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TUBULAR SECRETORY SOLUTE CLEARANCE AND HIV INFECTION

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Abstract

Background: Tubular secretion is an important kidney function responsible for the clearance of numerous medications including antibiotics and antivirals. It is unknown whether or not persons living with HIV have lower secretion compared with HIV-uninfected persons, which might predispose them to risk of progressive kidney disease or adverse drug events.

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DISCLOSURES

None

Setting and Methods: We evaluated a panel of 6 endogenous secretory solutes in 199 women living with HIV (WLWH) and 100 women without HIV enrolled in the Women's Interagency HIV Study (WIHS). Secretory clearance was estimated as the urine/plasma ratio (UPR) of each solute, with adjustment for urine tonicity. Using multivariable linear regression analysis, we compared differences in levels of secretory solute clearance between women with and without HIV and evaluated characteristics associated with secretion.

Results: WLWH were older (median 40 vs. 38 years) but had similar estimated glomerular filtration rate (eGFR, 96 vs. 100 ml/min/1.73m 2) compared to those without HIV. African American and Latino race, diabetes, diastolic blood pressure, smoking, Hepatitis C, peak HIV viral load, current and nadir CD4 count were associated with differences in clearance of at least one marker after multivariable adjustment. The secretory clearance of 3 solutes (cinnamoylglycine, kynurenic acid, and pyridoxic acid) were on average 10–15% lower among WLWH compared to those without HIV independent of eGFR, albuminuria and CKD risk factors, including HCV, and injection drug use.

Conclusions: HIV is associated with reduced secretion among women with preserved eGFR. The implications of these findings for drug dosing and adverse events need to be evaluated.

Keywords

kidney tubule; secretion; clearance; biomarker; HIV; women

INTRODUCTION

In the current era of antiretroviral therapy (ART), persons living with HIV (PLWH) have increased risk of several chronic diseases, including chronic kidney disease (CKD) and end-stage kidney disease (ESKD) compared to persons without HIV. [1–3] HIV infection has been specifically linked with several glomerular diseases, like HIV-associated nephropathy (HIVAN), immune complex disease, and membranoproliferative glomerulonephritis (often associated with hepatitis C co-infection). However, these are becoming progressively less common, and non-proteinuric tubulointerstitial kidney disease is increasing in PLWH,[4] accounting for nearly 25% of all cases in biopsy series.[5] While direct tubular damage from the HIV virus after uptake into the tubule cells may play a role[6], the mechanisms by which HIV infection promotes progressive kidney disease in those receiving ART remains to be elucidated.

The kidney tubules are responsible for a myriad of important functions which are needed to maintain homeostasis. Among them is secretion of toxins, both endogenous and exogenous, that are not filtered at the glomerulus and secretion of drugs including several used to treat HIV. It is unknown whether HIV involvement of kidney tubules leads to impairments of the kidney's secretory functions. Reductions in tubular secretion may lead to adverse drug effects due to medication accumulation or drug-drug interactions from polypharmacy.[7] Impaired secretion might also predispose to CKD through susceptibility to toxic exposures. Despite its potential importance, tubular secretion is only assessed in research settings due to a lack of simple non-invasive tools, and to our knowledge, it has never been studied in persons living with HIV.

Several endogenous solutes are highly secreted (5–10 times eGFR) by the kidney tubules via active transport, indicating the mammalian kidney's adaptation to effectively excrete these metabolites.[8] By simultaneously measuring each compound in urine and blood, their secretory clearance can be calculated, thereby providing an estimate of secretory function.[9] Given that HIV is associated with increased concentrations of proximal tubular injury and dysfunction biomarkers,[10] lower secretory function may also be an early manifestation of tubulopathy and CKD risk in persons with HIV. In this study of women with and without HIV enrolled in the Women's Interagency HIV Study (WIHS), we tested the hypothesis that tubular secretory clearance of endogenous solutes identified through prior work in knockout-out experimental models and in human studies would be worse in women living with HIV (WLWH) infection compared with those without after adjusting for traditional kidney disease risk factors.

METHODS

Study Population

WIHS was designed to investigate the progression of HIV disease in women. The study enrolled 3,766 WLWH and 966 women without HIV from six U.S. locations in 1994–95, and 2001–02.[11,12] A key design feature was the collection of comparable data among HIV-uninfected women through enrollment of seronegative persons with similar behavioral and demographic risk factors for infection. Participants underwent semiannual visits that included an interviewer-administered questionnaire, a physical examination, and the collection of laboratory specimens.

