AJKD
Original Investigation

Risk Factors for ESRD in HIV-Infected Individuals: Traditional and HIV-Related Factors

Vasantha Jotwani, MD,[1,2] Yongmei Li, PhD,[1] Carl Grunfeld, MD, PhD,[3] Andy I. Choi, MD, MAS,[4†] and Michael G. Shlipak, MD, MPH[1,2]

Background: Despite improvements in survival with human immunodeficiency virus (HIV) infection, kidney disease remains an important complication. Few studies have evaluated risk factors associated with the development of end-stage renal disease (ESRD) in HIV-infected individuals. We sought to identify traditional and HIV-related risk factors for ESRD in HIV-infected individuals and compare ESRD risk by estimated glomerular filtration rate (eGFR) and proteinuria levels.

Study Design: Retrospective cohort study.

Setting & Participants: 22,156 HIV-infected veterans without pre-existing ESRD receiving health care in the Veterans' Affairs medical system between 1996 and 2004.

Predictors: Hypertension, diabetes, cardiovascular disease, hypoalbuminemia (serum albumin $<$3.5 mg/dL), CD4 lymphocyte count, HIV viral load, hepatitis C virus coinfection, proteinuria, and eGFR were identified using the Veterans' Affairs electronic record system.

Outcomes: ESRD was ascertained by the US Renal Data System.

Results: 366 cases of ESRD occurred, corresponding to 3 cases/1,000 person-years. Hypertension (HR, 1.9; 95% CI, 1.5-2.4), diabetes (HR, 1.7; 95% CI, 1.3-2.2), and cardiovascular disease (HR, 2.2; 95% CI, 1.7-2.7) were associated independently with ESRD risk in multivariate-adjusted models, as were CD4 lymphocyte count $<$200 cells/μL (HR, 1.5; 95% CI, 1.2-2.0), HIV viral load $\geq$30,000 copies/mL (HR, 2.0; 95% CI, 1.5-2.8), hepatitis C virus coinfection (HR, 1.9; 95% CI, 1.5-2.4), and hypoalbuminemia (HR, 2.1; 95% CI, 1.8-2.5). Compared with persons without chronic kidney disease, defined as eGFR $>$60 mL/min/1.73 m^2 and no proteinuria, lower eGFR and higher proteinuria categories were associated jointly with exponentially higher ESRD rates, ranging from 6.6 events/1,000 person-years for persons with urine protein excretion of 30-100 mg/dL and eGFR $>$60 mL/min/1.73 m^2 to 193 events/1,000 person-years for persons with urine protein excretion $\geq$300 mg/dL and eGFR $<$30 mL/min/1.73 m^2.

Limitations: Results may not be generalizable to female and nonveteran populations.

Conclusions: In HIV-infected persons, ESRD risk appears attributable to a combination of traditional and HIV-related risk factors for kidney disease. Combining eGFR and proteinuria for chronic kidney disease staging is most effective for stratifying the risk of ESRD.

INDEX WORDS: End-stage renal disease; human immunodeficiency virus (HIV); chronic kidney disease; risk factors.

Kidney disease is a well-recognized complication of human immunodeficiency virus (HIV) infection.[1] Early in the HIV epidemic, HIV-associated nephropathy (HIVAN) emerged as the leading cause of HIV-related kidney disease.[2] This form of HIVAN, seen almost exclusively in black individuals, is characterized by heavy proteinuria and rapid progression to end-stage renal disease (ESRD). After the advent of antiretroviral therapy (ART), the incidence of clinically significant HIVAN decreased substantially in parallel with improvements in survival.[3,4] However, despite these initial improvements, rates of ESRD in HIV-infected individuals receiving care in the United States have remained stable since 1996.[5,6] We and others have previously shown that the burden of kidney disease in HIV infection is carried dispropor-

From the [1]Division of General Internal Medicine, San Francisco VA Medical Center; [2]Division of General Internal Medicine, University of California, San Francisco; and Divisions of [3]Endocrinology and [4]Nephrology, San Francisco VA Medical Center and University of California, San Francisco, CA.

† Deceased.

Received May 24, 2011. Accepted in revised form October 24, 2011.

Because the Editor-in-Chief recused himself from consideration of this manuscript, the Deputy Editor (Daniel E. Weiner, MD, MS) served as Acting Editor-in-Chief. Details of the journal's procedures for potential editor conflicts are given in the Editorial Policies section of the AJKD website.

