Published in final edited form as:

Am J Kidney Dis. 2010 November ; 56(5): 872–882. doi:10.1053/j.ajkd.2010.05.019.

Cystatin C, Albuminuria, and 5-Year All-Cause Mortality in HIV-Infected Persons

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Abstract

Background—Compared with controls, HIV-infected persons have a greater prevalence of kidney disease as assessed by high levels of cystatin C and albuminuria, but not as assessed by creatinine level. However, the clinical importance of elevated cystatin C and albuminuria in the HIV-infected population has not been studied.

Study Design—We conducted an observational cohort study to determine the association of kidney disease (measured by albuminuria, cystatin C, and serum creatinine) with mortality.

Setting & Participants—922 HIV-infected persons enrolled in the FRAM (Fat Redistribution and Metabolic Change in HIV infection) study.

Predictor—Serum cystatin C and serum creatinine were used to estimate glomerular filtration rate (eGFR). Albuminuria was defined as a positive urine dipstick ($\geq 1+$) or a urine albumin-creatinine ratio > 30 mg/g.

Outcome—5-year mortality

Results—At baseline, reduced kidney function ($\text{eGFR}_{\text{SCysC}} < 60$ mL/min/1.73m²) or albuminuria was present in 28% of participants. After five years of follow-up, mortality was 48% among those with both $\text{eGFR}_{\text{SCysC}} < 60$ mL/min/1.73m² and albuminuria, 23% in those with $\text{eGFR}_{\text{SCysC}} < 60$ mL/min/1.73m² alone, 20% in those with albuminuria alone, and 9% in those with neither condition. After multivariable adjustment for demographics, cardiovascular risk factors, HIV-related factors, and inflammatory markers, $\text{eGFR}_{\text{SCysC}} < 60$ mL/min/1.73m² and albuminuria were associated with nearly a twofold increase in mortality, whereas $\text{eGFR}_{\text{SCr}} < 60$ mL/min/1.73m² did

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not appear to have any substantial association with mortality. Together, $\text{eGFR}_{\text{SCysC}} < 60 \text{ mL/min/1.73m}^2$ and albuminuria accounted for 17% of the population-level attributable risk for mortality.

Limitations—Vital status was unknown in 261 participants from the original cohort.

Conclusions—Kidney disease marked by albuminuria or increased cystatin C levels appears to be an important risk factor for mortality in HIV-infected individuals. A substantial proportion of this risk may be unrecognized because of the current reliance on serum creatinine to estimate kidney function in clinical practice.

Keywords

kidney disease; mortality; HIV infection

HIV-infected persons now achieve near normal life spans with successful antiretroviral therapy.¹ The aging HIV-infected population faces a new set of challenges that have extended therapeutic goals beyond the treatment of HIV replication and AIDS-related illnesses. Many studies have found that HIV-infected persons are at greater risk for metabolic complications leading to premature, non-AIDS related conditions such as kidney disease. HIV-infected individuals have a 6-fold increased prevalence of impaired kidney function, a 5-fold increased prevalence of albuminuria, and a 10-fold greater risk of end-stage renal disease (ESRD), compared with HIV-uninfected controls.^{2–4}

Cystatin C is an alternative measure of kidney function approved by the Food and Drug Administration that has been found to be a more sensitive test than creatinine for the diagnosis of kidney disease in several populations.^{5–9} Elevated cystatin C also predicts the development of kidney disease, cardiovascular outcomes, and all-cause mortality more accurately than creatinine-based measures in HIV-uninfected persons.^{8, 10–12} In a previous analysis, we found that the prevalence of reduced kidney function in the FRAM (Fat Redistribution and Metabolic Change in HIV Infection) study was 31% based on cystatin C measurements ($>1 \text{ mg/L}$) and only 5% using creatinine-based measures of eGFR .³ Based on this finding, kidney disease may be significantly under-diagnosed in HIV-infected individuals.

Although the high risk of kidney disease in persons with HIV infection has been well documented, few studies have jointly evaluated the health consequences of reduced kidney function and albuminuria in this population. Using a large administrative database, we previously found that serum creatinine-based estimated glomerular filtration rate ($\text{eGFR}_{\text{SCr}} < 60 \text{ mL/min/1.73 m}^2$ and albuminuria both had strong and independent associations with risk for atherosclerotic cardiovascular disease and heart failure in HIV-infected persons, but mortality was not assessed.¹³ In the Women's Interagency HIV Study, albuminuria but not eGFR was associated with mortality in those receiving antiretroviral therapy.^{14, 15} However, in both of these studies, cystatin C levels were not available for comparison. In fact, no study to date has investigated the prognostic significance of cystatin C levels in HIV-infected persons.

We conducted this study to determine whether elevated cystatin C levels are independently associated with higher rates of death in HIV-infected persons after adjustment for established risk factors for mortality in the FRAM cohort, such as HIV-related and cardiovascular risk factors,¹⁶ and inflammation.¹⁷ Further, we compared the mortality risk associated with cystatin C to mortality risks of established markers of kidney disease, namely, serum creatinine-based eGFR and albuminuria.

Methods

Study Population

We determined the association between kidney disease and mortality in HIV-infected persons enrolled in the FRAM study. The methods, design, and sample characteristics of the FRAM cohort have been described previously in detail.¹⁸ Briefly, FRAM is a large, nationally representative, multicenter study of HIV-infection, originally designed to evaluate lipodystrophy and metabolic abnormalities in HIV-infected persons. Between June 2000 and September 2002, 1183 HIV-infected men and women from 16 geographically diverse sites were enrolled in FRAM, with a follow-up exam conducted approximately 5 years later (FRAM-2). We have described the vital status, retention, and observation time for FRAM-2 previously.¹⁶ At the second exam, 922 HIV-infected participants were known to be alive or known to be dead. Vital status could not be determined in 261 participants in whom contact could not be re-established. Linkage to the National Death Index was not possible because of patient confidentiality constraints. The institutional review boards at all sites approved the protocols for both FRAM examinations.