The WIHS Kidney Aging Study was a nested cohort study to investigate the onset of kidney disease in the setting of HIV-infection using stored urine and serum specimens collected between 1999 and 2000 when the prevalence of tenofovir disoproxil fumarate (TDF) use was <1%, therefore enabling us to uniquely study the effect of HIV-infection on kidney function decline independent of TDF effects. Among participants of the Kidney Aging Study who had stored serum and urine samples (HIV+ = 819, HIV− = 287), we created two random sub-cohorts of WLWH (n=200) and without HIV (n=100) and we measured secretory solutes using paired blood and urine samples. The institutional review boards of the participating institutions approved the study protocol at all WIHS study sites, and informed consent was obtained from all study participants. This kidney biomarker ancillary study was also approved by the Committee on Human Research of the University of California San Francisco (UCSF).

Exposure variable

HIV status was determined by enzyme-linked immunosorbent assay and Western blot confirmation[13] at the time of study enrollment.

Outcomes

The outcome of interest was the clearance of endogenous solutes suspected to be cleared primarily by tubular secretion. We initially selected a list of candidate solutes based on one or more of the following characteristics from the published literature: affinity for

OAT1/3 transporters, increase in plasma concentrations following transporter knockout in experimental models, high degree of protein binding suggesting minimal filtration, and/or kidney clearances that exceed GFR or creatinine clearance.[8,14] We then developed a mass spectroscopic assay for 16 solutes (3-hydroxy hippurate, adipic acid, cinnamoylglycine, dimethyluric acid, hippurate, indoxyl sulfate, isovalerylglycine, kynurenic acid, pantothenic acid, p-cresol sulfate, pyridoxic acid, suberic acid, succinic acid, tiglyglycine, trimethyluric acid and xanthosine). We initially excluded three solutes that could not be reliably quantified by our assay (adipic acid, suberic acid, succinic acid); two solutes that exhibited extremely higher diurnal variation in plasma, which violates the steady-state assumption for clearance (3-hydroxy hippurate, dimethyluric acid, trimethyluric acid); and one solute that was subsequently discovered to have a high degree of tubular reabsorption in literature review (pantothenic acid). Among the remaining nine solutes, we have subsequently focused on six that have appeared to best reflect tubule secretion in studies of CKD and the general population (cinnamoylglycine, indoxyl sulfate, isovalerylglycine, kynurenic acid, pyridoxic acid, and xanthosine).[15] Additional information about each secretory solute is available in the Human Metabolome Database (http://www.hmdb.ca).

All serum and urine specimens were stored at −80°C without prior freeze-thaw until biomarker measurement. Plasma samples underwent solid phase extraction after precipitation in organic solvent, and urine samples underwent two consecutive solid phase extractions (HLB or MCX µElution plates, Waters).[15,16] Reconstituted dried extracts were filtered through a large-pore filter plate (Millipore, MSBVN1210) to remove particulates before analysis by liquid chromatography-tandem mass spectrometry (Shimadzu and Sciex). Data were normalized based on stable isotope-labeled solutes added to each well. Calibration was achieved by a single point approach using pooled human serum and urine. All measurements included labeled internal standards and external calibrators, for which absolute solute concentrations were quantified by standard addition using spiking solutions characterized by nuclear magnetic resonance spectroscopy. The physical characteristics, limits of detection and coefficients of variation of these solutes have been previously described.[15] Laboratory personnel were blinded to clinical information, including their HIV status.

To account for the effect of tonicity on urine metabolite concentrations, we calculated the tubular secretion (TS) of each solute ‘X’ as $TS_x = U_x * V / P_x$, where U_x and P_x denote urine and plasma concentration of solute ‘X’, and the 24-hour urine volume (V) was estimated as exp(−1.351877*(urine creatinine/100)^0.5 + 1.369322). Serum creatinine was measured in local laboratories for each study site with assays using the modified Jaffé method traceable to isotope-dilution mass spectrometry. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI 2021) race-free equation using serum creatinine was used to estimate glomerular filtration rate as has been most recently recommended.[17] Urine albumin and creatinine were measured using a Siemens Dimension Xpand Plus HM clinical analyzer (Siemens) by particle-enhanced turbidimetry and colorimetric enzyme assay, respectively.

