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Chronic kidney disease and estimates of kidney function in HIV infection: a cross-sectional study in the Multicenter AIDS Cohort Study

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Abstract

Background—Cystatin C has been proposed as an alternative marker of kidney function among HIV-infected persons in whom serum creatinine is affected by extra-renal factors.

Methods—In this cross-sectional study, we compared estimated glomerular filtration rates (eGFR) using serum creatinine versus cystatin C between 150 HIV-uninfected and 783 HIV-infected men. We evaluated the prevalence of chronic kidney disease (CKD; eGFR < 60 mL/min/1.73 m²) and examined the influence of extra-renal factors on GFR-estimates among HIV-infected men.

Results—Estimated GFR_{SCR} was similar by HIV serostatus, but eGFR_{CYSC} was lower in HIV-infected men. A higher proportion of HIV-infected men were classified as having CKD when using eGFR_{CYSC} versus eGFR_{SCR} (7% vs. 5%, P < 0.01). In HIV-infected individuals without CKD, eGFR_{SCR} was higher than eGFR_{CYSC} while it was lower than eGFR_{CYSC} in persons with CKD. In HIV-infected men, older age, proteinuria, and prior clinical AIDS were inversely

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Results of this study have not been previously presented in part or whole.

Competing interests

All authors declare that they have no competing interests.

Authors' Contributions

All authors played a role in editing the manuscript and approved the text. M.M.E., R.S.P. and L.P.J. designed the study. M.M.E. wrote the manuscript. M.M.E. performed the data analysis, and L.P.J. and R.S.P. assisted in the interpretation of statistical data. R.S.P., B.C.A., R.B., R.W.E., F.J.P., and L.P.J. reviewed and edited the manuscript.

associated with both GFR-estimates. Higher serum albumin levels and ACE-inhibitor/ARB use were associated with lower eGFR_{SCR}. HIV viral load, hepatitis C co-infection, and serum alkaline phosphatase were inversely associated with eGFR_{CYSC}.

Conclusion—Among HIV-uninfected and HIV-infected men of similar social risk behaviors, GFR estimates differed by biomarker and kidney function level. Estimated GFR_{CYSC} classified a larger proportion of HIV-infected men with CKD compared to eGFR_{SCR}. Differences between these GFR-estimating methods may be due to the effects of extra-renal factors on serum creatinine and cystatin C. Until GFR-estimating equations are validated among HIV-infected individuals, current GFR estimates based on these biomarkers should be interpreted with care in this patient population.

Keywords

HIV; kidney disease; serum creatinine; cystatin C; glomerular filtration rate; Multicenter AIDS Cohort Study

INTRODUCTION

Since the introduction of highly active antiretroviral therapy (HAART) in 1996, a growing number of HIV-infected individuals are now developing non immunodeficiency related chronic medical illnesses such as chronic kidney disease (CKD) (1). In the context of HIV infection, CKD develops in response to several, often simultaneous risk factors including genetic predisposition (2,3), severity of HIV infection,(4) hepatitis C virus co-infection (5), HAART-related metabolic changes (6–8), and aging (9). As a result, nearly one-third of HIV-infected individuals have renal abnormalities (10).

Among HIV-infected persons, impaired kidney function is associated with faster progression to AIDS and death (11,12), and similar to the general population, severity of kidney dysfunction is positively associated with cardiovascular disease and mortality risk. HIV-infected persons who have estimated glomerular filtration rates (eGFRs) <15 mL/min/1.73 m² experience a 6-fold greater risk of developing cardiovascular disease (13) and death compared to persons with eGFRs ≥60 mL/min/1.73 m² (12).

Given these adverse associations, current guidelines recommend that all HIV-infected persons undergo screening for CKD by serum creatinine-based eGFR (eGFR_{SCR}) (14). However, serum creatinine-based eGFRs have not been rigorously validated among HIV-infected persons and are limited by their propensity to either under- or over-estimate true GFR across the full range of kidney function. These estimates are also particularly biased in HIV-infected individuals due to abnormalities in muscle mass and nutrition (15,16), liver disease (17), and exposure to several medications that alter urinary creatinine handling or serum creatinine measurement (18,19). Therefore, interest has focused on an alternative indicator of kidney function, serum cystatin C. Cystatin C is produced constantly by almost all human cells, is freely filtered by renal glomeruli and nearly completely metabolized by renal tubules. In addition, serum cystatin C is generally thought to be unaffected by lean muscle mass and thus a more accurate marker of kidney disease (20). Recent studies conducted in the general population, however, demonstrate that serum cystatin C is also dependent on age, sex, and race like creatinine (21). To account for these extra-renal influences, the CKD-Epidemiology Collaboration developed a cystatin C-based eGFR equation adjusted for age, sex, and race (22).

