Title

Associations of Urine Biomarkers with Kidney Function Decline in HIV-Infected and Uninfected Men.

Journal

American journal of nephrology, 50(5)

ISSN

0250-8095

Authors

Ascher, Simon B
Scherzer, Rebecca
Estrella, Michelle M
et al.

Publication Date

2019

DOI

10.1159/000502898

Peer reviewed

Published in final edited form as:

Am J Nephrol. 2019 ; 50(5): 401–410. doi:10.1159/000502898.

Associations of urine biomarkers with kidney function decline in HIV-infected and uninfected men

Simon B. Ascher[1,2], **Rebecca Scherzer**[1], **Michelle M. Estrella**[1], **Michael G. Shlipak**[1,3], **Derek K. Ng**[4], **Frank J. Palella**[5], **Mallory D. Witt**[6], **Ken Ho**[7], **Michael R. Bennett**[8], **Chirag R. Parikh**[9], **Joachim H. Ix**[10,11], **Vasantha Jotwani**[1]

[1]Kidney Health Research Collaborative, Department of Medicine, San Francisco Veterans Affairs Medical Center and University of California, San Francisco, CA

[2]Department of Medicine, University of California, Los Angeles, CA

[3]Department of Epidemiology, and Biostatistics, University of California, San Francisco, CA

[4]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[5]Department of Medicine, Division of Infectious Disease, Northwestern University Feinberg School of Medicine, Chicago, IL

[6]Department of Medicine, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California

[7]Department of Medicine, Division of Infectious Diseases, University of Pittsburgh, Pittsburgh, PA

[8]Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

[9]Division of Nephrology, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD

[10]Division of Nephrology-Hypertension, University of California, San Diego, CA

[11]Nephrology Section, Department of Medicine, Veterans Affairs San Diego Healthcare System, San Diego, CA

Abstract

Background: HIV-infected (HIV+) persons are at increased risk of chronic kidney disease (CKD), but serum creatinine does not detect early losses in kidney function. We hypothesized that urine biomarkers of kidney damage would be associated with subsequent changes in kidney function in a contemporary cohort of HIV+ and HIV- uninfected (HIV-) men.

Corresponding Author: Vasantha Jotwani, MD; 4150 Clement Street, Bldg 2, Rm 145, San Francisco, CA, 94121, USA; P: 415-221-4810 ext. 24903; F: 415-379-5573; Vasantha.Jotwani@ucsf.edu.

Authors' contributions:

S.B.A., R.S., M.M.E., M.G.S., and V.K.J. are responsible for the research idea and study design. D.K.N. and F.J.P. are responsible for data acquisition. S.B.A, R.S., M.M.E., M.G.S., V.K.J., D.K.N., F.J.P., M.D.W., K.H., M.R.B., C.R.P., and J.H.I. are responsible for data analysis and interpretation. R.S. is responsible for statistical analysis. V.K.J. is responsible for supervision and mentorship.

Disclosure Statement:

None declared. The results presented in this paper have not been published previously in whole or part, except in abstract format.

Methods: In the Multicenter AIDS Cohort Study, we measured baseline urine concentrations of five biomarkers from 2009–2011 in 860 HIV+ and 337 HIV- men: albumin, alpha-1-microglobulin (α1m), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), and procollagen type III N-terminal propeptide (PIIINP). We evaluated associations of urine biomarker concentrations with annual changes in estimated glomerular filtration rate (eGFR) using multivariable linear mixed models adjusted for demographics, traditional kidney disease risk factors, HIV-related risk factors, and baseline eGFR.

Results: Over a median follow-up of 4.8 years, the average annual eGFR decline was 1.42 ml/min/1.73m^2/year in HIV+ men and 1.22 ml/min/1.73m^2/year in HIV-men. Among HIV+ men, the highest vs. lowest tertiles of albumin (−1.78 ml/min/1.73m^2/year, 95% CI: −3.47, −0.09) and α1m (−2.43 ml/min/1.73m^2/year, 95% CI: −4.14, −0.73) were each associated with faster annual eGFR declines after multivariable adjustment. Among HIV- men, the highest vs. lowest tertile of α1m (−2.49 ml/min/1.73m^2/year, 95% CI: −4.48, −0.50) was independently associated with faster annual eGFR decline. Urine IL-18, KIM-1, and PIIINP showed no independent associations with eGFR decline, regardless of HIV serostatus.

Conclusions: Among HIV+ men, higher urine albumin and α1m are associated with subsequent declines in kidney function, independent of eGFR.

Keywords

HIV; urine biomarker; kidney damage; alpha-1-microglobulin; albuminuria

Introduction

In the era of combination antiretroviral therapy, HIV infection has become a chronic condition in which age-related comorbidities have become more common and may occur at an earlier age (1,2). Compared to uninfected individuals, HIV-infected individuals are at higher risk of developing proteinuria, chronic kidney disease (CKD), and end-stage kidney disease (3–5). In addition, HIV-infected individuals are at increased risk of cardiovascular disease, heart failure, and mortality, which are all endpoints strongly associated with CKD (6).

Clinical practice guidelines by the HIV Medicine Association of the Infectious Diseases Society of America recommend monitoring for kidney disease with serum creatinine and urine albumin, but both tests have limitations (7). Serum creatinine, which is used to calculate an estimated glomerular filtration rate (eGFR), lacks sensitivity for detecting early reductions in kidney function in HIV-infected individuals (4,8). In addition, substantial kidney injury can occur prior to a measurable reduction in kidney function. Urine albumin is the most common clinically used kidney injury marker and reflects endothelial damage to the glomerulus. However, kidney tubular epithelial cells are a long-term reservoir site for HIV infection, and kidney biopsy studies have shown that tubular injury and interstitial fibrosis are strong predictors of CKD progression in HIV-infected and uninfected populations (9–14).

Urine alpha-1-microglobulin (α1m), a marker of proximal tubular dysfunction, interleukin-18 (IL-18) and kidney injury molecule-1 (KIM-1), markers of proximal tubular injury, and procollagen type III N-terminal propeptide (PIIINP), a marker of renal interstitial fibrosis, are promising urine biomarkers of kidney tubule health. We previously found that HIV-infected women have significantly higher urine α1m, IL-18, KIM-1, and PIIINP levels compared to uninfected women (15–17). Furthermore, we observed among HIV-infected women that higher urine albumin, α1m, IL-18, and KIM-1 levels were each associated with faster eGFR decline over eight years of follow-up (18,19). Whether or not levels of these urine biomarkers are associated with kidney function decline in a more contemporary cohort, including HIV-infected men, is unclear.