Address correspondence to Michael Shlipak, MD, MPH, University of California, San Francisco, General Internal Medicine Section, Veterans Affairs Medical Center (111A1), 4150 Clement St, San Francisco, CA 94121. E-mail: michael.shlipak@ucsf.edu

0272-6386/$0.00
doi:10.1053/j.ajkd.2011.10.050

tionately by black individuals,[7,8] the racial group with the highest HIV prevalence in this country and worldwide. Furthermore, several contemporary cohort studies have shown that the natural history of HIV-related kidney disease is remarkably different from the case histories described early in the course of the HIV epidemic. Currently, HIV-related kidney disease is less characterized by proteinuria[9] and its progression appears to be influenced by control of viral replication,[10-12] coinfection with hepatitis C virus,[10,13] and comorbid conditions such as diabetes.[14-16]

Despite the evolving spectrum of HIV-related kidney disease, few studies have evaluated the risk factors associated with progression to ESRD in HIV-infected persons. Prior studies attempting to address this issue have been limited by small numbers of events[8] or were restricted to persons of black race[17] or patients undergoing kidney biopsy.[18] The primary objective of this study was to identify traditional and HIV-related risk factors associated with the development of ESRD and determine their relative contributions to ESRD risk in a large national cohort of HIV-infected individuals receiving care in the contemporary era of ART. We also aimed to determine whether these risk factors for ESRD differ between black and white patients. Finally, we compared ESRD risk in HIV-infected individuals across chronic kidney disease (CKD) staging categories based jointly on estimated glomerular filtration rate (eGFR) and proteinuria.

METHODS

Data Sources

We conducted a retrospective cohort study of HIV-infected veterans in the Department of Veterans' Affairs (VA) HIV Clinical Case Registry[19] between 1996 and 2004. The VA HIV Clinical Case Registry is a national database with demographic, clinical, laboratory, pharmacy, and vital status information from the VA electronic medical record system. As in prior studies published by our group,[7,20,21] this data source was linked to the VA National Patient Care Database, Medicare claims, and the VA Beneficiary Identification and Records Locator Subsystem Death File for supplemental demographic and clinical data.[22] We linked our database to the US Renal Data System,[6] a publicly funded national registry of kidney disease, to identify both prevalent ESRD cases at the time of entry into the cohort and incident ESRD cases during the period of follow-up.

Study Population

Target patients for this study were HIV-infected persons receiving clinical care in the contemporary era of ART. We therefore included all HIV-infected patients in the Veterans Health Administration who had either serum creatinine or urine protein measured between 1996 and 2004. Participants entered the study at the time of their earliest measurement of either serum creatinine or urine protein after December 31, 1995. Of the 22,324 HIV-infected veterans identified by serum creatinine or urine protein measurements, 168 patients were excluded due to pre-existing ESRD requiring long-term dialysis therapy or kidney transplant. The remaining 22,156 patients were included in the study.

Outcomes

The primary outcome was the development of ESRD, defined as the receipt of long-term dialysis treatment or kidney transplant, ascertained by the US Renal Data System.[6] Individuals were analyzed from their initial urine protein or serum creatinine assessment until ESRD and were censored by death or the end of follow-up at December 31, 2004.

Predictors and Covariates

Candidate predictors included traditional risk factors for advanced kidney disease, including hypertension, diabetes, cardiovascular disease, and dyslipidemia; and HIV-related characteristics, including lower CD4 lymphocyte count, higher HIV viral load, coinfection with hepatitis C virus, and hypoalbuminemia. Most of these factors are considered indications for annual screening for kidney disease according to the Infectious Diseases Society of America Guidelines for the Management of CKD in HIV-infected patients.[1] Although cardiovascular disease is not mentioned in these guidelines as a risk factor for CKD, it is associated strongly with kidney disease in HIV-uninfected persons.[23,24] Additional candidate predictors included age, race, body mass index, and use of specific classes of medications, including angiotensin-converting enzyme inhibitors, statins, and ART.

Demographic characteristics were obtained from the VA or Medicare health plan databases.[25] Diabetes, hypertension, cardiovascular disease, and HIV-related characteristics were ascertained by validated algorithms using a combination of ambulatory diagnoses, physician problem lists, hospitalization discharge diagnoses, procedures, laboratory results, and medication prescriptions.[26-30] Baseline hypertension was defined as the diagnosis of hypertension before or within the first year of follow-up. Hypoalbuminemia was defined as serum albumin level <3.5 mg/dL. Proteinuria was measured by spot urine dipstick. Baseline proteinuria was defined by the first urine dipstick measurement during follow-up. eGFR was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation based on age, sex, race, and serum creatinine level[31]; the MDRD Study equation remains in clinical use in the VA laboratory reporting system. Baseline eGFR was defined as either the average of the first 2 consecutive eGFR measurements separated by at least 3 months or the initial eGFR measurement if a subsequent measurement was unavailable. We used medication prescription records to account for exposure to specific classes of medications, including ART, statins, and angiotensin-converting enzyme inhibitors. For all variables, we included a missing indicator category to retain observations in the analysis.

