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Lucas, Gregory M
Jing, Yuezhou
Sulkowski, Mark
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Hepatitis C Viremia and the Risk of Chronic Kidney Disease in HIV-Infected Individuals

Gregory M. Lucas,[1] Yuezhou Jing,[1] Mark Sulkowski,[1] Alison G. Abraham,[1] Michelle M. Estrella,[1] Mohamed G. Atta,[1] Derek M. Fine,[1] Marina B. Klein,[2] Michael J. Silverberg,[3] M. John Gill,[4] Richard D. Moore,[1] Kelly A. Gebo,[1] Timothy R. Sterling,[5] and Adeel A. Butt,[6,7] for the NA-ACCORD of the IeDEA

[1]Johns Hopkins University, Baltimore, Maryland; [2]McGill University, Montreal, Quebec, Canada; [3]Kaiser Permanente Northern California, Oakland, California; [4]University of Calgary, Alberta, Canada; [5]Vanderbilt University, Nashville, Tennessee; [6]University of Pittsburgh, Pennsylvania; and [7]Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates

Background. The role of active hepatitis C virus (HCV) replication in chronic kidney disease (CKD) risk has not been clarified.

Methods. We compared CKD incidence in a large cohort of HIV-infected subjects who were HCV seronegative, HCV viremic (detectable HCV RNA), or HCV aviremic (HCV seropositive, undetectable HCV RNA). Stages 3 and 5 CKD were defined according to standard criteria. Progressive CKD was defined as a sustained 25% glomerular filtration rate (GFR) decrease from baseline to a GFR < 60 mL/min/1.73 m^2. We used Cox models to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

Results. A total of 52 602 HCV seronegative, 9508 HCV viremic, and 913 HCV aviremic subjects were included. Compared with HCV seronegative subjects, HCV viremic subjects were at increased risk for stage 3 CKD (adjusted HR 1.36 [95% CI, 1.26, 1.46]), stage 5 CKD (1.95 [1.64, 2.31]), and progressive CKD (1.31 [1.19, 1.44]), while HCV aviremic subjects were also at increased risk for stage 3 CKD (1.19 [0.98, 1.45]), stage 5 CKD (1.69 [1.07, 2.65]), and progressive CKD (1.31 [1.02, 1.68]).

Conclusions. Compared with HIV-infected subjects who were HCV seronegative, both HCV viremic and HCV aviremic individuals were at increased risk for moderate and advanced CKD.

Keywords. HIV; hepatitis C virus; chronic kidney disease; hepatitis C RNA; cohort study; glomerular filtration rate; injection drug use.

Hepatitis C virus (HCV) coinfection is present in 25% to 30% of HIV-infected persons in the United States [1]. Epidemiologic studies suggest that HCV seropositivity is linked to increased risk for chronic kidney disease (CKD) and end-stage renal disease (ESRD), in both the general population [2, 3] and human immunodeficiency virus (HIV)-infected individuals [4–6].

The association between HCV and CKD may be mediated by several potential mechanisms. First, HCV is associated with immune activation and immune complex glomerulonephritis [7–9]. Second, progressive liver disease, associated with longstanding HCV, may lead to hepatorenal syndrome. Third, HCV has been associated with an increased risk for diabetes [10], a leading cause of CKD and ESRD [11]. Additionally, the observed relationship between HCV and CKD may be confounded by heroin or cocaine use [12, 13], lower socioeconomic status [14, 15], and other factors that are associated with increased risk of CKD and ESRD.

Approximately 20% of individuals who are infected with HCV clear the viremia, although the rate of HCV clearance is lower in HIV-infected persons [16]. To explore the contribution of persistent HCV viremia on CKD risk, we compared CKD incidence in a large cohort of HIV-infected subjects in North America according to HCV exposure status: (1) HCV seronegative, (2) HCV viremic (detectable HCV RNA) and (3) HCV aviremic (HCV seropositive with undetectable HCV RNA).

METHODS

Study Design and Population

Our analysis included HIV-infected individuals who were part of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), a multisite consortium of 8 interval and 14 clinical cohort studies, with sites in the United States and Canada [17]. NA-ACCORD is part of the International Epidemiological Database to Evaluate AIDS project. Local institutional review boards approved each cohort's participation in the consortium. Contributing cohorts, using standardized data collection and reporting protocols, submitted demographic, behavioral, clinical, laboratory, treatment, and vital status data to a central data repository.

HCV Exposure Status and Covariate Definitions

The eligible population included HIV-infected adults who had (1) available sex, race (black vs nonblack), and age data; (2) an HCV antibody or HCV RNA test; and (3) 2 or more serum creatinine measurements after 1 January 1996. We used 4 domains to define HCV exposure status: HCV diagnosis code (either present or absent), HCV antibody assays, HCV RNA assays, and HCV recombinant immunoblot assays (RIBA) (Table 1). Individuals who could be categorized into an HCV exposure group were included in the analysis and those who could not be categorized were excluded.