Covariates

Potential confounding variables were chosen based on clinical knowledge including demographic characteristics, traditional risk factors for kidney disease, and HIV-related risk factors. The following characteristics were included in all multivariate models comparing HIV-infected and uninfected women: age, race/ethnicity, diabetes, hypertension, systolic and diastolic blood pressure, smoking status (current, former, never), hepatitis C coinfection, and injection drug use. Diabetes was defined using confirmatory criteria for fasting glucose ≥126mg/dL, self-reported diabetes, self-reported diabetes medication use, or HbA1c ≥6.5%. Hepatitis C co-infection was confirmed by detectable HCV RNA following a positive HCV antibody result. Models restricted to WLWH also included the following additional covariates: current CD4 count, nadir CD4 count, current HIV RNA level, and peak HIV RNA level from time of enrollment to time of sample collection.

Statistical Analysis

We compared demographic and clinical characteristics and secretion of the solutes between women with and without HIV. We also compared the baseline characteristics of participants included in our study compared to the entire WIHS cohort. Differences were tested using Wilcoxon rank sum tests for continuous variables and Chi-square tests for categorical variables. Correlations between secretory solutes and markers of glomerular function (eGFR and albuminuria), and tubular markers such as alpha-1 microglobulin (α1M), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) were calculated using Spearman correlation after adjusting for urine creatinine.

We used multivariable robust linear regression with MM estimation[18] to evaluate the associations of HIV infection and other factors with secretory clearance, in separate models for each secretory marker. Because the secretory clearances were right-skewed, we log-transformed each measure to normalize its distribution. Results were back transformed to produce estimated percentage differences in secretory clearance attributable to each factor. Within the HIV-only subgroup, we used Bayesian model averaging to identify parsimonious sets of risk factors that were independently associated with each clearance measure, retaining predictors with posterior probabilities > 35%.[19] Next, to determine whether HIV infection was independently associated with each secretory solute, multivariable models were sequentially adjusted for: 1) HIV status, 2) age and race, 3) diabetes, hypertension, smoking, HCV, injection drug use, SBP, and DBP. The final model included adjustment for eGFRcr.

In a sensitivity analysis we also excluded persons taking trimethoprim/sulfamethoxazole, which is known to block tubular secretion. All analyses were conducted using the SAS system, version 9.4 (SAS Institute, Inc., Cary, NC) and a p value <0.05 was considered statistically significant.

RESULTS

Clinical characteristics and secretory solute clearance

WLWH were 2 years older on average, had a higher proportion of hepatitis C infection, and had slightly lower systolic blood pressure and lower diastolic blood pressure compared to women without HIV, but were otherwise similar in clinical characteristics. (Table 1). The median eGFR (96 vs 100 ml/min/1,73m^2) and albuminuria prevalence (17 vs 14 %) were similar across groups. Approximately 58% of WLWH were being treated with highly active anti-retroviral therapy (HAART) and 29% had HIV viral load <80 copies/mL. Across a range of demographic and clinical characteristics, women with and without HIV selected for this study showed were not statistically significantly different from the overall WIHS cohort the overall WIHS cohort (Supplemental Table 1).

There was a wide range of secretory clearance rates among solutes with pyridoxic acid having the highest clearance and indoxyl sulfate having the lowest both in women with and without HIV. Secretory solute clearances were weakly correlated (Spearman r range −0.1 to 0.3) with eGFR and other tubular biomarkers in both women with and without HIV (Supplemental Figure 1).

Association of risk factors with secretory clearance among WLWH

We first evaluated demographic, kidney disease, and HIV-related risk factors with secretory clearance among WLWH using multivariable linear regression models (Table 2). Non-white race was independently associated with higher (or better) clearance of 4 of the 6 evaluated solutes (except for isovalerylglycine and xanthosine). By contrast, Black race was associated with worse clearance of xanthosine. Most other CKD risk factors (age, hypertension, systolic blood pressure, and injection drug use) showed no independent associations with secretory clearance or were significantly associated with certain solutes. Each 10 ml/min/ 1.73 m^2 higher eGFRcr was associated with higher secretion of cinnamoylglycine, indoxylsulfate, Isovalerylglycine and pyridoxic acid. In multivariable adjusted models, we found isolated associations for other factors with higher secretory clearance including diastolic blood pressure (for indoxyl sulfate), smoking (for cinnamoylglycine), hepatitis C (kynurenic acid, and pyridoxic acid), nadir CD4 (pyridoxic acid) and current HIV viral load (xanthosine). By contrast, diabetes was independently associated with worse clearance of cinnamoylglycine; higher current CD4 was associated with lower pyridoxic acid clearance; and higher peak HIV viral load was associated with lower xanthosine clearance.