In this longitudinal study of HIV-infected and uninfected men, we evaluated associations of levels of urine biomarkers of glomerular injury (albuminuria), tubular dysfunction (α1m), tubular injury (IL-18 and KIM-1), and interstitial fibrosis (PIIINP) with subsequent changes in kidney function. We hypothesized that more extensive kidney damage, as measured by higher urine biomarker concentrations, would be independently associated with faster eGFR decline.

Materials and Methods

Study Design

The Multicenter AIDS Cohort Study (MACS) is one of the largest cohort studies of HIV-infected individuals in the United States (U.S.). The design and methods have been described previously (20). In brief, 6,972 men who have sex with men with HIV infection or at high risk for HIV infection volunteered for enrollment in 1984–1985, 1987–1990, and 2001–2003 from four sites: Baltimore, Chicago, Los Angeles, and Pittsburgh. MACS participants attend semiannual visits for follow-up evaluations that include a standardized questionnaire, a physical examination, and collection of laboratory specimens.

The MACS Kidney Study was designed as a nested cohort to investigate the development and progression of kidney disease among HIV-infected and uninfected men. This longitudinal study included all 883 HIV-infected men with urine samples collected between October 1, 2009 and September 30, 2011, and a random sample of 350 uninfected men with available urine specimens from this time period. For the present study, we excluded 36 individuals who did not have a follow-up serum creatinine measurement, leaving a final analytic sample of 1197 (860 HIV-infected and 337 HIV-uninfected).

The institutional review boards of participating institutions approved the study protocol (IRB #10–00827) and informed consent was obtained from all study participants. The University of California, San Francisco and San Francisco Veterans Affairs Medical Center committees on human research approved this study.

Predictors

We measured urine concentrations of the following biomarkers: albumin, α1m, IL-18, KIM-1, and PIIINP. All biomarkers were measured at the Cincinnati Children's Hospital Medical Center Biomarker Laboratory. Details regarding the selected commercial assays and

inter-assay coefficients of variation are shown in Supplemental Table 1. Urine specimens were refrigerated immediately after collection and centrifuged at 5,000×*g* to remove cellular debris. The supernatant was aliquoted into 1-mL vials and then stored at −80°C until biomarker measurement without prior freeze-thaw. Laboratory personnel performing the biomarker assays were blinded to participants' clinical information.

Outcomes

The primary outcome was annual mean change in eGFR, expressed in ml/min/1.73m^2 per year. We calculated eGFR using the 2009 CKD Epidemiology Collaboration (CKD-EPI) creatinine equation (21). Serum creatinine was measured semi-annually at the clinical labs of each MACS site using the modified Jaffe method, traceable to isotope dilution mass spectrometry. Our secondary outcomes included: 1) incident CKD, defined as an eGFR < 60 ml/min/1.73m^2 on two consecutive visits separated by at least 3 months with at least 1 ml/min/1.73m^2 per year decline among persons with baseline eGFR >60 ml/min/1.73m^2; and 2) annual eGFR decline ≥5% of the baseline eGFR.

Covariates

Demographics, kidney disease risk factors, and HIV-related parameters were assessed at the baseline visit, except where noted below, and included in all multivariable models. Demographic variables included age and race/ethnicity. Metabolic health variables included diabetes mellitus (defined as fasting glucose ≥ 126 mg/dL, hemoglobin A_{1c} ≥ 6.5%, or self-reported history of diabetes and diabetes medication use) and body mass index. Cardiovascular health variables included systolic and diastolic blood pressure, hypertension (defined as systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, or self-reported history of hypertension and antihypertensive medication use), self-reported cardiovascular disease, and levels of low- and high-density lipoprotein cholesterol. Behavioral health risk factors included cigarette smoking status (current, past, or never), current heroin use, hepatitis C virus (HCV) infection (confirmed by detectable plasma HCV RNA following a positive HCV antibody result). HIV infection characteristics included CD4 T-lymphocyte count/mm^3 (nadir, baseline, and time-updated), plasma HIV-1 RNA level (peak, baseline, and time-updated), history of clinical AIDS diagnosis, current TDF use, and other highly active antiretroviral therapy (HAART) use.

Statistical Analysis

The percentage of missing observations for each baseline covariate ranged from <1% to 28%. While all participants had eGFR measured at baseline, the percentage of missing eGFR increased over time, from 11% at year 1 to 53% at year 5. Because 24% of urine α1m values were below the detectable limit of the assay (0.53 mg/dL), we used a left-censored Tobit regression model to impute undetectable α1m values. For all other variables we used pattern mixture models with the neighboring-case missing values method to impute missing data, using 100 imputations to ensure high relative efficiency and reliable estimation (22–24). This method is well-suited to handle longitudinal data with dropout patterns that may not represent data that are missing at random. Imputation models included eGFR as well as all exposures and covariates listed above.

We compared demographic and baseline characteristics by HIV serostatus using $\chi 2$ and Mann-Whitney U tests for categorical and continuous variables, respectively. We analyzed levels of urine biomarkers as continuous variables (log-transformed to achieve normality of right-skewness) and as categorical variables divided into tertiles. We also analyzed urine albumin as a dichotomous variable using the standard clinical cut-point (albumin-to-creatinine ratio [ACR] ≤30 mg/g versus >30 mg/g). We modeled the associations of each urine biomarker with annual mean change in eGFR using linear mixed effect models. All models were constructed separately by HIV serostatus. We accounted for serial within-subject correlations using a first-order autoregressive moving average covariance structure, and controlled for baseline eGFR and follow-up time so that coefficients would be interpretable as annual changes in eGFR attributable to each covariate (25). We estimated adjusted risk ratios for each two-fold higher level of each baseline urine biomarker with incident CKD and annual eGFR decline ≥ 5% using Poisson regression with a robust variance estimator (26). We adjusted for urine creatinine in all models to correct for tonicity.

To determine whether levels of individual urine biomarkers were independently associated with study outcomes, multivariable models were adjusted for demographics, traditional kidney disease risk factors, and HIV-related risk factors (as listed above in the Covariates section). We also modeled all biomarkers in combination, and evaluated all pairwise and three-way biomarker combinations in order to identify markers that were simultaneously statistically significant. We performed interaction testing to evaluate whether biomarker level associations with change in eGFR differed by TDF use. Because HIV infection may have direct effects on kidney tubular health and with eGFR, we also performed interaction testing to evaluate whether biomarker level associations with change in eGFR differed by HIV RNA levels. Based on observed findings, we additionally performed interaction testing to evaluate whether urine albumin associations varied by levels of α1m.

All analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

Results

At baseline, the median age was 52 years among the 860 HIV-infected men and 54 years among the 337 uninfected men (Table 1). Compared to uninfected men, HIV-infected men had a higher baseline prevalence of eGFR < 60 ml/min/1.73 m^2 (9% vs. 4%, P<0.001) and ACR > 30 mg/g (17% vs. 8%, P<0.001). Among the HIV-infected men, 85% were using HAART and 66% were using TDF; the median CD4 lymphocyte count was 576 cells/mm^3 and 78% had undetectable HIV RNA levels. Over a median follow-up period of 4.8 years (interquartile range: 4.4 to 5.3), the average rate of annual eGFR decline was 1.42 ml/min/1.73m^2 per year (95% confidence interval [95% CI]: 1.31, 1.53) in HIV-infected men and 1.22 ml/min/1.73m^2 per year (95% CI: 0.74, 1.70) in uninfected men.

In unadjusted analyses among the HIV-infected men, higher baseline urine albumin and α1m concentrations were associated with faster annual eGFR declines (Table 2). There was minimal attenuation of these associations after multivariable adjustment for traditional and HIV-related kidney disease risk factors. When biomarker levels were analyzed as continuous variables, each two-fold higher level of urine albumin at baseline was associated with a 0.58

ml/min/1.73m^2 per year faster rate of eGFR decline in multivariable-adjusted models. Compared to participants with baseline ACR ≤ 30 mg/g, those with ACR > 30 mg/g had faster eGFR declines. In tertile analyses, the highest vs. lowest tertiles of baseline urine albumin and α1m were each associated with faster eGFR declines in multivariable-adjusted models. By contrast, IL-18, KIM-1, and PIIINP were not significantly associated with eGFR decline in unadjusted or adjusted analyses. When we modeled levels of all five urine biomarkers simultaneously, higher urine albumin remained associated with faster eGFR decline (−0.61 ml/min/1.73m^2 annually per two-fold higher urine albumin, 95% CI: −1.13, −0.09), whereas the associations of levels of other markers, including α1m, with eGFR were attenuated and had weaker associations that did not reach statistical significance.

We next modeled associations of levels of urine biomarkers with annual changes in eGFR among HIV-uninfected men. In unadjusted analyses, higher baseline urine albumin and α1m concentrations were each associated with faster annual eGFR declines (Table 3). After multivariable adjustment, ACR > 30 mg/g vs. ≤ 30 mg/g and the highest vs. lowest tertile of α1m remained significantly associated with faster eGFR declines. When modeled as a continuous variable, each two-fold higher α1m at baseline also remained independently associated with faster eGFR declines. In models including levels of all five urine biomarkers simultaneously, only α1m remained associated with faster eGFR decline (−0.86, 95% CI: −1.58, −0.15 ml/min/1.73 m^2 annually per two-fold higher α1m).

To explore effect modification between kidney tubule dysfunction and glomerular injury, we evaluated whether urine levels of α1m modified the association of urine albumin with changes in eGFR. Among men who had simultaneously elevated levels of urine albumin and α1m (Figure 1, Supplemental Table 2), rates of eGFR decline were substantially faster compared to those with lower levels (*P*-value for interaction: 0.09 in HIV-infected and 0.03 in HIV- uninfected). Among HIV-infected men, the adjusted difference in annual eGFR decline was −3.02 (95% CI: −4.81, −1.23) ml/min/1.73 m^2 per year faster among those with levels in the highest tertile of both markers (N=159) relative to participants with lower levels of both markers (N=446). In HIV-uninfected men, the adjusted difference in annual eGFR decline was −2.09 (95% CI: −4.38, 0.20) ml/min/1.73 m^2 per year faster among those with levels in the highest tertiles of both markers (N=61) relative to participants with lower levels of both markers (N=174).

Because both tenofovir exposure and HIV viremia can impact kidney tubular health, we then evaluated whether TDF use and detectable HIV RNA levels at baseline modified the associations of the urine biomarkers with changes in eGFR in HIV-infected participants. Each two-fold higher urine albumin and IL-18 at baseline were associated with faster eGFR declines among non-TDF users compared to TDF users, whereas associations of urine α1m, KIM-1, and PIIINP with eGFR decline did not differ by TDF use (Supplemental Table 3). Higher urine biomarker levels were associated with faster eGFR declines in men with detectable HIV RNA levels compared to men with undetectable HIV RNA, although differences reached statistical significance only for IL-18 (*P*=0.023). Each two-fold higher IL-18 at baseline was associated with −0.39 ml/min/1.73 m^2 per year (95% CI: −1.02, 0.24) faster eGFR decline among men with detectable HIV RNA levels and +0.42 ml/min/1.73 m^2

per year (95% CI: 0.05, 0.79) slower eGFR decline among those with undetectable HIV RNA.

Among HIV-infected participants, 98 (12%) developed incident CKD and 155 (18%) had an annual eGFR decline ≥5% over the approximately five years of follow-up. In unadjusted analyses, higher baseline urine albumin and α1m concentrations were individually associated with risks of both incident CKD and ≥5% annual eGFR decline (Table 4). However, in multivariable models that adjusted for baseline eGFR, the associations were attenuated and none remained statistically significant.

Among HIV-uninfected participants, 23 (6.8%) developed incident CKD and 22 (6.8%) had an annual eGFR decline ≥5% during follow-up. In unadjusted analyses, only higher levels of urine albumin were associated with risk of incident CKD (risk ratio per two-fold higher urine albumin: 1.34, 95% CI: 1.00, 1.79), but this association was substantially attenuated and not statistically significant after multivariable adjustment including adjustment for baseline eGFR. None of the urine biomarkers were significantly associated with risk of ≥5% annual eGFR decline among HIV-uninfected participants; unadjusted point estimates were similar to those observed in the HIV-infected participants.

Discussion

As the burden of chronic, non-infectious comorbidities accumulates in an aging HIV population, early and accurate identification of kidney disease has become increasingly important. In this large ambulatory cohort, higher urine albumin and α1m concentrations at baseline were individually associated with faster kidney function decline in HIV-infected and uninfected men, independent of baseline eGFR and kidney disease risk factors. When we adjusted for all biomarkers simultaneously, associations with kidney function decline remained significant for urine albumin in HIV-infected individuals and for urine α1m in HIV-uninfected individuals. Participants in the highest tertiles for both urine albumin and α1m had substantially faster kidney function decline, as compared with participants in the lowest tertiles for each marker. By contrast, urine IL-18, KIM-1, and PIIINP did not show statistically significant associations with eGFR changes in either HIV-infected or uninfected participants.