Statistical Analysis

We used a Cox proportional hazards survival analysis to determine the multivariate-adjusted association of each predictor variable with ESRD risk. We used Schoenfeld residuals[32] to test the proportional hazards assumption and assessed individual risk factors in univariate Cox models. We then built the multivariate model using $P < 0.05$ for entry and retention of covariates. To account for potential bias due to the competing risk of death before ESRD, we performed a Fine-Gray competing-risks analysis, which extends the Cox proportional hazards model to competing-risks data by simultaneously evaluating hazards for the primary (ESRD) and competing (death) events.[33] Baseline values were used for age, eGFR, proteinuria, and hypertension. All other variables were time-updated using the last-value-carried-forward method.[26,34] Analyses also were stratified by white and black race to evaluate for possible effect modification. Finally, we used the C statistic[35]

to determine the ability of demographics (age and race), the 7 risk factors (hypertension, diabetes, cardiovascular disease, CD4 lymphocyte count, HIV viral load, hepatitis C virus coinfection, and hypoalbuminemia), proteinuria, and eGFR to discriminate risk of ESRD.

We then evaluated the combined ability of baseline eGFR and proteinuria to predict differential ESRD risk in HIV-infected individuals. We stratified the cohort by baseline eGFR (≥60, 30-59, or <30 mL/min/1.73 m^2) and baseline proteinuria (urine dipstick, 0, 30-100, or 300-1,000 mg/dL) and determined the ESRD event rate in each group. Using a baseline eGFR >60 mL/min/1.73 m^2 and negative urine dipstick result as the referent group, we calculated the multivariate-adjusted hazard ratio for ESRD in each joint category of baseline eGFR and proteinuria.

All analyses were conducted using Stata, version 11.0 (www.stata.com). This study was approved by the Committee on Human Research at the San Francisco VA Medical Center and the VA Public Health Strategic Health Care Group.

RESULTS

We analyzed 22,156 HIV-infected individuals who were followed up for a median of 69 months, during which 366 developed ESRD requiring long-term dialysis therapy. The overall rate of ESRD was 3.1 events/1,000 person-years. Compared with patients who did not develop ESRD, patients who developed ESRD were of similar age and sex, but were overwhelmingly of black race. Despite similar percentages of black and white veterans in the group without ESRD (42% and 36%, respectively), 85% of patients who developed ESRD were black compared with only 13% who were white (Table 1). As expected, patients who developed ESRD were more likely to have had proteinuria or eGFR <60 mL/min/1.73 m^2 at baseline compared with those who did not develop ESRD. Additionally, patients who developed ESRD were more likely to have comorbid conditions at baseline, including hypertension, diabetes, and cardiovascular disease, as well as lower CD4 lymphocyte counts and a higher prevalence of hypoalbuminemia and coinfection with hepatitis C virus. There was no significant difference in baseline HIV viral load between the 2 groups. The prevalence of ART use at baseline appeared modestly lower in individuals who developed ESRD, but this difference did not reach statistical significance ($P = 0.06$). Across the entire cohort, the percentage of individuals who ever received ART increased from 25% at baseline to 74% by the end of follow-up and did not

Table 1. Baseline Characteristics by ESRD Status

	No ESRD (n = 21,790)	ESRD (n = 366)	*P*
Age (y)	45 ± 10	45 ± 8	0.9
Women	2.2	2.2	0.9
Race			<0.001
White	36	13	
Black	42	85	
Other	4	3	
Unknown	18	0	
Body mass index (kg/m^2)	24.9 ± 4.5	24.6 ± 4.4	0.6
eGFR <60 mL/min/1.73 m^2	5	46	<0.001
Proteinuria			<0.001
0 mg/dL	84	32	
30-100 mg/dL	15	43	
300-1,000 mg/dL	1	26	
Hypertension	30	67	<0.001
Diabetes	5	20	<0.001
Cardiovascular disease	5	8	0.01
Dyslipidemia	8	8	0.7
CD4 count (cells/μL)	285 ± 289	236 ± 243	0.008
Viral load (copies/mL)	82,009 ± 166,484	96,007 ± 146,947	0.5
Hepatitis C virus infection	20	30	<0.001
Hypoalbuminemia[a]	18	37	<0.001
Antiretroviral therapy	25	21	0.06
Statin use	2	1	0.09
ACE-inhibitor use	2	4	0.02

Note: ESRD status defined at the end of observation. Categorical variables reported as proportion with condition (percentage); continuous variables reported as mean ± standard deviation.

Abbreviations: ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

[a]Serum albumin level <3.5 mg/dL.

