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Comparisons of creatinine and cystatin C for detection of kidney disease and prediction of all-cause mortality in HIV-infected women

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Abstract

Background—Cystatin C could improve chronic kidney disease (CKD) classification in HIV-infected women relative to serum creatinine.

Design—Retrospective cohort analysis.

Methods—Cystatin C and creatinine were measured from specimens taken and stored during the 1999–2000 exam among 908 HIV-infected participants in the Women's Interagency HIV study (WIHS). Mean follow-up was 10.2 years. The associations of baseline categories (<60, 60–90, and >90 mL/min/1.73m^2) of creatinine eGFR ($eGFR_{cr}$), cystatin C eGFR ($eGFR_{cys}$), and combined creatinine-cystatin C eGFR ($eGFR_{cr\text{-}cys}$) with all-cause mortality were evaluated using multivariable Cox regression. The net reclassification index (NRI) was calculated to evaluate the effect of cystatin C on reclassification of CKD staging.

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Conflicts of interest: None declared.

Results—The prevalence of CKD (eGFR<60) at baseline was higher with $eGFR_{cys}$ (10.1%) compared to $eGFR_{cr}$ (6.7%, p=0.0006) and $eGFR_{cr\text{-}cys}$ (7.5%, p=0.011). Relative to eGFR >90, the eGFR <60 category by $eGFR_{cys}$ (Adjusted HR: 2.56; 95% CI: 1.63, 4.02), $eGFR_{cr\text{-}cys}$ (3.11; 1.94–5.00), and $eGFR_{cr}$ (2.34; 1.44–3.79) was associated with increased mortality risk. However, the eGFR 60–90 category was associated with increased mortality risk for $eGFR_{cys}$ (1.80; 1.28–2.53) and $eGFR_{cr\text{-}cys}$ (1.91; 1.38–2.66) but not $eGFR_{cr}$ (1.20; 0.85–1.67). The overall NRI for mortality was 26% when reclassifying from $eGFR_{cr}$ to $eGFR_{cys}$ (p<0.001) and was 20% when reclassifying from $eGFR_{cr}$ to $eGFR_{cr\text{-}cys}$ (p<0.001).

Conclusion—Cystatin C detected a higher prevalence of CKD relative to creatinine and improves CKD staging relative to creatinine by reclassifying individuals at the highest mortality risk to lower eGFR categories.

Keywords

Creatinine; Cystatin C; Glomerular Filtration Rate; HIV; Mortality; Kidney; Women

Introduction

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines advocate for estimating glomerular filtration rate (GFR) with serum cystatin C in situations where serum creatinine is unreliable.[1] HIV infection is such a situation because of unpredictability in muscle mass.[2] As HIV survival increases, chronic kidney disease (CKD) is becoming increasingly common among HIV-infected individuals.[3–7] HIV-infected individuals have a 10-fold greater risk of end-stage renal disease (ESRD) and a 5-fold higher prevalence of microalbuminuria compared with uninfected persons.[8, 9] Detecting the presence of CKD is important in HIV-positive populations given the association of CKD with increased mortality risk and its potential impact on treatments, such as tenofovir.[10] While decreased creatinine-based glomerular filtration rate (GFR) is associated with adverse health outcomes in individuals with HIV,[4, 11–13] it may be an imperfect marker of kidney function because it is influenced by factors related to muscle mass, which is reduced in HIV infection.[14, 15]

The non-GFR determinants of serum creatinine have made serum cystatin C an alternative for estimating kidney function. In the general population, serum cystatin C shows stronger associations than serum creatinine with cardiovascular disease (CVD) and all-cause mortality.[16–19] In the HIV-infected population, serum cystatin C concentrations are elevated relative to HIV-negative persons, whereas creatinine levels are similar, thus potentially detecting changes in kidney function missed by creatinine.[20] Additionally, one study found that both cystatin C-based estimated glomerular filtration rate ($eGFR_{cys}$) <60 mL/min/1.73m^2 and albuminuria are independently associated with 2-fold increased risks of all-cause mortality, while creatinine eGFR ($eGFR_{cr}$) is not.[21]

While existing studies indicate that cystatin C may be superior to creatinine for detecting CKD and mortality risk in HIV patients, it has not been well studied in multiple high-risk populations, including women with HIV. We designed this study within the Women's Interagency HIV Study (WIHS) to address the following objectives: a) to compare mortality associations among eGFR categories based on cystatin C, creatinine, and combined creatinine-cystatin C; b) to compare eGFR values between HIV-infected and uninfected participants using each marker; c) to evaluate characteristics associated with differential eGFR based on creatinine versus cystatin C; and d) to evaluate the effect of cystatin C on reclassification of CKD stages.