The associations of higher urine albumin and α1m levels with kidney function decline among HIV-infected men are consistent with previous studies (18,19,27). By contrast, the null associations with incident CKD and rapid kidney function decline may have been due to loss of information from categorizing eGFR, reduced power, or the relatively preserved kidney function of MACS participants at baseline. In the Women's Interagency HIV Study (WIHS), a large, multicenter cohort of HIV-infected women, higher urine albumin levels were associated with faster eGFR decline, and higher urine α1m levels were associated with risk of incident CKD, independent of albuminuria and baseline eGFR (18,19). Urine albumin primarily reflects glomerular injury and is an established risk factor for CKD progression (28). Our results support current HIV guidelines that recommend monitoring for kidney damage with albuminuria (7) and suggest further investigation into potential use of urine α1m for risk stratification in future studies. In contrast to albumin, α1m is a freely

filtered, low-molecular-weight protein that is fully reabsorbed by the proximal tubule; elevated levels in urine indicate dysfunction of the proximal tubule (29). Our data suggest that albuminuria and urine α1m may provide complementary information about subsequent risk of declining kidney function, but further work is needed to validate these findings.

Similar to several previous studies in the general population, our study found no significant associations of urine IL-18, KIM-1 or PIIINP levels with eGFR decline (30–33). IL-18 is a proinflammatory cytokine released by proximal tubular cells in response to injury or inflammation, while KIM-1 is upregulated and overexpressed by dedifferentiated proximal tubular cells after injury (34,35). Urine PIIINP reflects the presence of type III collagen deposits in the renal interstitium during fibrosis, and higher urine PIIINP concentrations correlate with increased severity of fibrosis on kidney biopsy (36,37). We hypothesized that higher urine IL-18, KIM-1, and PIIINP levels would be associated with kidney function decline because tubulointerstitial injury and fibrosis are strong predictors of CKD progression (9,10,13,14). Contrary to our findings, higher urine IL-18 and KIM-1 levels among HIV-infected and uninfected participants of the Women's Interagency HIV Study were independently associated with larger eGFR declines (18). Additionally, a cohort study of middle-aged, ethnically diverse men and women also showed higher levels of KIM-1 was associated with an increased risk of incident CKD (38). Among ambulatory older adults, higher urine PIIINP levels have been associated with the risk of CKD progression (39). The discrepancy between our findings and previous work in HIV-infected individuals could be explained by differences in the study population. By comparison to the Women's Interagency HIV Study, our study consisted of men who were older, had higher prevalence of diabetes mellitus and hypertension, lower prevalence of smoking and hepatitis C, and higher prevalence of HIV viral suppression. Additional studies will be required to determine the optimal subset of urinary biomarkers for prognostication and monitoring of kidney health among HIV-infected individuals.

Strengths of our study include the use of a multicenter, diverse, contemporary cohort representative of HIV-infected men in the U.S. with a follow-up period of approximately five years, assessment of levels of multiple biomarkers of kidney damage, and inclusion of a similar group of HIV-uninfected men. Our study also has several limitations. First, we were unable to estimate GFR using serum cystatin C levels, which may be a more sensitive indicator of early losses in kidney function (4). Second, urine biomarkers were measured once at baseline, so we were unable to evaluate changes in biomarker levels over time. Repeated biomarkers may produce stronger associations with kidney-related outcomes that are several years after the exposure. Third, our observational study may not have accounted for all potential confounders given the numerous risk factors for kidney disease, although these models were comprehensively constructed with numerous potential confounders. Third, our results are not generalizable to HIV-infected women or to HIV-infected individuals not on antiretroviral therapy.

In summary, we observed that higher levels of urine albumin and α1m, a marker of kidney tubule dysfunction, were associated with faster declines in kidney function in a cohort of HIV-infected and uninfected men. Further studies are needed determine the utility of

monitoring levels of biomarkers of kidney tubular health, in addition to eGFR and albuminuria, among persons living with HIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The authors thank the participants and staff of the Multicenter AIDS Cohort Study (MACS), which has centers at Baltimore (U01-AI35042): The Johns Hopkins University Bloomberg School of Public Health: Joseph B. Margolick (PI), Jay Bream, Todd Brown, Barbara Crain, Adrian Dobs, Richard Elion, Richard Elion, Michelle Estrella, Lisette Johnson-Hill, Sean Leng, Anne Monroe, Cynthia Munro, Michael W. Plankey, Wendy Post, Ned Sacktor, Jennifer Schrack, Chloe Thio; Chicago (U01-AI35039): Feinberg School of Medicine, Northwestern University, and Cook County Bureau of Health Services: Steven M. Wolinsky (PI), John P. Phair, Sheila Badri, Dana Gabuzda, Frank J. Palella, Jr., Sudhir Penugonda, Susheel Reddy, Matthew Stephens, Linda Teplin; Los Angeles (U01-AI35040): University of California, UCLA Schools of Public Health and Medicine: Roger Detels (PI), Otoniel Martinez-Maza (Co-P I), Aaron Aronow, Peter Anton, Robert Bolan, Elizabeth Breen, Anthony Butch, Shehnaz Hussain, Beth Jamieson, Eric N. Miller, John Oishi, Harry Vinters, Dorothy Wiley, Mallory Witt, Otto Yang, Stephen Young, Zuo Feng Zhang; Pittsburgh (U01-AI35041): University of Pittsburgh, Graduate School of Public Health: Charles R. Rinaldo (PI), Lawrence A. Kingsley (Co-PI), James T. Becker, Phalguni Gupta, Kenneth Ho, Susan Koletar, Jeremy J. Martinson, John W. Mellors, Anthony J. Silvestre, Ronald D. Stall; Data Coordinating Center (UM1-AI35043): The Johns Hopkins University Bloomberg School of Public Health: Lisa P. Jacobson (PI), Gypsyamber D'Souza (Co-PI), Alison, Abraham, Keri Althoff, Jennifer Deal, Priya Duggal, Sabina Haberlen, Alvaro Muoz, Derek Ng, Janet Schollenberger, Eric C. Seaberg, Sol Su, Pamela Surkan. Institute of Allergy and Infectious Diseases: Robin E. Huebner; National Cancer Institute: Geraldina Dominguez. The MACS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional co-funding from the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH). Targeted supplemental funding for specific projects was also provided by the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute on Deafness and Communication Disorders (NIDCD). MACS data collection is also supported by UL1-TR001079 (JHU ICTR) from the National Center for Advancing Translational Sciences (NCATS) a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH), Johns Hopkins ICTR, or NCATS. The funders of this study had no role in study design; collection, analysis or interpretation of data; manuscript preparation; or the decision to submit the report for publication. The MACS website is located at http://www.statepi.jhsph.edu/macs/macs.html.

Funding sources:

This work was supported by the NIA (R01AG034853 for MGS/CRP) and NIDDK (K23DK109868 for VKJ).