Measures of Kidney Disease

Cystatin C was measured in previously frozen sera stored at -70°C , using a particle-enhanced immunonephelometric assay (BNII nephelometer, Dade Behring Inc, www.medical.siemens.com).³ The coefficient of variation for between-run imprecision was less than 2% for cystatin C.¹⁹ Additional characteristics of the assay have been reported.²⁰ In FRAM, serum creatinine was measured by the enzymatic method using an assay from Covance Laboratories (www.covance.com) and calibrated to an assay traceable to isotope-dilution mass spectrometry as currently recommended.²¹ We estimated glomerular filtration rate based on serum cystatin C using the CKD Epidemiology Collaboration (CKD-EPI) equation²²: $\text{eGFR}_{\text{SCysC}} = 76.7 \times \text{cystatin C}^{-1.19}$; eGFR_{SCr} was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation for standardized creatinine.^{21, 23} We converted both cystatin C and serum creatinine to eGFR to more accurately reflect actual GFR and to allow cross-comparisons between methods. We conducted analyses using eGFR as both a continuous and categorical variable (for the latter, we used a cutoff of $<60 \text{ mL/min/1.73m}^2$, the threshold level for CKD in the National Kidney Foundation's KDOQI guidelines).²³ Albuminuria was defined as a positive urine dipstick (1+ or greater) or a urine albumin-creatinine ratio greater than 30 mg/g .⁴

Covariates

Clinical information on FRAM participants was collected using standardized questionnaires, laboratory, and anthropometric measurement protocols. The following information was considered for inclusion in multivariable models: demographic characteristics (age, sex, and race), diabetes (medication use or fasting glucose $>125 \text{ mg/dl}$), smoking status (current, past, never), medication use (angiotensin converting enzyme inhibitors, other anti-hypertensives, hypolipidemics), clinical measurements (blood pressure, high density lipoprotein [HDL] and total cholesterol, waist circumference, lean body mass by MRI), inflammatory markers (C-reactive protein [CRP], fibrinogen), and HIV-related factors (HIV RNA level, CD4 count, AIDS,²⁴ hepatitis C virus co-infection [defined by detectable RNA]). In addition, both cumulative and past exposure to each antiretroviral drug and class were evaluated. Multiple imputation using the Markov chain Monte Carlo method was used to impute missing covariates.²⁵

Statistical Analysis

We determined the cumulative 5-year mortality of FRAM participants using multivariable logistic regression analysis. Since the exact dates of death were unknown in HIV-infected participants, those who died provided left-censored observations, meaning that death was only known to have occurred sometime before the contact attempt at approximately 5 years of follow-up. We therefore used logistic regression with an offset term for follow-up time, rather than Cox proportional hazards regression as our primary analysis, because this form of regression is appropriate for left-censored events. We also tested exponential regression survival models, but found that model fit was improved using logistic regression. Follow-up time was defined as elapsed time from baseline to follow-up exam or last contact. To account for those with missing vital status, we also adjusted estimates using an inverse probability of censor weighting approach by modeling the participant's probability of having known death status.²⁶ The inverse of this probability was then used as a weight applied to persons with known vital status in the logistic regression analysis of death.

To determine if kidney disease markers were independently predictive of mortality, multivariable models were sequentially adjusted for demographic information, smoking, diabetes, systolic and diastolic blood pressure, HDL and total cholesterol, medication exposure, waist circumference, lean body mass, and HIV-related factors. Interaction terms of African American race with markers of kidney disease were also tested in these models. We previously found that inflammatory markers are associated with mortality¹⁷ and it has been hypothesized that increased inflammation may be either an important confounder of cystatin C,²⁷ or a mediator in the pathway between kidney disease and mortality;³ therefore, we adjusted for inflammatory markers in a subsequent, final model. To ensure that models were not overfit, we built parsimonious models using a backward stepwise procedure. For all models, we tested the linearity of continuous variables such as eGFR, age, CD4 count and HIV RNA level, and we tested the additional benefit of log transformations and quadratic terms. Finally, in order to quantify the impact of kidney disease on mortality in HIV-infected persons at a population level, we estimated the attributable risk associated with kidney disease, a statistic that accounts not only for the strength of the association of a risk factor with mortality, but also how common the condition is in the population of interest. The population attributable risk percent was calculated using incidence rates of death predicted from fully adjusted multivariable models as: $100 * [(population\ mortality\ rate - mortality\ rate\ in\ unexposed) / population\ mortality\ rate]$.²⁸ All analyses were conducted using the SAS system, version 9.2 (SAS Institute, Inc., www.sas.com).

Supplemental Analyses

We conducted a number of analyses to assess the potential bias introduced to our results by limited vital status data. We compared the baseline characteristics of FRAM participants based on 5-year vital status (deceased, alive, or unknown) and further divided by eGFR category and albuminuria. We then conducted 3 sensitivity analyses that are reported in the final table. Sensitivity Analysis 1 was limited to persons with known vital status but did not incorporate a weighting procedure; this is the observed case analysis. The second and third sensitivity analyses modeled the likelihood of survival among persons with unknown vital status. In Sensitivity Analysis 2, we compared main model results with an analysis assuming that all participants who were lost to follow-up were alive. In the third sensitivity analysis, we used multiple imputation to assign vital status to those who were lost to follow-up. We did not perform a complete-case analysis instead of using multiple imputation for missing predictors, because this would be very likely to produce significant bias due to missing data rates of 0% to 23% for individual covariates, resulting in 40% of participants being excluded due to at least one missing predictor.²⁹

