Incidence and Predictors of Acute Kidney Injury in an Urban Cohort of Subjects with HIV and Hepatitis C Virus Coinfection

Shikha Garg, M.D., M.P.H.,¹ Melanie Hoenig, M.D.,² Erika M. Edwards, Ph.D., M.P.H.,³ Caleb Bliss, M.A.,⁴ Timothy Heeren, Ph.D.,⁴ Sheila Tumilty, R.N.,⁵ Alexander Y. Walley, M.D., M.Sc.,⁶ Margaret J. Koziel, M.D.,¹ Paul R. Skolnik, M.D.,⁷ C. Robert Horsburgh, M.D., M.U.S.,^{3,5} and Deborah Cotton, M.D., M.P.H.^{3,5}

Abstract

Coinfection with hepatitis C (HCV) significantly increases the risk of acute and chronic renal disease in HIV-infected individuals. However, the burden of acute kidney injury (AKI) directly attributable to HIV among HCV-infected individuals and associated risk factors are not well understood. Within a prospective cohort, AKI episodes were identified by a rise in creatinine of 0.5 mg/dL. Incidence of first AKI events was calculated for HIV/HCV coinfecting versus HCV monoinfected subjects, and multivariable analyses using Cox proportional hazards were performed to identify predictors of AKI. Throughout the study period, 35% HIV/HCV coinfecting and 17% HCV monoinfected subjects developed AKI, with incidence of 8.74/100 person-years and 3.53/100 person-years, respectively (hazard ratio (HR) 2.48; [95% confidence interval (CI) 1.50, 3.74]). In multivariable analysis, HIV coinfection (HR 2.19 [1.33, 3.62]), decompensated cirrhosis (HR 6.64 [3.81, 11.6]), and cocaine use (HR 2.06 [1.15, 3.71]) were independently associated with AKI. HCV genotype, HCV viral load, hazardous drinking, and heroin use were not associated with AKI. Study limitations included potential misclassification bias of HCV-infected individuals as serial HIV antibody testing was not routinely performed after study entry, and inability to adjust for tenofovir use in multivariable analysis. In conclusion, among subjects with HCV infection, decompensated cirrhosis, HIV coinfection, and cocaine use are associated with increased risk of AKI. These findings highlight the importance of preventing and treating cirrhosis, controlling HIV coinfection, and reducing cocaine use in HIV/HCV coinfecting persons.

Introduction

RENAL DISEASE is an increasingly important cause of morbidity and mortality among HIV-infected individuals.^{1,2} It is estimated that 30% of HIV-infected patients in the United States have abnormal renal function.¹ Recent epidemiologic studies have revealed that coinfection with hepatitis C virus (HCV) confers an even greater risk of both acute kidney injury (AKI) and chronic kidney (CKD) disease among individuals infected with HIV.³⁻⁷

AKI is a common complication among both ambulatory and hospitalized HIV-infected patients in the highly active antiretroviral therapy (HAART) era.^{3,4} In one study involving

hospitalized HIV patients by Wyatt and colleagues,³ AKI was associated with a 5.83 increased odds of in-hospital mortality. Franceschini and colleagues⁵ examined predictors of AKI among HIV-infected patients and found that coinfection with HCV was significantly associated with AKI, along with male gender, CD4 count less than 200 cells/mm³, HIV viral load (VL) greater than 10,000 copies per milliliter, and HAART exposure. A recent meta-analysis of studies involving HIV/HCV coinfection and renal disease found a pooled relative risk of 1.64 [95% confidence interval (CI) 1.21, 2.23] for AKI in HIV/HCV-coinfecting versus HIV-monoinfected patients. However, the authors commented that few of the studies provided a clear definition of HCV coinfection, and only one

¹Section of Infectious Diseases, ²Section of Nephrology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts.

³Department of Epidemiology, ⁴Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts.

⁵Section of Infectious Diseases, ⁶Section of General Internal Medicine, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts.