Some, but not all, cohorts had HCV diagnosis codes that were collected by manual medical record review. While we did not require HCV diagnosis code data for inclusion in the analysis, we considered a positive HCV diagnosis code to be an exclusion criterion for the HCV seronegative group. Individual HCV antibody and RIBA results were reported by the cohorts as positive, negative, or indeterminate. Individual HCV RNA values were classified by the cohorts as undetectable or detectable, depending on the dynamic range of the assay being used. We ignored indeterminate HCV antibody, RIBA, and HCV RNA results (which occurred in <0.1% of subjects) in HCV exposure classification.

We categorized longitudinal HCV antibody and RIBA results as always negative or always positive and categorized longitudinal HCV RNA results as always undetectable or always detectable. We excluded individuals who had mixed negative and positive HCV antibody or RIBA results or who had mixed undetectable and detectable HCV RNA results in order to exclude instances that might reflect new HCV infections, HCV treatment, or data errors. We required subjects included in the HCV aviremic group to have at least 1 undetectable HCV RNA result after a positive HCV antibody result (Table 1).

We estimated glomerular filtration rate (GFR) with the chronic kidney disease epidemiology collaboration (CKD-EPI) equation that uses serum creatinine concentration, age, race, and sex [18]. CKD stages were defined as 2 or more GFR values below a threshold for >90 days or last available GFR below a threshold, with thresholds of 60 mL/min/1.73 m^2 for stage 3 CKD and 15 mL/min/1.73 m^2 for stage 5 CKD [19]. Similar to other groups [20, 21], we defined progressive CKD as a ≥25% GFR decline from baseline to a GFR < 60 mL/min/1.73 m^2 that persisted for >90 days. As defined, progressive CKD avoids counting outcomes in which a threshold is reached, but the relative change in GFR is small. We defined diabetes as use of insulin or oral hypoglycemic medication, diagnostic code for diabetes, blood glucose >200 mg/dL, or glycosylated hemoglobin >6.5%. We defined hypertension as use of antihypertensive medication, diagnostic codes for hypertension, 2 or more systolic blood pressure readings >140 mm Hg, or 2 or more diastolic blood pressure readings >100 mm Hg. Cohorts provided data on history of injection drug use, although different methods of ascertainment were used, including self-report in a standardized questionnaire, self-report at an initial clinician visit, and an International Classification of Diseases coding algorithm.

Statistical Analysis

We compared baseline characteristics between included and excluded NA-ACCORD subjects and between HCV exposure groups using χ^2 test for categorical variables and Wilcoxon rank sum test for continuous variables. In order to control for the anticipated strong association of age with duration of HCV infection and CKD incidence [22], we used chronological age as the time scale, with an arbitrary origin (onset of risk) at age 25 years. Baseline was defined as the latest of 3 events: 25th birthday, 1 January 1996, or date of earliest serum creatinine measurement in the cohort. Subject follow-up time was censored at CKD events, death, or last available serum creatinine measurement.

We calculated incidence rates (events/1000 person-years) for stage 3 CKD, stage 5 CKD, and progressive CKD. Subjects were included in the analyses for these 3 outcomes if their baseline GFR was >60 mL/min/1.73 m^2, >15 mL/min/1.73 m^2, and >30 mL/min/1.73 m^2, respectively. We used Cox proportional hazard models to calculate unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for the 3 HCV exposure groups. Since age was used as the time scale, both unadjusted and adjusted HRs controlled for age. In the adjusted model, we included race, sex, baseline GFR, history of injection drug use, hepatitis B surface antigenemia, and time-varying covariates, including calendar year, CD4 cell count, HIV RNA, diabetes, hypertension, antiretroviral therapy use, tenofovir use, indinavir use, lopinavir/ritonavir use, and atazanavir use. Time-varying covariates were updated every 6 months after baseline, with last observation carried forward if new values were not available. Hypertension and diabetes were structured as monotonically increasing binary variables.

We conducted several supplementary analyses. First, to assess for a dose–response relationship between HCV RNA and CKD risk, we stratified the HCV viremic group at the median

Table 1. Hepatitis C Virus Exposure Group Definitions

Group	Pattern	Hepatitis C Diagnosis Code[a]	Hepatitis C Antibody[b]	Hepatitis C RNA Level[c]	Hepatitis C Recombinant Immunoblot Assay[b]	Other Factors
HCV seronegative	(. . .)	Absent	All results negative	All results undetectable or no results available	All results negative or no results available	
HCV viremic	A	Present or absent	All results positive	All results detectable	All results positive or no results available	
	B	Present	No results available	All results detectable	All results positive or no results available	
HCV aviremic	(. . .)	Present or absent	All results positive	All results undetectable	All results positive or no results available	At least 1 undetectable HCV RNA was measured after the earliest positive HCV antibody test

Abbreviation: HCV, hepatitis C virus.

