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HIV pre-exposure prophylaxis with tenofovir disoproxil fumarate/emtricitabine and changes in kidney function and tubular health

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Abstract

Objective: To evaluate the effects of HIV pre-exposure prophylaxis (PrEP) with tenofovir disoproxial fumurate (TDF)/emtricitabine (FTC) on kidney function and kidney tubular health.

Design: The Iniciativa Profilaxis Pre-Exposicion open-label extension (iPrEx-OLE) study enrolled former PrEP trial participants to receive open-label TDF/FTC. This study included 123 iPrEx-OLE participants who demonstrated PrEP adherence.

Methods: We compared estimated glomerular filtration rate calculated using serum creatinine (eGFRcr), serum cystatin C (eGFRcys), and in combination (eGFRcr-cys), and a panel of 14 urine biomarkers reflecting kidney tubular health before and six months after PrEP initiation.

Results: At baseline, mean eGFRcr, eGFRcys, and eGFRcr-cys were 108.3, 107.0, and 111.1 mL/min/1.73m^2, respectively. Six months after PrEP initiation, eGFRcr declined by −4.0% (95% CI: −5.7% to −2.4%), eGFRcys declined by −3.3% (95% CI: −8.3% to 1.9%), and eGFRcr-cys

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Conflicts of Interest

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declined by −4.1% (95% CI: −7.5% to −0.7%). From the urine biomarker panel, a1-microglobulin and P2-microglobulin increased by 22.7% (95% CI: 11.8% to 34.7%) and 14.1% (95% CI: −6.1% to 38.6%), whereas chitinase-3-like 1 protein and monocyte chemoattractant protein-1 decreased by −37.7% (95% CI: −53.0% to −17.3%) and −15.6% (95% CI: −31.6% to 4.2%), respectively. Ten of the 14 urine biomarkers, including albumin, had estimated changes of less than 12% with wide confidence intervals.

Conclusion: Six months of PrEP with TDF/FTC was associated with decreases in eGFRcr and eGFRcys. We also observed for the first time changes in four of 14 urine biomarkers reflecting kidney tubular health. These findings demonstrate that PrEP has direct effects on eGFR and the proximal tubule.

Keywords

HIV prevention; pre-exposure prophylaxis (PrEP); tenofovir; nephrotoxicity; urine biomarkers; alpha-1 microglobulin; cystatin C

Introduction

Despite the success of antiretroviral therapy, HIV transmission rates have not appreciably changed in the United States (U.S.), with nearly 40,000 new HIV diagnoses each year.[1] In 2012, the Food and Drug Administration (FDA) approved once-daily tenofovir disoproxil fumarate (TDF) in combination with emtricitabine (FTC) as the first drug for HIV pre-exposure prophylaxis (PrEP).[2–4] The Centers for Disease Control (CDC) clinical practice guidelines recommend PrEP with TDF/FTC for the prevention of HIV acquisition, estimating that 1.2 million high-risk adults in the U.S. may benefit.[5,6] With the awareness and use of PrEP expanding, surveillance for drug-related adverse events will become increasingly important.[7,8]

Tenofovir can lead to kidney damage through toxicity to the proximal tubule, where excessive intracellular tenofovir accumulation causes mitochondrial toxicity and acute tubular necrosis.[9–11] Among persons living with HIV (PLWH), TDF exposure is associated with increased risks of acute kidney injury, proteinuria, Fanconi syndrome, and chronic kidney disease.[12–14] Among HIV-uninfected persons enrolled in the PrEP trials, TDF has been associated with a small rise in serum creatinine, which appears to reverse after discontinuing PrEP.[15–21] As a result, current guidelines recommend monitoring individuals on PrEP with serum creatinine semi-annually.[5] However, because creatinine is both filtered and secreted by the proximal tubule, PrEP-associated increases in serum creatinine could potentially occur through either impaired tubular creatinine secretion or direct proximal tubular toxicity.[22] Cystatin C is another measure of kidney glomerular filtration, but unlike serum creatinine, cystatin C does not undergo secretion by the kidney tubules.[23,24] To our knowledge, no prior study has compared the effects of PrEP on both serum creatinine and cystatin C.