Methods

The WIHS is the longest observational study of HIV in U.S. women. The WIHS study design and methods have been described previously.[22, 23] In brief, 3,766 women (2,791 HIV-infected and 975 HIV-uninfected) were enrolled in either 1994–1995 (n=2,623) or 2001–2002 (n=1,143) from 6 sites (Bronx/Manhattan, Brooklyn, Chicago, Los Angeles, San Francisco and Washington, DC). HIV-infected women were recruited to be representative of HIV-infected women in each community. HIV-uninfected women were recruited from similar venues. Participants are interviewed and examined every six months.

For this nested cohort study, all HIV-infected women with available urine and serum specimens had their serum cystatin C, serum creatinine, and urine albumin and creatinine levels measured; these measures were also conducted among 289 representative participants without HIV infection. All specimens had been collected between October 1999 and March 2000 and stored in a −80°C freezer. Mean (SD) follow-up was 10.2 ± 2.4 years. WIHS was approved by the institutional review boards at all study sites. This study of kidney injury was also approved by the relevant committees on human research.

Primary predictors in this study were GFR estimates from serum creatinine, cystatin C, and combined creatinine and cystatin C. Creatinine measures were conducted at the clinical labs of each WIHS site at the time of collection. We estimated GFR using the 2009 CKD-EPI equation for creatinine ($eGFR_{cr}$).[24] Cystatin C was measured by a particle-enhanced immunoturbidometric assay (Gentian, Moss Norway), which has been calibrated against the new World Standard Reference material ERM-DA471/IFCC.[25] Intra-assay coefficients of variation for cystatin C based on 10 replicates were <2% at serum concentrations of 0.7 and 1.1 mg/L, and inter-assay coefficients of variation were 4.4% and 3.9% at serum concentrations of 0.8 and 2.2 mg/L, respectively. We estimated GFR using the 2012 CKD-EPI equations for cystatin C ($eGFR_{cys}$) and creatinine plus cystatin C ($eGFR_{cr\text{-}cys}$) which includes age, race and sex variables.[26, 27] In order to show stability of results, we conducted sensitivity analyses using the MDRD equation.[28]

Other characteristics included in multivariate analyses were demographic characteristics, traditional risk factors for CVD and CKD, and HIV-specific clinical factors; all were measured concurrently with the eGFR measures, except for CD4+ count and HIV-viral load, which were time-updated. The following characteristics were tested as candidate covariates in all multivariate models: age and race/ethnicity; antihypertensive use, diabetes (fasting glucose ≥126mg/dL, self-reported diabetes, self-reported diabetes medication use, or HbA1c ≥6.5%), cigarette smoking (current, former, never), menopause status, systolic and diastolic blood pressures, fasting LDL and HDL cholesterol, triglycerides, urinary albumin to creatinine ratio (ACR), body mass index (BMI), and waist circumference. We also tested the following HIV-related characteristics: hepatitis C virus (HCV) infection (confirmed by detectable HCV RNA following a positive HCV antibody result at or near the baseline WIHS enrollment visit), current heroin use, current CD4+ lymphocyte count, nadir CD4+ lymphocyte count, history of AIDS diagnosis, current HIV viral load, current highly active antiretroviral therapy (HAART) use, current nucleoside reverse transcriptase inhibitor (NRTI) use, current non-nucleoside reverse transcriptase inhibitor (NNRTI) use, and current protease inhibitor (PI) use. There was no use of tenofovir at the 1999–2000 WIHS visit, which is the baseline for this analysis.

All cause mortality was assessed via the WIHS protocol, which includes review of death certificates obtained from medical records and local health departments when the study staff became aware of a death. Additionally, National Death Index (NDI)-Plus searches were performed annually for all WIHS participants who were known to have died or to have been

lost to study follow-up. Patients were followed up until death, the end of the follow-up period in December 2007, or until the last completed study visit.