Comparison of solute clearance (TSx) between women with and without HIV infection

The median secretory clearances of all solutes except indoxyl sulfate were lower by 3–18% in WLWH compared to those without HIV. In demographic adjusted analyses, secretory clearances of cinnamoylglycine, kynurenic acid, pyridoxic acid and xanothosine were 10–15% lower on average among WLWH compared to those without HIV, although this difference was not statistically significant for xanthosine. After additional adjustment for traditional kidney disease risk factors, the clearances of cinnamoylglycine, kynurenic acid, and pyridoxic acid remained 12–20% lower on average among WLWH compared to those without HIV ($p<0.01$ for all) (Figure 1). In a sensitivity analysis after exclusion of 13

WLWH and 3 women without HIV who had reported current or past use of trimethoprim/sulfamethoxazole at the time of sample collection did not change these results.

DISCUSSION

In this analysis of a population-based and multicenter cohort of women with and without HIV, we found that the clearance of endogenous solutes by tubular secretion of the kidneys is lower in WLWH compared to those without. This relationship was independent of common CKD risk factors. These findings may be clinically relevant considering that numerous drugs are cleared by the kidney through tubular secretion with a potential to impact drug dosing among persons living with HIV. Impaired secretion may also be an early manifestation of HIV-associated tubulo-interstitial nephropathy.

Secretion in the proximal tubules is an active, energy driven process involving organic anion (OAT) and organic cation (OCT) transporters.[20–22] Relative diminution of secretory function or competitive inhibition of these transporters by the use of drugs may lead to drug-drug interactions and adverse events.[23] This is especially important in the setting of HIV, given the pill burden and polypharmacy associated with treatment, which puts this population at high risk of drug-drug interactions[24,25]. However, it is unknown what proportion of adverse events may be provoked by decreased secretory function of the kidney. Our main finding of our study resonates with similar results recently discovered in autosomal dominant polycystic kidney disease (ADPKD), a disease which has tubular damage as its central hallmark as opposed to glomerular involvement. Lower secretory clearance of endogenous solutes has been demonstrated in persons with ADPKD, relative to persons with other forms of CKD but with similar eGFR.[26] Another study in CKD patients showed that disorders of the tubules are associated with lower secretory solute clearance compared to those with glomerular or diabetic kidney disease [15]. These findings suggest that disease processes that primarily damage kidney tubules, as may occur with HIV, are important but may remain undetected with traditional measures of kidney function such as eGFR and albuminuria.

Over the last 3 decades, patterns of kidney injury associated with HIV have changed significantly. The incidence of HIV associated nephropathy (HIVAN) has decreased over time with the onset of antiretroviral therapy, and according to emerging data, tubulointerstitial disease may be the predominant pathology for nearly 26% of all persons with HIV undergoing a kidney biopsy. In persons without HIV, we recently demonstrated that greater severity of tubulo-interstitial fibrosis on kidney biopsy was strongly associated with less tubule secretion.[27] Thus, our findings of lower secretory solute excretion in persons with HIV are consistent with prior studies demonstrating abnormalities in tubular injury and fibrosis in the setting of HIV infection. In the Multicenter AIDS Cohort Study (MACS), urine levels of interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), and pro-collagen type III N-terminal pro-peptide (PIIINP), which are all biomarkers of tubule injury and fibrosis, were all higher among persons with HIV compared to those without.[28] Alpha 1-microglobulin is a molecule freely filtered by the glomerulus and reabsorbed in the proximal tubule. Its presence in the urine thus is an indication of impaired re-absorptive capacity. In analyses from the MACS, HIV was associated with higher levels of α1M.[10] In the same study, cumulative exposure to TDF, a tubule-toxin, was associated with an