[a] Hepatitis C diagnosis code was either present or absent, based on information abstracted from clinical records.

[b] Longitudinal patterns of test results categorized as (1) all results negative, (2) all results positive, (3) no results available, or (4) mixed positive and negative results.

[c] Longitudinal patterns of test results categorized as (1) all results undetectable, (2) all results detectable, (3) no results available, or (4) mixed detectable and undetectable results.

HCV RNA value and calculated adjusted HR for those above and below the median. Second, we repeated the Cox models for CKD events using a more rigorous definition for the HCV aviremic group, requiring 2 or more undetectable HCV RNA values (rather than 1 or more values) separated by more than 60 days and following the earliest positive HCV antibody. Third, we repeated time-to-event analyses using cohort entry as the time origin and adjusting for age, rather than using age as the time scale. Fourth, we assessed whether race modified the observed associations between HCV status and CKD by testing interaction terms in the models and inspecting associations stratified by race. Fifth, we conducted a sensitivity analysis in which stages 3 and 5 CKD were defined only by 2 GFR values below the respective thresholds for at least 90 days (ie, excluding events defined only by last available GFR below threshold).

RESULTS

Study Participants

A total of 93 495 individuals met the data requirements to be considered for the analysis. Of these, 63 023 met criteria for 1 of the 3 HCV exposure groups and were included in the analysis and 30 472 were excluded because HCV status could not be categorized according to the specified criteria (Figure 1). Among subjects included in the analysis, 52 602 were categorized as HCV seronegative, 9508 as HCV viremic, and 913 as HCV aviremic. Baseline characteristics of excluded subjects and included subjects, stratified by HCV status, are shown in Table 2. Excluded subjects were qualitatively similar to included subjects for most variables, although many differences were statistically significant due to large numbers of subjects. However, compared with included subjects, excluded subjects were more likely to have a history of injection drug use and a

hepatitis C diagnosis. The patterns of HCV test results in the 3 HCV exposure groups and in included and excluded subjects are shown in Supplementary Table 1. Compared with included subjects, excluded individuals were more likely to be missing HCV antibody test results. Consistent with the inclusion criteria, no subjects included in the analysis had mixed positive and negative results for HCV antibody, HCV RNA, or HCV RIBA, while 7.4%, 4.7%, and 0.1% of excluded subjects, respectively, had mixed results for these tests.

Compared with HCV seronegative subjects, both HCV viremic and HCV aviremic subjects were older and were substantially more likely to have a history of injection drug use (Table 2). Compared with HCV seronegative subjects, HCV viremic subjects (but not HCV aviremic subjects) were more likely to be male and black and had earlier baseline dates and higher serum concentrations of alanine aminotransferase. Baseline serum creatinine concentrations, median GFR, and distribution within GFR categories were qualitatively similar in the 3 HCV exposure groups.