Table 2. Risk Factors for ESRD in HIV-Infected Veterans

Risk Factors	Multivariate-Adjusted Model[a]		Competing-Risks Analysis[b]	
	HR (95% CI)	*P*	Sub-HR (95% CI)	*P*
Baseline age quartile				
<38 y	1.00 (reference)		1.00 (reference)	
38-44 y	0.90 (0.65-1.25)	0.5	0.84 (0.60-1.18)	0.3
45-49 y	0.59 (0.42-0.82)	0.002	0.55 (0.38-0.78)	0.001
≥50 y	0.36 (0.26-0.51)	<0.001	0.33 (0.23-0.48)	<0.001
Race				
White	1.00 (reference)		1.00 (reference)	
Black	3.06 (2.22-4.22)	<0.001	3.24 (2.18-4.82)	<0.001
Baseline hypertension	1.87 (1.46-2.40)	<0.001	2.04 (1.56-2.68)	<0.001
Diabetes	1.69 (1.32-2.16)	<0.001	1.54 (1.15-2.08)	0.004
Cardiovascular disease	2.17 (1.72-2.74)	<0.001	1.78 (1.34-2.36)	<0.001
Dyslipidemia	1.16 (0.91-1.49)	0.2	1.46 (1.11-1.94)	0.007
CD4 count				
>350 cells/μL	1.00 (reference)	—	1.00 (reference)	—
200-350 cells/μL	0.92 (0.65-1.29)	0.6	0.92 (0.64-1.32)	0.7
<200 cells/μL	1.54 (1.17-2.02)	0.002	1.30 (0.97-1.76)	0.08
Viral load				
<500 copies/mL	1.00 (reference)	—	1.00 (reference)	—
500-3,999 copies/mL	0.89 (0.60-1.32)	0.6	0.81 (0.52-1.27)	0.4
4,000-29,999 copies/mL	1.42 (0.99-2.03)	0.06	1.28 (0.88-1.87)	0.2
≥30,000 copies/mL	2.01 (1.46-2.76)	<0.001	1.44 (1.02-2.03)	0.04
Hepatitis C virus	1.90 (1.52-2.38)	<0.001	1.95 (1.53-2.50)	<0.001
Hypoalbuminemia[c]	2.14 (1.80-2.54)	<0.001	1.99 (1.69-2.34)	<0.001
Baseline eGFR				
≥60 mL/min/1.73 m^2	1.00 (reference)	—	1.00 (reference)	—
30-59 mL/min/1.73 m^2	6.43 (4.81-8.58)	<0.001	5.24 (3.72-7.39)	<0.001
<30 mL/min/1.73 m^2	28.09 (20.29-38.88)	<0.001	20.87 (13.73-31.73)	<0.001
Baseline proteinuria				
0 mg/dL	1.00 (reference)		1.00 (reference)	
30-100 mg/dL	5.63 (4.29-7.38)	<0.001	5.25 (3.88-7.11)	<0.001
300-1,000 mg/dL	18.09 (12.96-25.23)	<0.001	18.26 (12.40-26.89)	<0.001

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; HR, hazard ratio.

[a]Proportional hazards multivariate analysis adjusted for baseline age, race, body mass index, baseline eGFR, baseline proteinuria, baseline hypertension, diabetes, cardiovascular disease, CD4 lymphocyte count, HIV viral load, hepatitis C infection, hypoalbuminemia (serum albumin <3.5 mg/dL), and receipt of ACE inhibitor.

[b]Adjustment for the competing risk of death using Fine-Gray analysis. Competing-risks model estimates sub-HR for ESRD accounting for competing risk of death before ESRD.

[c]Serum albumin level <3.5 mg/dL.

differ between patients who did and did not develop ESRD (74% in each respective group; $P = 0.7$).

Several predictors were strongly and independently associated with higher ESRD risk after multivariate adjustment for demographics, traditional risk factors for kidney disease, and HIV-related characteristics (Table 2). Individuals of black race had a 3-fold higher risk of ESRD compared with nonblack individuals. Among the traditional risk factors for kidney disease, hypertension, diabetes, and cardiovascular disease were each associated with a 2-fold higher ESRD risk. HIV disease severity also predicted the risk of ESRD. Compared with CD4 lymphocyte count >350 cells/μL, CD4 lymphocyte counts <200 cells/μL were associated with a 50% increase in ESRD risk, whereas CD4 lymphocyte counts of 200-350 cells/μL were not independently associated with ESRD risk. Similarly, HIV viral load ≥30,000 copies/mL, hepatitis C coinfection, and hypoalbuminemia each portended a 2-fold increase in ESRD risk. Finally, lower baseline eGFR and higher baseline proteinuria predicted substantially higher ESRD risk in a dose-response fashion.

Modeling demographic characteristics with the 7 risk factors (hypertension, diabetes, cardiovascular