Statement of Ethics:

The institutional review boards of participating institutions approved the study protocol (IRB #10–00827) and informed consent was obtained from all study participants. The University of California, San Francisco and San Francisco Veterans Affairs Medical Center committees on human research approved this study.

References

1. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet. 2008 7 26;372(9635):293–9. [PubMed: 18657708]
2. Palella FJ, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 1999. 2006 9;43(1):27–34.
3. Eggers PW, Kimmel PL. Is there an epidemic of HIV Infection in the US ESRD program? J Am Soc Nephrol JASN. 2004 9;15(9):2477–85. [PubMed: 15339998]

4. Odden MC, Scherzer R, Bacchetti P, Szczech LA, Sidney S, Grunfeld C, et al. Cystatin C level as a marker of kidney function in human immunodeficiency virus infection: the FRAM study. Arch Intern Med. 2007 11 12;167(20):2213–9. [PubMed: 17998494]
5. Estrella MM, Parekh RS, Astor BC, Bolan R, Evans RW, Palella FJ, et al. Chronic Kidney Disease and Estimates of Kidney Function in HIV Infection: A Cross-Sectional Study in the Multicenter AIDS Cohort Study: JAIDS J Acquir Immune Defic Syndr. 2011 8;57(5):380–6. [PubMed: 21646913]
6. Choi AI, Li Y, Deeks SG, Grunfeld C, Volberding PA, Shlipak MG. Association between kidney function and albuminuria with cardiovascular events in HIV-infected persons. Circulation. 2010 2 9;121(5):651–8. [PubMed: 20100969]
7. Lucas GM, Ross MJ, Stock PG, Shlipak MG, Wyatt CM, Gupta SK, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis Off Publ Infect Dis Soc Am. 2014 11 1;59(9):e96–138.
8. Driver TH, Scherzer R, Peralta CA, Tien PC, Estrella MM, Parikh CR, et al. Comparisons of creatinine and cystatin C for detection of kidney disease and prediction of all-cause mortality in HIV-infected women. AIDS Lond Engl. 2013 9 10;27(14):2291–9.
9. Kassirer JP. Clinical evaluation of kidney function--glomerular function. N Engl J Med. 1971 8 12;285(7):385–9. [PubMed: 4933769]
10. Nath KA. Tubulointerstitial changes as a major determinant in the progression of renal damage. Am J Kidney Dis Off J Natl Kidney Found. 1992 7;20(1):1–17.
11. Winston JA, Bruggeman LA, Ross MD, Jacobson J, Ross L, D'Agati VD, et al. Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. N Engl J Med. 2001 6 28;344(26):1979–84. [PubMed: 11430327]
12. Ross MJ, Bruggeman LA, Wilson PD, Klotman PE. Microcyst formation and HIV-1 gene expression occur in multiple nephron segments in HIV-associated nephropathy. J Am Soc Nephrol JASN. 2001 12;12(12):2645–51. [PubMed: 11729233]
13. Wyatt CM, Morgello S, Katz-Malamed R, Wei C, Klotman ME, Klotman PE, et al. The spectrum of kidney disease in patients with AIDS in the era of antiretroviral therapy. Kidney Int. 2009 2;75(4):428–34. [PubMed: 19052538]
14. Rule AD, Amer H, Cornell LD, Taler SJ, Cosio FG, Kremers WK, et al. The association between age and nephrosclerosis on renal biopsy among healthy adults. Ann Intern Med. 2010 5 4;152(9): 561–7. [PubMed: 20439574]
15. Jotwani V, Scherzer R, Abraham A, Estrella MM, Bennett M, Devarajan P, et al. Does HIV infection promote early kidney injury in women? Antivir Ther. 2013;19(1):79–87. [PubMed: 23970313]
16. Jotwani V, Scherzer R, Estrella MM, Jacobson LP, Witt MD, Palella FJ, et al. HIV Infection, Tenofovir, and Urine α1-Microglobulin: A Cross-sectional Analysis in the Multicenter AIDS Cohort Study. Am J Kidney Dis Off J Natl Kidney Found. 2016 10;68(4):571–81.
17. Jotwani V, Scherzer R, Estrella MM, Jacobson LP, Witt MD, Palella F, et al. Association of HIV infection with biomarkers of kidney injury and fibrosis in the Multicenter AIDS Cohort Study. Antivir Ther. 2017 1 5;
18. Shlipak MG, Scherzer R, Abraham A, Tien PC, Grunfeld C, Peralta CA, et al. Urinary Markers of Kidney Injury and Kidney Function Decline in HIV-Infected Women: JAIDS J Acquir Immune Defic Syndr. 2012 12;61(5):565–73. [PubMed: 23023103]
19. Jotwani V, Scherzer R, Abraham A, Estrella MM, Bennett M, Cohen MH, et al. Association of urine α1-microglobulin with kidney function decline and mortality in HIV-infected women. Clin J Am Soc Nephrol CJASN. 2015 1 7;10(1):63–73. [PubMed: 25370597]
20. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. Am J Epidemiol. 1987 8;126(2):310–8. [PubMed: 3300281]
21. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 5 5;150(9):604–12. [PubMed: 19414839]