Incident CKD

Incidence rates with unadjusted and adjusted HRs for stage 3 CKD, stage 5 CKD, and progressive CKD are shown in Table 3. Compared with HCV seronegative subjects, HCV viremic subjects were at increased risk for stage 3 CKD (adjusted HR 1.36 [95% CI, 1.26, 1.46]), stage 5 CKD (1.94 [1.64, 2.30]), and progressive CKD (1.30 [1.18, 1.43]), while HCV aviremic subjects were also at increased risk for stage 3 CKD (1.19 [0.98, 1.45]), stage 5 CKD (1.68 [1.07, 2.65]) and progressive CKD (1.31 [1.02, 1.69]). Compared with HCV aviremic subjects, the risks of stage 3 CKD, stage 5 CKD, and progressive CKD were similar in HCV viremic subjects, adjusted HR 1.14 (95% CI, .94, 1.39), 1.16 (.74, 1.81), and 0.99 (.77, 1.28), respectively.
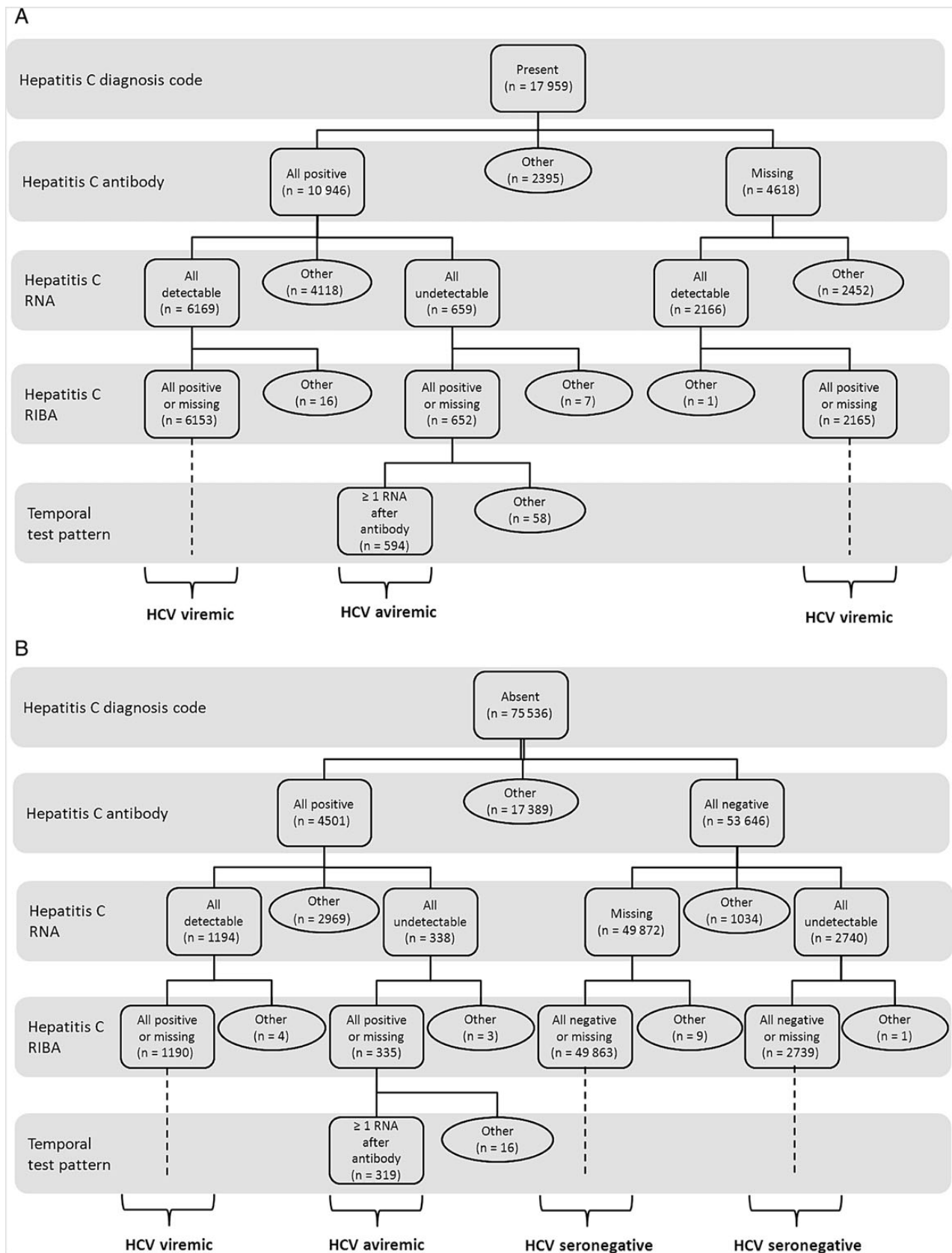
Figure 1. Disposition of human immunodeficiency virus–infected NA-ACCORD subjects who met the data requirements to be considered for the analysis, stratified by whether a hepatitis C diagnosis code was present (*A*) or absent (*B*). Rectangular and oval cells designate subjects who continued in the algorithm or were excluded from the analytic cohort, respectively. "Other" represents any pattern of results for a given factor that differs from those specified in sister cells. Abbreviations: RIBA, recombinant immunoblot assay; HCV, hepatitis C virus.

Table 2. Baseline Characteristics of Human Immunodeficiency Virus-Infected Subjects From NA-ACCORD According to Hepatitis C Exposure Group and Inclusion/Exclusion Status