Identification of impaired kidney function in the HIV-infected population often mandates changes to antiretroviral dosing, work-up for the etiology of kidney dysfunction, and initiation of CKD management strategies. Therefore, understanding additional factors which

alter serum creatinine and cystatin C and subsequently the estimates of kidney function is necessary for the clinical interpretation of GFR estimates in this high-risk population. In this study, we compared serum creatinine and cystatin C-based estimates of kidney function among HIV-uninfected and HIV-infected men with similar lifestyle and risk behaviors in the Multicenter AIDS Cohort Study (MACS). In addition, we sought to compare the prevalence of CKD among HIV-infected participants using the serum creatinine versus cystatin C-based estimates of GFR and evaluate the impact of extra-renal factors on these GFR estimates.

METHODS

Study Population

The MACS is an ongoing prospective cohort study of HIV-uninfected and HIV-infected men in four U.S. urban areas (23). A total of 6,972 men have been enrolled. Participants underwent semi-annual standardized interviews, physical examinations, and collection of blood and urine for laboratory testing and storage in repositories. The Institutional Review Board of each center approved the study protocols.

Our investigation was a cross-sectional study of HIV-uninfected and HIV-infected men. All participants had to have serum creatinine and urine protein excretion measured and stored serum available for cystatin C measurements at visits 45 (n=194) or 46 (n=739), corresponding with the calendar periods of March 20, 2006 to November 3, 2006 and September 12, 2006 to April 14 2007, respectively. HIV-uninfected were chosen randomly among those who had the above three components. A total of 150 HIV-uninfected and 783 HIV-infected men were included. Our sub-study was approved by the Johns Hopkins Institutional Review Board.

Estimation of Kidney Function

To standardize serum creatinine values which were previously measured by the modified Jaffe method across study sites, we re-measured serum creatinine on frozen samples in a separate, representative subset of 150 participants from corresponding visits. Secondary serum creatinine was analyzed enzymatically on the Roche ModP instrument (Roche Diagnostics Corp, Indianapolis, IN) at the University of Minnesota (Minneapolis, MN) in conjunction with National Institute of Standards and Technology SRM 967 reference materials traceable to isotope dilution mass spectrometry analysis. The original values were calibrated to standardized serum creatinine using errors-in-variables regression. The original serum creatinine values highly correlated with standardized values ($r=0.96$). Calibrated serum creatinine was used for this study. Serum cystatin C was measured on frozen samples using an automated particle-enhanced nephelometric assay (N Latex Cystatin C, Dade Behring, Deerfield, IL) run on the Dade Behring BN 100 Nephelometer. Serum creatinine-based eGFR was calculated using the CKD-EPI equation which adjusts for age and race according to the serum creatinine level (24). Serum cystatin C-based eGFR was calculated using the equation developed by the CKD-Epidemiology Collaboration ($eGFR_{CYSC} = 127.7 \times \text{serum cystatin C}[\text{mg/L}]^{-1.17} \times \text{age}[\text{y}]^{-0.13} \times 1.06$ if black) (22). An eGFR <60 mL/min/1.73m² was used to define CKD (25). Urine protein and creatinine were measured from untimed samples, and their ratio was used to estimate proteinuria. A ratio >200 mg/g defined proteinuria (25).

Extra-Renal Factors

Age, race, and history of injection drug use were self-reported. Interviews included questions regarding AIDS-defining illnesses and were confirmed through medical record review. Weight was measured using a standardized protocol and calibrated scales. Body mass index (BMI) was calculated from weight and height measurements. Diabetes mellitus

was defined as a fasting glucose concentration ≥ 126 mg/dL or a self-reported diabetes diagnosis with self-reported use of anti-diabetic medication. Hypertension was defined by a measured systolic blood pressure >140 mm Hg, or diastolic blood pressure >90 mm Hg, or self-reported hypertension diagnosis with self-reported use of anti-hypertensive medication. Dyslipidemia was defined as a fasting total cholesterol >200 mg/dL, triglyceride >150 mg/dL, high-density lipoprotein <50 mg/dL, or self-reported use of lipid-lowering medication.

