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Hepatitis C and the Risk of Kidney Disease and Mortality in Veterans With HIV

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Abstract

Objectives—To examine the effect of hepatitis C virus (HCV) on the prevalence of chronic kidney disease (CKD) among veterans with HIV and to evaluate independent associations of HCV and CKD with mortality.

Methods—We studied a national cohort of HIV-infected patients receiving care through the Veterans Healthcare Administration from 1998 to 2004. CKD was defined as an estimated glomerular filtration rate [eGFR (mL/min/1.73 m²)] < 60. Poisson regression was used to assess relationships between CKD, HCV, and mortality.

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Results—Among 23,155 HIV-infected veterans, 12% had CKD. Forty percent of the cohort was coinfecting with HCV, and a higher proportion of coinfecting subjects had CKD compared with monoinfected subjects (14% vs 11%, $P < 0.001$). During the median follow-up of 7.6 years, 37% of subjects died and a graduated increase in adjusted mortality rates occurred with lower levels of eGFR ($P < 0.001$). Adjusted mortality rates were consistently higher in HCV-coinfecting subjects across all levels of eGFR ($P < 0.001$). HCV was independently associated with increased mortality (incidence rate ratio 1.23, 95% confidence interval 1.17–1.29).

Conclusions—CKD is prevalent in HIV-infected veterans and associated with substantially higher mortality. Compared with their monoinfected counterparts, veterans coinfecting with HCV have significantly higher rates of CKD and mortality.

Keywords

death; HIV; hepatitis C; kidney failure; veterans

INTRODUCTION

Since the introduction of highly active antiretroviral therapy (HAART), life expectancy for persons with HIV infection has markedly increased.¹ As a consequence, chronic comorbid conditions are significantly influencing their health status and survival.² In the United States, up to 30% of HIV-infected individuals are coinfecting with hepatitis C virus (HCV), and many have liver disease and related complications that have been associated with increased morbidity and mortality.³ Furthermore, HIV–HCV coinfection has been hypothesized to accelerate the course of both diseases.^{4–11}

Chronic kidney disease (CKD) is a known consequence of HIV, HCV, and antiviral therapy, and HIV–HCV coinfection has been associated with an increased incidence and progression of CKD.^{12–23} CKD has been associated with higher mortality in HIV-infected patients; however, these studies have been limited by short follow-up periods, small sample sizes, or a lack of focus on the independent impact of HIV–HCV coinfection on mortality.^{15,16,23}

The Veterans Healthcare Administration (VHA) is the largest integrated provider of HIV care in the United States and has developed comprehensive clinical and administrative databases.²⁴ The VHA databases provide an opportunity to examine the relationships between HIV, comorbid conditions, and mortality. We examined the prevalence of CKD and HIV–HCV coinfection and their influence on mortality among a national cohort of HIV-infected veterans.

METHODS

The Veterans Aging Cohort Study (VACS) virtual cohort is described elsewhere²⁵ and includes 33,420 HIV-positive veterans identified from VHA medical records from October 1, 1997, to September 30, 2004. Baseline is defined as initiation of care in a VA Infectious Diseases clinic. The cohort was approved by the Institutional Review Boards of the VA Connecticut Healthcare System and Yale University and has been granted a waiver of informed consent.

Demographics and medical comorbidities were obtained from the National Patient Care databases at the Austin Automation Center, Austin, TX. Comorbidities were determined at baseline by International Classification of Diseases, 9th revision codes from hospitalizations and outpatient visits within 12 months before or 6 months after enrollment as previously described.^{25,26} Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) equation based on outpatient serum

creatinine at baseline.² If race was other or unknown, no correction was applied for African American race. eGFR was categorized according to the National Kidney Foundation classification system.²⁷ HCV coinfection was defined by either a HCV antibody or an International Classification of Diseases, 9th revision code for HCV. AIDS was defined by documentation of any AIDS-defining condition or a CD4+ cell count (CD4) < 200 cells/mm³ at baseline. HCV antibody, creatinine, CD4, and HIV-RNA (copies/mL) were obtained from Immunology Case Registry. Baseline use of antiretroviral agents was obtained from the VA Pharmacy Benefits Management. HAART was defined as the combination of at least 3 antiretroviral agents. Mortality data were obtained from the vital status mini file maintained by VA Information Resource Center and stored at the Austin Automation Center.