22. Little RJA. Pattern-Mixture Models for Multivariate Incomplete Data. J Am Stat Assoc. 1993;88(421):125–34.
23. Molenberghs G, Kenward M. Missing Data in Clinical Studies. John Wiley & Sons; 2007 529 p.
24. van Buuren S. Flexible Imputation of Missing Data [Internet]. Chapman and Hall/CRC; 2012 [cited 2018 Aug 23]. Available from: https://www.taylorfrancis.com/books/9781439868256
25. Fuller WA. Introduction to Statistical Time Series. New York: John Wiley & Sons; 1976.
26. Lumley T, Kronmal R, Ma S. Relative Risk Regression in Medical Research: Models, Contrasts, Estimators, and Algorithms. UW Biostat Work Pap Ser [Internet]. 2006 7 19; Available from: https://biostats.bepress.com/uwbiostat/paper293
27. Ando M, Yanagisawa N, Ajisawa A, Tsuchiya K, Nitta K. Kidney tubular damage in the absence of glomerular defects in HIV-infected patients on highly active antiretroviral therapy. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2011 10;26(10):3224–9.
28. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int. 2011 7;80(1): 93–104. [PubMed: 21289597]
29. Weber MH, Verwiebe R. Alpha 1-microglobulin (protein HC): features of a promising indicator of proximal tubular dysfunction. Eur J Clin Chem Clin Biochem J Forum Eur Clin Chem Soc. 1992 10;30(10):683–91.
30. Bhavsar NA, Köttgen A, Coresh J, Astor BC. Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1) as predictors of incident CKD stage 3: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis Off J Natl Kidney Found. 2012 8;60(2): 233–40.
31. O'Seaghdha CM, Hwang S- J, Larson MG, Meigs JB, Vasan RS, Fox CS. Analysis of a Urinary Biomarker Panel for Incident Kidney Disease and Clinical Outcomes. J Am Soc Nephrol JASN. 2013 11;24(11):1880–8. [PubMed: 23990678]
32. Fufaa GD, Weil EJ, Nelson RG, Hanson RL, Bonventre JV, Sabbisetti V, et al. Association of urinary KIM-1, L-FABP, NAG and NGAL with incident end-stage renal disease and mortality in American Indians with type 2 diabetes mellitus. Diabetologia. 2015 1;58(1):188–98. [PubMed: 25316431]
33. Nadkarni GN, Rao V, Ismail-Beigi F, Fonseca VA, Shah SV, Simonson MS, et al. Association of Urinary Biomarkers of Inflammation, Injury, and Fibrosis with Renal Function Decline: The ACCORD Trial. Clin J Am Soc Nephrol CJASN. 2016 8 8;11(8):1343–52. [PubMed: 27189318]
34. Parikh CR, Jani A, Melnikov VY, Faubel S, Edelstein CL. Urinary interleukin-18 is a marker of human acute tubular necrosis. Am J Kidney Dis Off J Natl Kidney Found. 2004 3;43(3):405–14.
35. Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int. 2002 7;62(1): 237–44. [PubMed: 12081583]
36. Ghoul BE, Squalli T, Servais A, Elie C, Meas-Yedid V, Trivint C, et al. Urinary procollagen III aminoterminal propeptide (PIIINP): a fibrotest for the nephrologist. Clin J Am Soc Nephrol CJASN. 2010 2;5(2):205–10. [PubMed: 20089486]
37. Soylemezoglu O, Wild G, Dalley AJ, MacNeil S, Milford-Ward A, Brown CB, et al. Urinary and serum type III collagen: markers of renal fibrosis. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 1997 9;12(9):1883–9.
38. Peralta CA, Katz R, Bonventre JV, Sabbisetti V, Siscovick D, Sarnak M, et al. Associations of urinary levels of kidney injury molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) with kidney function decline in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Kidney Dis Off J Natl Kidney Found. 2012 12;60(6):904–11.
39. Ix JH, Biggs ML, Mukamal K, Djousse L, Siscovick D, Tracy R, et al. Urine Collagen Fragments and CKD Progression-The Cardiovascular Health Study. J Am Soc Nephrol JASN. 2015 10;26(10):2494–503. [PubMed: 25655067]

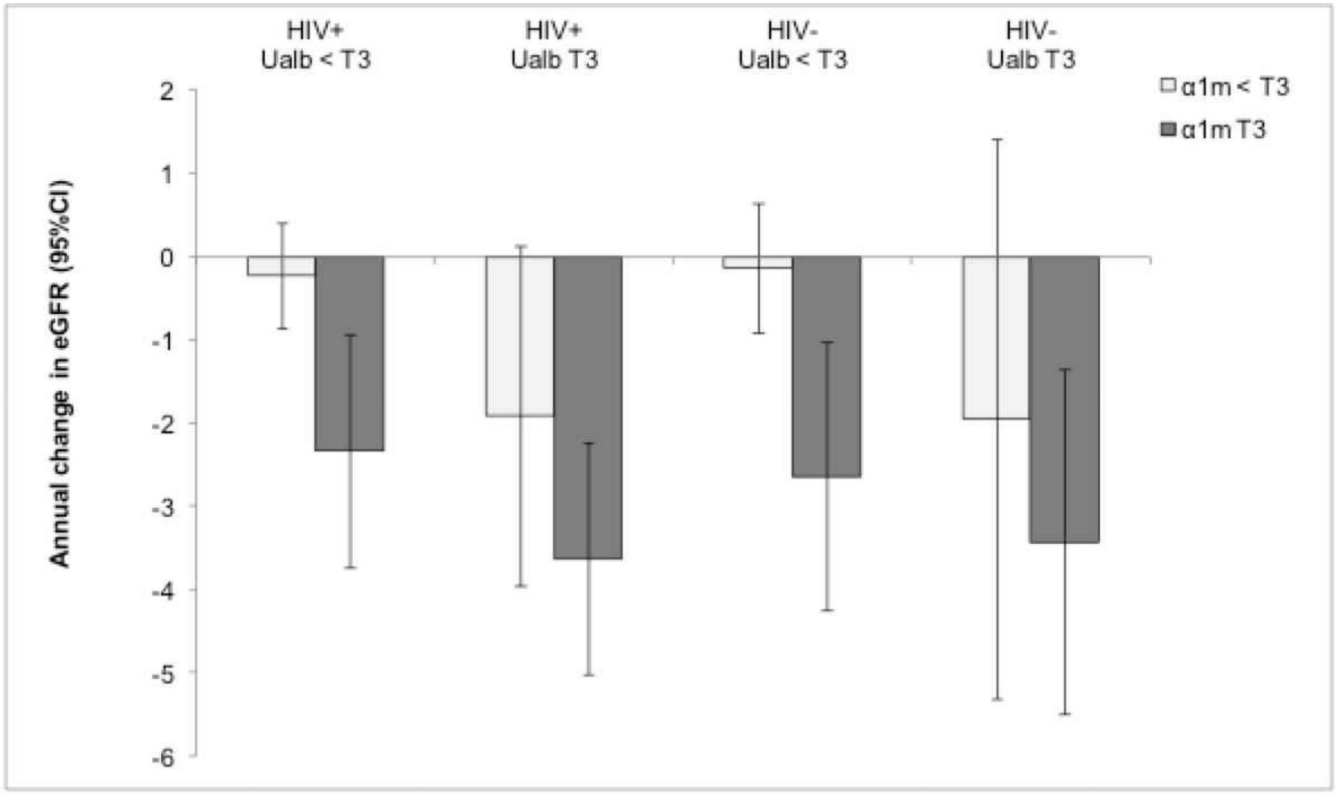

Figure 1: Annual change in eGFR across tertiles of urine albumin and α1m in HIV-infected and uninfected MACS participants

Bars represent unadjusted estimated annual change in eGFR in ml/min/1.73 m^2, with 95% confidence intervals displayed. Estimates are compared across the highest versus lower tertiles of urine albumin and α1m, and are derived from linear mixed effect models. Abbreviations: α1m, alpha-1-microglobulin; eGFR, estimated glomerular filtration rate; T3, highest tertile; < T3, first or second tertile; Ualb, urine albumin.

Table 1.