⁷Center for HIV/AIDS Care and Research, Boston University Medical Center, Boston, Massachusetts.

required HCV RNA testing for diagnosis.⁸ Thus, additional investigation is needed to understand the mechanisms underlying the association between HIV/HCV coinfection and renal disease.

Individuals with HIV/HCV coinfection demonstrate an accelerated course of liver disease progression to cirrhosis,⁹ and experience a high degree of liver-related morbidity and mortality.¹⁰ AKI is a frequent complication of decompensated cirrhosis in the general population, and in Franceschini's study,⁴ liver failure accounted for 18% of AKI events among HIV/HCV-coinfecting subjects. A subsequent study in the United Kingdom demonstrated that among 20 HIV/HCV-coinfecting patients with AKI, 7 had advanced cirrhosis while 5 experienced infectious complications of injection drug use (IDU).⁷

Although decompensated liver cirrhosis and infectious complications of IDU underlie some of the etiologies by which HIV/HCV coinfecting patients develop AKI, additional mechanisms remain unexplored. HCV has independently been associated with immune complex-mediated renal injury, but epidemiologic studies of the association between HCV mono-infection and renal disease have been inconclusive. Several studies have found increased associations between HCV infection and albuminuria, CKD, and end-stage renal disease (ESRD),^{11–13} while others have found no association.¹⁴ Since most studies of HIV/HCV infection and renal disease have relied solely on HCV antibody data, the impact of various HCV-specific factors such as viral load and genotype have not been well studied. In addition, despite the high prevalence of substance use among coinfecting patients, the associations between various substances of abuse and AKI have not been elucidated.

In this study, we sought to determine the incidence of AKI in HIV/HCV-coinfecting versus HCV-mono-infected subjects, and to examine the association between HCV-specific factors and exposure to various substances of abuse, and the subsequent development of AKI.

Methods

Study design/subject assembly

Subjects with HIV/HCV coinfection and HCV mono-infection were enrolled in a prospective cohort study of the natural history of liver disease progression. The present analysis covers the time period August 15, 2000 to December 31, 2007. Subjects were included if they had at least two creatinine (Cr) measures obtained a minimum of 3 months apart, and were excluded if they had less than 6 months of follow-up. Subjects were categorized as HCV mono-infected or HIV/HCV coinfecting based on their status at study entry.

Data collection

The study database contains information collected prospectively through semiannual patient surveys and annual electronic medical chart review. Data are available on self-reported illicit drug and alcohol use, clinical laboratory data, hospitalizations, liver events, and deaths.

Main exposures of interest Subjects reporting any quantity of heroin or cocaine use (through any route) within 6 months of interview were defined as having a positive ex-

posure. Hazardous alcohol use was defined as 5 or more drinks at least once per month. Nonhazardous alcohol use was defined as 5 or more drinks less than once per month or 1–4 drinks at any time. Nondrinkers were defined as having no alcohol use within 6 months of interview. Liver events, signifying the presence of decompensated cirrhosis, included: hepatic encephalopathy, ascites, spontaneous bacterial peritonitis, gastrointestinal variceal bleed, and hepatocellular carcinoma. HCV genotypes were grouped into categories 1 versus non-1 as the majority of subjects were infected with genotype 1. Subjects were defined as having a high versus low HCV VL, dichotomized at 750,000 copies per milliliter, which was the mean VL of the cohort. Among HIV/HCV-coinfecting subjects, HIV VL levels were defined as undetectable (<50 copies per milliliter), intermediate (50–4000 copies per milliliter), and high (>4000 copies per milliliter) based upon previous findings of an association between renal failure and HIV VL greater than 4000 copies per milliliter.¹⁵