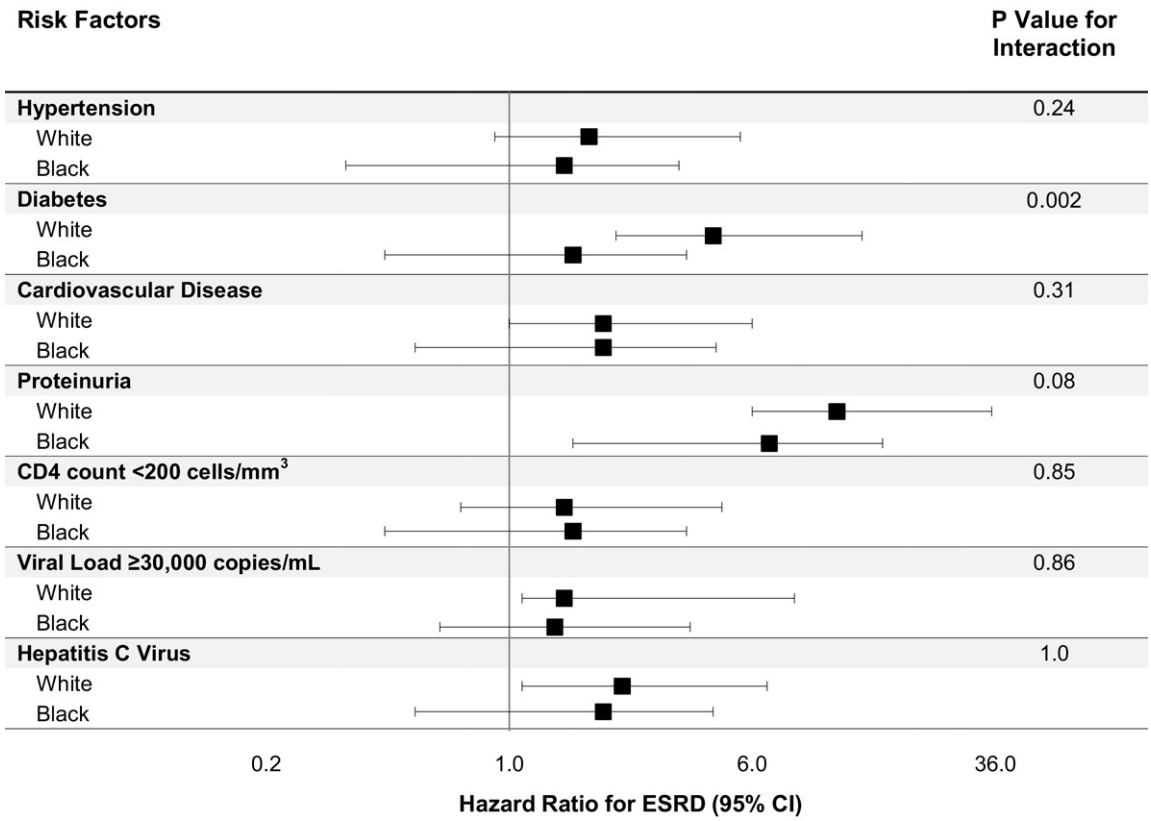

Figure 1. Risk factors for end-stage renal disease (ESRD) stratified by race. Multivariable model adjusted for baseline age, race, body mass index, baseline estimated glomerular filtration rate, baseline urine dipstick result, baseline hypertension, diabetes, cardiovascular disease, CD4 lymphocyte count, human immunodeficiency virus (HIV) viral load, hepatitis C infection, hypoalbuminemia (serum albumin <3.5 mg/dL), and receipt of angiotensin-converting enzyme inhibitor. Abbreviation: CI, confidence interval.

disease, CD4 lymphocyte count <200 cells/μL, HIV viral load ≥30,000 copies/mL, hepatitis C coinfection, and hypoalbuminemia) resulted in a C statistic of 0.87. Combined with baseline eGFR and proteinuria, the C statistic increased to 0.95.

When the competing risk of death before ESRD was accounted for (Table 2), the multivariate-adjusted associations of CD4 lymphocyte count <200 cells/μL and HIV viral load ≥30,000 copies/mL with ESRD were decreased in magnitude and rendered nonsignificant. All other predictors remained significantly associated with ESRD.

When stratified by race (Fig 1), the adjusted hazard ratios for ESRD for each risk factor were similar between the white and black race groups, with the exception of diabetes. Diabetes had a hazard ratio of 4.5 (95% confidence interval, 2.3-9.0) in white individuals compared with 1.6 (95% confidence interval, 1.2-2.1) in black individuals (P for interaction = 0.002).

We next stratified the cohort by baseline eGFR and proteinuria and observed exponential increases in ESRD event rates with lower eGFR and higher proteinuria (Fig 2). Notably, individuals with urine protein excretion of 300-1,000 mg/dL and preserved eGFR (>60 mL/min/1.73 m^2) had a 6-fold higher ESRD rate compared with individuals with decreased eGFR of 30-59 mL/min/1.73 m^2 but no proteinuria. Additionally, urine protein excretion of 30-100 mg/dL with preserved eGFR portended ESRD risk similar to decreased eGFR of 30-59 mL/min/1.73 m^2 without proteinuria. Based on the multivariate-adjusted hazard ratios for ESRD, individuals were categorized as having no, mild, moderate, or severe CKD.