Results

Baseline characteristics

At the time of enrollment in FRAM, kidney disease marked by albuminuria or $\text{eGFR}_{\text{SCysC}} < 60 \text{ mL/min/1.73m}^2$ was found in 28% of the study population. The prevalence of reduced kidney function, defined as an $\text{eGFR} < 60 \text{ mL/min/1.73m}^2$, was greater than two-fold higher when eGFR was calculated with cystatin C compared with creatinine (11% versus 5%). Albuminuria was also common, present in 22% of participants overall. In the subset of participants with normal kidney function, albuminuria was found in 19% of those with an $\text{eGFR}_{\text{SCysC}} \geq 60 \text{ mL/min/1.73m}^2$, and 20% of those with an $\text{eGFR}_{\text{SCr}} \geq 60 \text{ mL/min/1.73m}^2$. FRAM participants with an $\text{eGFR}_{\text{SCysC}} < 60 \text{ mL/min/1.73m}^2$ were older, and more likely to be African-American, current smokers, and receive antihypertensive medications compared with their counterparts with $\text{eGFR}_{\text{SCysC}} \geq 60 \text{ mL/min/1.73m}^2$ (Table 1). In terms of HIV-related factors, patients with an $\text{eGFR}_{\text{SCysC}} < 60 \text{ mL/min/1.73m}^2$ had higher HIV RNA levels and lower CD4 counts, and a larger proportion had a history of AIDS and hepatitis C virus co-infection. The unadjusted Spearman correlation between cystatin C and creatinine was $r=0.38$ ($p<0.001$); after adjustment for lean body mass, the correlation was $r=0.41$ ($p<0.001$). Factors independently associated with serum creatinine and cystatin C have been reported previously.³

Five-year mortality rates

After five years of observation, 34% ($n=35$) of those in the $\text{eGFR}_{\text{SCysC}} < 60 \text{ mL/min/1.73m}^2$ group and 11% ($n = 93$) in the $\text{eGFR}_{\text{SCysC}} \geq 60 \text{ mL/min/1.73m}^2$ group were deceased. In unadjusted analyses, individuals with albuminuria or $\text{eGFR}_{\text{SCysC}} < 60 \text{ mL/min/1.73m}^2$ alone each had an approximate 10% higher absolute risk of dying compared to those with neither condition, while nearly half of those with both conditions were dead at five years (Figure 1A). We also examined separately 877 HIV-infected FRAM participants who did not have kidney disease, using serum creatinine alone to measure kidney function ($\text{eGFR}_{\text{SCr}} \geq 60 \text{ mL/min/1.73m}^2$). In this subgroup, individuals with albuminuria and $\text{eGFR}_{\text{SCysC}} < 60 \text{ mL/min/1.73m}^2$ had higher rates of 5-year mortality compared to those without these conditions despite the presence of normal eGFR_{SCr} (Figure 1B).

Risk of death associated with kidney function among HIV-infected persons

Next, using multivariable models, we assessed whether the associations of markers of kidney disease with mortality were independent of confounding variables. When eGFR was analyzed as a continuous variable, eGFR_{SCr} did not appear to be associated with 5-year mortality, whereas $\text{eGFR}_{\text{SCysC}}$ was found to have a significant linear association with death in all models (Table 2). In multivariable adjusted models, each $10 \text{ mL/min/1.73m}^2$ decrement in baseline $\text{eGFR}_{\text{SCysC}}$ was associated with a 14% (95% CI, 3%-27%) increase in mortality.

Similarly, the presence of reduced kidney function at baseline, marked by an $\text{eGFR}_{\text{SCysC}} < 60 \text{ mL/min/1.73m}^2$, was associated with a four-fold unadjusted increase and nearly a two-fold fully adjusted increase in five-year mortality risk. In contrast, the association between $\text{eGFR}_{\text{SCr}} < 60 \text{ mL/min/1.73m}^2$ and mortality had a smaller effect size and reached statistical significance only in the unadjusted and demographic adjusted models. Furthermore, after accounting for inflammatory factors, the adjusted point estimate for the risk of mortality associated with $\text{eGFR}_{\text{SCr}} < 60 \text{ mL/min/1.73m}^2$ decreased from an OR of 1.4 down to 1.0 (p for attenuation=0.02). However, the association between $\text{eGFR}_{\text{SCysC}} < 60 \text{ mL/min/1.73m}^2$ with mortality remained statistically significant after accounting for inflammation.

Albuminuria was also a strong predictor of mortality, associated with an approximate two-fold increase in mortality in fully adjusted models. No interaction terms of African American race with markers of kidney disease reached statistical significance in models of mortality.

Population-level risk for mortality attributable to kidney disease

Based on multivariable adjusted models that accounted for inflammation, the attributable risk associated with the presence of either albuminuria or $\text{eGFR}_{\text{SCysC}} < 60 \text{ mL/min/1.73m}^2$ in the HIV-infected population was 17% (Figure 2). This corresponded to an absolute risk of 2.4 deaths per 100 HIV-infected persons attributable to kidney disease over five years. In multivariable adjusted models that excluded inflammatory markers, the population attributable risk was 9% for $\text{eGFR}_{\text{SCysC}} < 60 \text{ mL/min/1.73m}^2$, 14% for albuminuria, and 22% for the presence of either condition.

Supplemental Analyses

Compared to those who were either alive or had unknown vital status at 5-years, deceased persons had a higher prevalence of co-morbid conditions, albuminuria, and lower $\text{eGFR}_{\text{SCysC}}$ at baseline (Table S1; provided as online supplementary material available with this article at www.ajkd.org). Median levels of cystatin C and creatinine and the prevalence of albuminuria were similar between those known to be alive and those with unknown vital status. When analyses were repeated in those with known vital status without the application of inverse probability weights for vital status, point estimates for all markers of kidney disease were very similar to main model results (Table 3). In the sensitivity analysis that assumed all those who were lost to follow-up were alive, $\text{eGFR}_{\text{SCysC}}$ as a continuous variable remained statistically significantly associated with mortality [OR of 1.13 (95% CI, 1.01–1.26) per 10 mL/min/1.73m² decrement in $\text{eGFR}_{\text{SCysC}}$]. Finally, when multiple imputation was used to assign vital status to those who were lost to follow-up, the point-estimates for $\text{eGFR}_{\text{SCysC}}$, eGFR_{SCr} , and albuminuria, were similar, but with wider confidence intervals.