In addition, monitoring serum creatinine levels may not adequately detect early signs of tenofovir-induced nephrotoxicity because substantial tubular damage can occur prior to measurable losses in kidney function.[25,26] In the Partners PrEP study, participants in the

TDF/FTC arm had a higher risk of tubular proteinuria (defined as urine protein-to-creatinine ratio > 200mg/g with urine albumin-to-protein ratio < 0.4) and uricosuria compared to placebo, although there was no difference in risk of proximal tubulopathy, defined as ≥ 2 markers of proximal tubular dysfunction.[27] In the Iniciativa Profilaxis Pre-Exposicion (iPrEx) trial's renal substudy, there was no difference between TDF/FTC and placebo groups in risk of one or more indicators of proximal tubulopathy, although a substantial portion of participants randomized to TDF/FTC were not adherent.[15] In the iPrEX open label extension (iPrEx-OLE) study, a cohort of former participants of PrEP trials who subsequently enrolled in an open-label study of TDF/FTC-based PrEP, we recently reported that PrEP initiation was associated with a significant increase in urine levels of the proximal tubule dysfunction biomarker α1-microglobulin (α1m), even with low adherence to PrEP.[28] α1m is freely filtered at the glomerulus and normally fully reabsorbed by the proximal tubular epithelium, reflecting dysfunction of the proximal tubule when detected in the urine.[29,30] To our knowledge, no prior study has investigated the effects of PrEP on other urine biomarkers of kidney tubular health.

The objectives of this study were to evaluate the effects of PrEP on: 1) estimated glomerular filtration rate calculated by serum creatinine (eGFRcr), serum cystatin C (eGFRcys) and in combination (eGFRcr-cys); and 2) a panel of 14 urine biomarkers representative of varying pathophysiology within the nephron. We compared these measures of kidney health before and six months after PrEP initiation in participants of the iPrEx-OLE study.

Methods

Study Design

The iPrEx-OLE study provided PrEP free of charge to former participants of three placebo-controlled PrEP trials without restriction on renal function at the time of enrollment. The study assessed PrEP uptake, adherence and persistence in this cohort over 72 weeks.[31] A total of 1,225 HIV-seronegative men who have sex with men and transgender women from Brazil, Ecuador, Peru, South Africa, Thailand, and the U.S. received PrEP during follow-up. Two prior substudies measured drug adherence in iPrEx-OLE participants by tenofovir (TFV) concentrations in hair (N=220) or by TFV-diphosphate levels in dried-blood spot (DBS) specimens (N=353).[31–33] The present study of kidney health focused on iPrEx-OLE participants who had evidence of adherence to PrEP within the first year of follow-up, either by "ever-detectable" tenofovir (TFV) concentrations in hair or by TFV-diphosphate levels in DBS ≥ 700 fmol/punch, which is equivalent to ≥4 doses per week.[31] The rationale for this design was to enrich the study sample with participants who were adherent to PrEP, which is prescribed as a once-daily medication. Inclusion in the current study also required availability of serum specimens at baseline and at six months for measurement of serum creatinine and cystatin C levels. Among the 123 participants who met these inclusion criteria, urine specimens were also available at baseline and at six months in 102 participants (83%) for measurement of urine biomarkers.

The iPrEx-OLE study protocol was approved by institutional review boards of all participating sites, and all participants provided written informed consent in their preferred language. The present study was also approved by the University of California, San

Francisco (UCSF) and San Francisco Veterans Affairs Medical Center committees on human research.

Biomarker Measurements

Serum creatinine was measured in local laboratories for each study site with assays using the modified Jaffe method traceable to isotope dilute mass spectrometry. Serum cystatin C measurements before and after PrEP initiation were conducted in the same batch using a Siemens BNII (Siemens, Munich, Germany). Cystatin C was calibrated and standardized to the International Federation for Clinical Chemists reference.[34] We calculated eGFRcr, eGFRcys, and eGFRcr-cys based on the corresponding CKD Epidemiology Collaboration estimating equations.[35,36]

The urine biomarker panel included biomarkers representing proximal tubular dysfunction (α1m, beta-2 microglobulin [β2m)], and cystatin C [CysC]), proximal tubular injury (clusterin, trefoil factor 3, interleukin-18 [IL-18], kidney injury molecule-1 [KIM-1], and neutrophil gelatinase-associated lipocalin [NGAL]), inflammation, fibrosis and renal repair (monocyte chemoattractant protein-1 [MCP-1], chitinase-3-like 1 protein [YKL-40], and epidermal growth factor [EGF],), loop of Henle function (uromodulin [UMOD]), and glomerular injury (osteopontin and albumin).

