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Title

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Permalink

<https://escholarship.org/uc/item/61n9814p>

Journal

J AIDS Journal of Acquired Immune Deficiency Syndromes, 75(1)

ISSN

1525-4135

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Publication Date

2017-05-01

DOI

10.1097/qai.0000000000001302

Peer reviewed



Published in final edited form as:

J Acquir Immune Defic Syndr. 2017 May 01; 75(1): 45–51. doi:10.1097/QAI.0000000000001302.

Longitudinal assessment of proximal tubular dysfunction in HIV seropositive and seronegative persons: correlates and implications

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Abstract

Background—Proximal tubule dysfunction (PTD) is common in HIV-positive persons and has been associated with tenofovir disoproxil fumarate (TDF). However, few studies have assessed the natural history PTD in HIV-positive and –negative individuals, or the association of PTD with the subsequent trajectory of directly measured glomerular filtration rate (mGFR).

Methods—We followed 192 HIV-positive and 100 HIV-negative, non-diabetic participants for three years. We measured 3 PTD markers (normoglycemic glycosuria, fractional excretion of phosphorus, and tubular proteinuria) and mGFR (by iohexol disappearance from serum) annually. We used univariate and multivariate generalized estimating equation logistic regression to identify factors associated with PTD across all visits and linear mixed effects models to assess the association between baseline PTD and mGFR slope.

Results—Compared with HIV-negative participants, HIV-positive persons that were not taking antiretroviral therapy were at increased risk of PTD (adjusted OR 3.33; 95% CI 1.65, 6.71), while those taking a TDF-based or a TDF-sparing regimen were not at significantly increased risk of PTD. Among HIV-positive participants, uncontrolled viremia was a strong correlate of PTD.

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Conflicts of Interest: The remaining authors declared no conflicts.

Forty-nine of 55 (89%) participants with PTD at baseline had at least one subsequent visit without PTD. There was no association between baseline PTD and rate of decline in mGFR over time.

Conclusions—Poorly controlled HIV may be a stronger risk factor for PTD than TDF use. The individual-level variability of the PTD markers over time was high, potentially limiting their usefulness for routine screening in unselected patients. Baseline PTD was not associated with subsequent mGFR slope.

Keywords

HIV; proximal tubule dysfunction; tenofovir disoproxil fumarate; antiretroviral therapy; glomerular filtration rate

Introduction

Proximal tubular dysfunction (PTD) is thought to be common in HIV-positive individuals, with studies finding prevalence rates of 6% to over 50% (1, 2). PTD is defined as a decreased ability of the proximal tubule to reabsorb small molecules filtered by the glomerulus, such as glucose, phosphorous, and low molecular weight proteins. The current guidelines for chronic kidney disease in HIV-positive individuals describe laboratory findings supporting a diagnosis of PTD. However, due to limited information about the performance characteristics of PTD indicators and the unclear clinical significance of PTD in asymptomatic individuals, the guidelines do not recommend routine screening for PTD (3).

Many studies have identified tenofovir disoproxil fumarate (TDF), a commonly-prescribed nucleotide reverse transcriptase inhibitor, as a risk factor for PTD (1–9). TDF is excreted in the urine partially through tubular secretion (10, 11). Accumulation of TDF within proximal tubular cells is thought to cause PTD through mitochondrial damage (6, 12, 13). Current guidelines recommend avoiding TDF in patients with an estimated glomerular filtration rate (eGFR) of $< 60 \text{ mL/min/1.73 m}^2$ (Infectious Disease Society of America) or a creatinine clearance of $< 50 \text{ mL/min/1.73 m}^2$ (United States Department of Health and Human Services) (3, 8).

Despite the high prevalence of PTD among people with HIV, there are key gaps in our knowledge of the natural history of HIV-related and TDF-associated PTD. In particular, there are few studies assessing PTD in demographically similar HIV-negative persons, the persistence of PTD indicators over time, or the implication of PTD for subsequent GFR change (3, 14–16). Using data from a cohort of HIV-positive participants, many with long treatment histories, and HIV-negative participants followed over three years, our objectives were to (1) assess the associations between HIV serostatus, TDF use and PTD, (2) assess changes in the prevalence of PTD over the course of the study, and (3) assess the association between PTD at baseline and measured GFR (mGFR) trajectory. We used three indicators of PTD that have been proposed in guidelines and are readily available in clinical practice: phosphaturia, tubular proteinuria, and glycosuria with normoglycemia (3).