Case ascertainment Electronic chart reviews were performed to identify episodes of incident AKI. For subjects with baseline Cr 1 mg/dL or less, AKI was defined as an absolute rise in Cr to more than 1.5 mg/dL or a relative rise of 0.5 mg/dL. For subjects with baseline Cr 1–2 mg/dL, AKI was defined as a rise in Cr of 0.5 mg/dL or more. For those with baseline Cr 2–4.9 mg/dL, AKI was defined as a rise in Cr of 1.0 mg/dL or more. For those with baseline Cr greater than 5 mg/dL, AKI was defined as a rise in Cr of 1.5 mg/dL or more, as described previously.¹⁴ When a rise in serum Cr occurred, available clinical data were reviewed to determine the probable cause. Events were categorized as prerenal, intrinsic renal, obstructive, or unknown. An event was attributed to prerenal azotemia when there was a clinical history of volume depletion and/or hypotension and renal function improved with hydration. Events were attributed to intrinsic renal disease from ischemic or toxic injury, based on available clinical data. Events were attributed to obstructive renal disease if clinical or radiographic evidence of nephrolithiasis or other forms of obstructive disease were identified. If data were insufficient, cause was characterized as unknown. Cases were reviewed by a nephrologist (M.H.) to ensure that criteria were met and events consistently characterized.

Statistical analysis

Data were analyzed using SAS version 9.1 (SAS Institute, Cary, NC). AKI incidence rates (IR) were calculated by dividing number of events by person time at risk. IRs were calculated for first AKI events, but not for subsequent events. χ^2 and Fisher exact tests were utilized to compare baseline characteristics between HIV/HCV-coinfecting and HCV-mono-infected subjects. Kaplan-Meier estimates of time to AKI were produced and stratified by infection status. For subjects who died or were lost to follow-up, data was censored at the time of study drop out. Data was censored on December 31, 2007 for all subjects who reached this date without developing AKI. Cox proportional hazards were utilized to determine risk factors for AKI. Variables significant in univariate analysis, as well as potential confounders, were included in multivariable analysis. Due to concern for collinearity between heroin, cocaine, and alcohol use, adjusted models were run separately for each of these variables prior to their inclusion

into a final model. Certain variables including liver event history and heroin, cocaine, or hazardous alcohol use within the past 6 months, were also evaluated as time-varying covariates at 6-month intervals. All tests were two tailed with a significance level of 0.05.

Results

Two hundred sixteen HIV/HCV-coinfected and 151 HCV-monoinfected subjects were included in the analysis. Other than higher rates of cocaine use among coinfecting subjects, no significant differences in baseline characteristics were found. Table 1 summarizes baseline characteristics. A substantial percentage of HIV/HCV coinfecting and HCV monoinfected subjects demonstrated use of cocaine, heroin, or hazardous alcohol within 6 months of study entry.

AKI incidence

Among HIV/HCV-coinfected subjects, 75 first AKI events occurred over 858 person-years, with an IR of 8.74 per 100 person-years. Among HCV-monoinfected subjects, 25 first AKI events occurred over 708 person-years, with an IR of 3.53 per 100 person-years. Kaplan Meier estimates of time to AKI by infection status are displayed in Fig. 1.

Etiology of AKI

Of the 100 AKI events, 45% were due to prerenal causes, 31% were due to intrinsic renal causes, and one case was due to obstructive nephrolithiasis from indinavir use. In 23% of cases, the mechanisms of AKI could not be determined. Of the 31 cases of AKI due to intrinsic renal etiologies, three cases each were due to acute interstitial nephritis, acute tubular necrosis, and rhabdomyolysis. Two cases each were attributed to renal crystaluria secondary to high-dose acyclovir, amphotericin B treatment for cryptococcal meningitis, and

staphylococcal sepsis. One case each was attributed to complications of chemotherapy and pentamidine treatment for PCP pneumonia. Only one case was attributed to HIV-associated nephropathy. The etiology of intrinsic AKI could not be determined for 13 cases.

Univariate analysis

Table 2 summarizes results of univariate analysis of baseline risk factors for AKI. Significant predictors of AKI included black race, hypertension, HIV/HCV coinfection, liver event, cocaine use, and hazardous drinking within 6 months of study entry.