Urine specimens were in continuous storage at −80°C until biomarker measurement. All urine biomarker concentrations were measured at the UCSF Kidney Health Research Collaboration Biomarker Laboratory. Urine α1m was measured by immunonephelometry with a commercially available assay using a Siemens BNII (Siemens, Munich, Germany). Urine creatinine was measured using a commercially available colorimetric kit from R&D Systems (Minneapolis, MN). All other urine biomarker measurements were performed with Meso Scale Discovery (MSD, Gaithersburg, MD) assay kits according to manufacturer protocols. The MSD platform is a multiplex solid-phase electrochemiluminescence-based assay system; MSD plates were read and analyzed on the QuickPlex SQ 120 (MSD). Biomarkers measured in Kidney Injury Panel 3 include urine clusterin (intra-assay coefficient of variation [CV] 8.8%), KIM-1 (CV 4.7%), and TFF-3 (CV 5.3%). Kidney Injury Panel 5 contains urine albumin (CV 5.7%), β2m (CV 4.9%), CysC (CV 4.9%), EGF (CV 7.2%), NGAL (CV 4.9%), osteopontin (CV 7.1%), and UMOD (CV 4.0%). A custom MSD panel was used to measure IL-18 (CV 4.7%), MCP-1 (CV 4.4%), and YKL-40 (CV 2.5%). Laboratory personnel performing the biomarker assays were blinded to participants' clinical information.

Statistical analysis

We summarized baseline demographics and clinical characteristics of the study population and we evaluated the geometric mean and 95% confidence interval (CI) of each eGFR and urine biomarker at the baseline visit and the six-month on-PrEP visit. We then estimated six-month relative changes in eGFR and urine biomarker concentrations using linear mixed models and random intercepts to account for within-subject correlations. In addition, we used Huber-White standard errors, which are designed to be robust to non-normally distributed residuals. Due to their right-skewed distributions, the urine biomarker measures

were log-transformed to normalize their distributions, and results were back-transformed to produce relative changes from baseline. Models of urine biomarkers adjusted for urine creatinine to correct for urine tonicity. For urine biomarkers with significant six-month changes, we additionally performed interaction testing to determine whether estimates varied by age and nonsteroidal anti-inflammatory drug (NSAID) use.[18] To explore whether hair TFV levels were associated with urine biomarker and eGFR changes, we used robust linear regression adjusting for urine creatinine to estimate the association between each doubling of six-month hair TFV concentrations and relative changes in urine biomarker concentrations and eGFRcr, eGFRcys, and eGFRcr-cys over six months. Hair TFV levels and urine biomarker measures were both log-transformed due to their right-skewed distribution. Results were back-transformed to produce relative urine biomarker and eGFR changes from baseline.

Results

Characteristics of PrEP-adherent iPrEx-OLE participants

Among the 123 participants included in this iPrEx-OLE substudy with evidence of adherence to PrEP by drug level measurement either in hair or DBS specimens, 66% were less than 40 years of age, 3% were transgender, 14% were black, and 8% were Asian (Table 1). Compared to the overall iPrEX-OLE cohort, participants in this substudy were older, fewer were transgender or Latino, and baseline systolic and diastolic blood pressures were higher. At baseline, the mean serum creatinine and cystatin C were 0.88 mg/dL and 0.78 mg/L, respectively. The geometric mean eGFRcr, eGFRcys, and eGFRcr-cys were 108.3, 107.0, and 111.1 ml/min/1.73m^2, respectively. Overall, 17 participants had an eGFRcr 60–90 ml/min/1.73m^2 and 21 participants had eGFRcys 60–90 ml/min/1.73m^2 at baseline. Only 2 participants had an eGFRcr < 60 ml/min/1.73m^2, whereas 7 participants had eGFRcys < 60 ml/min/1.73m^2 at baseline.