Discussion

In this large contemporary cohort of HIV-infected persons, 28% of participants had either albuminuria or $\text{eGFR}_{\text{SCysC}} < 60 \text{ mL/min/1.73m}^2$. These markers of kidney damage and reduced kidney function, respectively, were each independently associated with a nearly two-fold increase in mortality risk, whereas eGFR_{SCr} did not have a significant association with mortality. Albuminuria and $\text{eGFR}_{\text{SCysC}} < 60 \text{ mL/min/1.73m}^2$ provided complementary prognostic information, collectively accounting for 17% of the population-level mortality in HIV-infected persons. These findings suggest that kidney disease, marked by albuminuria and decreased $\text{eGFR}_{\text{SCysC}}$, is an important source of mortality in HIV-infected individuals, and that a substantial proportion of this risk is unrecognized because of the current reliance on serum creatinine to estimate kidney function in clinical practice. Alternatively, the mortality associations of either albuminuria, decreased $\text{eGFR}_{\text{SCysC}}$, or both in HIV-infected persons may in part reflect an unknown process that is unrelated to the kidney.

Few studies have jointly assessed the risk of death associated with reduced kidney function and albuminuria in the contemporary era of antiretroviral therapy. While we and others have observed a graded, independent relationship between eGFR_{SCr} levels and mortality, these studies lacked information on albuminuria and were unable to account for important characteristics such as HIV viral load, blood pressure, or inflammatory markers.^{30, 31} Our results are consistent with studies that have analyzed both eGFR_{SCr} and albuminuria as risk factors for mortality among individuals receiving antiretroviral therapy, and found that

albuminuria is independently associated with death, but $eGFR_{SCr}$ is not.^{14, 15} Our study builds on these prior reports, which were limited to women, by establishing the independent association of both kidney damage (albuminuria) and reduced kidney function ($eGFR_{SCysC}$) with mortality in a diverse population of antiretroviral treated patients. We also describe the population attributable risk associated with joint measures of kidney disease to help understand its relevance to the HIV-infected population at large, given the high prevalences of albuminuria and reduced $eGFR_{SCysC}$ and their strong associations with mortality. Collectively, these findings strongly suggest that kidney disease is a critical source of mortality in patients with HIV and demand further investigations into underlying mechanisms.

To our knowledge, no prior study has reported an association between cystatin C levels and mortality in HIV-infected persons. A strength of this study is the demonstration of this relationship in a large, geographically and ethnically diverse, population-based sample of HIV-infected persons, and the availability of comprehensive clinical information and specialized measures of physiologic status which allowed us to test the robustness of this association. Consistent with findings in HIV-uninfected persons, cystatin C appears to capture mortality risk not characterized by established measures of kidney function, such as creatinine.^{10, 12} Interestingly, this result was not affected by adjustment for lean body mass, which has been hypothesized to confound the association between creatinine and mortality, since creatinine is a derivative of muscle mass. We have previously shown that cystatin C levels are not associated with muscle mass.³

While studies of $eGFR_{SCysC}$ in HIV-uninfected patients have revealed that it is a sensitive test of kidney disease and an accurate predictor of gold standard GFR, no studies of adequate sample size have been conducted in HIV-infected persons.⁵⁻⁹ It is unknown, therefore, whether abnormal levels of cystatin C are predominantly a manifestation of reduced GFR or if there is a substantial contribution from non-GFR determinants of cystatin C. In addition, the impact of muscle mass on the validity of serum creatinine as a marker of kidney function has not been definitively addressed. To date, neither of the currently available measures of kidney function, cystatin C or creatinine, has been validated in an HIV-infected population using gold standard techniques. Such studies are urgently needed to aid the interpretation of increased cystatin C levels in the HIV-infected population.

Some have expressed concern that cystatin C may be confounded by increased cell turnover, leading to excessive cystatin C production in high inflammatory states such as HIV infection.^{32, 33} In addition, inflammation itself is associated with mortality in HIV-infected persons, which raises the possibility of a spurious association between $eGFR_{SCysC}$ and mortality due to confounding.³⁴ However, it is notable that inflammation had similar attenuating effects on the associations of reduced kidney function defined by $eGFR_{SCr}$ or $eGFR_{SCysC}$ with mortality. Furthermore, both $eGFR_{SCysC} < 60$ mL/min/1.73m² and albuminuria remained independent predictors of mortality despite adjustment for inflammatory factors. These results do not rule out the possibility that the mortality associations of cystatin C or albuminuria could still be subject to residual confounding by inflammation or other unmeasured factors, but they suggest that $eGFR_{SCr}$ may be differentially affected by inflammation or associated malnutrition and muscle wasting. Further study is needed to identify determinants of serum creatinine and cystatin C in HIV-infected persons in conjunction with measurements of gold standard GFR.

In this study, markers of kidney disease were independent risk factors for mortality in HIV-infected persons after accounting for traditional and HIV-related risk factors for mortality, including comorbid illnesses, health behaviors, physiologic measurements, CD4 count, HIV viremia, hepatitis C virus co-infection, and medication exposures. It is plausible that kidney

disease could lead to increased mortality among HIV-infected individuals through a number of different pathways. Both albuminuria and decreased kidney function are associated with cardiovascular disease in studies conducted among both HIV-infected and uninfected persons.^{13,35} Cardiovascular disease has become a leading cause of death in the HIV-infected population^{36–38} and both kidney and heart complications have become increasingly common as the HIV-infected population ages.^{31, 39–42} In addition, several studies conducted *in vitro* and in humans have established an association between uremia and immune activation, which is widely accepted as an important mechanism by which HIV disease progresses.^{43, 44} Similarly, other studies have suggested that kidney disease is associated with progression to AIDS and loss of CD4+ T cells.^{15, 45} Finally, another report suggested that the effectiveness of antiretroviral therapy may be compromised in the setting of kidney disease because of decreased renal clearance of these medications, inadequate dose adjustments, and increased side effects.³⁰ The next key step will be to investigate causes of death associated with kidney disease and to determine whether mortality is due to cardiovascular causes, immune-related mechanisms, or interactions between the host and the reservoir of HIV residing in the kidney.