Baseline characteristics by HIV status

	HIV+ (N=860)	HIV− (N=337)	P-value
Age, y	52 (46, 58)	54 (49, 62)	<0.001
Race			
African American	264 (31%)	94 (28%)	0.15
Caucasian	526 (61%)	224 (66%)	
Other	70 (8%)	19 (6%)	
Diabetes mellitus	107 (16%)	43 (15%)	0.75
Body mass index, kg/m^2	26 (24, 30)	27 (24, 32)	0.015
Hypertension	360 (46%)	150 (47%)	0.75
History of cardiovascular disease	56 (7%)	17 (5%)	0.34
Systolic blood pressure, mmHg	126 (116, 135)	128 (117, 136)	0.14
Diastolic blood pressure, mmHg	78 (71, 84)	78 (71, 84)	0.64
LDL, mg/dL	108 (88, 132)	115 (92, 137)	0.011
HDL, mg/dL	45 (38, 55)	50 (41, 60)	<0.001
Smoking			
Current	250 (30%)	76 (23%)	0.05
Past	378 (45%)	170 (52%)	
Never	210 (25%)	82 (25%)	
Hepatitis C virus infection	83 (10%)	30 (9%)	0.69
Current heroin use	11 (1%)	4 (1%)	0.90
eGFR, ml/min/1.73m^2	91 (76, 103)	89 (78, 100)	0.71
eGFR < 60 ml/min/1.73m^2	74 (9%)	12 (4%)	0.002
Albumin-creatinine ratio > 30 mg/g	142 (17%)	28 (8%)	<0.001
HAART use	723 (85%)		
TDF use	555 (66%)		
NRTI use	728 (85%)		
NNRTI use	401 (47%)		
PI use	383 (45%)		
Current CD4, cells/mm^3	576 (411, 740)		
Nadir CD4, cells/mm^3	287 (177, 408)		
History of AIDS	123 (14%)		
Current HIV RNA > 40 copies/mL	188 (22%)		
Peak HIV RNA > 100,000 copies/mL	331 (40%)		

AIDS, acquired immunodeficiency syndrome; eGFR, estimated glomerular filtration rate; HAART, highly active antiretroviral therapy; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate.

Data are presented as median (IQR) or numbers (percent). P-values are from $\chi 2$ tests for categorical variables and Mann-Whitney U tests for continuous variables.

Table 2.

Association of urine biomarkers with annual eGFR change in HIV+ MACS participants

Biomarker	Annual eGFR change (mL/min/1.73 m^2/yr) (95% CI)	Unadjusted difference (mL/min/1.73 m^2/yr) (95% CI)	Adjusted difference* (mL/min/1.73 m^2/yr) (95% CI)
Albumin			
Continuous**		−0.63 (−1.12, −0.15)	−0.58 (−1.03, −0.12)
T1: < 0.6 mg/dL	−0.64 (−1.57, 0.29)	Reference	Reference
T2: 0.6–1.6 mg/dL	−0.73 (−1.57, 0.11)	−0.09 (−1.49, 1.31)	−0.17 (−1.54, 1.21)
T3: >1.6 mg/dL	−2.87 (−4.00, −1.73)	−2.23 (−3.97, −0.48)	−1.78 (−3.47, −0.09)
ACR ≤ 30 mg/g	−0.88 (−1.32, −0.44)	Reference	Reference
ACR > 30 mg/g	−4.02 (−5.83, −2.21)	−3.14 (−5.20, −1.08)	−3.00 (−4.88, −1.11)
α1m			
Continuous		−0.47 (−0.91, −0.02)	−0.40 (−0.87, 0.06)
T1: < 0.9 mg/dL	−0.32 (−1.33, 0.69)	Reference	Reference
T2: 0.9–2.4 mg/dL	−0.86 (−1.73, 0.01)	−0.54 (−2.02, 0.95)	−0.40 (−1.87, 1.07)
T3: >2.4 mg/dL	−3.10 (−4.04, −2.16)	−2.78 (−4.40, −1.15)	−2.43 (−4.14, −0.73)
IL-18			
Continuous		0.07 (−0.26, 0.41)	0.19 (−0.15, 0.52)
T1: < 22.9 pg/mL	−1.18 (−2.11, −0.26)	Reference	Reference
T2: 22.9–51.2 pg/mL	−1.45 (−2.31, −0.58)	−0.26 (−1.68, 1.16)	0.10 (−1.29, 1.49)
T3: > 51.2 pg/mL	−1.64 (−2.72, −0.57)	−0.46 (−2.14, 1.22)	0.31 (−1.35, 1.97)
KIM-1			
Continuous		0.03 (−0.43, 0.49)	0.13 (−0.33, 0.59)
T1: < 0.49 ng/mL	−1.20 (−2.18, −0.21)	Reference	Reference
T2: 0.49–1.02 ng/mL	−2.03 (−2.83, −1.24)	−0.84 (−2.25, 0.58)	−0.35 (−1.74, 1.04)
T3: > 1.02 ng/mL	−1.04 (−2.08, −0.00)	0.15 (−1.54, 1.84)	0.38 (−1.28, 2.03)
PIIINP			
Continuous		−0.45 (−1.09, 0.18)	−0.49 (−1.10, 0.12)

Biomarker	Annual eGFR change (mL/min/1.73 m^2/yr) (95% CI)	Unadjusted difference (mL/min/1.73 m^2/yr) (95% CI)	Adjusted difference* (mL/min/1.73 m^2/yr) (95% CI)
T1: <4.70 ng/mL	−0.71 (−1.77, 0.35)	Reference	Reference
T2: 4.70–10.09 ng/mL	−1.60 (−2.46, −0.73)	−0.88 (−2.41, 0.64)	−0.79 (−2.28, 0.69)
T3: > 10.09 ng/mL	−1.97 (−2.96, −0.97)	−1.25 (−3.01, 0.50)	−1.43 (−3.15, 0.30)

ACR, albumin-to-creatinine ratio; α1m, alpha-1-microglobulin; eGFR, estimated glomerular filtration rate; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; PIIINP, procollagen type III N-terminal propeptide Biomarkers modeled individually, not jointly.

*Adjusted for age, race/ethnicity, urine creatinine, baseline eGFR, diabetes mellitus, systolic and diastolic blood pressure, hypertension, cardiovascular disease, low- and high-density lipoprotein cholesterol levels, triglyceride level, body mass index, waist circumference, cigarette smoking status, serum albumin, current heroin use, hepatitis C virus infection, current CD4 lymphocyte count, plasma HIV-1 RNA level, history of clinical AIDS diagnosis, TDF use, and highly active antiretroviral therapy use.

**Continuous predictors are modeled per two-fold higher level of biomarker at baseline.

Table 3.

