OPEN

Frequent injection cocaine use increases the risk of renal impairment among hepatitis C and HIV coinfected patients

Carmine Rossi[a], Joseph Cox[a], Curtis Cooper[b], Valérie Martel-Laferrière[c], Sharon Walmsley[d], John Gill[e], Ruth Sapir-Pichhadze[f], Erica E.M. Moodie[a], Marina B. Klein[g], for the Canadian Co-infection Cohort Investigators

Objective: To examine the association between injection cocaine use, hepatitis C virus (HCV) infection, and chronic renal impairment (CRI).

Design: Prospective observational cohort study of HIV–HCV coinfected patients.

Methods: Data from 1129 participants in the Canadian Co-Infection Cohort with baseline and follow-up serum creatinine measurements between 2003 and 2014 were analyzed. Prevalent and incident cohorts were created to examine the association between self-reported past, current, and cumulative cocaine use and chronic HCV with CRI. CRI was defined as an estimated glomerular filtration rate below 70 ml/min per 1.73 m^2. Multivariate logistic regression was used to calculate odds ratios, and discrete-time proportional-hazards models were used to calculate hazard ratios for cocaine use, in the two respective cohorts, adjusted for HCV RNA and important demographic, HIV disease stage, and comorbidity confounders.

Results: Eighty-seven participants (8%) had prevalent CRI. Past injection cocaine use was associated with a two-fold greater risk of prevalent CRI [odds ratio 2.03, 95% confidence interval (CI) 0.96, 4.32]. During follow-up, 126 of 1061 participants (12%) developed incident CRI (31 per 1000 person-years). Compared to nonusers, heavy ($\geq$ 3 days/week) and frequent injection cocaine users ($\geq$75% of follow-up time) experienced more rapid progression to CRI (hazard ratio 2.65, 95% CI 1.35, 5.21; and hazard ratio 1.82, 95% CI 1.07, 3.07, respectively). There was no association between chronic HCV and CRI in either cohort.

Conclusion: After accounting for HCV RNA, frequent and cumulative injection cocaine abuse was associated with CRI progression and should be taken into consideration when evaluating impaired renal function in HIV–HCV coinfection.

AIDS 2016, **30**:1403–1411

Keywords: chronic hepatitis C, cocaine, coinfection, HIV, intravenous substance abuse, renal insufficiency

[a]McGill University, Department of Epidemiology, Biostatistics and Occupational Health, Montréal, Québec, [b]The Ottawa Hospital-General Campus, Ottawa, Ontario, [c]Centre Hospitalier de l'Université de Montréal – Notre-Dame, Montréal, Québec, [d]University Health Network, University of Toronto, Toronto, Ontario, [e]Southern Alberta HIV Clinic, Calgary, Alberta, [f]McGill University, Division of Nephrology and Multi-Organ Transplant Program, Department of Medicine, Montréal, Québec, and [g]Chronic Viral Illness Service, McGill University Health Centre, Montréal, Québec, Canada.

Correspondence to Dr Marina B. Klein, Professor of Medicine, McGill University Health Centre, Division of Infectious Diseases and Chronic Viral Illness Service, 1001 Decarie Boulevard, Montréal, QC H4A 3J1, Canada.

Tel: +1 514 843 2090; fax: +1 514 843 2092; e-mail: marina.klein@mcgill.ca
Received: 24 November 2015; revised: 28 January 2016; accepted: 29 January 2016.

DOI:10.1097/QAD.0000000000001060

ISSN 0269-9370

Introduction

Chronic kidney disease (CKD) is a prevalent comorbidity among HIV-infected persons [1,2]. It is estimated that 5–11% of people living with HIV have mild to moderately reduced kidney function [3–5], increasing their risk of cardiovascular disease and premature mortality [6,7]. HIV-associated nephropathy (HIVAN), which is associated with rapid progression to end-stage renal disease (ESRD), is the classic kidney disease presentation among HIV patients, particularly in African Americans [8]. With the introduction of antiretroviral therapy (ART), which has been effective in the prevention and treatment of HIVAN [9,10], the spectrum of CKD among HIV-infected persons has changed. Of late, the increasing CKD burden among HIV-infected persons has been attributed to aging, metabolic changes associated with a greater prevalence of diabetes and hypertension, and direct nephrotoxic complications from prolonged ART use [1,11].