The most important limitation of the study was the analytic challenge presented by limited vital status information. We used a number of statistical methods to deal with this problem, including multivariable logistic regression with an offset term for follow-up time and inverse probability of censor weights to account for those with missing vital status. In addition, we performed a number of sensitivity analyses to test our analytic approach, which further supported a significant association between eGFR_{SCysC} with mortality. Unfortunately, cause of death information was not available to us to provide additional evidence that these deaths were related to kidney disease. Our data support the concept that cystatin C should be measured in future studies of HIV-infected cohorts in which cause of death can be ascertained.

In this nationally representative cohort of HIV-infected persons, kidney disease marked by albuminuria and impaired kidney function was common, and strongly associated with mortality. Cystatin C based estimates of kidney function appear to improve the prognostic value of eGFR, compared with serum creatinine based estimates of kidney function that are the current clinical standard. Further study is needed to confirm these findings and to determine whether cystatin C may be a useful tool for detecting unrecognized kidney disease and identifying HIV-infected persons at increased risk for mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Tekeda Ferguson, and Anthony Goudie). FRAM-2 Data Coordinating Center: University of Washington, Seattle (Richard A. Kronmal, PhD, Mary Louise Biggs, PhD, and John Pearce). Image Reading Centers: St Luke's-Roosevelt Hospital Center: (Steven Heymsfield, MD, Jack Wang, MS and Mark Punyanitya). Tufts New England Medical Center, Boston: (Daniel H. O'Leary, MD, Joseph Polak, Anita P. Harrington). Office of the Principal Investigator: University of California, San Francisco, Veterans Affairs Medical Center and the Northern California Institute for Research and Development: (Carl Grunfeld, MD, PhD, Phyllis Tien, MD, Peter Bacchetti, PhD, Dennis Osmond, PhD*, Michael Shlipak, MD, Rebecca Scherzer, PhD, Mae Pang, RN, MSN, Heather Southwell, MS, RD).

Support: This study was supported by NIH grants R01 DK57508, R01 HL74814, R01 HL53359, K23 AI66943, and K23 DK080645-01A1, as well as NIH center grants P30 AI027767, M01 RR00036, M01 RR00051, M01 RR00052, M01 RR00054, M01 RR00083, M01 RR0636, M01 RR00865, KL2 RR024130, and UL1 RR024131. The funding agency played no role in the conduct of the study, collection of the data, management of the study, analysis of data, interpretation of the data or preparation of the manuscript. A representative of the funding agent participated in planning the protocol.

References

1. Lohse N, Hansen AB, Pedersen G, et al. Survival of persons with and without HIV infection in Denmark, 1995–2005. *Ann Intern Med.* Jan 16; 2007 146(2):87–95. [PubMed: 17227932]
2. Eggers PW, Kimmel PL. Is there an epidemic of HIV Infection in the US ESRD program? *J Am Soc Nephrol.* Sep; 2004 15(9):2477–2485. [PubMed: 15339998]
3. Odden MC, Scherzer R, Bacchetti P, et al. Cystatin C level as a marker of kidney function in human immunodeficiency virus infection: the FRAM study. *Arch Intern Med.* Nov 12; 2007 167(20):2213–2219. [PubMed: 17998494]
4. Szczech LA, Grunfeld C, Scherzer R, et al. Microalbuminuria in HIV infection. *Aids.* May 11; 2007 21(8):1003–1009. [PubMed: 17457094]
5. Perkins BA, Ficociello LH, Ostrander BE, et al. Microalbuminuria and the Risk for Early Progressive Renal Function Decline in Type 1 Diabetes. *J Am Soc Nephrol.* Feb 28; 2007
6. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *Am J Kidney Dis.* Aug; 2002 40(2):221–226. [PubMed: 12148093]
7. Shlipak MG, Praught ML, Sarnak MJ. Update on cystatin C: new insights into the importance of mild kidney dysfunction. *Curr Opin Nephrol Hypertens.* May; 2006 15(3):270–275. [PubMed: 16609294]
8. Perkins BA, Nelson RG, Ostrander BE, et al. Detection of renal function decline in patients with diabetes and normal or elevated GFR by serial measurements of serum cystatin C concentration: results of a 4-year follow-up study. *J Am Soc Nephrol.* May; 2005 16(5):1404–1412. [PubMed: 15788478]
9. Hoek FJ, Kemperman FA, Krediet RT. A comparison between cystatin C, plasma creatinine and the Cockcroft and Gault formula for the estimation of glomerular filtration rate. *Nephrol Dial Transplant.* Oct; 2003 18(10):2024–2031. [PubMed: 13679476]
10. Shlipak MG, Sarnak MJ, Katz R, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med.* May 19; 2005 352(20):2049–2060. [PubMed: 15901858]
11. Sarnak MJ, Katz R, Stehman-Breen CO, et al. Cystatin C concentration as a risk factor for heart failure in older adults. *Ann Intern Med.* Apr 5; 2005 142(7):497–505. [PubMed: 15809461]
12. Shlipak MG, Katz R, Sarnak MJ, et al. Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. *Ann Intern Med.* Aug 15; 2006 145(4):237–246. [PubMed: 16908914]
13. 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.* Feb 9; 2005 111(5):651–658. [PubMed: 20100969]
14. Wyatt CM, Hoover DR, Shi Q, et al. Microalbuminuria Is Associated With All-Cause and AIDS Mortality in Women With HIV Infection. *J Acquir Immune Defic Syndr.* Jan 21.
15. Szczech LA, Hoover DR, Feldman JG, et al. Association between renal disease and outcomes among HIV-infected women receiving or not receiving antiretroviral therapy. *Clin Infect Dis.* Oct 15; 2004 39(8):1199–1206. [PubMed: 15486845]