DISCUSSION

In the present era of ART, ESRD remains an important clinical complication of HIV infection. Our observed ESRD rate of 3.1 events/1,000 person-years is nearly as high as the rate of myocardial infarction, 3.5 events/1,000 person-years, observed in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study.[36] An important outcome of this study is our finding that traditional risk factors for kidney disease and HIV-related factors had relatively similar associations with ESRD. Furthermore, we found that staging CKD jointly by eGFR and proteinuria resulted in remarkable risk stratification for ESRD in HIV-infected individuals and should be used broadly in clinical practice.

	Proteinuria		
	0 mg/dL	30-100 mg/dL	300-1,000 mg/dL
eGFR ≥60 ml/min/1.73m^2			
Number of Patients at Risk	15,348	2,390	185
ESRD Rate per 1,000 Person-Years	1.0	6.6	35.4
Hazard Ratio (95% CI)†	Reference	6.3 (4.6-8.6)	24.6 (16.0-37.7)
eGFR 30-59 ml/min/1.73m^2			
Number of Patients at Risk	484	350	85
ESRD Rate per 1,000 Person-Years	5.5	31.1	115.6
Hazard Ratio (95% CI)†	7.4 (4.0-13.8)	37.1 (25.3-54.6)	88.7 (56.0-140.5)
eGFR <30 ml/min/1.73m^2			
Number of Patients at Risk	38	106	60
ESRD Rate per 1,000 Person-Years	46.1	111.1	192.9
Hazard Ratio (95% CI)†	42.6 (18.3-99.4)	132.8 (87.1-202.5)	523.0 (323.6-845.4)

Figure 2. Chronic kidney disease (CKD) staging by risk of progression to end-stage renal disease (ESRD). ESRD rate per 1,000 person-years stratified by baseline estimated glomerular filtration rate (eGFR) and proteinuria (measured by urine dipstick). Severity of CKD shown by intensity of shading (no CKD vs mild, moderate, and severe CKD). †Multivariate-adjusted hazard ratios for ESRD adjust for baseline age, race, body mass index, baseline eGFR, baseline proteinuria, baseline hypertension, diabetes, cardiovascular disease, CD4 lymphocyte count, human immunodeficiency virus (HIV) viral load, hepatitis C infection, hypoalbuminemia (serum albumin <3.5 mg/dL), and receipt of angiotensin-converting enzyme inhibitor. Abbreviation: CI, confidence interval.

This is the first large cohort study in support of the clinical practice guideline published by the Infectious Diseases Society of America recommending routine screening for kidney disease in specific groups of HIV-infected patients, including black individuals and those with hypertension, diabetes mellitus, low CD4 lymphocyte count, high HIV viral load, and hepatitis C coinfection.[1] Prior studies in support of this recommendation were few and limited by their small sample sizes.[10,37,38] We found that most of these factors predicted higher risk of ESRD in a large population of HIV-infected veterans, even when the competing risk of death before ESRD was accounted for. The observed decreases in effect sizes of CD4 lymphocyte count and HIV viral load in competing-risks analyses likely represent the strong association of these factors with death in the HIV-infected patient population.

Our findings also reinforce the dramatic effect of race on the incidence and progression of HIV-related kidney disease, which has been reported previously.[7,8] Despite similar risk factors for the development of ESRD and similar access to health care in this study, black individuals had a 3-fold higher ESRD risk compared with whites. Unfortunately, biopsy data were not available to us and we were unable to distinguish cases of HIVAN from other forms of HIV-related kidney disease. However, others have reported that blacks with non-HIVAN histopathology still experience faster progression to ESRD than whites.[8] This racial predilection for ESRD in HIV infection is consistent with the epidemiology of ESRD in the general population, for which the risk of progression from CKD to ESRD has been reported as 4-fold higher in blacks compared with whites.[39] Recent literature suggests there may be genetic polymorphisms that predispose black individuals to kidney disease to a greater degree than white individuals.[40] Given their disproportionate burden of ESRD, further studies should evaluate the utility of early screening and monitoring of kidney function in black HIV-infected individuals, perhaps with a combination of creatinine level, urine protein excretion, and cystatin C level.[41]

There is concern that long-term exposure to ART may unintentionally promote the development of traditional risk factors for kidney disease, such as hypertension and diabetes.[14,15,42] The present study was not designed to evaluate the long-term effects of ART on

the kidney, and the prevalence of ART exposure by the end of follow-up was similar between patients who developed ESRD and those who did not. However, our findings that high viremia and low CD4 lymphocyte counts remain associated with ESRD suggest that viral suppression and reversal of immunosuppression by ART is beneficial to the kidney. Data from the Strategies for Management of Antiretroviral Therapy (SMART) Study also support the concept that continuous use of ART is associated with fewer cardiovascular, renal, and hepatic complications compared with episodic use of ART,[43] although the number of renal events in the study was small. Finally, ART-related decreases in mortality rates from infectious complications may have allowed patients to survive long enough to reach ESRD.