Methods

Study design and population

The Mr. Bean study is a prospective cohort in Baltimore, MD, recruited in 2011–2012 to assess demographic, behavioral, and viral (HIV and hepatitis C virus [HCV]) factors associated with the progression of kidney and cardiovascular disease among individuals with initially normal estimated kidney function(17). We recruited HIV-positive participants from the Johns Hopkins HIV clinic and HIV-negative participants from the community in a 2:1 ratio. We recruited HIV-negative subjects through local media advertising and from a cohort of persons with a history of injection drug use, the latter to achieve comparable behavioral characteristics and HCV seropositivity rates to the HIV-positive sample(18). Inclusion criteria included age 18 years or older and eGFR ≥ 60 mL/min/1.73 m² based on the MDRD equation(19). Exclusion criteria included history of radiocontrast allergy, pregnancy, diabetes mellitus, uncontrolled hypertension (systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg), collagen vascular disease, or life-threatening comorbidity. After screening and enrollment, participants completed a baseline study visit and up to three annual follow-up visits. Laboratory results from this study were not routinely made available to clinicians caring for enrolled patients. The study was approved by the Johns Hopkins Medicine Institutional Review Board and participants provided written informed consent.

Data collection and measurements

At each study visit, we collected demographic, behavioral, clinical, and pharmacologic data by interview and medical record review, and measured blood pressure, height, and weight. Laboratory testing at each study visit included plasma concentrations of creatinine, phosphorous, CD4 cell count, and HIV RNA level (lower limit of detection of 400 copies/mL). Additionally, we measured fasting urine concentrations of creatinine, albumin, protein, and phosphorus from fresh urine samples at each study visit. Plasma and urine chemistry testing was done by The Johns Hopkins Hospital clinical laboratory with a Cobas 8000 c701 analyzer (Roche Diagnostics, Indianapolis, IN) using an enzymatic creatinase method for creatinine, spectrophotometry for phosphorus, a turbidimetric assay for protein, and an immunoturbidimetric assay for albumin. Urine glucose was assessed with a fully automated dipstick method (Aution 9EB, Arkray, Inc. Kyoto, Japan) using a glucose oxidation reaction.

We measured glomerular filtration rate at each study visit using iohexol disappearance from plasma (mGFR), as has been previously described(17). HCV serostatus was determined at baseline by HCV serology with reflex to HCV RNA if seropositive. Participants with detectable HCV RNA were considered to have active hepatitis C infection.

Definitions

Participants were considered “ever smokers” if they reported having smoked at least 100 cigarettes during their lifetime. Participants were considered “current smokers” if they reported active cigarette use at baseline. Time since ART initiation was defined as the number of months since ART initiation, with no adjustments for possible lapses in therapy.

Cumulative exposure to TDF was defined as the number of months of TDF use prior to start of the study, excluding lapses in TDF use.

Urine measures of kidney injury and proximal tubular function included albumin-creatinine ratio (ACR), protein-creatinine ratio (PCR), albumin-protein ratio (APR), and fractional excretion of phosphorous (FE_{phos}). The APR was calculated as ACR/PCR and FE_{phos} was calculated as $[(\text{urine phosphorous concentration}) * (\text{serum creatinine concentration}) / (\text{urine creatinine concentration}) * (\text{serum phosphorous concentration})] * 100$. Consistent with guidelines(20), we defined albuminuria as an $ACR \geq 30$ mg/g and proteinuria as $PCR \geq 200$ mg/g. Subjects who met criteria for proteinuria were further categorized as having glomerular proteinuria ($APR > 0.4$) or tubular proteinuria ($APR \leq 0.4$). Tubular proteinuria has been proposed as a marker of PTD, as low-molecular weight proteins (which are normally resorbed by the proximal tubule) account for a large relative share of total proteinuria compared with albumin (21, 22). A recent study of biopsy-proven TDF nephrotoxicity suggested that low urine APR (i.e., non-albumin proteinuria) is a reliable feature of TDF-associated nephrotoxicity (23). We defined low serum phosphate (hypophosphatemia) as serum phosphate < 2.5 mg/dL.