Hepatitis C virus (HCV) coinfection has also been implicated as an important risk factor for CKD and ESRD among HIV patients [12–16]. Because of shared routes of transmission, approximately 25% of people living with HIV are also coinfected with HCV [17]. Membranoproliferative glomerulonephritis (MPGN) is more common in HCV coinfected compared to HIV monoinfected patients [18,19]. MPGN is associated with type II mixed cryoglobulinemia, which may represent a pathway by which HCV affects the kidney [20]. A recent epidemiologic study, however, found no association between HCV RNA and CKD, suggesting that the excess risk associated with HCV infection may be attributable to other exposures in this population [21].

Injection drug use (IDU), the primary route of HCV infection, remains a common behavior for many coinfected individuals [22]. Cocaine itself has been associated with rhabdomyolysis and acute kidney injury, and is a known nephropathic drug [23,24]. However, there is little epidemiological evidence about the role that cocaine has on renal function or whether its use may explain the observed association between HCV and CKD. The aim of this study was to examine the association between injection cocaine use and chronic renal impairment (CRI) among HIV–HCV coinfected patients receiving clinical care.

Methods

Study population

Data were obtained from the Canadian Co-Infection Cohort (CCC). This study has been described previously [25]. Briefly, after providing informed consent, all eligible participants at least 16 years of age with a confirmed HIV infection and serologic evidence of HCV exposure completed a baseline questionnaire to provide socio-demographic information and self-reported injection drug histories. Medical records were abstracted to obtain ART treatment histories, and AIDS, liver disease, and other comorbidities. Standard laboratory analyses were used to measure $CD4^+$ T-cell counts, HIV viral load, and HCV viremia, using qualitative or quantitative molecular HCV RNA assays. A serum biochemistry panel was also performed, which included measurement of serum creatinine (SCr). All information was updated at bi-annual follow-up visits. The study was approved by the community advisory committee of the Canadian Institutes of Health Research (CIHR) – Canadian HIV Trials Network – and by all institutional ethics boards of participating centers.

We included 1366 CCC participants enrolled between January 2003 and October 2014, who had at least one SCr measurement. The first study visit with an available SCr measurement was defined as the index visit; 98% of participants had their first SCr measurement at enrollment. The study population was divided into prevalent and incident cohorts for two separate analyses (Fig. 1). For the prevalent cohort, we included all participants who enrolled after February 2007, the date after which study questionnaires introduced a question on injection drug histories. For the incident cohort, we included all participants without CRI (see definition below) at the index visit and who were followed for at least two study visits. No exclusion based on the older questionnaire was used for the incident cohort because questions on current injection use were available on all questionnaires.

Chronic renal impairment

Prevalent CRI was defined as an estimated glomerular filtration rate (eGFR) below 70 ml/min per 1.73 m^2 at the index visit. For those who did not have CRI at the index visit, incident CRI was defined as two consecutive eGFR values of less than 70 ml/min per 1.73 m^2 [26]. We calculated eGFR using the 2009 SCr-based CKD-epidemiology (EPI) equation [27]. This equation has been validated in HIV-infected populations [28,29]. A confirmed eGFR decline to less than 70 ml/min per 1.73 m^2 was chosen to maximize study power, but it is also clinically relevant as renal interventions can be initiated to prevent kidney disease progression [30].

Exposure and covariate definitions

For the prevalent cohort, past injection cocaine use was defined as any self-reported use prior to the index visit. For the incident cohort, current injection cocaine use was defined as any self-reported use in the past 6 months. Frequency of injection cocaine use was categorized as: no use in the past month (referent), occasional use ($<$1 day/week), regular use (1 or 2 days/week), or heavy use ($\geq$3 days/week). Cumulative exposure to injection cocaine was defined using the proportion of total follow-