The strengths of this study include its large size, national scope, the relatively uniform health care system available to US veterans, and the reliable data source for the outcome of ESRD. There are important limitations to this study. First, as a study of predominantly male veterans receiving care in the Department of VA Health Care System, results may not be generalizable to female patients, nonveteran patients, patients without access to health care, or other racial and ethnic groups not represented in this cohort. Compared with HIV-infected nonveterans, HIV-infected veterans previously have been shown to have higher CD4 lymphocyte counts and a lower prevalence of AIDS-defining conditions.[44] The incidence of ESRD in this study therefore could be an underestimate of ESRD incidence in the nonveteran HIV population. Second, as noted, biopsy data were not available for patients who progressed to ESRD; thus, we were unable to distinguish cases of HIVAN from other forms of HIV-related kidney disease. The presence of biopsy data could have enabled us to differentiate the risk factors specific to HIVAN versus other forms of HIV-related kidney disease. Biopsy data also may have allowed us to evaluate whether proteinuria portends differential risk of HIVAN versus traditional forms of kidney disease. Third, as noted, this study was not designed to evaluate the long-term effects of ART on the kidney. Our data regarding ART use is limited to whether patients were exposed to ART during follow-up. We were unable to determine whether exposure to specific classes of ART medications is beneficial or harmful to the kidney. Fourth, we had no knowledge of veterans' *APOL1* (apolipoprotein L-I) or *MYH9* (nonmuscle myosin, heavy chain 9) genotypes and therefore could not evaluate whether genetic polymorphisms in blacks might interact with clinical risk factors or add to ESRD prediction. Finally, the identified clinical variables may not necessarily be in the causal pathway, and despite our multivariate-adjusted analysis, we cannot exclude the possibility of residual confounding.

In conclusion, in this large contemporary cohort of HIV-infected veterans, the risk of ESRD appeared to be attributable to a combination of traditional risk factors for kidney disease, such as hypertension and diabetes, and HIV disease severity. A combined assessment of eGFR and proteinuria constitutes a novel method for CKD staging in HIV-infected individuals and effectively stratifies individual risk of progression to ESRD. This updated staging method should be evaluated further as a potential framework for targeting renoprotective interventions in this unique population.

ACKNOWLEDGEMENTS

This report is dedicated to the memory of Andy I. Choi, MD, MAS.

Support: This study was supported by National Institutes of Health grants K23DK080645-01A1 (A.I.C.), 1R03AG034871-01 (A.I.C.), R01 DK066488-01 (M.G.S.), which were administered by the Northern California Institute for Research and Education, and with resources of the VA Medical Center, San Francisco, CA. These funding sources had no involvement in the design or execution of this study.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

REFERENCES

1. Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2005;40(11):1559-1585.

2. Humphreys MH. Human immunodeficiency virus-associated glomerulosclerosis. *Kidney Int*. 1995;48(2):311-320.

3. Lucas GM, Eustace JA, Sozio S, Mentari EK, Appiah KA, Moore RD. Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: a 12-year cohort study. *AIDS*. 2004;18(3):541-546.

4. Ross MJ, Klotman PE. HIV-associated nephropathy. *AIDS*. 2004;18:1089-1099.

5. Eggers PW, Kimmel PL. Is there an epidemic of HIV infection in the US ESRD program? *J Am Soc Nephrol*. 2004;15:2477-2485.

6. US Renal Data System. USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. *Am J Kidney Dis*. 2011;57(1)(suppl 1):e1-e526.

7. Choi AI, Rodriguez RA, Bacchetti P, Bertenthal D, Volberding PA, O'Hare AM. The impact of HIV on chronic kidney disease outcomes. *Kidney Int*. 2007;72(11):1380-1387.

8. 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*. 2008;197(11):1548-1557.

9. Szczech LA, Grunfeld G, Scherzer R, et al. Microalbuminuria in HIV infection. *AIDS*. 2007;21(8):1003-1009.

10. Szczech LA, Gange SJ, van der Horst C, et al. Predictors of proteinuria and renal failure among women with HIV infection. *Kidney Int*. 2002;61:195-202.

11. 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*. 2004;39:1199-1206.

12. Mocroft A, Wyatt C, Szczech L, et al. Interruption of antiretroviral therapy is associated with increased plasma cystatin C. *AIDS*. 2009;23(1):71-82.

13. Tsui J, Vittinghoff E, Anastos K, et al. Hepatitis C seropositivity and kidney function decline among women with HIV: data from the Women's Interagency HIV Study. *Am J Kidney Dis*. 2009;54(1):43-50.

14. Brown TT, Cole SR, Li X, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch Intern Med*. 2005;165(10):1179-1184.

15. De Wit S, Sabin CA, Weber R, et al. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study. *Diabetes Care*. 2008;31(6):1224-1229.

16. El-Sadr WM, Mullin CM, Carr A, et al. Effects of HIV disease on lipid, glucose and insulin levels: results from a large antiretroviral-naive cohort. *HIV Med*. 2005;6(2):114-121.