We defined PTD as the presence of at least one the following(3): non-diabetic glycosuria (>100 mg/dL by semiquantitative dipstick) in the presence of normoglycemia (serum glucose <126 mg/dL), phosphaturia, defined as $FE_{\text{phos}} > 18\%$ (1, 24), or the presence of tubular proteinuria. Data from study visits at which urine samples were abnormally dilute (creatinine concentration < 10 mg/dL) or where more than one of the three PTD criteria could not be assessed were excluded.

Statistical analysis

We compared baseline demographic, behavioral, and laboratory characteristics in four groups: 1) HIV-positive participants taking TDF-based ART, 2) HIV-positive participants taking TDF-sparing ART, 3) HIV-positive participants not taking ART, and 4) HIV-negative participants. We used Fisher's exact tests and Kruskal-Wallis tests for categorical and continuous variables, respectively. We used a logistic regression to assess the association between cumulative ART/TDF exposure and baseline PTD. The duration of ART and TDF exposure were natural log-transformed due to the wide range of cumulative exposure.

We used univariate and multivariate generalized estimating equation logistic regression with an exchangeable correlation structure to identify factors associated with PTD across all visits. The time-fixed covariates were HIV-infection status, sex, race, baseline smoking status, history of hypertension, history of cardiovascular disease, and active HCV infection. The time-varying covariates were age, body mass index (BMI), plasma creatinine, systolic blood pressure, diastolic blood pressure, glycosylated hemoglobin, use of ART and TDF among HIV-positive subjects, use of nonsteroidal anti-inflammatory drugs (NSAIDs), and use of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). Covariates for the multivariate model were selected in a backwards stepwise manner; covariates with a p -value of < 0.05 were retained in the final model and tested for interactions. We also assessed an alternate categorization scheme for participants: 1) HIV-negative, 2) HIV-positive not on ART, 3) HIV-positive on ART with a detectable viral load,

and 4) HIV-positive on ART with an undetectable viral load. In this case, use of ART and viral suppression status were time-varying.

We used linear mixed effects models to assess the association between baseline PTD and mGFR slope, stratified by HIV serostatus. In multivariate slope models, we controlled for age, race, sex, and viral suppression. STATA 14.1 (STATA Corp, College Station, TX, USA) was used for all analyses.

Results

A total of 292 participants (192 HIV-positive and 100 HIV-negative) were included in the study. These participants completed a total of 1,030 study visits, with individuals completing a median (25th percentile, 75th percentile) of 4 (3, 4) study visits. We excluded 8 study visits due to abnormally dilute urine or more than 1 missing measure of PTD, leaving 1,022 visits in the analysis of risk factors for PTD. Of the 1,022 total study visits, 952 had valid mGFR measurements for the mGFR slope analysis.

Baseline clinical characteristics

The HIV-status/ART groups were similar in age, BMI, race, and smoking status (Table 1). The HIV-positive groups had higher proportions of women, were more likely to have active HCV infection, and were more likely to be taking an ACEi or ARB at baseline. However, there was no significant difference in hypertension or hemoglobin A1c between the groups.

HIV-positive individuals not taking ART were significantly more likely than other HIV-positive participants to have a detectable viral load. HIV-positive individuals taking ART (with or without TDF) had lower CD4 nadirs than HIV-positive participants not taking ART. HIV-positive participants taking ART with and without TDF had similar durations of ART use prior to the beginning of the study. Seven of the 17 subjects not on ART at baseline were ART naïve; the other ten had prior ART exposure. As expected, cumulative exposure to TDF was highest in HIV-positive subjects receiving TDF at baseline.

Baseline plasma creatinine was statistically significantly different between the groups, although the differences were not clinically significant, with the median baseline plasma creatinine in all groups between 0.9 and 1.0 mg/dL. Baseline mGFR was lowest in participants on TDF-sparing ART (80 mL/min/1.73 m²), and highest in HIV-negative participants (96 mL/min/1.73 m²). The prevalence of hypophosphatemia was similar among the groups at baseline (Table 1) and during follow-up (data not shown). Compared with HIV-negative participants, the prevalence of PTD at baseline was higher in the HIV-positive groups, particularly the group not taking ART.