We began our analyses by comparing the baseline characteristics of HIV-infected and HIV-uninfected participants. The associations of $eGFR_{cr}$, $eGFR_{cys}$, and $eGFR_{cr\text{-}cys}$, with all-cause mortality were assessed initially using spline analyses. We tested the linearity assumption for the relationship of eGFR with mortality by examining generalized additive models.[29] Because eGFR showed non-linear associations with mortality, we then categorized each eGFR as <60, 60–90, and >90mL/min/1.73m^2. We used multivariate proportional hazards models to determine the associations of $eGFR_{cr}$, $eGFR_{cys}$, and $eGFR_{cr\text{-}cys}$ categories with time to all-cause mortality; the multivariable Cox models were unadjusted and then adjusted for other risk factors. Plots of the Schoenfeld residuals and formal tests suggested no violation of the proportional hazards assumption. We selected covariates using a stepwise backward selection with a significance level of α=0.05 to remove candidate covariates that were not associated with the outcome. As an alternative model building approach, we used Bayesian model averaging and retained predictors with posterior probabilities >35%.[30] Models constructed using the two approaches were very similar. Multiple imputation with the Markov chain Monte Carlo method was used to impute missing covariates, with 5 imputations to yield approximately 95% relative efficiency.[31] The percentage of observations with missing covariates ranged from less than 1% to 15%.

We next compared each GFR estimate among participants with and without HIV infection. To determine the association of HIV-infection with kidney function cross-sectionally, we used age-adjusted linear regression. Because the findings appeared to differ by race, we repeated the analyses among HIV-infected participants, stratified by Black and White race.

Based on the above analyses, we investigated characteristics that were associated with different results in estimated GFR values. We constructed multivariate linear regression models with the raw difference of $eGFR_{cys}$-$eGFR_{cr}$ or $eGFR_{cr\text{-}cys}$-$eGFR_{cr}$ as the outcome. Candidate covariates were chosen from those listed above and retained in the final model as previously described.

Finally, we evaluated whether reclassifying HIV-infected participants' $eGFR_{cr}$ values with either $eGFR_{cys}$ or $eGFR_{cr\text{-}cys}$ would improve risk classification. Using cut points of <60, 60–90, and >90 mL/min/1.73m^2 based on creatinine and cystatin C, we considered reclassifications by cystatin C as appropriate if deceased participants were reclassified to a lower eGFR stage or if surviving participants were reclassified to a higher eGFR stage. Conversely, reclassifications by cystatin C were deemed inappropriate if deceased participants were reclassified to a higher eGFR category or if surviving participants were reclassified to a lower eGFR category. Overall improvement in reclassification based on cystatin C was calculated by the net reclassification improvement (NRI).[32, 33] We used chi-squared tests to determine if differences in risk classification were statistically significant.

Bayesian model averaging was performed using the BMA package for the R statistical computing language (R Development Core Team, Vienna, Austria). All other analyses were conducted using the SAS system, version 9.2 (SAS Institute, Inc., Cary, NC).

Results

A total of 908 HIV-infected women and 289 HIV-uninfected women were studied. Demographic, CVD risk factors, anti-retroviral therapies, and HIV disease study measures are shown in Table 1. Hepatitis C virus infection and albuminuria prevalence were higher in the HIV-infected women than in the HIV-uninfected women (Table 1).

Among HIV-infected WIHS participants, graphical examination of the association of eGFR with all-cause mortality suggested that only $eGFR_{cr}$ levels below 70 mL/min/1.73m^2 were linearly associated with higher mortality risks. In contrast, $eGFR_{cys}$ showed a strong, linear inverse association with higher mortality risk across the full range. $eGFR_{cr\text{-}cys}$ showed a similar association with all cause mortality, although the association appeared to be slightly weaker than for $eGFR_{cys}$ (Figure 1). We next categorized the eGFR of HIV-infected women as <60, 60–90, and >90 mL/min/1.73m^2 using each equation (Table 2). Relative to an $eGFR_{cr}$ >90 mL/min/1.73m^2, having an $eGFR_{cr}$ < 60 was associated with a 2-fold adjusted mortality risk, while the association in the 60–90 category was not statistically significant. In contrast, the adjusted mortality risks in the $eGFR_{cys}$ categories of <60 and 60–90 mL/min/1.73m^2, were 2.5-fold and 2-fold, respectively. When using combined $eGFR_{cr\text{-}cys}$, 3-fold and 2-fold adjusted mortality risks were observed for the <60 and 60–90 mL/min/1.73m^2 categories, respectively.