AIDS status, comorbidities, and use of HAART or specific antiretroviral agents at baseline were considered as binary variables. Age, CD4, HIV-RNA were analyzed as continuous variables. HIV-RNA was log₁₀ transformed and CD4 was square root transformed to approximate a normal distribution. Descriptive analyses were stratified by eGFR grouping and HCV status. Characteristics were compared using chi-squared or *t* tests, and those that approached significance were entered into multivariate Poisson regression models to allow the reporting of adjusted survival rates.²⁸ Variables were removed from the model if they were neither statistically significant nor clinically relevant. Two-tailed *P* values < 0.05 were considered significant. Statistical analyses were conducted with SAS, version 9.1.3 (Cary, NC).

RESULTS

The current analysis is restricted to 23,155 HIV-infected veterans with complete data and at least one serum creatinine value at cohort conception (Table 1). Compared with the overall cohort, included subjects had a higher HCV prevalence (40% vs 32%), higher median CD4 (336 vs 230 cells/mm³), and lower HIV-RNA (1007 vs 2444 copies/mL).

Baseline eGFR (mL/min/1.73 m²) was <60 in 12% of the cohort (Table 1). Compared with subjects with an eGFR ≥ 60, subjects with reduced eGFR were older, more often African American, and had a higher prevalence of comorbidities (*P* < 0.001). With lower levels of eGFR, a graduated trend toward more advanced HIV disease was seen as indicated by AIDS status, CD4, and HIV-RNA (*P* < 0.001). Patients with eGFR < 15 had the lowest receipt of HAART at baseline (*P* = 0.003).

Overall, 40% of the cohort was coinfecting with HCV (Table 1). A higher proportion of HIV-HCV coinfecting subjects had an eGFR < 60 (14% vs 11%), and both AIDS and non-AIDS comorbidities were more common (*P* < 0.05). Coinfecting subjects had a lower median CD4, higher median HIV-RNA, and were less likely to have received HAART at baseline (*P* < 0.05).

During a median of 7.6 years of follow-up, 37% of the cohort died. Adjusted mortality was consistently higher in coinfecting subjects across the spectrum of eGFR (Fig. 1). Moreover, a consistent, graduated, and significant trend existed between higher adjusted mortality rates and decreasing eGFR (*P* < 0.0001) with a plateau at eGFR < 30. The difference in adjusted mortality rates between coinfecting and monoinfecting subjects became smaller upon adjustment for eGFR with the adjusted mortality rate ratio decreasing from 1.27 to 1.20.

In multivariable analysis (Table 2), reduced eGFR was associated with significantly increased mortality compared with eGFR ≥ 60 [incidence rate ratio (IRR) 1.61, 95% confidence interval (CI) 1.50–1.73 and IRR 2.75, 95% CI 2.50–3.03 for eGFR 30–59 and eGFR 15–29, respectively]. No further increase in mortality was found with eGFR < 15

(IRR 2.46, 95% CI 2.25–2.71). HCV coinfection was also independently associated with higher mortality (IRR 1.23, 95% CI 1.17–1.29).

DISCUSSION

In this large national cohort of HIV-infected veterans, we found a high prevalence of CKD as defined by an eGFR < 60 mL/min/1.73 m². This observed prevalence of 12% is higher than that recently reported in a smaller study, where between 7.1% and 8.5% of HIV-infected veterans had CKD.^{14,16} In nonveteran populations with HIV, previous studies have reported a broad range of CKD prevalence between 2% and 15%.^{12,13,15,18} Differences in patient characteristics probably account for the high prevalence of CKD in our cohort, including a higher prevalence of African American race and traditional CKD risk factors, more advanced HIV disease, and low receipt of HAART.^{12,13–16,29–31} Associations between advanced HIV disease and CKD have been well described^{12,13,31} and HAART may attenuate the course of HIV-associated nephropathy.^{2,32,33}

Consistent with previous studies, we found a significant and graduated relationship between mortality and lower eGFR. Eighty percent of HIV-infected veterans with an eGFR < 30 died during follow-up compared with only one-third of those with normal baseline kidney function, and reduced eGFR was independently associated with substantially increased mortality. In a study of 534 veterans with CKD, Choi et al²⁹ found that African Americans with HIV and CKD had twice the rate of death compared with African Americans with diabetes and CKD. The cause of this exaggerated relationship between CKD and death in HIV-infected patients remains unclear and incompletely understood.^{17,34}