Among HIV-positive participants, cumulative exposure to TDF was not significantly associated with baseline PTD, in either the unadjusted analysis (odds ratio [OR] 0.97 per 1 log_e increase in exposure time [months], 95% confidence interval [CI] 0.78, 1.20) or when adjusting for time since ART initiation (adjusted OR 1.11 per 1 log_e increase in TDF exposure time, 95% CI 0.85, 1.44).

Patterns and prevalence of PTD

Table 2 shows the frequencies for different patterns of PTD components among those with PTD at baseline. Tubular proteinuria was the most common PTD criterion detected, followed by $FE_{\text{phos}} > 0.18$. Tubular proteinuria and phosphaturia were poorly correlated, and did not co-occur in individual participants any more frequently than would be expected by chance (Kappa 0.05, 95% CI -0.06, 0.17). Only a single participant had non-diabetic glycosuria at baseline and this individual also had tubular proteinuria. There were only 24 visits (out of 1,022 visits) by 20 different participants (out of 292 subjects) at which more than one criterion for PTD was met.

Table 3 shows the prevalence of PTD over time according to the baseline HIV-serostatus/ART groups. Group differences in PTD were significantly different at baseline and the 24-month visit. One hundred and thirteen participants (39%) had a change in their PTD status over the course of the study. Among subjects with at least 2 visits, 49 of 55 (89%) with PTD at baseline had at least one subsequent visit without PTD, and 65 of 217 (30%) without PTD at baseline had at least one subsequent visit with PTD.

Association of clinical factors with PTD

Table 4 shows the associations of clinical factors with PTD in a repeated measures analysis. Compared with HIV-negative individuals in the unadjusted analysis, all HIV-positive groups had significantly higher odds of PTD, with subjects who were not on ART having the highest odds (OR 4.67; 95% CI 2.37, 9.18). There were no significant associations of age, smoking status, history of cardiovascular disease, systolic/diastolic blood pressure, hemoglobin A1c, NSAID use, or ACEi/ARB use with PTD.

Compared with HIV-negative subjects, a significant association between HIV/ART status and PTD remained only for HIV-positive subjects not taking ART (OR 3.33; 95% CI 1.65, 6.71) in the adjusted analysis. Additionally, among HIV-positive individuals, those not taking ART were significantly more likely to have PTD than participants on TDF-based or TDF-sparing ART (OR 2.25; 95% CI 1.22, 4.15 and OR 2.40; 95% CI 1.21, 4.77, respectively). Among ART-treated individuals, use of tenofovir was not significantly associated with PTD in the adjusted analysis (OR 1.07; 95% CI 0.66, 1.71). Other factors associated with PTD in the adjusted analysis were female gender, Caucasian race, lower BMI, hypertension, active HCV infection, and higher plasma creatinine. The above analysis was repeated excluding HIV-positive participants who had ever received TDF from the TDF-sparing group, with no substantial changes in the results of the adjusted analysis (Appendix I).

In a supplementary analysis in which participants were categorized by HIV status, ART use, and viral suppression, HIV-positive individuals not on ART (reference HIV-negative participants; adjusted OR [aOR] 3.48, 95% CI 1.73, 6.99) and HIV-positive individuals on ART with a detectable viral load (aOR 2.61, 95% CI 1.38, 4.92) had similar odds of PTD (Appendix II). The odds of PTD for HIV-positive individuals on ART with an undetectable viral load were similar to that of HIV-negative participants (aOR 1.30, 95% CI 0.80, 2.08).

In an additional supplemental analysis restricted to HIV-positive participants, there was both an unadjusted (OR 2.01; 95% CI 1.30, 3.10) and an adjusted (OR 1.81, 95% CI 1.10, 3.00) association between a detectable viral load and PTD (Appendix III). Logarithmically-transformed CD4 count was negatively associated with PTD in the unadjusted model (OR 0.71, 95% CI 0.56, 0.89), but did not reach statistical significance in the adjusted model (OR 0.78, 95% CI 0.61, 1.01).