Changes in kidney function

Over a median of 23.9 weeks (interquartile range: 23.6 to 24.3 weeks) following PrEP initiation, mean serum creatinine levels increased by 4.6% (95% CI: 2.5% to 6.7%) with a corresponding decrease in eGFRcr from 108.3 to 104.0 ml/min/1.73m^2 (adjusted relative change: −4.0%; 95% CI: −5.7% to −2.4%) (Table 2). Mean cystatin C levels similarly increased by 5.5% (95% CI: −0.4% to 11.8%), and eGFRcys decreased from 107.0 to 103.5 ml/min/1.73m^2 (adjusted relative change: −3.3%; 95% CI: −8.3% to 1.9%). eGFRcr-cys decreased from 111.1 to 106.5 ml/min/1.73m^2, with an estimated relative change of −4.1% (95% CI: −7.5% to −0.7%). The prevalence of eGFRcr < 90 ml/min/1.73m^2 increased from 15% to 21% (P=0.04) over time, but there were no significant changes in the prevalence of eGFRcys or eGFRcr-cys < 90 ml/min/1.73m^2.

Changes in kidney tubular health

Correlations between baseline urine biomarkers and six-month changes in urine biomarkers are shown in Supplemental Table 1 http://links.lww.com/QAD/B591. The strongest baseline urine biomarker correlations were between CysC and α1m, β2m, and UMOD (Spearman correlation coefficients: 0.469, 0.489, and 0.685, respectively); α1m and β2m (0.486); IL-18

and MCP-1 (0.457); and clusterin and KIM-1 (0.450). The strongest correlations of six-month change in urine biomarker were between UMOD and α1m, CysC, NGAL, and EGF (0.597, 0.752, 0.495, and 0.463, respectively); CysC and α1m, NGAL, and EGF (0.674, 0.519, and 0.478, respectively); β2m and EGF (0.525); and clusterin and KIM-1 (0.515).

In unadjusted comparisons of six-month changes in urine biomarker concentrations following PrEP initiation, α1m and β2m increased, whereas YKL-40 and MCP-1 decreased (Table 3). In analyses adjusting for urine creatinine to correct for tonicity, the mean urine α1m concentration increased by 22.7% (95% CI: 11.8% to 34.7%) and β2m increased by 14.1% (95% CI: −6.1% to 38.6%). Conversely, YKL-40 decreased by −37.7% (95% CI: −53.0% to - 17.3%) and MCP-1 decreased by −15.6% (95% CI: −31.6% to 4.2%). Ten of the 14 urine biomarkers, including albumin, had estimated relative changes less than 12% with wide confidence intervals. In interaction testing, relative changes in urine α1m and YKL-40 did not differ significantly by age or recent NSAID use. Six-month tenofovir hair levels ranged from 0.002 to 0.51 ng/mg. There were no statistically significant associations between higher six-month hair tenofovir levels and relative changes in the urine biomarkers or eGFR following PrEP initiation (Supplemental Table 2, http://links.lww.com/QAD/B591).

Discussion

In this longitudinal substudy of iPrEx-OLE participants adherent to PrEP, we observed small increases in serum creatinine and cystatin C over six months following PrEP initiation, with corresponding declines in eGFRcr, eGFRcys, and eGFRcr-cys. Using a urine biomarker panel representative of diverse glomerular and tubular pathophysiologic mechanisms, we also found that PrEP initiation was associated with increases in biomarkers reflecting proximal tubular dysfunction, and decreases in biomarkers reflecting renal repair. PrEP with TDF/FTC substantially reduces the risk of HIV transmission and will play a central role in public health strategies to prevent HIV infection.[37] With PrEP use expected to increase in the future, evaluation of the optimal surveillance strategy for nephrotoxicity is warranted. Our study suggests that PrEP with TDF/FTC may lead to small changes in kidney glomerular filtration and subclinical changes in kidney tubular health.

Due to the concern for nephrotoxicity, the Partners PrEP and iPrEx trials excluded individuals with pre-existing kidney disease, and CDC clinical practice guidelines do not support PrEP use in patients with a creatinine clearance < 60 ml/min.[5] Similar to our findings, previous studies of TDF-based combination antiretroviral therapy in PLWH and TDF/FTC in PrEP users have shown modest declines in creatinine-based eGFR.[12–20] Unlike previous studies, however, we additionally measured cystatin C to evaluate whether creatinine-based eGFR changes following PrEP initiation reflect a direct effect on glomerular filtration or tubular creatinine secretion.[22] Our data demonstrate decreases in both eGFRcr and eGFRcys following six months of PrEP use, suggesting a direct effect on glomerular filtration. To our knowledge, there are no known effects of tenofovir on glomerular hemodynamics, as seen with NSAIDs and angiotensin converting enzyme inhibitors. The magnitude of change in eGFR was small, but these changes were observed after only six months of PrEP use, and many patients receive PrEP for much longer

durations. Although we found no association between higher six-month tenofovir hair levels and changes in eGFR or urine biomarkers, hair levels may not have been an accurate reflection of cumulative tenofovir exposure. Further studies will be needed to determine whether these small changes in eGFR are associated with subsequent CKD risk among PrEP users, and to identify whether specific subgroups with existing CKD risk factors warrant closer monitoring to avoid nephrotoxicity.