Association of urine biomarkers with annual eGFR change in HIV- MACS participants

Biomarker	Annual eGFR change (mL/min/1.73 m^2/yr) (95% CI)	Unadjusted difference (mL/min/1.73 m^2/yr) (95% CI)	Adjusted difference* (mL/min/1.73 m^2/yr) (95% CI)
Albumin			
Continuous**		−0.47 (−0.90, −0.03)	−0.22 (−0.61, 0.18)
T1: < 0.4 mg/dL	−0.24 (−1.61, 1.13)	Reference	Reference
T2: 0.4–0.9 mg/dL	−1.07 (−2.16, 0.01)	−0.83 (−2.80, 1.13)	−0.22 (−2.14, 1.71)
T3: >0.9 mg/dL	−2.35 (−3.78, −0.92)	−2.11 (−4.50, 0.28)	−0.85 (−3.12, 1.42)
ACR ≤ 30 mg/g	−0.82 (−1.34, −0.30)	Reference	Reference
ACR > 30 mg/g	−5.54 (−8.67, −2.40)	−4.72 (−8.03, −1.40)	−3.13 (−6.19, −0.08)
α1m			
Continuous		−1.15 (−1.73, −0.56)	−0.74 (−1.34, −0.14)
T1: < 0.5 mg/dL	0.69 (−0.53, 1.92)	Reference	Reference
T2: 0.5–0.9 mg/dL	−1.17 (−2.40, 0.05)	−1.87 (−3.85, 0.12)	−0.76 (−2.79, 1.26)
T3: > 0.9 mg/dL	−3.17 (−4.40, −1.95)	−3.87 (−5.86, −1.88)	−2.49 (−4.48, −0.50)
IL-18			
Continuous		−0.20 (−0.59, 0.18)	−0.04 (−0.42, 0.34)
T1: < 15.4 pg/mL	−0.40 (−1.75, 0.96)	Reference	Reference
T2: 15.4–33.6 pg/mL	−1.57 (−2.66, −0.47)	−1.17 (−3.11, 0.76)	−0.52 (−2.39, 1.35)
T3: > 33.6 pg/mL	−1.69 (−2.99, −0.38)	−1.29 (−3.52, 0.94)	−0.04 (−2.28, 2.21)
KIM-1			
Continuous		−0.19 (−0.75, 0.37)	0.02 (−0.55, 0.59)
T1: < 0.32 ng/mL	−0.87 (−2.20, 0.46)	Reference	Reference
T2: 0.32–0.85 ng/mL	−1.10 (−2.17, −0.03)	−0.23 (−2.16, 1.69)	−0.31 (−2.08, 1.46)
T3: >0.85 ng/mL	−1.68 (−2.98, −0.38)	−0.81 (−2.99, 1.37)	−0.01 (−2.13, 2.11)
PIIINP			
Continuous		0.18 (−0.60, 0.96)	0.08 (−0.67, 0.84)

Biomarker	Annual eGFR change (mL/min/1.73 m^2/yr) (95% CI)	Unadjusted difference (mL/min/1.73 m^2/yr) (95% CI)	Adjusted difference* (mL/min/1.73 m^2/yr) (95% CI)
T1: < 3.75 ng/mL	−0.98 (−2.35, 0.39)	Reference	Reference
T2: 3.75–7.99 ng/mL	−1.38 (−2.49, −0.27)	−0.40 (−2.38, 1.59)	−0.96 (−2.91, 0.98)
T3: >7.99 ng/mL	−1.29 (−2.54, −0.04)	−0.31 (−2.48, 1.86)	−0.72 (−2.85, 1.42)

ACR, albumin-to-creatinine ratio; α1m, alpha-1-microglobulin; eGFR, estimated glomerular filtration rate; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; PIIINP, procollagen type III N-terminal propeptide Biomarkers modeled individually, not jointly.

*Models adjust for age, race/ethnicity, urine creatinine, baseline eGFR, diabetes mellitus, systolic and diastolic blood pressure, hypertension, cardiovascular disease, low- and high-density lipoprotein cholesterol levels, triglyceride level, body mass index, waist circumference, cigarette smoking status, serum albumin, current heroin use, hepatitis C virus infection.

**Continuous predictors are modeled per two-fold higher level of biomarker at baseline

Table 4:

Association of urine biomarkers with rapid eGFR decline and incident CKD in HIV+ MACS participants

	Unadjusted RR (95% CI)	Multivariable-Adjusted* RR (95% CI)	Multivariable-Adjusted*+eGFR RR (95% CI)
5% annual eGFR decline (N=155/860)			
Albumin	1.16 (1.03, 1.30)	1.12 (1.00, 1.27)	1.11 (0.98, 1.25)
α1m	1.13 (1.01, 1.28)	1.12 (0.99, 1.26)	1.09 (0.97, 1.23)
IL-18	1.17 (0.96, 1.43)	1.10 (0.92, 1.33)	1.10 (0.92, 1.32)
KIM-1	1.03 (0.86, 1.230	1.00 (0.84, 1.19)	1.00 (0.85, 1.19)
PIIINP	1.05 (0.89, 1.25)	1.03 (0.87, 1.21)	1.00 (0.85, 1.17)
Incident CKD (N=98/786)			
Albumin	1.18 (1.04, 1.34)	1.16 (0.99, 1.35)	1.08 (0.96, 1.22)
α1m	1.23 (1.08, 1.40)	1.17 (1.01, 1.35)	1.09 (0.93, 1.27)
IL-18	1.11 (0.91, 1.35)	1.06 (0.87, 1.30)	1.11 (0.90, 1.37)
KIM-1	1.11 (0.92, 1.35)	1.00 (0.81, 1.23)	1.03 (0.85, 1.26)
PIIINP	1.17 (0.96, 1.43)	1.10 (0.90, 1.35)	1.04 (0.88, 1.24)

α1m, alpha-1-microglobulin; eGFR, estimated glomerular filtration rate; IL-18, interleukin-18; RR, risk ratio; KIM-1, kidney injury molecule-1; PIIINP, procollagen type III N-terminal propeptide

Biomarkers are modeled per two-fold higher level at baseline and are modeled individually, not jointly.

*Models adjust for age, race/ethnicity, urine creatinine, diabetes mellitus, systolic and diastolic blood pressure, hypertension, cardiovascular disease, low- and high-density lipoprotein cholesterol levels, triglyceride level, body mass index, waist circumference, cigarette smoking status, serum albumin, current heroin use, hepatitis C virus infection, current CD4 lymphocyte count, plasma HIV-1 RNA level, history of clinical AIDS diagnosis, TDF use, and highly active antiretroviral therapy use.