Association of PTD with mGFR slope

Among HIV-positive participants with and without PTD at baseline, the mGFR slopes were -2.96 and -1.31 mL/min/1.73m² per year, respectively ($P=0.084$ for difference between slopes). In a model adjusting for age, sex, race, and viral suppression the difference in mGFR slopes between HIV-positive participants with and without PTD was -1.58 mL/min/1.73m² per year (95% CI -3.56 , 0.40 , $p=0.12$). Similarly, there was no significant difference in mGFR slopes between HIV-negative participants with and without baseline PTD (difference in slopes 0.67 mL/min/1.73m² per year; 95% CI -3.00 , 4.33 ; $p=0.72$).

Discussion

Our first objective was to assess the associations of HIV status and TDF use with PTD, characterized by recommended measures of proximal tubular function that are widely available in clinical practice. Compared with HIV-negative participants, HIV-positive persons that were not taking antiretroviral therapy were at over 3-fold the odds of having PTD, while those taking ART were not at significantly increased risk of PTD. Among HIV-positive individuals, there were no significant associations between current or cumulative TDF exposure and PTD. Other factors independently associated with an increased risk of PTD included low BMI, female sex, Caucasian race, active HCV infection, and higher plasma creatinine. Our second objective was to assess changes in the prevalence of PTD over the course of the study. We found that 39% of subjects had a change in PTD status over the three years of this study. More than 80% of participants with PTD at baseline had at least one follow-up visit with no PTD. Our third objective was to assess the association between PTD at baseline and mGFR trajectory. We found that PTD at baseline was not significantly associated with mGFR slope in HIV-positive or -negative subjects.

Previous studies have yielded mixed findings regarding whether TDF is a risk factor for PTD(1, 2, 4, 15, 16, 25–27). A review noted that most studies finding an association between TDF and PTD were case-control or retrospective cohort studies; whereas randomized-controlled trials have not typically found differences in adverse kidney events in TDF recipients compared with those treated with alternative agents (6). However, recent trials comparing tenofovir alafenamide with TDF-based therapy have reported higher levels of urine retinol binding protein and β_2 -microglobulin (alternative PTD markers) in the latter group, although the clinical implications of this are unknown (28, 29). Our results, suggest that poorly-controlled HIV may be a stronger risk factor for PTD than TDF in a non-diabetic population with long HIV treatment histories, but without clinically decreased kidney function. Consistent with this, increased levels of urine β_2 -microglobulin have been observed in patients with advanced HIV prior to the use of TDF (30).

We also found higher rates of PTD in participants with low BMI, female sex, Caucasian race, active HCV infection, and higher plasma creatinine. Low BMI is a commonly reported risk factor for PTD in HIV, although this association has generally been attributed to increased TDF exposure in smaller individuals (6, 26, 31). Fewer studies have looked at associations between gender, race, and PTD. In particular, many cohorts used to study PTD have been predominantly male or of a single ethnicity (4, 9, 15, 27, 31). While HCV serostatus has been included in many analyses, results have been mixed regarding whether HCV infection is an independent risk factor for PTD (1, 9, 26, 27). Of note, female gender and HCV are risk factors for the development of reduced GFR in HIV-infected persons(3). However, while we found higher rates of PTD in Caucasians, HIV-positive Caucasians are at lower risk of progressive impairment in GFR compared with African Americans (3). Thus, our results highlight potential parallels, and one difference, between risk factors for PTD and risk factors for CKD in HIV.

In follow-up visits over 36 months, we found surprising variability in the presence or absence of PTD laboratory indicators. Over one-third (39%) of participants had a change in their PTD status over the three years of the study; 81% of subjects with PTD at baseline had at least one subsequent visit without PTD. Moreover, despite the increased risk of PTD in HIV-positive individuals, 34% of HIV-negative subjects had PTD detected at least once. There is little published on the variability of PTD indicators over time. However, our findings suggest that routine screening for PTD with the clinically available indicators we studied in HIV-infected patients may be insufficiently reliable to guide clinical management.