HIV infection was determined by positive serum antibody tests. Use of antiretroviral drugs, co-trimoxazole, angiotensin-converting enzyme inhibitor (ACEi), and angiotensin receptor blocker (ARB) were assessed at each visit along with medications taken since the last visit. Antiretroviral drugs were subdivided into three classes: 1) nucleoside/nucleotide reverse transcriptase inhibitors (NRTI); 2) non-nucleoside reverse transcriptase inhibitors (NNRTI); and 3) protease inhibitors (PI). The definition of HAART was guided by the U.S. Department of Health and Human Services guidelines (26). The duration of HAART exposure was calculated for individuals exposed to HAART.

CD4⁺ cell counts were measured using standardized flow cytometry. Plasma HIV-1 RNA levels were measured using an ultrasensitive RNA polymerase chain reaction assay. Hepatitis C virus infection was based on a positive hepatitis C virus antibody serostatus and a detectable RNA level. Serum albumin levels were measured using a kinetic colorimetric method while liver enzymes were measured enzymatically. CRP levels were measured using a high-sensitivity nephelometric assay, and were carried forward from the prior visits over a median period of 1.4 years (interquartile range [IQR]: 1.2 – 1.5 years) if they were missing (n=164).

Statistical methods

Statistical analyses were performed using Stata/MP 11 (StataCorp LP, College Station, TX). Variables with skewed distributions were log₁₀-transformed. Variables were compared using Student's t-test or Wilcoxon rank-sum test and chi-square or Fisher exact test, as appropriate. Bland-Altman plots depicting the average of log₁₀-eGFR_{SCR} (X) and log₁₀-eGFR_{CYSC} (Y) versus their difference were used to evaluate the agreement between the two methods among HIV-infected men. We calculated the slope and intercept of the linear regression of the difference (X–Y) on the average of the two methods ($[X+Y]/2$) to evaluate the ratio of the standard deviations (SD) of X and Y and assess bias, respectively (27). The analyses were stratified by eGFR_{SCR} <60 and ≥ 60 mL/min/1.73 m². Influential points were determined by evaluating both their leverages and residuals and were excluded. The agreement between eGFR_{SCR} and eGFR_{CYSC} in classifying individuals with CKD was evaluated using the κ -statistic with 95% confidence intervals (CI) determined by bootstrapping. Unadjusted and adjusted linear regression models were constructed to evaluate the association of extra-renal factors with each GFR-estimating method, presented as percent change in eGFR. Factors which were significant at P-values <0.10 in unadjusted analysis were included in the adjusted model.

RESULTS

Clinical characteristics of HIV-uninfected and HIV-infected men are presented in Table 1. Compared with HIV-uninfected participants, a greater proportion of HIV-infected men were co-infected with hepatitis C and had elevated liver enzymes. The two groups were similar with regard to other risk factors for CKD such as diabetes and hypertension. HIV-infected men had a lower median BMI and a higher median CRP level. Co-trimoxazole use was noted only among HIV-infected men. Among HIV-infected participants, 15% previously received HAART; 73% were currently receiving HAART. The median duration of HAART receipt was 4.03 years (interquartile range [IQR]: 2.90–13.71 years) and 8.21 years (IQR:

4.42–9.79 years) among prior and current HAART-users, respectively. Although both HIV-uninfected and HIV-infected men had similar levels of kidney function by $eGFR_{SCR}$, HIV-infected men had lower $eGFR_{CYS}$. A greater proportion of HIV-infected participants had proteinuria compared to HIV-uninfected men (17% versus 2%, respectively; $P < 0.01$).

Comparison of kidney function estimates

The agreement between the two GFR estimates for CKD classification was only moderate ($\kappa = 0.53$, 95% CI: 0.40, 0.65). The proportion of HIV-infected men with CKD was higher by $eGFR_{CYS}$ compared with $eGFR_{SCR}$ (7% versus 5%, respectively; $P < 0.01$). When we defined CKD based on $eGFR_{SCR}$, $eGFR_{SCR}$ was generally 9% higher than $eGFR_{CYS}$ among HIV-infected men without CKD ($P < 0.01$) (Figure 1A); the degree of discordance between the two GFR estimates varied by level of kidney function (P for equality of SDs < 0.01). Conversely, $eGFR_{SCR}$ was generally 7% lower than $eGFR_{CYS}$ among HIV-infected men with kidney dysfunction ($P < 0.01$) (Figure 1B).