Characteristic	Analytic Cohort (n = 63 023)			Included in Analysis (n = 63 023)	Excluded from Analysis (n = 30 472)
	HCV Seronegative (n = 52 602)	HCV Viremic (n = 9508)	HCV Aviremic (n = 913)		
Male, n (%)	42 883 (81.5)	8419 (88.5)[a]	722 (79.1)	52 024 (82.5)	26 086 (85.6)[b]
Age, years, median (P$_{25}$, P$_{75}$)	41 (34, 48)	47 (43, 52)[a]	47 (40, 51)[a]	42 (35, 49)	45 (38, 52)[b]
Black, n (%)	19 903 (37.8)	5511 (58.0)[a]	342 (37.5)	25 756 (40.9)	13 657 (44.8)[b]
Baseline date, median (P$_{25}$, P$_{75}$)	01/17/2003 (02/22/2000, 08/15/2006)	11/25/2000 (12/02/1999, 05/24/2004)[a]	01/27/2003 (04/18/2000, 08/09/2006)	09/05/2002 (01/31/2000, 05/08/2006)	08/24/2001 (12/15/1999, 07/14/2005)[b]
CD4 count, cells/mm^3, median (P$_{25}$, P$_{75}$)	342 (160, 538)	334 (172, 536)[c]	353 (170, 563)	340 (162, 538)	335 (161, 533)[d]
HIV RNA, log$_{10}$ copies/mL, median (P$_{25}$, P$_{75}$)	3.8 (2.3, 4.8)	3.5 (2.5, 4.6)[a]	3.6 (2.3, 4.7)[c]	3.8 (2.3, 4.8)	3.5 (2.3, 4.7)[b]
HIV RNA <500 copies/mL, n (%)	15 686 (34.3)	2939 (38.0)[a]	295 (38.6)[c]	18 920 (34.9)	9145 (38.0)[b]
History of AIDS-defining illness, n (%)	7223 (14)	1082 (11)[a]	118 (13)	8423 (13)	4096 (13)
Taking antiretroviral therapy n (%)	22 591 (42.9)	4227 (44.5)[c]	383 (41.9)	27 201 (43.2)	13 980 (45.9)[b]
Tenofovir, n (%)	5743 (10.9)	590 (6.2)[a]	86 (9.4)	6419 (10.2)	2907 (9.5)[d]
Indinavir, n (%)	565 (1.1)	66 (0.7)[c]	13 (1.4)	644 (1.0)	229 (0.8)[b]
Lopinavir/ritonavir, n (%)	5863 (11.1)	1581 (16.6)[a]	112 (12.3)	7556 (12.0)	4562 (15.0)[b]
Atazanavir, n (%)	1111 (2.1)	121 (1.3)[a]	19 (2.1)	1251 (2.0)	661 (2.2)
History of injection drug use, n (%)	5063 (9.6)	5667 (59.6)[a]	464 (50.8)[b]	11 194 (17.8)	9476 (31.1)[b]
Hypertension, n (%)	13 161 (25.0)	2374 (25.0)	204 (22.3)	15 739 (25.0)	7114 (23.3)[b]
Diabetes, n (%)	2346 (4.5)	737 (7.8)[a]	49 (5.4)	3132 (5.0)	2347 (7.7)[b]
Alanine aminotransferase, U/L, median (P$_{25}$, P$_{75}$)	26 (18, 40)	48 (31, 75)[a]	25 (17, 44)	28 (19,44)	31 (20, 49)[b]
Hepatitis B surface antigen positive, n (%)	1406 (2.7)	94 (1.0)[a]	33 (3.6)	1533 (2.4)	485 (1.6)[b]
Creatinine, mg/dL, median (P$_{25}$, P$_{75}$)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)[a]	0.9 (0.8, 1.1)[c]	0.9 (0.8, 1.1)	1.0 (0.8, 1.1)[b]
GFR, mL/min/1.73 m^2, median (P$_{25}$, P$_{75}$)	102 (86, 115)	103 (88, 116)[a]	100 (83, 112)	102 (86 115)	99 (82 112)[b]
GFR category, mL/min/1.73 m^2, n (%)					
>90	35 894 (69.4)	6754 (71.3)	619 (68.1)	43 267 (69.7)	19 344 (64)
60–89	13 535 (26.2)	2193 (23.1)	241 (26.5)	15 969 (25.7)	8894 (29.4)
30–59	1742 (3.4)	353 (3.7)	36 (4.0)	2131 (3.4)	1490 (4.9)
15–29	218 (0.4)	56 (0.6)	5 (0.6)	279 (0.4)	184 (0.6)
<15	305 (0.6)	120 (1.3)[a]	7 (0.8)	432 (0.7)	327 (1.1)[b]

Abbreviations: GFR, glomerular filtration rate; HCV, hepatitis C virus; HIV, human immunodeficiency virus; P$_{25}$, 25th percentile; P$_{75}$, 75th percentile.

[a] $P < .001$ compared with HCV seronegative subjects.

[b] $P < .001$ compared with included subjects.

[c] $0.05 > P \geq .001$ compared with HCV seronegative subjects.

[d] $0.05 > P \geq .001$ compared with included subjects.

Table 3. Incidence Rates and Relative Hazards of Chronic Kidney Disease Among Human Immunodeficiency Virus–Infected Individuals According to Hepatitis C Exposure Group

Outcome Exposure Group	Number of Events	Person-Years	Rate per 1000 Person-Years (95% CI)	Hazard Ratios (95% CI) Unadjusted[a]	Hazard Ratios (95% CI) Adjusted[a,b]
Stage 3 CKD[c]					
HCV seronegative	5090	269 805	18.9 (18.4, 19.4)	1.0	1.0
HCV viremic	1666	57 854	28.8 (27.5, 30.2)	1.22 (1.16, 1.30)	1.36 (1.26, 1.46)
HCV aviremic	122	4769	25.6 (21.4, 30.6)	1.14 (.96, 1.37)	1.19 (.98, 1.45)
Stage 5 CKD[c]					
HCV seronegative	699	287 386	2.4 (2.3, 2.6)	1.0	1.0
HCV viremic	376	61 833	6.1 (5.5, 6.7)	2.30 (2.02, 2.63)	1.95 (1.64, 2.31)
HCV aviremic	23	5139	4.4 (2.9, 6.7)	1.74 (1.15, 2.64)	1.69 (1.07, 2.65)
Progressive CKD[d]					
HCV seronegative	2885	279 096	10.3 (9.9, 10.7)	1.0	1.0
HCV viremic	984	59 892	16.4 (15.4, 17.5)	1.32 (1.22, 1.42)	1.31 (1.19, 1.44)
HCV aviremic	76	4952	15.4 (12.3, 19.2)	1.29 (1.02, 1.62)	1.31 (1.02, 1.68)

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HCV, hepatitis C virus.