17. Lucas GM, Mehta SH, Atta MG, et al. End-stage renal disease and chronic kidney disease in a cohort of African-American HIV-infected and at-risk HIV-seronegative participants followed between 1988 and 2004. *AIDS*. 2007;21(18):2435-2443.

18. Szczech LA, Gupta SK, Habash R, et al. The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. *Kidney Int*. 2004;66:1145-1152.

19. Backus L, Mole L, Chang S, Deyton L. The Immunology Case Registry. *J Clin Epidemiol*. 2001;54(1)(suppl 1):S12-S15.

20. Choi AI, Li Y, Deeks SG, Grunfeld C, Volberding PA, Shlipak MG. Association between kidney function and albuminuria with cardiovascular events in HIV-infected persons. *Circulation*. 2010;121(5):651-658.

21. Choi AI, Li Y, Parikh C, Volberding PA, Shlipak MG. Long-term clinical consequences of acute kidney injury in the HIV-infected. *Kidney Int*. 2010;78(5):478-485.

22. Maynard C, Chapko MK. Data resources in the Department of Veterans Affairs. *Diabetes Care*. 2004;27(2)(suppl 2):B22-B26.

23. Elsayed EF, Tighiouart H, Griffith J, et al. Cardiovascular disease and subsequent kidney disease. *Arch Intern Med*. 2007;167(11):1130-1136.

24. Shlipak MG, Katz R, Kestenbaum B, Fried LF, Siscovick D, Sarnak MJ. Clinical and subclinical cardiovascular disease and kidney function decline in the elderly. *Atherosclerosis*. 2009;204(1):298-303.

25. Sohn MW, Zhang H, Arnold N, et al. Transition to the new race/ethnicity data collection standards in the Department of Veterans Affairs. *Popul Health Metr*. 2006;4(7):7.

26. 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*. 2004;351(13):1296-1305.

27. Miller DR, Safford MM, Pogach LM. Who has diabetes? Best estimates of diabetes prevalence in the Department of Veterans Affairs based on computerized patient data. *Diabetes Care*. 2004;27(2)(suppl 2):B10-B21.

28. Goulet JL, Fultz SL, McGinnis KA, Justice AC. Relative prevalence of comorbidities and treatment contraindications in HIV-mono-infected and HIV/HCV-co-infected veterans. *AIDS*. 2005;19(3)(suppl 3):S99-S105.

29. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. *Hepatology*. 2004;39(4):1147-1171.

30. Justice AC, Lasky E, McGinnis KA, et al. Medical disease and alcohol use among veterans with human immunodeficiency infection: a comparison of disease measurement strategies. *Med Care*. 2006;44(8)(suppl 2):S52-S60.

31. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139(2):137-147.

32. Schoenfeld D. Residuals for the proportional hazards regression model. *Biometrika*. 1982;69(1):239-241.

33. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509.

34. Dekker FW, de Mutsert R, van Dijk PC, Zoccali C, Jager KJ. Survival analysis: time-dependent effects and time-varying risk factors. *Kidney Int*. 2008;74(8):994-997.

35. Newson RB. Comparing the predictive power of survival models using Harrell's C or Somer's D. *Stata J*. 2010;10:339-358.

36. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med*. 2003;349(21):1993-2003.

37. Gupta SK, Mamlin BW, Johnson CS, Dollins MD, Topf JM, Dube MP. Prevalence of proteinuria and the development of chronic kidney disease in HIV-infected patients. *Clin Nephrol*. 2004;61:1-6.

38. Laradi A, Mallet A, Beaufils H, Allouache M, Martinez F. HIV-associated nephropathy: outcome and prognosis factors. Groupe d' Etudes Nephrologiques d'Ile de France. *J Am Soc Nephrol*. 1998;9(12):2327-2335.

39. Hsu CY, Lin F, Vittinghoff E, Shlipak MG. Racial differences in the progression from chronic renal insufficiency to end-stage renal disease in the United States. *J Am Soc Nephrol*. 2003;14(11):2902-2907.

40. Rosset S, Tzur S, Behar DM, Wasser WG, Skorecki K. The population genetics of chronic kidney disease: insights from the MYH9-APOL1 locus. *Nat Rev Nephrol.* 2011;7(6):313-326.

41. Choi A, Scherzer R, Bacchetti P, et al. Cystatin C, albuminuria, and 5-year all-cause mortality in HIV-infected persons. *Am J Kidney Dis*. 2010;56(5):872-882.

42. Seaberg EC, Munoz A, Lu M, et al. Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003. *AIDS*. 2005;19(9):953-960.

43. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355(22):2283-2296.

44. Zingmond DS, Kilbourne AM, Justice AC, et al. Differences in symptom expression in older HIV-positive patients: the Veterans Aging Cohort 3 Site Study and HIV Cost and Service Utilization Study experience. *J Acquir Immune Defic Syndr*. 2003;33(suppl 2):S84-S92.