Clinical factors which influence $eGFR_{SCR}$ and $eGFR_{CYS}$ and therefore CKD classification in the context of HIV infection are displayed in Tables 2 and 3, respectively. In general, fewer clinical factors were associated with $eGFR_{SCR}$ than $eGFR_{CYS}$ in unadjusted analyses. In adjusted analyses, older age, history of clinical AIDS and ACEi or ARB use, higher serum albumin, and proteinuria were associated with lower $eGFR_{SCR}$. With the exception of ACEi or ARB use and serum albumin, $eGFR_{CYS}$ was associated with the same factors. In addition, $eGFR_{CYS}$ was lower with hepatitis C co-infection, higher HIV viral loads, and higher serum alkaline phosphatase levels. In contrast to $eGFR_{SCR}$, cystatin C-based GFR estimates were affected by race, with African Americans having nearly 3% higher $eGFR_{CYS}$ levels compared with persons of other ethnicities.

DISCUSSION

In a large population of HIV-uninfected and HIV-infected men of similar social risk behaviors, we demonstrated that GFR estimates differed by the biomarker used and by kidney function level. Estimates of GFR based on serum cystatin C differed by HIV status. Among HIV-infected men, estimates of GFR based on serum cystatin C classified a larger proportion of individuals with moderate to severe CKD compared with GFR estimates based on serum creatinine. These discordant classifications are clinically relevant as drug dosing and the institution of a multitude of CKD management strategies are advocated at the threshold of $eGFR$ below 50 to 60 mL/min/1.73m² by national guidelines (25).

The differences between these two GFR-estimating methods and therefore CKD classification reflect the differential factors associated with the respective biomarkers. We observed that more clinical factors correlated with $eGFR_{CYS}$ than $eGFR_{SCR}$, supporting ongoing concerns of cystatin C's utility as an uninfluenced biomarker of kidney function. Since HIV infection can be accompanied by systemic inflammation and multiple non-AIDS co-morbidities that may alter markers of kidney function independently of kidney function, our study is an important step in understanding the relationship of these concurrent factors with indicators of renal function among HIV-infected persons and may help with interpretation of GFR estimates in this patient population.

Similar to prior studies, we demonstrated that HIV-infected individuals have higher serum cystatin C levels compared with social and demographically similar HIV-uninfected individuals (28,29). Whether these elevated serum cystatin C levels in HIV-infected persons necessarily reflect decrements in kidney function, however, remains unclear. In the Study of Fat Redistribution and Metabolic Change (FRAM) study, HIV-infected individuals who had traditional CKD risk factors (older age, higher baseline or greater increase in HIV RNA

levels, higher serum glucose levels, and dyslipidemia) were more likely to have a decline in $eGFR_{CYSC}$ (30). Conversely, individuals with improved HIV RNA levels had improvement in $eGFR_{CYSC}$. While these findings by Longenecker and colleagues suggests that elevated serum cystatin C levels seen in HIV-infected individuals may be explained by subclinical kidney disease, our data suggest that additional factors occurring in HIV-infected persons are differentially associated with serum creatinine and cystatin C, and thus their corresponding estimates of kidney function. While some clinical factors, such as age and proteinuria, were consistent in their influence across GFR-estimating methods, others factors affected only one or the other method. For example, ACEi or ARB use and higher serum albumin levels were inversely associated with $eGFR_{SCR}$ but not $eGFR_{CYSC}$; in this context, ACEi or ARB use may reflect a drug-related reduction in true GFR via vasodilatation of the renal efferent arteriole or may serve as a surrogate for hypertension, a risk factor for CKD. On the other hand, serum albumin's effect on serum creatinine may be reflective of one's nutritional state and protein stores rather than kidney function. Prior studies comparing various GFR-estimating equations to an exogenous indicator of GFR have shown that both $eGFR_{SCR}$ and $eGFR_{CYSC}$ are considerably biased (-10 to -29 mL/min/1.72 m²) in HIV-infected persons (31). Moreover, Barraclough and colleagues demonstrated that cystatin C-based estimates of kidney function were less accurate than those based on serum creatinine, with 41% versus 89% falling within 30% of the measured GFR, respectively (31,32). These studies, however, consisted of no more than 30 participants, limiting their generalizability to the HIV-infected population at large. While our study also underscores the need for large studies which rigorously validate GFR-estimating equations in the HIV-infected population, clinicians currently rely on available GFR-estimating equations (which were developed in studies excluding HIV-infected persons) to inform management of their HIV-infected patients. Therefore, recognition and understanding of extra-renal factors which affect these estimates are important in the application of these GFR-estimating equations to HIV-infected persons.