[a] Age used as analysis time, so estimates account for age.

[b] Adjusted for sex, race, history of injection drug use, hepatitis B surface antigen positivity, baseline glomerular filtration rate, and time-updated covariates including, calendar year, CD4 cell count, human immunodeficiency virus RNA, antiretroviral therapy use, tenofovir use, indinavir use, lopinavir/ritonavir use, atazanavir use, hypertension, and diabetes.

[c] Stage 3 and stage 5 CKD were defined as glomerular filtration rates (GFR) that persisted below the threshold (60 mL/min/1.73 m^2 and 15 mL/min/1.73 m^2, respectively) for at least 90 days or last available GFR below the respective threshold among subjects with baseline GFR above the respective threshold.

[d] Progressive CKD was defined as a ≥25% GFR decline from baseline to a GFR < 60 mL/min/1.73 m^2 that persisted for at least 90 days among subjects with baseline GFR ≥ 30 mL/min/1.73 m^2.

Supplementary Analyses

First, we assessed for a dose–response relationship between HCV viremia level and CKD risk by stratifying the HCV viremic group into those above and below the median HCV RNA level (1 060 000 IU/mL). Compared with those with HCV RNA values below the median, those with HCV RNA values above the median were at similar risk for stage 3 CKD (HR 0.93; 95% CI, .84, 1.05), stage 5 CKD (HR 0.90; 95% CI, .71, 1.15), and progressive CKD (HR 1.05; 95% CI, .91, 1.21). Figure 2 shows adjusted HRs for CKD outcomes in HCV aviremic subjects and in HCV viremic subjects, stratified at the median HCV RNA level relative to HCV seronegative subjects. Second, we conducted a supplementary analysis using a rigorous definition of HCV aviremia, in which subject were required to have 2 or more undetectable HCV RNA measurements, separated by 60 or more days, occurring after a positive HCV antibody result. Compared with the definition used in the primary analysis, the rigorous definition reduced the number of subjects in the HCV aviremic group from 913 to 329. Although the CIs were wider, risk estimates with the rigorously defined HCV aviremic group were similar to those in the primary analysis. Specifically, compared with HCV seronegative subjects, the adjusted HRs (95% CI) for HCV aviremic subjects (rigorous definition) were 1.18 (.88, 1.58), 1.87 (.99, 3.54), and 1.38 (.96, 1.98) for stage 3 CKD, stage 5 CKD, and progressive CKD, respectively.

Third, we repeated the analysis using time from enrollment as the time scale (rather than age), with adjustment for age as a time-dependent covariate in the adjusted analysis. Compared with HCV seronegative subjects, the adjusted HR (95% CI) for HCV viremic and HCV aviremic subjects were similar for stage 3 CKD (1.48 [1.38, 1.58] and 1.46 [1.20, 1.78], respectively), stage 5 CKD (2.04 [1.75, 2.38] and 2.86 [1.82, 4.50], respectively), and progressive CKD (1.28 [1.16, 1.41] and 1.41 [1.10, 1.82], respectively). Fourth, to assess whether racial differences in cohorts might explain different findings in NA-ACCORD and Eurosyndrome de inmuno-deficiencia Adquirida (SIDA), we assessed for effect modification of HCV associations with CKD by race. The P values for interactions between race and HCV status were 0.17, 0.08, and 0.002 for stage 3 CKD, stage 5 CKD, and progressive CKD, respectively. However, confidence intervals were wide and racial differences were inconsistent across outcomes when adjusted HR estimates were stratified by race (Supplementary Table 2).