incremental increase in α1M levels. Further, in analyses from WIHS, WLWH in the highest α1M category had over 2-fold risk of developing CKD compared with women without HIV. Thus, prior studies have demonstrated worse tubule fibrosis on biopsy, and biomarker studies have demonstrated greater tubule injury, fibrosis, and reabsorprtive capacity. This study demonstrates worse tubule secretory capacity for the first time. Thus, we conclude that HIV infection is associated with a state of widespread kidney tubule dysfunction and injury that may be manifest even when eGFR is normal (>95ml/min/1.73m^2 in this cohort). These and other studies [29] also highlight the potential prognostic utility of evaluating tubular biomarkers in assessing kidney health beyond traditional glomerular markers such as blood creatinine and urinary albumin.

This study has important limitations. First, this is a cross-sectional study and so causation and direction of association cannot be inferred. Second, the study only included women and is limited in size. Third, we cannot comment on the clearance of secretory markers in persons with HIV receiving TDF or tenofovir alafenamide (TAF), which are among the most common anti-retrovirals used for pre-exposure prophylaxis (PrEP), and have known potential to cause proximal tubule damage, where secretion occurs. Fourth, we used spot urine specimens to calculate secretory clearance instead of 24-hour urine measures; however, prior data suggest good correlation between measures of secretory solutes conducted using 24-hour and spot urine samples.[9] Fifth, given changes in HIV treatment, the effect of drugs on secretion may be different today and needs further evaluation in a more contemporary cohort.

Our study also has a number of strengths including the use of targeted mass spectrometry assays to quantify secretory solute concentrations as done in prior studies; use of biospecimens prior to the initiation of TDF therapy, therefore negating any possible tubulotoxic effects; and the utilization of a well-phenotyped cohort of women with and without HIV which has provided important information on other kidney tubule biomarkers.

In conclusion, we demonstrate that endogenous secretory solute clearance by the kidney tubules is lower among WLWH, compared to those without HIV, even after adjusting for traditional kidney disease risk factors, eGFR, and albuminuria. Larger studies are needed in persons with a wider range of kidney function, and those receiving different anti-retroviral medications to confirm these findings and evaluate the potential effects of medications of tubular secretion, and conversely the effects of tubular secretion on drug clearance in HIV. Finally, given the importance of tubule secretion for systemic clearance of a wide range of medications, the impact of these findings on drug dosing, and drug related adverse events require evaluation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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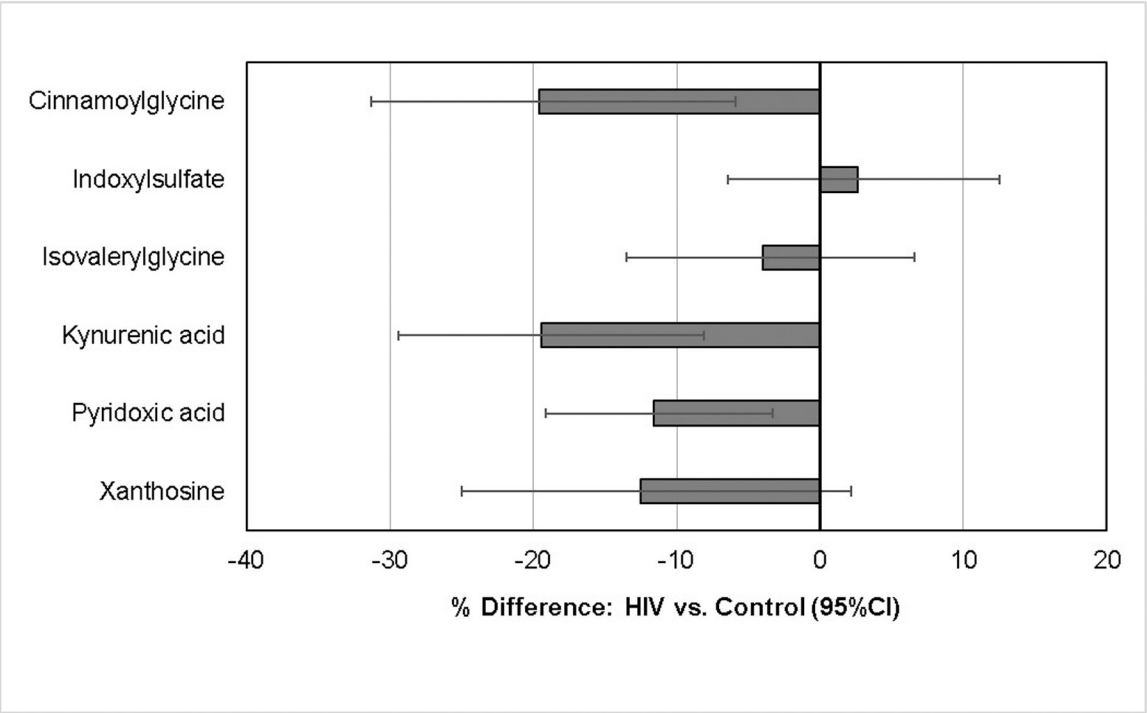