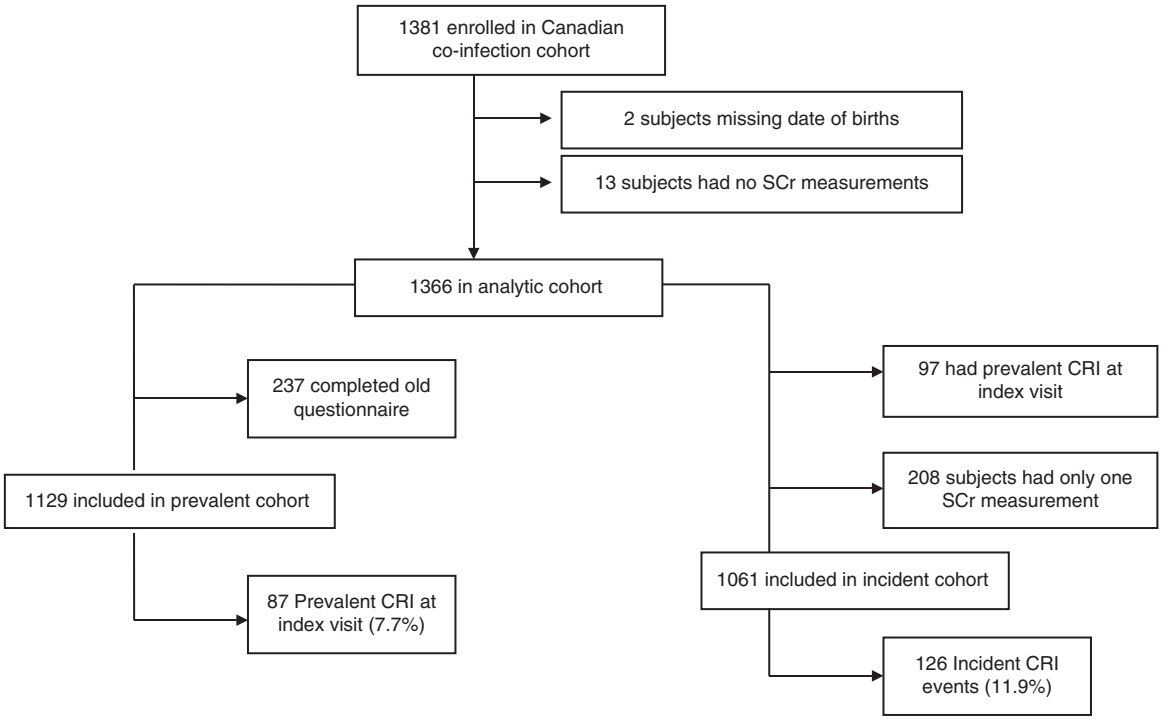

Fig. 1. Study participant flow chart for prevalent and incident cohorts. CRI, chronic renal impairment; SCr, serum creatinine.

up time when a participant self-reported using any amount of the drug by injection. The following categories were used: no use during follow-up (referent), low (≥1% to <33% of follow-up time), moderate (≥33% to <75%), and high (≥75%). All injection cocaine exposures in the incident cohort analysis were time-updated.

Hepatitis C virus viremia was measured with either a qualitative (e.g. Amplicor HCV Test v2.0) or quantitative molecular HCV RNA assay (e.g. Abbott Real Time PCR) according to study center-specific laboratory standards. Any participant with detectable HCV viremia from a qualitative or quantitative assay was considered to have a chronic HCV infection.

On the basis of low-income cut-offs from Statistics Canada, annual income was dichotomized at 24 000 Canadian dollars [31]. Hypertension was defined by clinical diagnosis, SBP above 140 mmHg or DBP above 90 mmHg, or the use of any antihypertensive drug. Diabetes was defined by clinical diagnosis or the use of insulin or any oral hypoglycemic agents. End-stage liver disease (ESLD) was defined by any diagnosis of cirrhosis, ascites, varices, spontaneous bacterial peritonitis, portal hypertension, encephalopathy, or hepatocellular carcinoma. In the incident cohort, hypertension and ESLD were coded as time-updated ever diagnosed variables. AIDS was defined as a diagnosis of any opportunistic infection or AIDS-related illness, regardless of $CD4^+$ cell count.