16. Cockerham L, Scherzer R, Zolopa A, et al. Association of HIV Infection, Demographic and Cardiovascular Risk Factors With All-Cause Mortality in the Recent HAART Era. *J Acquir Immune Defic Syndr*. Sep 4.2009
17. Tien, P.; Choi, A.; Zolopa, A., et al. Inflammation and Mortality in HIV-infected Adults: Analysis of the FRAM Study Cohort. Paper presented at: Conference on Retroviruses and Opportunistic Infections; 2009; San Francisco, CA.
18. Tien PC, Benson C, Zolopa AR, Sidney S, Osmond D, Grunfeld C. The study of fat redistribution and metabolic change in HIV infection (FRAM): methods, design, and sample characteristics. *Am J Epidemiol*. May 1; 2006 163(9):860–869. [PubMed: 16524955]
19. Erlandsen EJ, Randers E, Kristensen JH. Evaluation of the Dade Behring N Latex Cystatin C assay on the Dade Behring Nephelometer II System. *Scand J Clin Lab Invest*. Feb; 1999 59(1):1–8. [PubMed: 10206092]
20. Shlipak MG, Wassel Fyr CL, Chertow GM, et al. Cystatin C and mortality risk in the elderly: the health, aging, and body composition study. *J Am Soc Nephrol*. Jan; 2006 17(1):254–261. [PubMed: 16267155]
21. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. Aug 15; 2006 145(4):247–254. [PubMed: 16908915]
22. Stevens LA, Coresh J, Schmid CH, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis*. Mar; 2008 51(3):395–406. [PubMed: 18295055]
23. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. Jul 15; 2003 139(2): 137–147. [PubMed: 12859163]
24. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep*. Dec 18; 1992 41(RR-17):1–19.
25. Gilks, WR.; Richardson, S.; DJ, S. Markov chain Monte Carlo in practice. London: Chapman & Hall; 1996.
26. Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests. *Biometrics*. Sep; 2000 56(3):779–788. [PubMed: 10985216]
27. Mocroft A, Wyatt C, Szczech L, et al. Interruption of antiretroviral therapy is associated with increased plasma cystatin C. *Aids*. Jan 2; 2009 23(1):71–82. [PubMed: 19050388]
28. Luepker, RV.; Evans, A.; McKeigue, P.; Reddy, KS. Cardiovascular Survey Methods. 3. Geneva: World Health Organization; 2004.
29. Schafer, JL. Analysis of Incomplete Multivariate Data. New York: Chapman and Hall; 1997.
30. Choi AI, Rodriguez RA, Bacchetti P, et al. Low rates of antiretroviral therapy among HIV-infected patients with chronic kidney disease. *Clin Infect Dis*. Dec 15; 2007 45(12):1633–1639. [PubMed: 18190326]
31. Mulenga LB, Kruse G, Lakhi S, et al. Baseline renal insufficiency and risk of death among HIV-infected adults on antiretroviral therapy in Lusaka, Zambia. *Aids*. Sep 12; 2008 22(14):1821–1827. [PubMed: 18753939]
32. Knight EL, Verhave JC, Spiegelman D, et al. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. *Kidney Int*. Apr; 2004 65(4): 1416–1421. [PubMed: 15086483]
33. Stevens LA, Schmid CH, Greene T, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int*. Mar; 2009 75(6):652–660. [PubMed: 19119287]
34. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med*. Oct 21.2008 5(10):e203. [PubMed: 18942885]
35. Ninomiya T, Perkovic V, de Galan BE, et al. Albuminuria and Kidney Function Independently Predict Cardiovascular and Renal Outcomes in Diabetes. *J Am Soc Nephrol*. May 14.2009
36. Hooshiyar D, Hanson DL, Wolfe M, Selik RM, Buskin SE, McNaghten AD. Trends in perimortal conditions and mortality rates among HIV-infected patients. *Aids*. Oct 1; 2007 21(15):2093–2100. [PubMed: 17885300]

37. Sackoff JE, Hanna DB, Pfeiffer MR, Torian LV. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. *Ann Intern Med.* Sep 19; 2006 145(6): 397–406. [PubMed: 16983127]
38. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* Sep 23; 2004 351(13):1296–1305. [PubMed: 15385656]
39. Mocroft A, Kirk O, Gatell J, et al. Chronic renal failure among HIV-1-infected patients. *Aids.* May 31; 2007 21(9):1119–1127. [PubMed: 17502722]
40. Choi AI, Rodriguez RA, Bacchetti P, Bertenthal D, Volberding PA, O'Hare AM. The impact of HIV on chronic kidney disease outcomes. *Kidney Int.* Sep 5.2007
41. Lucas GM, Lau B, Atta MG, Fine DM, Keruly J, Moore RD. Chronic kidney disease incidence, and progression to end-stage renal disease, in HIV-infected individuals: a tale of two races. *J Infect Dis.* Jun 1; 2008 197(11):1548–1557. [PubMed: 18422458]
42. Friis-Moller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med.* Apr 26; 2007 356(17):1723–1735. [PubMed: 17460226]
43. Meier P, Spertini F, Blanc E, Burnier M. Oxidized low-density lipoproteins activate CD4+ T cell apoptosis in patients with end-stage renal disease through Fas engagement. *J Am Soc Nephrol.* Jan; 2007 18(1):331–342. [PubMed: 17182885]
44. Meier P, Dayer E, Blanc E, Wauters JP. Early T cell activation correlates with expression of apoptosis markers in patients with end-stage renal disease. *J Am Soc Nephrol.* Jan; 2002 13(1): 204–212. [PubMed: 11752039]
45. Wools-Kaloustian, K.; Owino, On G'or W.; Wafula, S., et al. The Relationships between Renal Dysfunction and Clinical Outcomes in HIV-Infected Kenyans Not Requiring Immediate ART. 16th Conference on Retroviruses and Opportunistic Infections; Montréal, Québec. 2009.