Figure 1: Adjusted difference in secretory solute clearance among WLWH compared with those without HIV.

The above figure depicts the % difference in secretory solute clearance among WLWH compared to women without HIV after adjusting for age, race, diabetes, hypertension, smoking, hepatitis-C infection, injection drug use, systolic and diastolic blood pressure. Values below the 0 indicate worse secretory solute clearance among WLWH compared with women without HIV.

Table 1:

Summary of demographic and clinical characteristics by HIV status

Parameter	WLWH N=199	No HIV N=100
Age (year)	40 (36, 45)	38 (32, 45)
Race/ethnicity		
African American	117 (59%)	60 (60%)
Other	51 (26%)	27 (27%)
White	31 (16%)	13 (13%)
Hispanic	49 (25%)	28 (28%)
Diabetes	14 (7%)	11 (11%)
Hypertension	44 (22%)	26 (26%)
Current Smoking	105 (53%)	55 (55%)
Hepatitis C	58 (29%)	18 (18%)
Injection drug use	8 (4%)	3 (3%)
Systolic BP (mmHg)	118 (106, 126)	120 (110, 130)
Diastolic BP (mmHg)	70 (64, 80)	74 (65, 80)
Albuminuria[a]	33 (17%)	14 (14%)
eGFRcr (ml/min per 1.73 m^2)	94 (75, 109)	94 (75, 108)
Current CD4 (cells/mm^3)	385 (232, 539)	
Nadir CD4 (cells/mm^3)	214 (100, 308)	
Current HIV RNA < 80 (copies/ml)	56 (29%)	
Peak HIV RNA > 10,000 (copies/ml)	164 (83%)	
HAART use	114 (58%)	

Data are presented as Median (IQR) or numbers (percent).

WLWH- women living with HIV

[a]defined urine albumin to creatinine ratio >30mg/g of creatinine

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Table 2:

Adjusted associations of traditional and HIV-related factors with secretory markers in WLWH (n=199)