We next compared eGFR between HIV-infected and HIV-uninfected women, stratified by race. In both races, HIV-infected and uninfected women showed similar levels of $eGFR_{cr}$ (age-adjusted difference for Blacks: 2.8 mL/min/1.73m^2, p=0.086; for Whites: 0.0 mL/min/1.73m^2, p=0.99). By contrast, HIV infection was associated with lower $eGFR_{cys}$ in both races (age-adjusted difference for Blacks: −11.1 mL/min/1.73m^2, p<0.0001; for Whites: −10.0 mL/min/1.73m^2, p=0.0084). Moderately lower $eGFR_{cr\text{-}cys}$ values were also observed in HIV-infected individuals (age-adjusted difference for Blacks: −4.7 mL/min/1.73m^2, p=0.0010; for Whites: −5.8 mL/min/1.73m^2, p=0.028). Of note, both Black and White HIV-infected individuals had similar baseline $eGFR_{cys}$, while baseline $eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$ were approximately 10 mL/min/1.73m^2 and 6 mL/min/1.73m^2 higher in HIV-infected Black women when compared to Whites, respectively (see Figure, Supplemental Digital Content 1, which shows the association of HIV infection with median eGFR levels at baseline, stratified by race).

Given these differences among the HIV-infected women, we next investigated risk factors associated with differences in eGFR using the three equations. Demographic factors that are included in the GFR equations were associated with significant differences: older age was associated with higher estimated $eGFR_{cys}$ relative to $eGFR_{cr}$, whereas Black race was associated with lower $eGFR_{cys}$. CVD risk factors including larger waist circumference and current smoking were associated with lower $eGFR_{cys}$, whereas higher HDL was associated with higher $eGFR_{cys}$ relative to $eGFR_{cr}$. Three indices of worse HIV status – higher viral load, lower CD4+ count, and HCV co-infection – were associated with significantly lower $eGFR_{cys}$ relative to $eGFR_{cr}$. Findings were similar with the combined equation, but the magnitude of the effect sizes were smaller (Table 3).

Given the differential GFR estimates, we investigated if mortality risk classification would be improved by using $eGFR_{cys}$ or $eGFR_{cr\text{-}cys}$ instead of $eGFR_{cr}$. When eGFR was recalculated using cystatin C instead of creatinine, we found that 34% of those with $eGFR_{cr}$>90 and 14% of those with $eGFR_{cr}$ 60–90 mL/min/1.73m^2 were reclassified downward. Conversely, 33% and 45% were reclassified upward in the 60–90 and <60 mL/min/1.73m^2 $eGFR_{cr}$ categories, respectively. Findings were similar with the combined equation, but the percentages reclassified were smaller (see Figure, Supplemental Digital Content 2, which illustrates the effect of reclassifying participants from $eGFR_{cr}$ to $eGFR_{cys}$ or $eGFR_{cr\text{-}cys}$ categories). for the mortality endpoint, the overall NRI of converting CKD staging from $eGFR_{cr}$ to $eGFR_{cys}$ was 26%, while the NRI was 20% when converting from $eGFR_{cr}$ stages to $eGFR_{cr\text{-}cys}$ stages (Table 4).

Sensitivity analyses with the MDRD equation produced similar results (see Tables, Supplemental Digital Content 3–5 and Figures, Supplemental Digital Content 6–7, which

show the results of the sensitivity analyses with the MDRD equation). The associations of MDRD eGFR categories with mortality were similar to those with the CKD-EPI creatinine equation. The MDRD equation produced a moderately larger race gradient with MDRD $eGFR_{cr}$ being 7.8 and 4.5 mL/min/1.73m^2 higher than $eGFR_{cys}$ and $eGFR_{cr\text{-}cys}$, respectively. Finally, when converting from CKD staging based on the MDRD equation to either $eGFR_{cys}$ or $eGFR_{cr\text{-}cys}$, the overall NRI values were slightly larger than those associated with the CKD-EPI equation, 31.1% and 23.8%, respectively.