Multivariable analysis

Successive multivariable Cox proportional hazards regression models showed the following variables to be significant independent risk factors for AKI: cocaine use within 6 months of study entry (HR 2.06 [95% CI 1.15, 3.71]), history of liver event ever (HR 6.64 [95% CI 3.81, 11.6]), and HIV/HCV coinfection (HR 2.19 [95% CI 1.33, 3.62]). HCV-specific factors, including genotype and HCV VL, did not show significant associations in univariate or adjusted analyses. Results of multivariable analyses are summarized in Table 3. While hazardous alcohol use is associated with AKI in univariate analysis, the association loses statistical significance in the adjusted analysis. Heroin use appears to be significantly associated with AKI in an adjusted model, but loses statistical significance when cocaine use is subsequently added into the model.

Certain variables, including liver event, cocaine, heroin, and hazardous alcohol use, were also evaluated as time-varying covariates over 6-month intervals throughout the study period. In an adjusted model, liver event (HR 4.70 [95% CI 2.85, 7.75]) and cocaine use (HR 1.92 [1.10, 3.36]) within the past 6 months remained significantly associated with AKI over time.

Subgroup analysis in HIV/HCV-coinfected subjects

Among subjects with HIV/HCV coinfection, additional analysis of risk factors for AKI was performed with adjustment for CD4 cell count and HIV VL. In univariate analysis, baseline CD4 cell count less than 200/mm³ was significantly associated with AKI (HR 1.90 [95% CI 1.17, 3.31]) compared to CD4 cell count greater than 350/mm³. HIV VL greater than 4000 copies per milliliter was also associated with AKI (HR 1.53 [95% CI 0.90, 2.60]) compared to HIV VL less than 50 copies per milliliter, although not statistically significant. Results of multivariable analyses among coinfecting subjects, adjusting first for CD4 cell count and then for HIV viral load, are summarized in Tables 4 and 5. Cocaine use within 6 months of study entry and history of a liver event remained significantly associated with AKI, even after adjustment for CD4 cell count and HIV VL.

HAART and AKI

Antiretroviral regimens (ARVs) at the time of AKI were examined for the 75 HIV/HCV-coinfected subjects. Forty percent of subjects were not on ARVs at the time of AKI. Of the 45 subjects on ARVs, 38% were on tenofovir-containing regimens, 7% were on indinavir-containing regimens, and

TABLE 1. BASELINE CHARACTERISTICS BY INFECTION STATUS

Characteristic	HIV/HCV n = 216 (%)	HCV n = 151 (%)	p Value
Male gender	143 (66)	86 (57)	0.15
Age ≤ 45 years	119 (55)	74 (49)	0.25
Race/ethnicity			
Black/not Hispanic	110 (51)	70 (46)	0.18
White	49 (23)	49 (32)	
Latino/Hispanic	52 (24)	28 (19)	
Hypertension ^a	82 (38)	63 (42)	0.49
Diabetes ^a	40 (19)	38 (25)	0.13
Liver event	27 (13)	14 (9)	0.33
HCV genotype			
1	154 (72)	118 (78)	0.18
2–4	39 (18)	26 (17)	
HCV viral load ≥750,000 copies/mL	106 (49)	60 (40)	0.11
Cocaine use ^b	56 (26)	26 (17)	0.04
Heroin use ^b	48 (22)	35 (23)	0.81
Hazardous alcohol ^b	54 (25)	41 (27)	0.78

^aIndicates presence of characteristic at any point during study period.

^bIndicates use within 6 months of study entry.

HCV, hepatitis C virus.

FIG. 1. Kaplan Meier curves of time to incident acute kidney injury (AKI) stratified by infection status. Mean follow up time was 5.15 years.

55% were on other ARV regimens. Collection of tenofovir data for the cohort did not begin until 2005 and was inconsistent. Upon query of medication logs, we determined that 74 (34%) of HIV/HCV-coinfected subjects reported ever taking tenofovir. In univariate analysis, the RR of AKI for HIV/HCV coinfected subjects reporting tenofovir use versus no use was 0.70 (95% CI [0.44–1.13]); *p* value 0.137.