	Cinnamoylglycine	Indoxylsulfate	Isovalerylglycine	Kynurenic acid	Pyridoxic acid	Xanthosine
Parameter	% Estimate (95%CI) p-value	% Estimate (95%CI) p-value	% Estimate (95%CI) p-value	% Estimate (95%CI) p-value	% Estimate (95%CI) p-value	% Estimate (95%CI) p-value
Age (per decade)	−9.4 (−22.1, 5.3) p=0.20	0.085 (−9.1, 10.2) p=0.99	−5.5 (−15.0, 5.1) p=0.30	−10.3 (−21.4, 2.3) p=0.10	−6.5 (−14.5, 2.3) p=0.14	−4.4 (−17.8, 11.2) p=0.56
African American vs. Caucasian	**52.0 (13.0, 104.5) p=0.0056**	**37.0 (12.2, 67.4) p=0.0020**	0.52 (−18.7, 24.2) p=0.96	29.3 (−0.95, 68.8) p=0.059	**39.9 (16.1, 68.5) p=0.0004**	**−26.6 (−45.9, −0.47) p=0.047**
Other/Latinx vs. Caucasian	**64.6 (19.5, 126.8) p=0.0023**	**42.5 (15.3, 76.1) p=0.0010**	11.2 (−11.1, 39.0) p=0.35	**42.5 (7.0, 89.8) p=0.015**	**50.3 (23.4, 83.1) p<.0001**	2.4 (−26.2, 42.0) p=0.89
Diabetes	**−50.0 (−66.4, −25.7) p=0.0006**	−7.3 (−28.6, 20.4) p=0.57	28.3 (−4.1, 71.6) p=0.093	−9.9 (−36.2, 27.2) p=0.55	−13.8 (−31.8, 9.0) p=0.21	−3.4 (−34.7, 43.0) p=0.86
Hypertension	6.2 (−22.0, 44.7) p=0.70	6.5 (−12.8, 30.1) p=0.53	1.95 (−18.0, 26.8) p=0.86	8.3 (−17.4, 42.1) p=0.56	5.9 (−12.0, 27.5) p=0.54	−17.4 (−39.8, 13.3) p=0.24
SBP (per 10 mmHg)	−3.7 (−12.1, 5.6) p=0.43	−5.2 (−10.7, 0.67) p=0.082	−2.4 (−8.3, 3.9) p=0.45	−5.5 (−12.7, 2.3) p=0.16	−0.15 (−5.5, 5.5) p=0.96	3.6 (−5.6, 13.7) p=0.46
DBP (per 10 mmHg)	2.3 (−9.2, 15.3) p=0.71	**10.7 (2.3, 19.7) p=0.011**	3.2 (−5.2, 12.4) p=0.46	3.5 (−6.8, 14.9) p=0.52	0.28 (−6.5, 7.6) p=0.94	3.7 (−8.0, 16.9) p=0.55
Current smoker	**52.3 (16.0, 99.9) p=0.0024**	−2.9 (−18.3, 15.4) p=0.74	0.02 (−16.9, 20.4) p=0.99	17.7 (−7.2, 49.2) p=0.18	12.0 (−5.0, 31.9) p=0.18	3.6 (−21.1, 36.1) p=0.80
Past smoker	22.7 (−8.7, 64.9) p=0.18	−8.5 (−24.1, 10.2) p=0.35	11.6 (−9.0, 37.0) p=0.29	4.4 (−19.1, 34.6) p=0.74	5.6 (−11.5, 25.9) p=0.55	−10.6 (−33.1, 19.7) p=0.45
Hepatitis C	22.9 (−3.4, 56.5) p=0.094	5.2 (−9.8, 22.5) p=0.52	−5.2 (−19.7, 11.9) p=0.53	**34.9 (9.3, 66.4) p=0.0053**	**22.0 (5.7, 40.9) p=0.0067**	24.3 (−2.4, 58.4) p=0.078
Injection drug use	24.7 (−25.6, 109.0) p=0.40	2.7 (−26.1, 42.9) p=0.87	2.5 (−28.1, 46.1) p=0.89	36.7 (−13.2, 115.2) p=0.18	9.3 (−19.6, 48.4) p=0.57	−1.9 (−41.3, 63.9) p=0.94
Current CD4 (per doubling)	9.7 (−1.62, 22.3) p=0.096	−5.2 (−11.7, 1.84) p=0.14	**−9.7 (−16.5, −2.4) p=0.010**	−3.5 (−12.3, 6.2) p=0.46	**−7.3 (−13.4, −0.78) p=0.029**	−7.5 (−17.1, 3.2) p=0.16
Nadir CD4 (per doubling)	−2.3 (−9.4, 5.4) p=0.55	3.4 (−1.66, 8.7) p=0.19	3.3 (−2.1, 9.1) p=0.24	3.0 (−3.6, 9.9) p=0.38	**5.3 (0.39, 10.5) p=0.034**	1.9 (−5.7, 10.1) p=0.63
Current HIV RNA (per 10-fold increase)	8.7 (−2.5, 21.1) p=0.13	−0.58 (−7.2, 6.5) p=0.87	−3.0 (−10.2, 4.6) p=0.43	0.29 (−8.8, 10.2) p=0.95	−2.7 (−8.8, 3.9) p=0.42	**14.7 (2.9, 27.8) p=0.013**
Peak HIV RNA (per 10-fold increase)	10.5 (−3.5, 26.4) p=0.15	1.1 (−7.3, 10.3) p=0.81	1.1 (−8.0, 11.1) p=0.82	4.7 (−7.0, 17.9) p=0.44	7.0 (−1.25, 16.0) p=0.098	**−16.1 (−26.8, −3.9) p=0.011**
eGFRcr (per 10 ml/min per 1.73 m^2)	**6.3 (0.45, 12.4), p=0.034**	**8.0 (4.3, 11.8), p<.0001**	**9.3 (5.2, 13.6), p<.0001**	4.7 (−0.20, 9.8), p=0.060	**6.4 (3.0, 9.9), p=0.0002**	3.6 (−1.88, 9.5), p=0.20

Outcomes are log-transformed; results are back-transformed to produce estimated percentage differences in biomarker attributable to each factor.