The relationship between PTD and GFR trajectory in patients with HIV is unclear (4, 9, 15). Although we found that PTD was associated with lower GFR (or higher serum creatinine) at baseline, we found no association between baseline PTD and subsequent mGFR slope over 3 years. In contrast, Kinai *et al.* found that higher levels of urine β_2 -microglobulin were associated with greater declines in eGFR among HIV-positive subjects on TDF(4). Ando *et al.* showed that HIV-positive patients with evidence of baseline tubular damage were more likely than patients without baseline tubular damage to have a decline in their eGFR at one year (9). Our findings suggest that PTD (defined by the indicators we used) may be correlated with decreased kidney function, but it remains unclear whether PTD is predictive of future GFR decline.

The strengths of our study include prospective 3-year follow-up of well-characterized demographically-similar HIV-positive and HIV-negative participants. As data obtained for the study were not routinely shared with treating clinicians, these data were unlikely to have affected treatment decisions. Limitations include potential treatment selection bias, particularly as many patients had long treatment histories at the beginning of the study; absence of data on bone mineral density (a potential complication of PTD); and limited generalizability as the cohort was predominantly African American. Finally, we characterized PTD according to readily available markers in clinical practice (glycosuria, tubular proteinuria, and FE_{phos}). Other studies have included alternative PTD markers, such as fractional excretion of uric acid, β_2 -microglobulin, retinol binding protein, neutrophil gelatinase-associated lipocalin, and others, which limits the ability to make cross-study comparisons (4, 9, 15, 28, 32).

In conclusion, we found a higher prevalence of PTD in HIV-positive than HIV-negative individuals. Among HIV-positive participants, uncontrolled viremia was the strongest correlate of PTD, while TDF use was not significantly associated with PTD. There was striking within-subject variability in the presence of PTD indicators over time, and the 2 most common indicators (tubular proteinuria and phosphaturia) occurred independently of one another. We found similarities between CKD and PTD risk factors, but no association between baseline PTD and GFR trajectory. Our results highlight the need for a consensus definition of PTD and further studies examining the association between HIV viremia, PTD, and GFR over time, in both HIV-positive and HIV-negative populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding: This study was supported by the National Institute on Drug Abuse (R01DA026770, K24DA035684). Other support was provided by the National Institute of Allergy and Infectious Diseases (T32AI102623), the National Institute of Diabetes and Digestive and Kidney Disease (U01DK082194, P01DK056492), the Johns Hopkins Institute for Clinical and Translational Research (ICTR), which is funded in part by grant number UL1-TR000424 from the National Center for Advancing Translational Sciences (NCATS), a component of the NIH, and by the Johns Hopkins Center for AIDS Research (P30AI094189). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

M.G.A. has received an institutional grant from and served as an advisor to Gilead Sciences, Inc.

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Table 1

Baseline clinical characteristics of participants, stratified by HIV status and use of tenofovir disoproxil fumarate (TDF)-containing or TDF-sparing antiretroviral therapy.

	HIV-positive (n = 192)			HIV-negative (n = 100)	p-value [†]
	ART with TDF (n = 130)	ART without TDF (n = 45)	No ART (n = 17)		
Demographics					
Age, years, median (P ₂₅ , P ₇₅)	48 (44, 52)	50 (48, 56)	47 (41, 52)	49 (45, 54)	0.011
Body mass index, kg/m ² , median (P ₂₅ , P ₇₅)	25 (22, 31)	27 (23, 32)	25 (23, 32)	27 (23, 33)	0.41
Sex					
Female, n (%)	48 (37%)	13 (29%)	6 (35%)	19 (19%)	0.025
Male, n (%)	82 (63%)	32 (71%)	11 (65%)	81 (81%)	
Race					
White, n (%)	8 (6%)	1 (2%)	2 (12%)	8 (8%)	0.39
Black, n (%)	122 (94%)	44 (98%)	15 (88%)	92 (92%)	
Medical history					
Ever smoker, n (%)	98 (75%)	34 (76%)	14 (82%)	73 (73%)	0.91
Current smoker, n (%)	84 (65%)	28 (62%)	12 (71%)	61 (61%)	0.88
Ever intravenous drug use, n (%)	52 (40%)	12 (27%)	7 (41%)	37 (37%)	0.44
History of hypertension, n (%)	45 (35%)	15 (33%)	7 (41%)	21 (21%)	0.080
History of cardiovascular disease, n (%)	16 (12%)	8 (18%)	2 (12%)	5 (5%)	0.072
Active hepatitis C, n (%)	63 (48%)	19 (42%)	10 (59%)	23 (23%)	<0.001
Systolic blood pressure, mm HG, median (P ₂₅ , P ₇₅)	118 (107, 132)	121 (111, 128)	122 (113, 138)	126 (113, 135)	0.034
Diastolic blood pressure, mm HG, median (P ₂₅ , P ₇₅)	70 (64, 76)	71 (67, 77)	73 (64, 81)	73 (66, 82)	0.22
Glycosylated hemoglobin, %, median (P ₂₅ , P ₇₅)	5.4 (5.2, 5.7)	5.3 (5.0, 5.7)	5.5 (5.1, 5.7)	5.5 (5.3, 5.8)	0.12
NSAID ² use, n (%)	83 (64%)	25 (56%)	13 (76%)	59 (59%)	0.43
ACEi or ARB use ³ , n (%)	20 (15%)	5 (11%)	5 (29%)	8 (8%)	0.073
HIV characteristics					
Nadir CD4 count, cells/mm ³ , median (P ₂₅ , P ₇₅)	134 (33, 296)	127 (42, 235)	301 (148, 410)	NA	0.015
Current CD4 count, cells/mm ³ , median (P ₂₅ , P ₇₅)	437 (248, 617)	522 (335, 669)	417 (177, 681)	NA	0.21