FIGURE 1.

Unadjusted 5-year mortality rates in HIV-infected participants, stratified by presence of reduced serum cystatin C-based estimated glomerular filtration rate (eGFR_{Cys} <60 mL/min/1.73m²) or albuminuria. In Panel (A), mortality rates in all 922 HIV-infected FRAM (Fat Redistribution and Metabolic Change in HIV Infection) participants are shown. In Panel (B), mortality rates in 877 HIV-infected individuals with normal kidney function, defined as a serum creatinine-based eGFR ≥60 mL/min/1.73m², are displayed.*

FIGURE 2. Population-Level Risk of Mortality Attributable to Kidney Disease in HIV-Infected Persons. eGFR_{Cys} (serum cystatin C-based estimated glomerular filtration rate) reported in mL/min/1.73m². “Combined” category includes those with either eGFR_{Cys} <60 mL/min/1.73m² or microalbuminuria.

TABLE 1

Baseline Characteristics by eGFR_{SCysC} Category

Characteristic	eGFR _{SCysC} <60* (n=104)	eGFR _{SCysC} ≥60* (n=818)	P value
Age (y)	45 (40, 50)	40 (36, 47)	0.01
Gender			0.3
Female	35%	30%	
Male	66%	71%	
Race			0.01
African American	53%	38%	
Caucasian	38%	49%	
Other	9%	13%	
Diabetes	7%	9%	0.4
Smoking Status			0.02
Current	52%	40%	
Past	16%	25%	
Never	32%	35%	
Medications			
Antihypertensive use	43%	19%	0.01
ACEi use	13%	9%	0.09
Hyperlipidemia Treatment	19%	15%	0.3
Clinical Measurements			
Systolic BP, (mmHg)	119 (105, 128)	115 (106, 123)	0.06
Diastolic BP, (mmHg)	79 (70, 85)	78 (70, 83)	0.5
Waist Circumference, (cm)	90 (81, 97)	88 (81, 96)	0.3
Lean Body Mass, (L)	27 (23, 31)	28 (25, 32)	0.04
Total Cholesterol Level, (mg/dL)	177 (145, 226)	191 (160, 228)	0.07
HDL Cholesterol, (mg/dL)	38 (30, 48)	41 (34, 52)	0.02
HIV-Related Factors			
HIV RNA level (log copies/mL)	3.1 (2.6, 4.5)	2.6 (2.5, 4.0)	0.02
Detectable HIV RNA	58%	49%	0.06
CD4 count (cells/μL)	292 (140, 473)	375 (225, 558)	0.01
Hepatitis C virus infection	39%	19%	0.01
Prior AIDS	81%	70%	0.01
HAART	88%	88%	0.9
Inflammation			
C-Reactive Protein, (mg/L)	3.1 (1.5, 5.1)	1.7 (0.7, 3.9)	0.01
Fibrinogen, (mg/dL)	438 (351, 531)	353 (291, 420)	0.01
Markers of Kidney Disease			
Cystatin C (mg/L)	1.4 (1.3, 1.6)	0.9 (0.8, 1.0)	0.01

Characteristic	eGFR _{SCysC} <60* (n=104)	eGFR _{SCysC} ≥60* (n=818)	P value
Creatinine (mg/dL)	1.0 (0.8, 1.3)	0.8 (0.7, 0.9)	0.01
eGFR _{SCysC} (ml/min/1.73m ²)	52 (44, 56)	88 (75, 103)	0.01
eGFR _{SCr} (ml/min/1.73m ²)	78 (58, 92)	101 (87, 118)	0.01
Albuminuria	43%	19%	0.01

Note Continuous data are represented as median (25th, 75th percentile). Conversion factors for units: total and HDL cholesterol in mg/dL to mmol/L, x0.02586; fibrinogen in mg/dL to μmol/L, x0.0294; creatinine in mg/dL to μmol/L, x88.4. Abbreviations: BP, blood pressure; eGFR = estimated glomerular filtration rate. eGFR_{SCysC} = cystatin C-based eGFR. eGFR_{SCr} = serum creatinine-based eGFR. HDL, high-density lipoprotein; ACEi = angiotensin-converting enzyme inhibitor. HAART = highly active antiretroviral therapy; HIV, human immunodeficiency virus

* eGFR given in ml/min/1.73m²; factor for conversion to mL/s/1.73m², x0.01667.

TABLE 2

The association of eGFR_{SCr}, eGFR_{SCysC}, and Albuminuria with 5-year Mortality in HIV-infected FRAM participants*

	Unadjusted	Demographic Adjusted	Multivariable Adjusted	Multivariable + Inflammation Adjusted
Linear eGFR				
eGFR _{SCr} (per 10 ml/min/1.73m ² decrease)	1.03 (0.95–1.11)	1.03 (0.94–1.12)	1.05 (0.95–1.15)	1.01 (0.92–1.12)
eGFR _{SCysC} (per 10 ml/min/1.73m ² decrease)	1.37 (1.26–1.49)	1.36 (1.25–1.48)	1.20 (1.09–1.32)	1.14 (1.03–1.27)
Kidney Disease Category				
eGFR _{SCr} <60 ml/min/1.73m ²	2.31 (1.25–4.28)	2.05 (1.09–3.88)	1.44 (0.65–3.19)	0.98 (0.42–2.26)
eGFR _{SCysC} <60 ml/min/1.73m ²	4.03 (2.67–6.09)	3.71 (2.43–5.64)	2.26 (1.34–3.80)	1.86 (1.09–3.19)
Albuminuria	3.10 (2.11–4.56)	2.88 (1.95–4.27)	2.22 (1.32–3.71)	1.91 (1.15–3.19)