Discussion

In this cohort of HIV-infected and HIV-uninfected women, $eGFR_{cys}$ and $eGFR_{cr\text{-}cys}$ were associated with all-cause mortality over a wider range of kidney function than $eGFR_{cr}$ and identified a higher prevalence of CKD in HIV-infected women. Both the serum cystatin C and combined creatinine-cystatin C eGFR were associated with all-cause mortality risk in the pre-CKD stages (eGFR 60–90 mL/min/1.73m^2), whereas $eGFR_{cr}$ only detected the mortality risk in those with established CKD. HIV infection was associated with lower eGFR when estimated from $eGFR_{cys}$ and $eGFR_{cr\text{-}cys}$ but not by $eGFR_{cr}$. When exploring characteristics associated with differences between $eGFR_{cys}$ and $eGFR_{cr}$, we found that Black race and most established risk factors for CKD were associated with lower eGFR values by cystatin C-containing equations. In aggregate, these findings suggest that cystatin C is likely to be a more sensitive and accurate measure of kidney function than creatinine in HIV-infected women.

The associations of cystatin C with mortality have been previously observed. Studies in the general population have shown that $eGFR_{cys}$ is more strongly associated with CVD and mortality than $eGFR_{cr}$.[16–19] In the study of Fat Redistribution and Metabolic Change in HIV infection (FRAM), a predominantly male cohort, both $eGFR_{cys}$ <60 mL/min/1.73m^2 and albuminuria were independently associated with a doubling of all-cause mortality, while $eGFR_{cr}$ showed little association with mortality risk.[21] Our findings extend this association to HIV-infected women in WIHS. We found that $eGFR_{cr}$ <60 mL/min/1.73m^2 was associated with a 2-fold mortality risk; however, a stronger association of $eGFR_{cys}$ with mortality risk was observed, which appeared linear throughout the distribution.[34] Recently, the combined creatinine-cystatin C equation has been reported to be the most accurate eGFR equation in studies with measured GFR; we observed similar associations of $eGFR_{cr\text{-}cys}$ and $eGFR_{cys}$ with mortality risk, although the NRI was larger for $eGFR_{cys}$ because more participants were re-classified appropriately. [26]

The second major finding was that the association of HIV-infection with reduced kidney function differs strikingly by GFR estimate. As we had previously observed in the FRAM study, HIV-infected participants had lower kidney function than HIV-uninfected participants, when estimated by cystatin C, but had no significant difference in kidney function when estimated by creatinine.[20] Similarly, within the Nutrition for Healthy Living (NFHL) cohort, HIV-infected individuals had significantly lower serum creatinine levels than HIV-uninfected individuals, but had a higher prevalence of CKD when defined by cystatin C ($eGFR_{cys}$ <60 mL/min/1.73m^2).[35] The association of HIV infection with kidney function was similar with the new combined creatinine-cystatin C equation, but somewhat smaller than seen with $eGFR_{cys}$. Given the strong association of HIV infection with ESRD risk and albuminuria, we believe that the cystatin C results are more likely to be accurate.[8, 9, 36] Among Black women, our findings are especially concerning because their $eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$ levels were 10 mL/min/1.73m^2 and 6 mL/min/1.73m^2 higher than their White HIV-infected counterparts, respectively. Blacks have substantially higher ESRD risk than Whites, regardless of HIV infection status. As a result, cystatin C is likely to be a less biased measure than creatinine, particularly in Blacks, since the equations for both

$eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$ require race adjustments that inflate eGFR, but $eGFR_{cys}$ has no race coefficient.[8, 9, 24, 36, 37]

To further explore these two markers, we conducted analyses to evaluate determinants of differential $eGFR_{cys}$ or $eGFR_{cr\text{-}cys}$ versus $eGFR_{cr}$ values. Age was associated with lower $eGFR_{cr}$ than $eGFR_{cys}$ and $eGFR_{cr\text{-}cys}$ values, perhaps because the creatinine CKD-EPI equation has a larger age coefficient than the cystatin C CKD-EPI equation.[24, 26] All remaining characteristics associated with lower $eGFR_{cys}$ and $eGFR_{cr\text{-}cys}$ values relative to $eGFR_{cr}$ are known risk factors for kidney disease. Therefore, patients at the highest risk of kidney disease are the most likely to have $eGFR_{cr}$ values that may overestimate kidney function relative to $eGFR_{cys}$ and $eGFR_{cr\text{-}cys}$.