Our findings of increased urine α1m, modestly increased urine β2m, and unchanged urine albumin levels following PrEP initiation are consistent with tenofovir's pathophysiology localizing to the proximal tubule.[9,29] Unlike albumin, α1m and β2m are low molecular weight proteins that are freely filtered at the glomerulus and fully reabsorbed in the proximal tubule.[30,38] Increased urine α1m and β2m are therefore specific for impaired proximal tubular function, and these and other tubule dysfunction markers are used by the FDA to evaluate for drug-induced nephrotoxicity. We previously reported a similar increase in urine α1m in this cohort among participants with variable PrEP adherence.[28] In PLWH, one study showed TDF initiation was associated with 32% relative increase in urine α1m, and another study demonstrated each cumulative year of TDF exposure was associated with 7.6% higher urine α1m levels.[26,39] However, the clinical implications of observing proximal tubular dysfunction in HIV-uninfected persons following PrEP initiation are unknown. Two studies in cohorts of PLWH found higher urine α1m was associated with longitudinal kidney function decline.[40,41] Another study in PLWH found greater increases in urine α1m and β2m from baseline to one year following TDF initiation were associated with subsequent kidney function decline.[25] Current CDC clinical practice guidelines recommend renal safety monitoring in PrEP users only with serum creatinine.[5] Although our findings must be replicated in additional longitudinal studies, our data suggest there may be utility to measuring urine low molecular weight proteins to monitor for nephrotoxicity in PrEP users.

We also observed that PrEP initiation was associated with subsequent decreases in urine YKL-40 and MCP-1. Urine YKL-40 is produced by kidney macrophages that secrete YKL-40 in response to kidney injury, and may in some settings mark adaptive renal repair processes.[42,43] Urine MCP-1 is a cytokine that mediates the inflammatory response in the kidney by recruiting and activating monocytes and macrophages.[44] To our knowledge, no prior study has evaluated urine YKL-40 and MCP-1 in the setting of monitoring drug-induced nephrotoxicity in otherwise healthy adults. Because these biomarkers are not standardized for clinical use, comparing results from different labs is difficult. In addition, prior studies reported markedly higher biomarker levels compared to the levels we observed in our study participants, which may have been due to differences in participants' kidney health across studies, or differences in the timing of urine measurements relative to the inciting injury. In a study among PLWH initiating TDF-based combination antiretroviral therapy, aviremic participants had one-year increases in urine YKL-40 without changes in MCP-1.[26] However, YKL-40 and MCP-1 levels were nearly twice the levels we observed in our study. In hospitalized patients with acute kidney injury (AKI), urine YKL-40 levels ≥ 5,000 pg/mL were associated with higher risk of AKI progression and/or in-hospital death.[45] In contrast, among deceased donor kidney transplant recipients, urine YKL-levels greater than 3,330 pg/mL in donors were associated with lower risk of delayed graft

function, improved eGFR after transplantation, and lower risk of graft failure.[43] Taking the above into consideration, we hypothesize that the finding of declining urine YKL-40 and MCP-1 concentrations on PrEP could indicate subclinical changes in renal repair and inflammatory processes. However, these urine biomarkers remain investigational, and our findings require confirmation in other cohorts.