The most common comorbid condition in this veteran cohort was HCV coinfection, affecting more than one-third of subjects. Although the observed prevalence of HCV coinfection is similar to other urban and veteran cohorts, it is nearly twice that in many prior studies.^{3,9,11–13,35,36} A graduated increase in prevalence of HCV coinfection occurred with worsening eGFR, ranging from 39% in those with normal kidney function to 60% in those with eGFR < 15. Several reasons may account for this finding, including the known association between HCV and acute kidney injury, proteinuria, CKD, and ESRD^{18–20,22,30} and other known risk factors for CKD being more common in HCV-coinfected subjects.^{9,32,33}

We demonstrated consistently higher adjusted mortality rates among HCV-coinfected veterans at all levels of eGFR, and it seems that only approximately 25% of this excess mortality in HCV-coinfected veterans can be attributed to the higher prevalence of CKD. Moreover, HCV coinfection independently increased the likelihood of death by nearly 25%, after adjustment for other important HIV- and HCV-related factors. Known complications of HCV such as end-stage liver disease and commonly associated behaviors such as substance abuse were also associated with increased mortality, consistent with previous studies.^{3,36,37} These findings corroborate those of a recent small biopsy series of 100 patients with HIV, HCV, and HIV–HCV coinfection where HIV–HCV coinfection was independently associated with a 2.7-fold increase in mortality.²³ The reasons for the effect of HCV coinfection on mortality in patients with HIV remain unclear and controversial. Impaired immunologic or virologic response in the setting of HCV coinfection has been suggested as an explanation for worse health outcomes observed in patients with HIV–HCV coinfection in some studies,^{9–11,15,17} whereas other investigators have attributed higher hospitalization and mortality rates to non-AIDS complications such as liver disease.^{3,9,10,33,35,36} Finally, others have not observed an increase in adverse health outcomes among patients with HCV coinfection.³² The heterogeneity of these findings has been attributed to differences in cohorts, time intervals, antiviral therapies, and outcome measures.

There are limitations to this study. First, the VACS virtual cohort consists of veterans; therefore, these findings may be less generalizable to non-veteran populations. Second, identification of subjects with CKD was limited by the use of a single creatinine value and lack of data on proteinuria, which may be present in up to one-third of HIV-infected patients.^{13,15,17} However, our methodology has been widely utilized in previous publications, and the Modification of Diet in Renal Disease eGFR estimate has been endorsed by consensus guidelines for CKD management in patients with HIV.^{2,14,16} Third, although we capitalized on robust data sources within the VA, we did not consider information regarding disease management, such as blood pressure control, serial medication data, and repeat measures of HIV-RNA. Although this may lead to residual confounding, it is unlikely that our findings would be significantly different given the magnitude and graduated nature of the relationship between eGFR, HCV, and mortality. Repeat measures of CD4 were available and were generally stable during follow-up (data not shown). Finally, we relied on antibody assays to detect HCV, and so some misclassification of HCV is possible.⁹

The results of the current study demonstrate that CKD affects more than 1 in 8 HIV-infected veterans and is associated with significantly higher mortality. Veterans coinfecting with HCV incur even higher rates of CKD and mortality than those with only HIV infection. Efforts should be targeted toward optimizing medical care for mono- and coinfecting veterans, including HAART therapy, HCV antiviral therapy, and treatment of comorbid medical conditions.

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TABLE 1
Demographic and Clinical Characteristics of HIV⁺ VACS Cohort by EGFR and HCV Status

Variables	GFR Groupings					Overall	HIV Only	HIV-HCV
	≥60	30–59	15–29	<15				
N	20,322 (88%)	1602 (7%)	556 (2%)	675 (3%)		23,155	13,825 (60%)	9330 (40%)
Age (median [25th, 75th])	44 (38, 49)*	49 (43, 56)*	47 (42, 53)*	46 (41, 51)*		44 (39, 50)	43 (36, 51)*	45 (41, 49)*
Male sex (%)	98	98	99	99		98	98	98
Race (%)								
Black	52*	49*	69*	81*		52	44*	66*
White	38*	41*	29*	15*		38	43*	29*
Other/unknown	10	10	2*	4*		10	13*	5*
Hispanic ethnicity (%)	8	9	10	8		8	7*	10*
Kidney disease groups (%)								
GFR: >60	—	—	—	—		88	89*	86*
GFR: 30–60	—	—	—	—		7	7*	7*
GFR: 15–30	—	—	—	—		2	2*	3*
GFR: <15	—	—	—	—		3	2*	4*
Comorbidities (%)								
Hepatitis C	39*	40*	51*	60*		40	*	*
Hepatitis B	3*	4*	6*	6*		4	2*	5*
Liver disease (end stage/decompensated/cirrhosis)	1*	3*	8*	5*		1	1*	3*
Diabetes	13*	21*	24*	26*		15	13*	17*
Hypertension	15*	29*	35*	49*		17	16*	19*
Cardiovascular disease (CAD, CHF)*	3*	8*	11*	12*		4	4*	3*
Cerebrovascular disease (stroke, TIA)*	1*	2*	3*	3*		1	1	1
Peripheral vascular disease (PVD)*	1*	1*	3*	3*		1	0.8	0.7
Pulmonary diseases (pulmonary disorder, COPD)*	7*	9*	10*	8*		7	7*	8*