Our study has several limitations to consider. Results of the agreement between $eGFR_{SCR}$ and $eGFR_{CYSC}$ should be interpreted cautiously at the extremes of $eGFR$ since we had few individuals with either very high or low $eGFR$ s; therefore, these results may have been unduly influenced by the few participants at the $eGFR$ extremes. In addition, we relied upon only one time point for GFR estimation. Our calibration of the original serum creatinine values to standardized serum creatinine across sites may have introduced bias or additional measurement error which may have affected our results; however, the high correlation and excellent agreement between the original and repeated serum creatinine values across sites indicate that these potential effects were minimal. A systematic downward drift in cystatin C values due to changes in the assay has been noted since the development of the CKD-EPI $eGFR_{CYSC}$ equation (33). This may have led to an underestimation of the CKD prevalence based on $eGFR_{CYSC}$ in our study. Direct comparisons of cystatin C concentrations from our study to previous studies of HIV-infected populations should account for the change in the assay over time.

Kidney function estimates based on serum creatinine versus cystatin C differentially classified individuals with CKD. This discordance in identifying some individuals with CKD may be due to the effects of extra-renal factors on both serum creatinine and cystatin C. Until GFR-estimating equations are rigorously validated among HIV-infected individuals, current estimates of kidney function based on these biomarkers should be interpreted cautiously in this patient population in light of these potential extra-renal influences.

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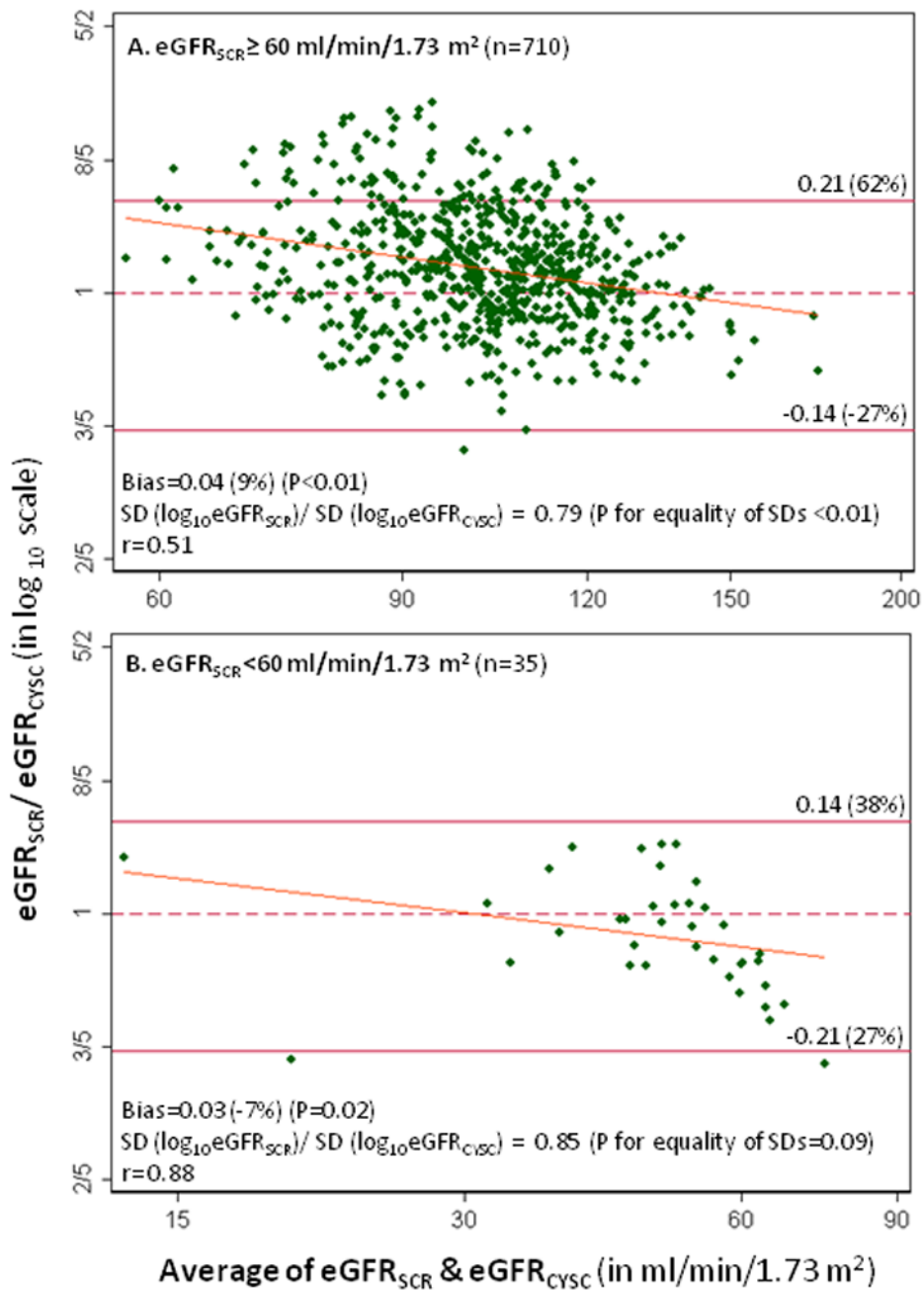