Our study has several limitations. First, kidney function and tubular health biomarkers were measured once before and after PrEP initiation, so we could not evaluate trajectories over time. Second, our sample size was small and the duration of follow-up was only six months, so we had limited power for interaction testing by subgroups or evaluating a potential dose-response between tenofovir exposure levels and kidney health. Because PrEP is often taken as a long-term medication, larger studies with longer follow-up will be necessary to determine the subgroups of PrEP users that would benefit from closer nephrotoxicity monitoring. Third, we did not measure urine biomarker changes in iPrEx-OLE participants with undetectable drug levels for comparison. We believe our findings reflect the effects of PrEP initiation because the iPrEx-OLE cohort is comprised of young, otherwise healthy participants with no major interventions other than PrEP. In addition, we previously reported changes in nine urine biomarkers among participants in the SPRINT trial with and without CKD, and found that nearly all biomarkers in the standard treatment arm did not significantly change over 12 months.[46] Fourth, our findings in young, otherwise healthy HIV-uninfected participants may not generalize to individuals at higher risk of kidney disease. Fifth, although this study evaluated several urine biomarkers, we did not include formal adjustments for multiple comparisons. This is because we hypothesized *a priori* that PrEP initiation would be associated with changes in multiple, inter-related biomarkers reflecting proximal tubular pathology in a pattern that should be mutually reinforcing. However, spurious positive findings are still possible. Finally, our study was designed prior to the widespread availability of tenofovir alafenamide fumarate (TAF), a less nephrotoxic alternative to TDF. Although TDF-based PrEP remains the only FDA-approved regimen, a recent study demonstrated that PrEP with TAF/FTC is non-inferior to TDF/FTC for prevention of HIV acquisition.[47] Whether or not TAF-based PrEP leads to similar changes in kidney health will require future investigation.

In summary, initiation of PrEP with TDF/FTC was associated with a small decrease in creatinine-based eGFR, and for the first time we demonstrate an associated small decrease in cystatin C-based eGFR. We also found that PrEP initiation was associated with increases in urine biomarkers of proximal tubule dysfunction and decreases in urine biomarkers of renal repair. Future studies are needed to validate these findings in other cohorts and to evaluate the long-term implications of these changes in kidney health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline characteristics of iPrEx-OLE and renal substudy participants

Parameter	iPrEx-OLE (N=1225)	Renal substudy (N=123)
Age, y		
< 40	956 (78%)	81 (66%)
40–50	181 (15%)	23 (19%)
>50	88 (7%)	19 (15%)
Transgender	151 (12%)	4 (3%)
Race		
Black	126 (10%)	17 (14%)
White	279 (23%)	37 (30%)
Mixed/other	756 (62%)	59 (48%)
Asian	64 (5%)	10 (8%)
Ethnicity		
Latino	773 (63%)	59 (48%)
Non-Latino	452 (37%)	64 (52%)
Body mass index, kg/m^2	25 (22, 28)	26 (23, 30)
Systolic blood pressure, mmHg	113 (104, 120)	118 (110, 129)
Diastolic blood pressure, mmHg	70 (70, 80)	76 (70, 82)
Hypertension	77 (6%)	12 (10%)
NSAID use in prior 30 days	160 (13%)	25 (20%)

NSAID, nonsteroidal anti-inflammatory drug.

Data presented as median (interquartile range) or numbers (percent).

Table 2.

Summary of kidney function measures before and six months after PrEP initiation

Measure	Baseline (95% CI)	Follow-up (95% CI)	Relative % Change (95% CI)
Serum creatinine (mg/dL)	0.88 (0.86, 0.91)	0.92 (0.89, 0.95)	4.6 (2.5, 6.7)
Serum cystatin C (mg/L)	0.78 (0.74, 0.83)	0.82 (0.78, 0.87)	5.5 (−0.4, 11.8)
eGFRcr (ml/min/1.73m^2)	108.3 (104.7, 112.0)	104.0 (100.2, 107.9)	−4.0 (−5.7, −2.4)
eGFRcys (ml/min/1.73m^2)	107.0 (101.5, 112.9)	103.5 (98.4, 108.8)	−3.3 (−8.3, 1.9)
eGFRcr-cys (ml/min/1.73m^2)	111.1 (106.5, 115.9)	106.5 (102.1, 111.1)	−4.1 (−7.5, −0.7)

eGFRcr, estimated glomerular filtration rate by creatinine; eGFRcr-cys, estimated glomerular filtration rate by creatinine and cystatin C; eGFRcys, estimated glomerular filtration rate by cystatin C.

Data presented as geometric mean (95% CI).

Table 3.