Estimates from robust multivariable linear regression models.

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Values in bold indicate a p-value <0.05

WLWH- women living with HIV

Table 3:

Association of HIV status with secretory solute clearance

Parameter		WLWH (N = 199)	No HIV (N = 100)
Cinnamoylglycine			
	Median (IQR)	209 (134, 325)	256 (185, 342)
	Mean ± SD	297±344	282±160
	Range	16, 2724	53, 1123
% Difference for HIV-infected vs. Controls (95% CI)			
Adjusted for demographics ‡		**−15.5 (−27.6, −1.46), p=0.032**	
Multivariable adjusted §		**−19.6 (−31.3, −5.9), p=0.0067**	
Multivariable adjusted § + eGFRcr		**−21.4 (−32.6, −8.4), p=0.0021**	
Indoxylsulfate			
	Median (IQR)	91 (67, 112)	90 (74, 113)
	Mean ± SD	95±44	96±40
	Range	15, 297	27, 302
% Difference for HIV-infected vs. Controls (95% CI)			
Adjusted for demographics ‡		0.40 (−8.4, 10.1), p=0.93	
Multivariable adjusted §		2.6 (−6.4, 12.5), p=0.58	
Multivariable adjusted § + eGFRcr		1.95 (−6.6, 11.3), p=0.67	
Isovalerylglycine			
	Median (IQR)	475 (358, 600)	493 (402, 637)
	Mean ± SD	519±270	529±202
	Range	89, 1906	197, 1554
% Difference for HIV-infected vs. Controls (95% CI)			
Adjusted for demographics ‡		−4.9 (−13.9, 5.2), p=0.33	
Multivariable adjusted §		−4.0 (−13.5, 6.6), p=0.44	
Multivariable adjusted § + eGFRcr		−5.6 (−15.0, 4.9), p=0.29	
Kynurenic acid			
	Median (IQR)	303 (195, 438)	348 (257, 455)
	Mean ± SD	342±190	383±170
	Range	52, 1134	92, 963
% Difference for HIV-infected vs. Controls (95% CI)			
Adjusted for demographics ‡		**−14.5 (−25.3, −2.2), p=0.023**	
Multivariable adjusted §		**−19.4 (−29.4, −8.1), p=0.0013**	
Multivariable adjusted § + eGFRcr		**−19.7 (−29.7, −8.4), p=0.0012**	
Pyridoxic acid			
	Median (IQR)	1111 (800, 1442)	1239 (1046, 1499)
	Mean ± SD	1174±748	1266±416
	Range	91, 9068	257, 2393

Parameter	WLWH (N = 199)	No HIV (N = 100)
% Difference for HIV-infected vs. Controls (95% CI)		
Adjusted for demographics ‡	**−10.2 (−18.1, −1.47), p=0.023**	
Multivariable adjusted §	**−11.6 (−19.1, −3.3), p=0.0069**	
Multivariable adjusted § + eGFRcr	**−12.0 (−19.4, −4.0), p=0.0042**	
Xanthosine		
Median (IQR)	85 (50, 133)	97 (72, 133)
Mean ± SD	100±69	112±78
Range	5, 446	4, 673
% Difference for HIV-infected vs. Controls (95% CI)		
Adjusted for demographics ‡	−13.2 (−25.7, 1.30), p=0.072	
Multivariable adjusted §	−12.5 (−25.0, 2.2), p=0.092	
Multivariable adjusted § + eGFRcr	−12.0 (−24.7, 2.7), p=0.11	

Outcome is log-transformed; results are back-transformed to produce estimated percentage differences in biomarker of HIV vs. Control.

Estimates from robust multivariable linear regression models.

‡Adjusted for age and race,

§Adjusted for age, race, diabetes, hypertension, smoking, HCV, injection drug use, SBP, and DBP.

Values in bold represent p<0.05, WLWH- women living with HIV