Figure 1.

Bland-Altman plots of the average vs. the difference between \log_{10} -transformed $eGFR_{SCR}$ and $eGFR_{CYSC}$ among HIV-infected men with $eGFR_{SCR} \geq 60$ (A) and $eGFR_{SCR} < 60 \text{ mL/min/1.73 m}^2$ (B). The diagonal lines are the slope of the linear regression of the difference on the mean of $eGFR_{SCR}$ and $eGFR_{CYSC}$. Thirty-six and two influential points were excluded in Panels A and B, respectively.

Table 1

Demographic and clinical characteristics of HIV-uninfected and infected men

Characteristics	HIV Serostatus		P-value
	Uninfected (n=150)	Infected (n=783)	
Black, n (%)	52 (35)	261 (33)	0.77
Median age, y (IQR)	47(41–57)	47 (42 – 53)	0.46
Injection drug use, n (%)	1 (<1)	18 (2)	0.34
Hepatitis C co-infection, n (%)	6 (4.0)	75 (10)	0.03
Diabetes, n (%)	11 (10)	75 (13)	0.53
Hypertension, n (%)	52 (38)	270 (37)	0.85
Hypercholesterolemia, n (%)	113 (75)	564 (72)	0.43
ACEi or ARB use, n(%)	20 (13)	108 (14)	0.88
Co-trimoxazole, n(%)	0 (0)	58 (7)	<0.01
Median BMI, kg/m ² (IQR)	26.9 (23.9 – 29.6)	24.9 (22.7 – 27.8)	<0.01
Median CD4 ⁺ cell count, cells/mm ³ (IQR)	---	511 (348 – 695)	---
Median HIV-1 RNA level, copies/mL (IQR)	---	<50 (<50 – 1830)	---
Median CRP level, mg/L (IQR)	0.9 (0.5 – 2.5)	1.5 (0.7 – 3.6)	0.01
Median serum albumin, g/dL (IQR)	4.5 (4.3 – 4.7)	4.4 (4.2 – 4.6)	0.02
Median AST, U/L (IQR)	22 (18 – 26)	25 (21 – 33)	<0.01
Median ALT, U/L (IQR)	22 (17–19)	25 (19–37)	<0.01
Medianalkaline phosphatase, U/L (IQR)	68 (57 – 80)	80 (64 – 102)	<0.01
Median serum creatinine, mg/dL (IQR)	1.0 (0.9 – 1.1)	0.9 (0.7 – 1.0)	0.41
Median serum cystatin C, mg/L (IQR)	0.76 (0.70 – 0.85)	0.85 (0.75 – 0.98)	<0.01
Median eGFR _{SCR} , mL/min/1.73m ² (IQR)	103.1 (91.0 – 117.9)	105.2 (91.3 – 118.8)	0.78
Median eGFR _{CYSC} , mL/min/1.73m ² (IQR)	108.0 (92.5 – 124.0)	94.6 (80.2 – 110.3)	<0.01
Median urine PCR, mg/g (IQR)	60 (50–83)	98 (68 – 159)	<0.01