Fifth, we conducted sensitivity analyses in which stage 3 and stage 5 CKD were defined only by 2 GFR values below the respective thresholds for at least 90 days (ie, excluding events defined only by the last available GFR below threshold). A total of 4708 of 6878 (68%) stage 3 CKD events and 710 of 1098 (65%) stage 5 CKD events were defined by 2 GFR values below the respective thresholds. The results of this sensitivity analysis
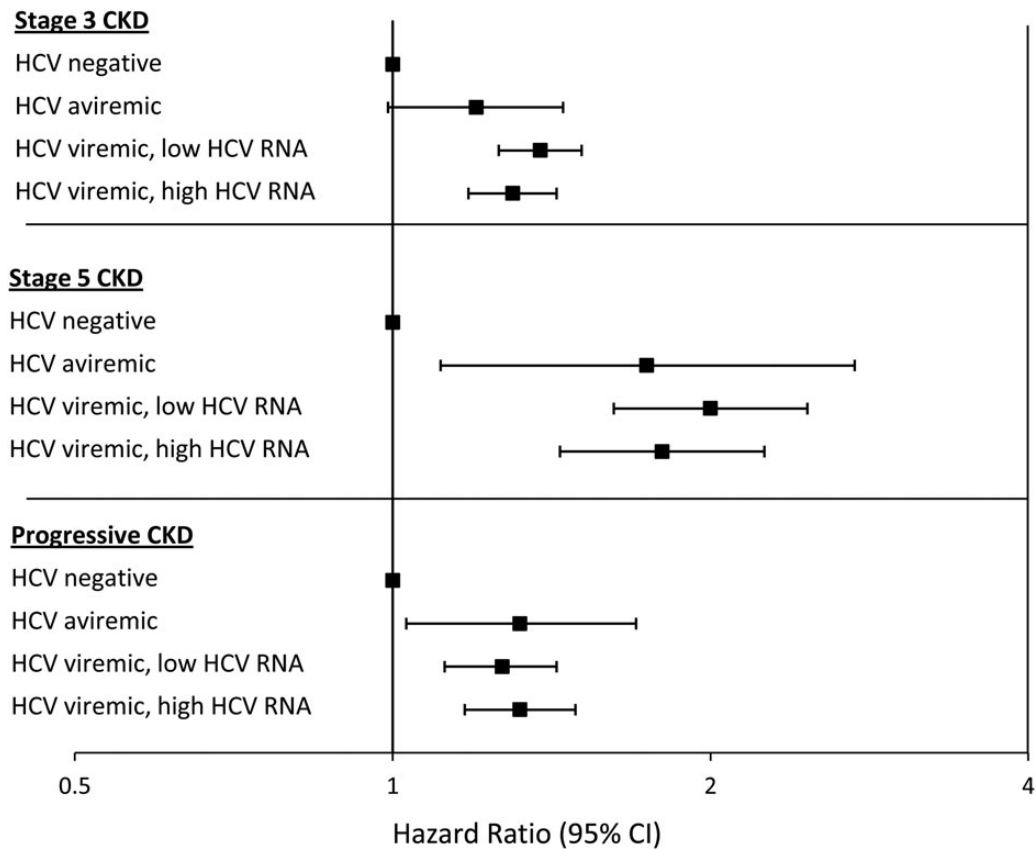
Figure 2. Adjusted hazard ratio point estimates and 95% confidence intervals (CIs) for stage 3 chronic kidney disease (CKD), stage 5 CKD, and progressive CKD, according to hepatitis C virus (HCV) exposure groups in human immunodeficiency virus (HIV)-infected subjects from NA-ACCORD. Low and high HCV RNA represent values below and above, respectively, the median value (1 060 000 IU/mL) for the subjects with detectable HCV viremia. Estimates were adjusted for age, sex, race, history of injection drug use, hepatitis B surface antigen positivity, baseline glomerular filtration rate, and time-updated variables including calendar year, CD4 cell count, HIV RNA, antiretroviral therapy use, tenofovir use, indinavir use, lopinavir/ritonavir use, atazanavir use, hypertension, and diabetes.

(Supplementary Table 3) showed trends that were similar to those in the primary analysis, although with wider CIs due to fewer events, particularly for stage 5 CKD.

DISCUSSION

In this consortium of HIV cohorts from the United States and Canada, we found that, compared with HCV seronegative individuals, prior HCV infection was associated with increased risk for stage 3 CKD, stage 5 CKD, and progressive CKD. Unexpectedly, we found that prior HCV infection was associated with excess CKD risk irrespective of the presence or absence of HCV viremia. Compared with HCV seronegative subjects, HCV viremic individuals were at significantly increased risk for all 3 CKD outcomes, while HCV aviremic subjects were at significantly increased risk for stage 5 CKD and progressive CKD, with a nonsignificant trend toward increased risk for stage 3 CKD. Moreover, there were no significant differences in risk

between HCV viremic and HCV aviremic subjects for any of the CKD outcomes.

An observed difference in CKD risk between HCV viremic and HCV aviremic individuals would be expected to reflect the role of ongoing HCV replication in CKD risk independent of behavioral or other characteristics that HCV-exposed individuals might share. Our results suggest that chronic HCV viremia is not the primary factor mediating increased CKD risk in HIV-infected persons with prior HCV exposure. However, our data do not rule out a small independent effect of HCV viremia, as HR point estimates were slightly higher in HCV viremic compared with HCV aviremic subjects for stage 3 and stage 5 CKD and CIs for the HCV aviremic group were relatively wide.

In our cohort, HCV viremic subjects were more likely to be male and black than HCV aviremic subjects. These differences are consistent with data that men and black individuals are less likely to clear HCV than women or nonblacks, respectively [23]. Racial differences in HCV clearance appear to be largely

or wholly explained by differences in the *IL28B* haplotypes [24]. We controlled for sex and race in adjusted models.