AKI associated morbidity and mortality

The majority of AKI events were associated with either an emergency department visit or hospitalization, including 68% of episodes among HCV-monoinfected subjects and 89% of episodes among HIV/HCV coinfected subjects. While no AKI

events among HCV-monoinfected subjects resulted in need for hemodialysis, six (8%) events among HIV/HCV-coinfected subjects led to a transient need for hemodialysis. AKI resulted in death in one (0.4%) HCV-monoinfected subject and six (8%) HIV/HCV coinfected subjects. Results are displayed in Fig. 2.

Discussion

In this analysis, AKI incidence was 2.2 times higher in subjects with HIV/HCV coinfection than in HCV mono-infection. In comparison to Franceschini's study,⁵ in which subjects with HIV/HCV coinfection and HIV monoinfection had a combined incidence of first AKI event of 4.3 per 100 person-years, AKI incidence was twofold higher (8.74 per 100 person-years) among HIV/HCV-coinfected subjects in our

TABLE 2. UNIVARIATE ANALYSIS OF RISK FACTORS FOR ACUTE KIDNEY INJURY

Variable	HR (95% CI)	p Value
Male gender	1.03 (0.69, 1.53)	0.89
Age ≤ 45	0.72 (0.49, 1.07)	0.11
Black race ^a	1.60 (1.07, 2.39)	0.02
Hypertension	1.80 (1.22, 2.67)	<0.001
Diabetes	1.54 (0.99, 2.41)	0.06
Liver event	4.68 (2.96, 7.41)	<0.001
HIV/HCV infection ^b	2.48 (1.57, 3.89)	<0.001
HCV genotype 2–4 ^c	0.93 (0.52, 1.65)	0.80
HCV VL ≥ 750,000 copies/mL	1.05 (0.69, 1.60)	0.82
Cocaine use	1.72 (1.13, 2.61)	0.01
Heroin use	1.18 (0.75, 1.87)	0.43
Hazardous alcohol use ^d	1.70 (1.08, 2.67)	0.02

Reference groups are as follows:

^aNon-black race/ethnicity (including white, Latino/Hispanic, Asian, and other).

^bHCV monoinfection.

^cHCV genotype 1.

^dModerate alcohol use or no alcohol use.

HR, hazard ratio; CI, confidence interval; HCV, hepatitis C virus; VL, viral load.

TABLE 3. MULTIVARIABLE ANALYSIS OF RISK FACTORS FOR ACUTE KIDNEY INJURY

Model	Variable	HR (95% CI)	p Value
1	Cocaine use	1.93 (1.23, 3.02)	0.004
2	Heroin use	1.62 (1.01, 2.60)	0.045
3	Hazardous alcohol	1.49 (0.94, 2.36)	0.092
4	Cocaine use	1.76 (1.07, 2.87)	0.025
	Heroin use	1.28 (0.76, 2.14)	0.352
5	Cocaine use	2.06 (1.15, 3.71)	0.016
	Heroin use	0.97 (0.53, 1.77)	0.910
	Hazardous alcohol	1.33 (0.76, 2.32)	0.314
	HCV genotype 2–4	0.84 (0.44, 1.60)	0.595
	HCV viral load	0.96 (0.60, 1.54)	0.877
	≥ 750,000 copies/mL		
	Liver event	6.64 (3.81, 11.6)	<0.001
	HIV/HCV infection	2.19 (1.33, 3.62)	0.002

All Cox proportional hazards regression models adjusted for age, gender, race/ethnicity, diabetes, hypertension, liver event ever, and infection status.

HR, hazard ratio; HCV, hepatitis C virus.

TABLE 4. MULTIVARIABLE ANALYSIS OF RISK FACTORS FOR ACUTE KIDNEY INJURY, ADJUSTED FOR CD4 CELL COUNT

Variable	HR (95% CI)	p Value
CD4 cell count		
>350/mm ³ (reference group)	—	—
201–350/mm ³	0.59 (0.31, 1.10)	0.0960
<200/mm ³	1.76 (1.02, 3.05)	0.0424
Liver event	5.63 (3.11, 10.21)	<0.0001
Cocaine use	2.32 (1.39, 3.88)	0.0013

Cox proportional hazard regression model is adjusted for age, race/ethnicity, diabetes, and hypertension.