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine transaminase; eGFR_{SCR}, serum creatinine-based estimated glomerular filtration rate; eGFR_{CYSC}, cystatin C-based estimated glomerular filtration rate, PCR, protein-to-creatinine ratio

Table 2
Unadjusted and adjusted associations of serum creatinine-based eGFR with extra-renal factors

Variable	Unadjusted % change in eGFR _{SCr} (95% CI)	P-value	Adjusted % change in eGFR _{SCr} (95% CI)	P-value
Age, per 10-y increase	-4.71 (-5.37, -4.06)	<0.001	-4.11 (-4.92, -3.29)	<0.001
Black vs. non-black	3.94 (2.42, 5.47)	<0.001	1.05 (-0.55, 2.67)	0.20
History of clinical AIDS	-8.02 (-10.17, -5.82)	<0.001	-5.44 (-7.46, -3.38)	<0.001
History of hypertension	-5.07 (-6.46, -3.67)	<0.001	-1.21 (-2.88, 0.48)	0.16
History of hypercholesterolemia	-3.00 (-4.50, -1.47)	<0.001	0.67 (-0.98, 2.37)	0.42
Use of ACEi or ARB vs. neither	-8.51 (-10.53, -6.44)	<0.001	-2.82 (-5.08, -0.51)	0.02
HIV-1 RNA, per 1-log increase	1.20 (0.55, 1.85)	<0.001	3.47 (-0.25, 9.56)	0.26
C-reactive protein, per 1 mg/L increase	-0.22 (-0.35, -0.08)	0.002	-0.08 (-0.20, 0.04)	0.20
Serum albumin, per 1 g/dL increase	-1.81 (-3.66, 0.07)	0.06	-4.79 (-6.73, -2.82)	<0.001
Proteinuria, per 100 mg/g increase	-1.18 (-0.13, -0.10)	<0.001	-1.03 (-1.25, -0.81)	<0.001

Abbreviations: eGFR_{SCr}, serum creatinine-based estimated glomerular filtration rate; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

Table 3
Unadjusted and adjusted associations of serum cystatin C-based GFR with extra-renal factors

Variable	Unadjusted % change in eGFR _{CYS} C (95% CI)	P-value	Unadjusted % change in eGFR _{CYS} C (95% CI)	P-value
Age, per 10-y increase	-4.23 (-4.99, -3.47)	<0.001	-3.76 (-4.69, -2.82)	<0.001
Black vs. non-black	2.57 (0.89, 4.28)	0.003	2.62 (0.76, 4.51)	0.006
History of clinical AIDS	-7.55 (-10.12, -5.33)	<0.001	-3.50 (-5.88, -1.05)	0.005
History of hypertension	-3.98 (-5.73, -2.22)	<0.001	-1.01 (-2.91, 0.92)	0.30
Hepatitis C infected vs. uninfected	-3.37 (-4.72, -2.00)	<0.001	-2.22 (-3.62, -0.84)	0.002
Use of ACEi or ARB vs. neither	-8.51 (-10.53, -6.44)	<0.001	-2.22 (-4.81, 0.45)	0.10
CD4 cell count, per 100 cells/mm ³	0.57 (0.25, 0.89)	<0.001	0.14 (-0.18, 0.46)	0.40
HIV-1 RNA, per 1-log increase	-1.53 (-2.22, -0.84)	<0.001	-1.84 (-2.56, -1.11)	<0.001
C-reactive protein, per 1mg/L increase	-0.25 (-0.40, -0.09)	0.001	-0.09 (-0.22, 0.04)	0.21
Serum albumin, per 1 g/dL increase	5.70 (3.35, 8.10)	<0.001	1.69 (-0.73, 4.19)	0.17
AST, per 100 U/L increase	-0.03 (-0.06, -0.01)	0.005	3.54 (-0.50, 7.75)	0.09
ALT, per 100 U/L increase	-0.03 (-0.05, <0.01)	0.04	-2.71 (-6.61, 1.36)	0.19
Alkaline phosphatase, per 100 U/L increase	-0.07 (-0.09, -0.04)	<0.001	-3.92 (-6.38, -1.39)	0.003
Proteinuria, per 100 mg/g increase	-0.01 (-0.02, -0.01)	<0.001	-0.92 (-1.18, -0.65)	<0.001

Abbreviations: eGFR_{CYS}C, serum cystatin C-based estimated glomerular filtration rate; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; ALT, alanine transaminase