There may be clinical implications to our findings for the treatment of HIV-infected women. Our findings are consistent with recommendations from the recently released 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines that state: “we suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate.”[1] Cystatin C may be useful to improve CKD staging and prognosis in HIV-infected persons. Based on our findings, using $eGFR_{cys}$ to screen HIV-infected women without CKD by $eGFR_{cr}$ would identify approximately 7% with CKD by cystatin C, making the number needed to screen approximately 14 to detect an additional case of CKD. Cystatin C or creatinine-cystatin C eGFR values could assist in selection of antiretroviral therapy, specifically, by avoiding nephrotoxic drugs such as tenofovir or atazanavir in those with kidney impairment.[10] $eGFR_{cys}$ or $eGFR_{cr\text{-}cys}$ could also assist with dosing of medications, could more accurately risk-stratify HIV-infected patients for procedures, could inform appropriate exposure to contrast agents, and could identify persons in whom nephrotoxic medications, such as non-steroidal anti-inflammatory drugs, should be avoided.[38–40]

An important limitation of this study is the lack of measured GFR in the study population; to our knowledge, there have been no studies comparing mortality associations of $eGFR_{cys}$, $eGFR_{cr\text{-}cys}$, or $eGFR_{cr}$ with measured GFR in HIV-infected women.[27, 41, 42] The serum creatinine concentrations were measured at multiple sites, which could introduce measurement variability. We also lacked specific causes for the deaths in our study. The generalizability of this study is limited by our findings being exclusively in women, though we observed similar results in the predominantly male FRAM cohort.

Conclusion

Detecting the presence of CKD is important in the HIV-infected population given its association with increased mortality risk and potential impact on treatment choices. In this cohort of HIV-infected women, serum cystatin C estimates of GFR were more strongly associated with mortality risk and appeared more sensitive in detecting reduced kidney function than the current clinical standard, $eGFR_{cr}$. Additionally, those at the highest risk of kidney disease were most likely to have higher eGFR by creatinine relative to eGFR by cystatin C, and thus to be at risk for having undetected CKD. These findings suggest that cystatin C may provide a better measure of kidney function than creatinine in HIV-infected women and should be considered as a complement to creatinine in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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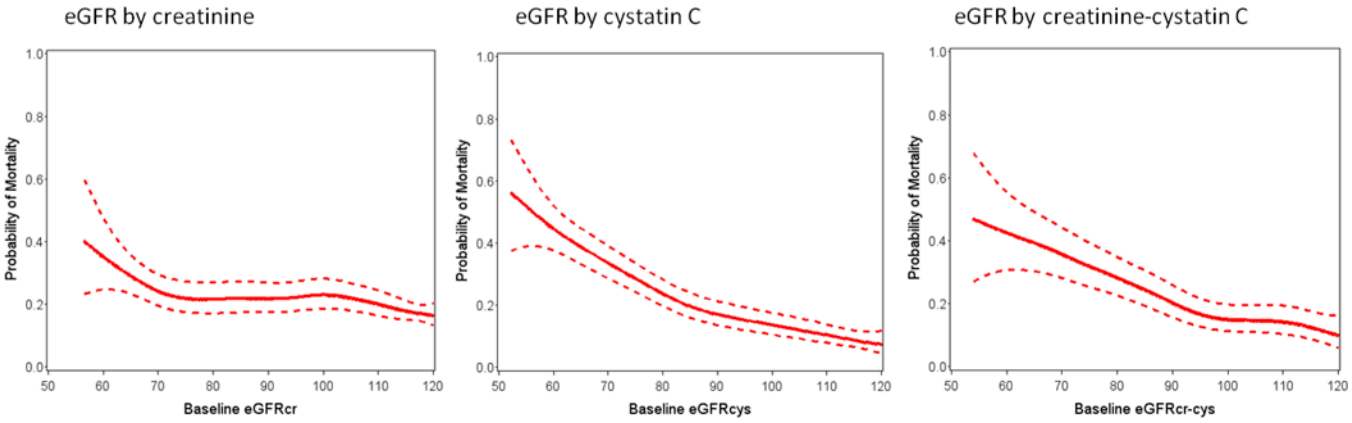