HR, hazard ratio; CI, confidence interval.

current analysis. After adjusting for the elevated risk of AKI attributed to HIV coinfection, additional significant risk factors for AKI included decompensated liver cirrhosis and cocaine use. These risk factors remained significant among HIV/HCV-coinfected subjects, even after adjustment for CD4 cell count and HIV VL.

In contrast to findings that higher HIV VL is associated with increased risk of AKI, we did not find an association between HCV VL and AKI incidence in our analysis. While several studies have demonstrated that HIV infection may be linked to renal disease through direct viral infection of renal parenchyma,¹⁶ a similar mechanism has not been demonstrated for HCV infection. HCV has been linked to several types of glomerular lesions including membranoproliferative glomerulonephritis (MPGN) and membranous glomerulopathy. These pathologic lesions appear to result from deposition of circulating immune complexes that contain HCV and anti-HCV antibody. Although a few reports of immunohistochemical localization of HCV antigen in renal tissue have been published, results have not been consistently demonstrated.^{16,17} Although in our study, higher HCV VL and genotype were not associated with AKI, these findings add important information to currently available data as other epidemiologic studies examining the relationship between HCV and renal disease have not included HCV VL or genotype data.^{11–14}

In addition to HIV/HCV coinfection and decompensated liver cirrhosis, cocaine but not heroin use was strongly associated with AKI. Indeed, the entity previously known as heroin nephropathy has greatly decreased in recent years and likely represented primary focal and segmental glomerulo-

sclerosis (FSGS) rather than a consequence of heroin use.¹⁸ FSGS is now the most common cause of nephrosis in African American individuals in the United States. In contrast, cocaine clearly causes deleterious effects on the kidney and can lead to AKI both from rhabdomyolysis and malignant hypertension.^{19,20} This study further supports the existence of an association between cocaine use and AKI among persons with HIV/HCV coinfection.

Among the HIV/HCV-coinfected subjects, there was only a single case of HIV-associated nephropathy identified. No cases of other diagnoses attributable to HIV infection, such as HIV immune complex kidney disease, IgA nephropathy or thrombotic thrombocytopenic purpura (TTP), were found. The bulk of cases were related to prerenal azotemia or drug toxicity. In multivariable analyses, lower CD4 cell count and higher HIV VL were both associated with AKI, although only CD4 cell count less than 200 was statistically significant. Lower CD4 count may have been associated with AKI through higher rates of nephrotoxic drug use for opportunistic infections and ARV toxicity. Indinavir-associated renal dysfunction is well documented and there is also growing evidence of an association between tenofovir use and loss of renal function.^{22–27} In a recent meta-analysis that included 17 studies to assess the renal safety of tenofovir in HIV-infected patients, a statistically significant greater loss in creatinine clearance was observed among tenofovir recipients compared to control subjects, as well as a significantly greater risk of acute renal failure among tenofovir recipients.²² Of subjects on ARVs at the time of AKI, 45% were receiving indinavir or tenofovir-containing regimens, reflecting evolving drug availability and prescribing practices during the study period. However, sufficient data were not available to examine the independent association between tenofovir use and AKI. The interrelationships between CD4 cell count, HIV VL, exposure to ARVs, and the subsequent development of AKI warrant further investigation among HIV/HCV-coinfected subjects.

There were several limitations to this analysis. Serial HIV antibody testing was not performed as part of the research protocol after study entry, and could have resulted in misclassification of some dually infected subjects as having HCV mono-infection. Such a misclassification may have dampened the true impact of HIV coinfection on the incidence of AKI among subjects with HCV infection. HCV VL and genotype data was missing for 12% of the cohort and may have diminished the power to detect a true association between HCV VL and AKI. Furthermore, kidney biopsies were not performed in this study to look for direct HCV viral effects on renal tissue. Data on tenofovir use were not consistently collected for the cohort and the data presented likely underestimates the true proportion, of individuals that were taking tenofovir. Due to concerns with the quality of the tenofovir data and associated biases, we did not adjust for tenofovir use in the final multivariable analyses. Thus, tenofovir use may have been a potential confounder of the association between variables of interest and AKI among coinfecting subjects. As no standard definition for AKI exists, a traditional definition of AKI, which has been shown to affect mortality in hospitalized patients without HIV or HCV, was utilized.⁴ Recently, smaller changes in serum Cr have been found to be of clinical import, such that a rise in Cr of 0.5 mg/dL is utilized in the RIFLE criteria (Risk Injury Failure Loss End Stage) and a rise of only 0.3 mg/dL is utilized in the AKIN criteria (Acute Kidney