	HIV-positive (n = 192)			HIV-negative (n = 100)	p-value ^f
	ART with TDF (n = 130)	ART without TDF (n = 45)	No ART (n = 17)		
HIV RNA >400 copies/mL, n (%)	20 (15%)	4 (9%)	16 (94%)	NA	<0.001
HIV RNA in subjects with values > 400 copies/mL, median (P ₂₅ , P ₇₅)	6121 (3084, 52451)	52408 (442, 142645)	18875 (8007, 53177)	NA	0.53
Time since ART initiated, months, median (P ₂₅ , P ₇₅)	100 (46, 162)	140 (69, 172)	19 (0, 59)	NA	<0.001
Cumulative exposure to TDF, months, median (P ₂₅ , P ₇₅)	38 (17, 62)	5 (0, 36)	0 (0, 8)	NA	<0.001
Measures of kidney function					
Serum creatinine, mg/dL, median (P ₂₅ , P ₇₅)	0.9 (0.7, 1.0)	1.0 (0.9, 1.2)	0.9 (0.7, 1.1)	1.0 (0.8, 1.1)	0.0087
Measured GFR, ⁴ mL/min/1.73 m ² , median (P ₂₅ , P ₇₅)	92 (79, 104)	80 (71, 95)	88 (73, 108)	96 (84, 111)	<0.001
<i>Glomerular injury markers</i>					
Urine albumin-cr ratio, mg/g, median (P ₂₅ , P ₇₅)	6 (3, 16)	11 (3, 23)	18 (2, 33)	4 (2, 9)	0.0012
Urine albumin-cr ratio > 30 mg/g, n (%)	22 (17%)	11 (24%)	6 (35%)	6 (6%)	0.001
Urine protein-cr ratio, mg/g, median (P ₂₅ , P ₇₅)	107 (74, 182)	100 (67, 153)	131 (73, 223)	70 (55, 100)	<0.001
Urine protein-cr ratio > 200 mg/g, n (%)	29 (22%)	10 (22%)	5 (31%)	6 (6%)	0.001
<i>Tubular injury markers</i>					
Glycosuria ⁵ , n (%)	1 (0.8%)	0	0	0	1
Serum phosphate, median (P ₂₅ , P ₇₅)	3.6 (3.3, 4.0)	3.4 (3.1, 3.9)	3.6 (3.3, 3.8)	3.4 (3.0, 3.9)	0.17
Low serum phosphate (< 2.5 mg/dL)	5 (4%)	1 (2%)	0	4 (4%)	1
Fractional excretion of phosphate, %, median (P ₂₅ , P ₇₅)	11 (7, 14)	10 (7, 15)	10 (7, 14)	10 (7, 13)	0.51
Fractional excretion of phosphate > 18%, n (%)	12 (9%)	7 (16%)	3 (19%)	6 (6%)	0.13
Tubular proteinuria ⁶ , n (%)	23 (18%)	5 (11%)	5 (31%)	3 (3%)	<0.001
PTD at baseline ⁷	33 (26%)	10 (22%)	7 (41%)	9 (9%)	0.001

^f Fisher's exact tests and Kruskal-Wallis tests for categorical and continuous variables, respectively.² Nonsteroidal anti-inflammatory drug (NSAID)³ Angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB)⁴ Measured using an iohexol clearance from plasma⁵ Nondiabetic, as patients with diabetes were excluded from this study.