Variables	GFR Groupings					Overall	HIV Only	HIV-HCV
	≥60	30–59	15–29	<15				
Anemia	9*	20*	33*	27*		11	11	11
Hypertlipidemia	3*	6*	3*	3*		4	5*	2*
Any psychiatric disorder [†]	25*	23*	21*	19*		25	21*	31*
Substance abuse (%)								
Alcohol abuse	19*	16*	21*	17*		19	12*	30*
Drug abuse	22*	17*	21*	21*		21	11*	37*
Any substance abuse [‡]	27*	23*	30*	27*		27	15*	44*
HIV parameters								
AIDS (%)	29*	46*	62*	53*		32	30*	34*
CD4 [median (range)]	334 (0–2000)*	226 (0–1558)*	133 (0–1452)*	177 (0–1068)*		336 (0–2000)	349 (0–2000)*	316 (0–2000)*
Viral load [median (range)]	886 (9–75 × 10 ⁴)*	1750 (18–75 × 10 ⁴)*	9981 (27–75 × 10 ⁴)*	10,518 (25–75 × 10 ⁴)*		1007 (9–75 × 10 ⁴)	944 (9–75 × 10 ⁴)*	1127 (9–75 × 10 ⁴)*
HIV medications at baseline								
Indinavir	11*	15*	13*	9*		11	13*	9*
Ritonavir-boosted protease inhibitor	2*	4*	1*	2*		2	3*	2*
Tenofovir	0.16	0.19	0	0		0.2	0.2	0.1
HAART	17*	19*	16*	13*		17	20*	13*

* $P < 0.05$.

[†] Any psychiatric disorder comprised of bipolar, mild and major depression, post-traumatic stress disorder (PTSD), and schizophrenia.

[‡] Any substance abuse comprised of drug, alcohol, or cocaine.

CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; TIA, transient ischemic attack.

TABLE 2Factors Associated With Mortality in HIV⁺ VACS Cohort

Variables	IRR	95% CI
eGFR (30–59)	1.61	1.50–1.73
eGFR (15–29)	2.75	2.50–3.03
eGFR < 15	2.46	2.25–2.71
Age/10 yrs	1.50	1.46–1.54
African American race	0.90	0.86–0.94
Hepatitis C	1.23	1.17–1.29
Liver disease (end stage, decompensated, cirrhosis)	2.50	2.20–2.85
Diabetes	0.96	0.90–1.02
Hypertension	1.04	0.98–1.11
Cardiovascular disease (CAD, CHF)	1.34	1.21–1.48
Cerebrovascular disease (stroke, TIA)	1.31	1.11–1.53
Peripheral vascular disease (PVD)	1.20	0.98–1.48
Pulmonary diseases (pulmonary disorder, COPD)	1.11	1.03–1.20
Any psychiatric disorder [*]	0.97	0.92–1.03
Any substance abuse [†]	1.14	1.08–1.20
AIDS	1.10	1.01–1.19
CD4 ⁺ cell count	0.93	0.93–0.94
HIV-RNA level	1.33	1.31–1.36
HAART baseline	0.96	0.90–1.03

GFR ≥ 60 was the reference group; model adjusted for hepatitis B, hyperlipidemia, anemia, indinavir, boosted ritonavir, and tenofovir. IRR for CD4⁺ cell count was per one square root unit increase and the IRR for HIV-RNA level was per one log₁₀ unit increase.

^{*} Any psychiatric disorder is comprised of bipolar, mild and major depression, post-traumatic stress disorder (PTSD), and schizophrenia.

[†] Any substance abuse is comprised of illicit drug, alcohol, and cocaine use.

CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; IRR, incidence rate ratio; PVD, peripheral vascular disease; TIA, transient ischemic attack.