TABLE 5. MULTIVARIABLE ANALYSIS OF RISK FACTORS FOR ACUTE KIDNEY INJURY, ADJUSTED FOR HIV VIRAL LOAD

Variable	HR (95% CI)	p Value
HIV viral load		
<50 copies/mL (reference group)	—	—
51–4000 copies/mL	0.97 (0.53, 1.79)	0.9321
>4000 copies/mL	1.72 (0.98, 3.03)	0.0583
Liver event	5.85 (3.23, 10.61)	<0.0001
Cocaine use	2.19 (1.31, 3.67)	0.0028

Cox proportional hazards regression model is adjusted for age, race/ethnicity, diabetes, and hypertension.

HR, hazard ratio; CI, confidence interval.

FIG. 2. Percentage of acute kidney injury (AKI) episodes associated with emergency department visit, clinic visit, hospital admission, need for transient or permanent dialysis, and death. Results are broken down by infection status.

Injury Network).²⁸ In our study, we chose to utilize the more conservative definition of AKI to capture the most serious events.

The findings of the association between AKI and decompensated liver cirrhosis, HIV coinfection, and cocaine use in this study, highlight the importance of controlling HIV infection in coinfected individuals and preventing liver disease progression and cocaine use in persons with both HIV/HCV coinfection and HCV monoinfection. While the relationship between AKI and other substances of abuse, including heroin and hazardous alcohol, was not statistically significant after adjusting for cocaine use, intermediate multivariable models did demonstrate a positive association between these agents and AKI. Thus, targeted interventions to reduce heroin and alcohol use may further reduce the burden of renal disease among these individuals. Further studies are required to determine the association between HCV VL and AKI, and whether lowering HCV VL may impact AKI incidence. By addressing the identified modifiable risk factors, a reduction in AKI-associated morbidity and mortality, including rates of hospitalization, transient hemodialysis and death, may potentially be achieved in this population.

Acknowledgments

Funding for the CHARM cohort at Boston Medical Center is supplied by National Institute on Drug Abuse Grant 5R01DA019841-09. Additional funding provided to S.G. through National Institute of Health Institutional Research Training Grants 5T32AI007433-18 and 5T32AI007438-17. The authors thank the study participants, investigators, study coordinators, and research interviewers at Boston Medical Center, and the data coordinating center at Boston University School of Public Health, for making this study possible.

Author Disclosure Statement

No competing financial interests exist.

References

1. Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney diseases in HIV- infected patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2005;40:1559–1585.
2. Fine DM, Atta MG. Kidney disease in the HIV-infected patient. *AIDS Patient Care STDs* 2007;21:813–824.
3. Wyatt CM, Arons RR, Klotman PE, Klotman ME. Acute renal failure in hospitalized patients with HIV: Risk factors and impact on in-hospital mortality. *AIDS* 2006;20:561–5605.
4. Franceschini N, Napravnik S, Eron JJ Jr, Szczech LA, Finn WF. Incidence and etiology of acute renal failure among ambulatory HIV- infected patients. *Kidney Int* 2005;67:1526–1531.
5. Franceschini N, Napravnik S, Finn WF, Szczech LA, Eron JJ Jr. Immunosuppression, hepatitis C infection, and acute renal failure in HIV- infected patients. *J Acquir Immune Defic Syndr* 2006;42:368–372.
6. Lopes JA, Fernandes J, Jorge S, Neves J, Antunes F, Prata MM. Acute renal failure in critically ill HIV- infected patients. *Crit Care* 2007;11:404.
7. Roe J, Campbell LJ, Ibrahim F, Hendry BM, Post FA. HIV Care and Incidence of Acute Renal Failure. *Clin Infect Dis* 2008;47:242–249.
8. Wyatt CM, Malvestutto C, Coca SG, Klotman PE, Parikh CR. The impact of hepatitis C virus coinfection on HIV-related kidney disease: A systematic review and meta-analysis. *AIDS* 2008;22:1799–1807.
9. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: A meta-analysis. *Clin Infect Dis* 2001;33:562–569.
10. Weber R, Sabin CA, Friis-Moller N et al. Liver-related deaths in persons infected with the human immunodeficiency virus: The D:A:D study. *Arch Intern Med* 2006;166:1632–1641.
11. Tsui JI, Vittinghoff E, Shlipak MG, O'Hare AM. Relationship between hepatitis C and chronic kidney disease: Results