Figure 1. Association of Baseline eGFR with Mortality among HIV-infected WIHS participants

Solid lines denote the predicted probability of mortality (with dotted 95% CI bounds) calculated from unadjusted generalized additive models. The lowest 5% of eGFR values and all above 120 are truncated.

Table 1

Baseline characteristics of HIV-infected and uninfected women

Parameter		HIV-infected (N = 908)	HIV-uninfected (N = 289)	P-value
Baseline Age (y)		41 (36–46)	40 (34–45)	0.0086
Race				
African American		524 (58%)	178 (62%)	0.0058
Caucasian		175 (19%)	33 (11%)	
Other		209 (27%)	78 (27%)	
Menopause		185 (21%)	40 (14%)	0.0076
Cigarette smoking				
Current		464 (51%)	170 (59%)	0.071
Past		224 (25%)	62 (21%)	
Never		220 (24%)	57 (20%)	
Diabetes mellitus		86 (9%)	26 (9%)	0.91
Systolic BP (mmHg)		118 (108–129)	120 (110–131)	0.0076
Diastolic BP (mmHg)		72 (66–80)	73 (68–80)	0.31
Hypertension		228 (25%)	80 (28%)	0.40
Antihypertensive use		98 (11%)	35 (12%)	0.52
LDL (mg/dL)		103 (80–132)	104 (86–129)	0.30
HDL (mg/dL)		44 (36–56)	51 (42–62)	<.0001
TG (mg/dL)		133 (93–196)	101 (73–150)	<.0001
BMI (kg/m^2)		27 (23–31)	29 (24–34)	<.0001
Waist Circ (cm)		88 (80–99)	93 (80–104)	0.0064
Current HAART use		533 (59%)		
Current NRTI use		606 (67%)		
Current NNRTI use		246 (27%)		
Current PI use		381 (42%)		
Current CD4		397 (245–576)		
Nadir CD4		212 (109–326)		
History of AIDS		445 (49%)		
Plasma HIV RNA:	≤80	276 (31%)		
	81–1999	204 (23%)		
	2000–9999	147 (16%)		
	>10000	275 (30%)		
Hepatitis C		281 (31%)	62 (22%)	0.0021
Current heroin use		43 (5%)	23 (8%)	0.053
Albuminuria *		183 (20%)	29 (10%)	<.0001

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

Abbreviations: NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

* Defined as urine albumin-creatinine ratio >30mg/g

Table 2

Association of baseline eGFR with all-cause mortality in HIV-infected WIHS participants

	Total Number	Death rate (per 1,000 person-years) (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Creatinine				
• >90 mL/min/1.73m^2	694	18.9 (15.7, 22.7)	Reference	Reference
• 60–90 mL/min/1.73m^2	154	23.5 (18.3, 30.1)	1.25 (0.92, 1.71), p=0.15	1.20 (0.85, 1.67), p=0.30
• < 60 mL/min/1.73m^2	60	43.6 (29.2, 65.0)	2.53 (1.62, 3.95), p<.0001	2.34 (1.44, 3.79), p=0.0006
Cystatin C				
• >90 mL/min/1.73m^2	479	11.3 (8.8, 14.6)	Reference	Reference
• 60–90 mL/min/1.73m^2	337	28.5 (23.3, 34.8)	2.59 (1.87, 3.58), p<.0001	1.80 (1.28, 2.53), p=0.0007
• < 60 mL/min/1.73m^2	92	59.4 (44.7, 79.1)	5.78 (3.93, 8.49), p<.0001	2.56 (1.63, 4.02), p<.0001
Creatinine-Cystatin C				
• >90 mL/min/1.73m^2	524	13.4 (10.7, 16.8)	Reference	Reference
• 60–90 mL/min/1.73m^2	316	30.1 (24.6, 36.8)	2.29 (1.69, 3.11), p<.0001	1.91 (1.38, 2.66), p=0.0001
• < 60 mL/min/1.73m^2	68	53.8 (38.1, 76.1)	4.44 (2.93, 6.74), p<.0001	3.11 (1.94, 5.00), p<.0001

