners PrEP Study population [1]. Kidney injury cases were older than controls (median age 39 versus 34 years, $P = 0.04$), but there were no other

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Table 1. Baseline characteristics and kidney injury outcomes of participants with elevations in both kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin.

	Age (years)	Sex	BMI (kg/m^2)	Serum creatinine (mg/dl)	NGAL (ng/ml)	KIM-1 (ng/ml)	Kidney injury
Cases							
1	38	Female	19.1	0.5	137.3	3.2	Tubular proteinuria
2	57	Male	24.2	0.5	156.3	2.1	Tubular proteinuria
3	39	Female	22.1	0.7	132.1	2.2	Proximal tubulopathy; eGFR decline of 39%
4	30	Male	19.2	0.8	164.7	2.3	Tubular proteinuria
5[a]	47	Male	20.5	0.7	476.9	2.9	Proximal tubulopathy; eGFR decline of 58%
6	29	Male	21.0	0.8	742.0	2.4	eGFR decline of 37%
7	29	Male	21.0	0.7	131.2	2.3	Tubular proteinuria
Controls							
1	23	Female	18.7	0.5	121.4	2.2	None
2	30	Male	21.2	0.9	256.9	2.8	None
3	25	Female	20.5	0.7	118.9	2.1	None
4	28	Male	19.5	0.9	102.2	2.0	None
5	45	Female	21.4	0.9	235.9	3.2	None

Kidney injury cases were participants randomized to emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) preexposure prophylaxis (PrEP) who experienced a decline of at least 25% in estimated glomerular filtration rate (eGFR) from baseline and/or evidence of proximal tubulopathy or non-albumin ('tubular') proteinuria at month 24. Controls were randomly selected from among participants in the FTC/TDF arm who did not have proximal tubulopathy or tubular proteinuria at month 24 and who experienced less than 10% decline in eGFR. KIM-1, kidney injury molecule 1; NGAL, neutrophil gelatinase-associated lipocalin.
[a]Case 5 was previously reported to have multiple indicators of proximal tubulopathy and eGFR below 60 ml/min/1.73 m^2. Although data on proximal tubulopathy were not available for safety monitoring during the trial, study drug was discontinued in this participant based on the decline in creatinine clearance [8].

significant differences between the groups. Baseline eGFR was similar in cases and controls (median 131 versus 128 ml/min/1.73 m^2, $P = 0.07$).

At month 12, urine NGAL and KIM-1 levels were similar in cases and controls [median NGAL 50, interquartile range (IQR) 20–113 versus 46, IQR 22–109, respectively, $P = 0.8$; median KIM-1 0.8, IQR 0.4–1.7 versus 0.8, IQR 0.3–1.6, respectively, $P = 0.6$]. Although urine NGAL and KIM-1 levels were undetectable or low in most participants, 29 of 73 cases and 31 of 66 controls had a urine NGAL greater than 100 ng/ml or a urine KIM-1 greater than 2 ng/ml. Among these, seven cases and five controls had both urine NGAL greater than 100 ng/ml and urine KIM-1 greater than 2 ng/ml (Table 1).

In this nested case–control analysis within the FTC/PrEP arm of a randomized trial, the tubular injury biomarkers NGAL and KIM-1 did not differ significantly at 12 months between subjects who subsequently developed clinically evident kidney injury and those who did not. Notably, more than one-third of subjects had a clinically meaningful elevation in at least one of the biomarkers, whereas a smaller number had elevations in both.

Urine biomarkers were measured at a single time point, and it is possible that the elevations in KIM-1 and NGAL observed in some participants at month 12 reflect preexisting kidney injury or the effect of concomitant insults rather than an effect of FTC/TDF. It is also possible that the control group included some participants who would have developed clinical evidence of kidney injury with longer follow-up. This is a particular concern for the small number who had elevations in both KIM-1 and NGAL. As this was an unanticipated finding, urine biomarkers were not available for participants in the placebo arm to serve as a second control group. We did not measure plasma drug concentrations, so it is possible that the absence of subsequent kidney injury in those participants reflects a decline in PrEP adherence over time. Nonetheless, self-reported adherence was more than 95% in the Partners PrEP Study, and more than 80% of participants in a previous substudy had plasma drug exposure consistent with daily use [1]. Although we lacked the power to detect small differences in urinary biomarker levels between cases and controls, the absence of large and consistent differences suggests that urinary KIM-1 and NGAL have limited utility for the early identification of individuals at risk for clinically significant kidney injury with TDF use. Nonetheless, the finding of elevated kidney injury biomarker levels in more than one-third of the subjects in our sample may suggest the potential for kidney injury with long-term PrEP use and reinforces the need for kidney injury monitoring in this setting.

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Conflicts of interest

T.L.N. and J.B., CUIMC has licensed patents for the use of NGAL as a diagnostic marker. J.M.B., C.C., and R.H. have received donations of study medication from Gilead Sciences. J.M.B. serves on Advisory Committees for Gilead Sciences, Merck, and Janssen; C.C. serves on the Advisory Committee for Merck. C.M.W. serves as a consultant for Epividian. All other authors declare no relevant conflicts of interest.

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