- from Third NHANES Survey. *J Am Soc Nephrol* 2006; 17:1168–1174.
12. Dalrymple LS, Koepsell T, Sampson J, et al. Hepatitis C Virus Infection and the Prevalence of Renal Insufficiency. *Clin J Am Soc Nephrol* 2007;2:715–721.
 13. Tsui JJ, Vittinghoff E, Shlipak MG, et al. Association of hepatitis C seropositivity with increased risk for developing end-stage renal disease. *Arch Intern Med* 2007;167: 1271–1276.
 14. Moe SM, Pampalone AJ, Ofner S, Rosenman MD, Teal E, Hui SL. Association of hepatitis C virus infection with prevalence and development of kidney disease. *Am J Kidney Dis* 2008;51:885–892.
 15. 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.
 16. Alpers CE, Kowalewska J. Emerging paradigms in the renal pathology of viral diseases. *Clin J Am Soc Nephrol* 2007;2:S6–S12.
 17. Barsoum RS. Hepatitis C virus: From entry to renal injury-facts and potentials. *Nephrol Dial Transplant* 2007;22:1840–1848.
 18. Jaffe JA, Kimmel PL. Chronic nephropathies of cocaine and heroin abuse: A critical review. *Clin J Am Soc Nephrol* 2006;1:655–667.
 19. Fine DF, Garg N, Haas M, et al. Cocaine use and hypertensive renal changes in HIV-infected individuals. *Clin J Am Soc Nephrol* 2007;2:1125–1130.
 20. Norris KC, Thornhill-Joynes M, Robinson C, et al. Cocaine use, hypertension, and end-stage renal disease. *Am J Kidney Dis* 2001;38:523–528.
 21. Glauser J, Queen JR. An overview of non-cardiac cocaine toxicity. *J Emerg Med* 2007;32:181–186.
 22. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: Renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis* 2010;51:496–505.
 23. Gallant JE, Staszewski S, Pozniak AI, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: A 3-year randomized trial. *JAMA* 2004;292:191–201.
 24. Young B, Buchacz K, Moorman A, Wood K, Brooks JT; the HIV Outpatient Study (HOPS) Investigators. Renal function in patients with preexisting renal disease receiving tenofovir-containing highly active antiretroviral therapy in the HIV outpatient study. *AIDS Patient Care STDs* 2009;23:589–592.
 25. Crum-Cianflone N, Ganesan A, Teneza-Mora N et al. Prevalence and factors associated with renal dysfunction among HIV-infected patients. *AIDS Patient Care STDs* 2010;24:353–360.
 26. Verhelst D, Monge M, Meynard JL, et al. Fanconi syndrome and renal failure induced by tenofovir: A first case report. *Am J Kidney Dis* 2002;40:1331–1333.
 27. Szczech LA. Renal dysfunction and tenofovir toxicity in HIV infected patients. *Top HIV Med* 2008;16:122–126.
 28. Mehta RL, Kellum JA, Shah SV, et al. Acute kidney injury network: Report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;11:R31.

Address correspondence to:

Shikha Garg
1600 Clifton Road
Mailstop A-32
Atlanta, GA 30333

E-mail: shikhagarg75@yahoo.com