* Fully adjusted Cox models control for age, ethnicity, traditional kidney risk factors†, and HIV-related risk factors‡ (all measured at baseline, except for CD4+ count and HIV RNA, which are time-updated)

† Traditional kidney risk factors include smoking, hypertension, diabetes, and ACR

‡ HIV-related risk factors include CD4+ count, HIV RNA, and HCV

Table 3

Factors associated with difference between $eGFR_{cys}$ and $eGFR_{cr}$ or $eGFR_{cr\text{-}cys}$ and $eGFR_{cr}$ among WIHS HIV-infected participants.

Selected Model:	**Adjusted difference in mL/min/1.73m^2 ($eGFR_{cys}$-$eGFR_{cr}$) (95% CI)**	**Adjusted difference in mL/min/1.73m^2 ($eGFR_{cr\text{-}cys}$-$eGFR_{cr}$) (95%CI)**
Demographic factors:		
Age (per decade)	5.5 (3.5, 7.5), p<0.001	1.51 (0.54, 2.5), p=0.0023
Black vs. White	−5.6 (−10.4, −0.86), p=0.021	−2.3 (−4.4, −0.10), p=0.039
Cardiovascular disease risk factors:		
Current Smoker	−6.7 (−9.9, −3.5), p<0.001	−3.8 (−5.3, −2.2), p<0.0001
SBP (per 10 mmHg)	−1.26 (−2.5, −0.01), p=0.049	N/A*
Hypertension	N/A*	−2.2 (−4.3, −0.070), p=0.042
HDL (per 10 mg/dL)	1.65 (0.41, 2.9), p=0.0056	0.72 (0.18, 1.26), p=0.0068
Waist Circumference (per 10 cm)	−1.71 (−2.8, −0.59), p=0.0028	−0.96 (−1.50, −0.42), p=0.0005
HIV-related factors:		
Current CD4 < 200 cells/mcL	−6.6 (−11.0, −2.3), p=0.0028	−3.6 (−5.8, −1.41), p=0.0013
HIVRNA (per 10-fold increase)	−4.5 (−6.4, −2.6), p<0.001	−2.4 (−3.2, −1.63), p<0.0001
HCV	−7.8 (−11.9, −3.6), p=0.0002	−4.7 (−6.6, −2.8), p<.0001

Adjusted for standard clinical measures including age, ethnicity, traditional cardiovascular risk factors†, and HIV-related risk factors‡ (all measured at baseline, except for CD4+ count and HIV RNA, which are time-updated)

† Traditional cardiovascular risk factors include smoking, hypertension, HDL, and waist circumference

‡ HIV-related risk factors include CD4+ count, HIV RNA, and HCV

* Excluded from model (not statistically significant)

Table 4

Appropriateness of reclassifying participants from $eGFR_{cr}$ to $eGFR_{cys}$ or $eGFR_{cr\text{-}cys}$ among HIV-infected WIHS participants

	eGFRcys	**eGFRcr-cys**
Participants deceased	201	201
Appropriately reclassified (as higher risk)	86 (42.8%)	53 (26.4%)
No change	97 (48.3%)	142 (70.7%)
Inappropriately reclassified (as lower risk)	18 (9.0%)	6 (3.0%)
NRI (95% CI), Cases	33.8% (23.9%, 43.8%), p<.0001	23.4% (15.9%, 30.9%), p<.0001
Participants alive	707	707
Inappropriately reclassified (as higher risk)	152 (21.5%)	73 (10.3%)
No change	461 (65.2%)	583 (82.5%)
Appropriately reclassified (as lower risk)	94 (13.3%)	51 (7.2%)
NRI (95% CI), Non-cases	8.2% (3.9%, 12.6%), p=0.0002	3.1% (0.0%, 6.2%), p=0.048
Overall NRI (95% CI)	25.6% (14.8%, 36.5%), p<.0001	20.3% (12.2%, 28.4%), p<.0001

* NRI = net reclassification index