Summary of urine biomarker concentrations before and six months after PrEP initiation

Urine Biomarker	Baseline (95% CI)	Follow-up (95% CI)	Relative % Change (95% CI)
α1m (mg/dL)			
Unadjusted	0.79 (0.72, 0.87)	0.98 (0.86, 1.12)	23.8 (11.3, 37.8)
Adjusted *	0.80 (0.72, 0.87)	0.98 (0.87, 1.10)	22.7 (11.8, 34.7)
β2m (ng/mL)			
Unadjusted	64.1 (54.2, 75.7)	74.7 (60.6, 92.0)	16.6 (−5.2, 43.3)
Adjusted	64.8 (56.8, 73.9)	73.9 (61.8, 88.4)	14.1 (−6.1, 38.6)
Cystatin C (ng/mL)			
Unadjusted	45.9 (41.1, 51.3)	44.8 (39.6, 50.8)	−2.3 (−14.1, 11.1)
Adjusted	45.0 (40.7, 49.7)	42.0 (37.7, 46.8)	−6.6 (−18.3, 6.8)
Clusterin (ng/mL)			
Unadjusted	28.4 (21.6, 37.2)	26.1 (20.2, 33.7)	−8.0 (−32.1, 24.7)
Adjusted	29.0 (24.0, 35.0)	25.6 (21.5, 30.5)	−11.6 (−28.7, 9.5)
Trefoil factor 3 (pg/mL)			
Unadjusted	42.1 (31.9, 55.6)	39.9 (29.6, 53.8)	−5.4 (−31.0, 29.8)
Adjusted	42.5 (32.5, 55.5)	39.6 (29.6, 52.9)	−6.9 (−31.2, 26.1)
IL-18 (pg/mL)			
Unadjusted	33.9 (27.7, 41.5)	35.0 (28.2, 43.5)	3.3 (−18.8, 31.4)
Adjusted	34.4 (29.8, 39.7)	34.5 (28.8, 41.3)	0.38 (−15.5, 19.3)
KIM-1 (pg/mL)			
Unadjusted	279.0 (216.3, 359.9)	289.5 (223.6, 374.7)	3.7 (−20.4, 35.2)
Adjusted	284.2 (238.5, 338.8)	284.1 (235.7, 342.5)	−0.04 (−16.4, 19.6)
NGAL (ng/mL)			
Unadjusted	23.7 (18.8, 30.0)	25.2 (20.2, 31.4)	6.2 (−11.9, 27.9)
Adjusted	23.9 (19.3, 29.7)	25.0 (20.4, 30.6)	4.6 (−12.2, 24.6)
MCP-1 (pg/mL)			
Unadjusted	111.8 (88.8, 140.6)	97.1 (75.4, 125.0)	−13.1 (−33.0, 12.7)
Adjusted	113.4 (95.2, 135.0)	95.7 (77.1, 118.8)	−15.6 (−31.6, 4.2)
YKL-40 (pg/mL)			
Unadjusted	437.1 (348.3, 548.5)	278.7 (201.5, 385.5)	−36.2 (−52.8, −13.9)
Adjusted	442.1 (365.7, 534.5)	275.6 9202.8, 374.5)	−37.7 (−53.0, −17.3)
Epidermal growth factor (ng/mL)			
Unadjusted	12.4 (10.6, 14.6)	11.8 (9.9, 14.1)	−4.7 (−20.9, 14.8)
Adjusted	12.6 (11.5, 13.8)	11.7 (10.5, 13.0)	−7.4 (−17.7, 4.2)
Uromodulin (mg/L)			
Unadjusted	9.6 (8.1, 11.5)	9.4 (8.0, 11.1)	−2.2 (−16.8, 15.0)
Adjusted	9.7 (8.2, 11.5)	9.4 (8.0, 11.0)	−2.9 (−17.6, 14.5)

Urine Biomarker	Baseline (95% CI)	Follow-up (95% CI)	Relative % Change (95% CI)
Osteopontin (μg/dL)			
Unadjusted	52.9 (42.8, 65.3)	59.1 (48.6, 71.9)	11.8 (−9.9, 38.7)
Adjusted	53.6 (45.8, 62.8)	58.2 (50.9, 66.6)	8.6 (−9.0, 29.6)
Albumin (mg/L)			
Unadjusted	2.1 (1.7, 2.6)	2.2 (1.7, 2.9)	5.5 (−17.4, 34.9)
Adjusted	2.1 (1.7, 2.6)	2.2 (1.7, 2.8)	3.1 (−16.3, 27.0)

α1m, alpha-1-microglobulin; β2m, beta-2-microglobulin; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; MCP-1, monocyte chemoattractant protein-1; NGAL, neutrophil gelatinase-associated lipocalin; YKL-40, chitinase-3-like 1 protein.

Data presented as geometric mean (95% CI).

*Adjusted for urine creatinine