Several factors distinct from HCV viremia may mediate the observed association between HCV seropositivity and CKD. Heroin and cocaine use are major risk factors for HCV infection and have been implicated in the pathogenesis of kidney disease [25]. Cocaine has established mechanisms of vascular toxicity [26], is linked to cardiovascular disease [27], and has been associated with arterial intimal fibrosis and arteriosclerosis on kidney pathology [12, 28]. Although we adjusted for history of injection drug use, this variable was not collected systematically by the various cohorts, is subject to underreporting bias, does not include noninjection drug use, and does not distinguish between active and inactive use. Consequently, residual confounding from drug use behaviors is possible. Additionally, HCV seropositivity has been associated with antiretroviral therapy nonadherence and lower rates of HIV RNA suppression [29], and uncontrolled HIV increases the risk of CKD [30]. However, we controlled for time-updated antiretroviral therapy use, HIV RNA level, and CD4 cell count in our adjusted models. Finally, injection drug use and HCV coinfection are associated with lower socioeconomic status in HIV-infected individuals [31], and lower socioeconomic status has consistently been found to be a risk factor for kidney disease outcomes in the general population [14, 15]. Unfortunately, socioeconomic data were not available in NA-ACCORD, preventing us from examining this factor.

The results from the present study should be considered in context with other studies that examined the association of HCV viremia with CKD. Our findings are consistent with a study of more than 40 000 HCV seropositive and seronegative US male veterans, all of whom were HIV negative [2]. In this study, HCV seropositive patients were at 30% higher risk for stage 3 CKD than seronegative individuals, with similarly increased risk in HCV seropositive persons with detectable and undetectable HCV RNA levels.

However, our findings contrast with a recent analysis from the EuroSIDA cohort [21]. In an analysis of 8235 HIV-infected subjects, the investigators found no significant difference in the risk of CKD between HCV seronegative subjects and HCV aviremic subjects. In contrast, HCV viremic subjects had a statistically significant 2-fold increased risk of CKD compared with HCV seronegative subjects. However, the EuroSIDA study included fewer than 200 HCV aviremic individuals and the CIs around the point estimate for this group were wide. One difference between the 2 studies is that only 6% of subjects in the EuroSIDA study were black, whereas approximately 40% of subjects in NA-ACCORD were black. Black individuals are at increased risk for CKD compared with white individuals [32, 33]. When we stratified our outcome analyses by race, we could find no consistent evidence that HCV associations with CKD differed by race, although CIs were wide. A second study, by Mocroft and colleagues, analyzed data from 2 HIV clinical trials and reported a marginally statistically significant trend for increased CKD risk with increasing HCV RNA levels [20]. In contrast, we found no association between HCV RNA magnitude and CKD risk. Compared with our cohort, the population in the Mocroft study was less likely to have a history of injection drug use, less likely to be black, more likely to be receiving antiretroviral therapy at baseline, and had higher CD4 cell counts and lower HIV RNA levels at baseline. It is possible that the greater participant homogeneity and uniformity of treatment experience in the clinical trials cohort allowed a small HCV viremia association with CKD to be identified.

Our study has strengths, including centralized data mapping and harmonization and a large sample size that is representative of individuals receiving care for HIV in North America [34]. Our study also has several limitations. First, we did not have data on proteinuria, which is an independent predictor of clinical outcomes in CKD [19]. Second, individuals in the HCV aviremic group may have become reinfected with HCV, which may, in turn, have increased their risk for CKD. While reinfection has been documented in individuals who have previously cleared HCV, it appears that such individuals are also likely to clear reinfections [23, 35]. Additionally, we conducted a sensitivity analysis, using a more rigorous definition of HCV aviremia that required 2 undetectable HCV RNA measurements separated in time, in which inferences were unchanged. Third, we had minimal data on HCV treatment. However, we excluded subjects who had both undetectable and detectable HCV RNA values, as might be seen in the context of treatment, with the goal of selecting an HCV aviremic group composed primarily of subjects with prior immune clearance. Fourth, a large number of individuals in NA-ACCORD were excluded because insufficient data were available to categorize them into HCV exposure groups. If excluded subjects differed systematically from included subjects in ways relevant to the association between HCV status and CKD, our findings could be biased. However, we have no reason to suspect this is the case, and we have shown detailed comparisons of included and excluded subjects in Table 2 and Supplementary Table 1.

In summary, we found that HIV-infected individuals with prior HCV coinfection were at increased risk for moderate and advanced CKD, regardless of the presence HCV viremia. We found no significant differences in CKD risk in HCV viremic and aviremic subjects, although our data cannot rule out a small independent effect of HCV viremia for CKD. The mechanism behind increased CKD risk in HCV aviremic subjects is unclear but may include confounding effects from drug use, poorer control of HIV infection, lower socioeconomic status, or other unidentified factors.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of

data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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