* Results reported as odds ratio (95% confidence interval). Demographic adjusted models control for age, sex and race. Multivariable adjusted models additionally control for smoking, non-HDL cholesterol, waist circumference, lean body mass, CD4 count, and total duration of lopinavir, efavirenz, indinavir, and amprenavir exposure; eGFR estimates are adjusted for albuminuria and albuminuria estimates are adjusted for eGFR_{SCysC}. Inflammation adjusted models additionally control for CRP and fibrinogen. Note that alternative versions of eGFR are shown entering the model individually, not simultaneously.

Abbreviations: eGFR = estimated glomerular filtration rate. eGFR_{SCysC} = cystatin C based eGFR. eGFR_{SCr} = serum creatinine based eGFR. FRAM, Fat Redistribution and Metabolic Change in HIV Infection; HIV, human immunodeficiency virus

TABLE 3

Sensitivity Analyses of the Associations between Kidney Function and Albuminuria with All-Cause Mortality in HIV-Infected Persons*

	Unadjusted	Demographic Adjusted	Multivariable Adjusted	Multivariable + Inflammation Adjusted
Sensitivity Analysis 1: Limited to Persons with Known Vital Status at Follow-up (n=922)				
Linear eGFR				
eGFR _{SCr} (per 10 ml/min/1.73m ² decrease)	1.03 (0.94–1.13)	1.03 (0.94–1.14)	1.05 (0.94–1.17)	1.02 (0.91–1.13)
eGFR _{SCysC} (per 10 ml/min/1.73m ² decrease)	1.36 (1.24–1.50)	1.35 (1.23–1.48)	1.19 (1.07–1.33)	1.14 (1.02–1.28)
Kidney Disease Category				
eGFR _{SCr} <60 ml/min/1.73m ²	2.25 (1.14–4.46)	1.98 (0.98–4.01)	1.36 (0.56–3.29)	0.95 (0.37–2.40)
eGFR _{SCysC} <60 ml/min/1.73m ²	3.92 (2.47–6.20)	3.58 (2.24–5.72)	2.18 (1.22–3.89)	1.80 (0.99–3.28)
Albuminuria	3.04 (1.98–4.68)	2.82 (1.82–4.38)	2.25 (1.29–3.91)	1.95 (1.11–3.40)
Sensitivity Analysis 2: Assumes all individuals lost to follow-up remained alive (n=1183)				
Linear eGFR				
eGFR _{SCr} (per 10 ml/min/1.73m ² decrease)	1.05 (0.96–1.15)	1.04 (0.95–1.14)	1.04 (0.94–1.15)	1.02 (0.92–1.13)
eGFR _{SCysC} (per 10 ml/min/1.73m ² decrease)	1.36 (1.24–1.49)	1.34 (1.22–1.46)	1.17 (1.06–1.30)	1.13 (1.01–1.26)
Kidney Disease Category				
eGFR _{SCr} <60 ml/min/1.73m ²	2.51 (1.29–4.90)	2.17 (1.09–4.33)	1.54 (0.68–3.48)	1.25 (0.54–2.91)
eGFR _{SCysC} <60 ml/min/1.73m ²	3.91 (2.50–6.09)	3.49 (2.22–5.49)	2.12 (1.24–3.62)	1.84 (1.06–3.18)
Albuminuria	3.02 (1.99–4.58)	2.76 (1.80–4.22)	1.79 (1.08–2.97)	1.48 (0.89–2.47)
Sensitivity Analysis 3: Multiple imputation procedure to predict vital status in those lost to follow-up (n=1183)				
Linear eGFR				
eGFR _{SCr} (per 10 ml/min/1.73m ² decrease)	1.04 (0.96–1.13)	1.04 (0.96–1.13)	1.05 (0.95–1.16)	1.02 (0.92–1.13)
eGFR _{SCysC} (per 10 ml/min/1.73m ² decrease)	1.37 (1.24–1.51)	1.35 (1.22–1.50)	1.19 (1.04–1.36)	1.14 (0.99–1.30)
Kidney Disease Category				
eGFR _{SCr} <60 ml/min/1.73m ²	2.17 (1.14–4.14)	1.92 (0.99–3.71)	1.37 (0.61–3.05)	1.06 (0.46–2.45)
eGFR _{SCysC} <60 ml/min/1.73m ²	3.65 (2.06–6.47)	3.31 (1.78–6.14)	1.95 (0.76–4.97)	1.62 (0.62–4.22)
Albuminuria	3.29 (2.03–5.32)	2.97 (1.76–5.03)	2.38 (1.27–4.46)	1.81 (0.95–3.43)

* Results reported as odds ratio (95% confidence interval). Sensitivity analysis 1 is restricted to those where the outcome could definitively be ascertained.

Demographic adjusted models control for age, sex and race. Multivariable adjusted models additionally control for smoking, non-HDL cholesterol, waist circumference, lean body mass, CD4 count, and total duration of lopinavir, efavirenz, indinavir, and amprenavir exposure; eGFR estimates are adjusted for albuminuria and albuminuria estimates are adjusted for eGFR_{cys}. Inflammation adjusted models additionally control for CRP and fibrinogen. Note that alternative versions of eGFR are shown entering the model individually, not simultaneously.

Abbreviations: eGFR = estimated glomerular filtration rate. eGFR_{SCysC} = cystatin C based eGFR. eGFR_{SCr} = serum creatinine based eGFR.
HIV, human immunodeficiency virus