Tubular proteinuria is defined as a urine protein-creatinine ratio of >200 (proteinuria) AND an urine albumin-protein ratio of <0.4

PTD is defined as non-diabetic glycosuria, fractional excretion of phosphate > 18%, OR tubular proteinuria

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Table 2

Patterns of proximal tubular dysfunction components at baseline.

PTD classification conditions ¹			Number with combination (% of total with PTD)
Non-diabetic glycosuria	Tubular proteinuria	FE _{phos} > 0.18	
1	0	0	0
0	1	0	30 (51%)
0	0	1	23 (39%)
1	1	0	1 (2%)
1	0	1	0
0	1	1	5 (8%)
1	1	1	0

FE_{phos}, fractional excretion of phosphorous; PTD, proximal tubular dysfunction

¹The number 1 indicates component was present, 0 absent

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Prevalence of proximal tubular dysfunction over time according to baseline HIV and antiretroviral use status. The number in each group was different at each visit.

Table 3

	HIV-positive		HIV-negative ¹	p-value	
	ART with TDF ¹	ART without TDF ¹			No ART ¹
Baseline	33 of 129 (26%)	10 of 45 (22%)	7 of 17 (41%)	9 of 98 (9%)	0.001
12 months	23 of 114 (20%)	8 of 43 (19%)	3 of 15 (20%)	9 of 84 (11%)	0.31
24 months	32 of 104 (31%)	6 of 42 (14%)	3 of 13 (23%)	12 of 79 (15%)	0.043
36 months	23 of 101 (23%)	7 of 42 (17%)	6 of 13 (46%)	13 of 83 (16%)	0.083
Anytime	64 (50%)	19 (42%)	8 (47%)	33 (34%)	0.14

ART, antiretroviral therapy; TDF, tenofovir disoproxil fumarate

¹Based on HIV/ART categories at baseline

Table 4

Factors associated with proximal tubule dysfunction using a repeated measures analysis: univariate and multivariate analyses.

		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
HIV-negative		1	1
HIV-positive	ART with TDF	1.98 (1.22, 3.22)	1.48 (0.91, 2.42)
	ART without TDF	2.10 (1.19, 3.62)	1.39 (0.79, 2.45)
	No ART	4.67 (2.37, 9.18)	3.33 (1.65, 6.71)
Age ¹ (per 10 year increase in age)		1.03 (0.80, 1.32)	
BMI		0.97 (0.94, 1.0)	0.96 (0.93, 0.99)
Female (reference: male)		1.78 (1.19, 2.66)	2.35 (1.51, 3.65)
Caucasian race		1.88 (0.92, 3.84)	2.72 (1.31, 5.62)
Ever smoker		1.12 (0.70, 1.79)	
History of hypertension		1.76 (1.18, 2.63)	1.63 (1.08, 2.44)
History of cardiovascular disease		1.68 (0.94, 2.99)	
Active Hepatitis C		2.05 (1.38, 3.04)	1.49 (1.00, 2.22)
Systolic blood pressure ² (per 10mmHg increases)		1.04 (0.94, 1.15)	
Diastolic blood pressure ²		1.08 (0.92, 1.26)	
Glycosylated hemoglobin		0.91 (0.63, 1.33)	
non-steroidal anti-inflammatory drug use		1.21 (0.89, 1.64)	
ACEi or ARB use		1.34 (0.83, 2.16)	
Serum creatinine ³		1.95 (1.05, 3.60)	3.78 (1.81, 7.91)

OR, odds ratio; ART, antiretroviral therapy; TDF, tenofovir disoproxil fumarate; BMI, body mass index; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers

¹ Per 10 year increase in age

² Per 10mmHg increase in blood pressure

³ Per 1 mg/mL increase in serum creatinine