Statistical analysis

Prevalent cohort

Logistic regression was used to calculate crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between past injection cocaine use and prevalent CRI. The multivariate model was adjusted for age, sex, income, chronic HCV infection, detectable HIV viral load (>50 copies/ml), any past tenofovir, ritonavir-boosted or unboosted atazanavir, and lopinavir use, and prevalent hypertension. Covariates were selected *a priori* based on their plausibility as confounders for the past injection cocaine and kidney disease relationship. Missing data were imputed using fully conditional specification multiple imputation (FCS-MI) [32]. Continuous covariates were imputed using linear regression, and dichotomous variables were imputed using logistic regression. The imputation model included all covariates in the multivariate model and an indicator for CRI. We created 10 imputed data sets and combined regression results using Rubin's rules [32].

Incident cohort

Participants were followed from the index visit until they developed incident CRI, died, were lost to follow-up, or had their last visit prior to 1 October 2014. Person-time was censored for participants not developing CRI at their last visit. Discrete-time proportional-hazards models were used to estimate crude and adjusted hazard ratios and 95% CIs for CRI [33]. Three separate models were fit for current injection cocaine use, current frequency of use, and cumulative exposure to injection cocaine. All

multivariate models were adjusted for age, sex, income, chronic HCV infection, $CD4^+$ cell count, detectable HIV viral load, tenofovir, atazanavir and lopinavir use, AIDS diagnosis in the past 6 months, and prevalent hypertension, and ESLD, using time-updated covariates. We tested for interaction between the three injection cocaine exposures and all covariates. Missing longitudinal data were also imputed. STATA version 13.1 (College Station, Texas, USA) was used for all analyses.

Supplemental analyses

In a supplemental analysis, we modeled continuous eGFR using generalized estimating equations (GEEs) to compare longitudinal rates of change in eGFR per year between injection cocaine users and nonusers. To examine if any observed association was related to cocaine and not the injection route of administration, we also considered the role of current and cumulative exposure to noninjection cocaine and CRI using discrete-time proportional-hazards models.

Results

Prevalent cohort

Of the 1366 participants included, 1129 (83%) met the inclusion criteria (Fig. 1). Overall, most participants were men, aged over 45 years and who had been infected with HCV for a median of 20 years. At the index visit, 847 participants (75%) reported a history of injection cocaine use and 937 (83%) had a chronic HCV infection. Of those without evidence of HCV viremia, 100 (59%) had spontaneously cleared their infection and 63 (41%) had cleared following prior HCV treatment. Participant characteristics with and without a history of injection cocaine use are shown in Table 1. Compared to participants who did not inject cocaine, those who had a history of use were younger, were more likely to be women, have low income, have been smokers, currently have a detectable HIV viral load, and have used an atazanavir-containing ART regimen.

In univariate analysis, past injection cocaine use was associated with a significantly increased risk of CRI among HIV–HCV coinfected patients (Table 2). After adjustment, past injection cocaine use increased the risk of CRI, but was no longer significant. Presence of HCV viremia was not associated with CRI in either univariate or multivariate models. Increasing age, female sex, past tenofovir, lopinavir, and atazanavir use were also associated with CRI in the multivariate analysis. Results for injection cocaine use were qualitatively similar when the model was further adjusted for smoking, nadir $CD4^+$ cell count, AIDS, diabetes, and ESLD (OR 2.06, 95% CI 0.96, 4.43), and when eGFR below 60 ml/min per 1.73 m^2 was used to define prevalent CRI (OR 1.92, 95% CI 0.75, 4.91).

Incident cohort

Among the 1366 participants with available eGFR measurements, 1061 (78%) did not have prevalent CRI at the index visit and were followed for at least two study visits (Fig. 1). During follow-up, 126 participants (12%) developed incident CRI and the remaining 935 were censored without having the event. Of those who did not develop CRI, 678 were administratively censored, 94 died, 87 were lost-to-follow-up, and 76 withdrew from the study. Overall, the median duration of follow-up was

Table 1. Baseline characteristics of 1129 Canadian Co-Infection Cohort participants by history of injection cocaine use[a].

Characteristics[b]	History of injection cocaine use (n = 847) [n (%)]	No history of injection cocaine use (n = 277) [n (%)]
Median age, years (IQR)	45 (39, 50)	47 (41, 53)
Women	276 (33%)	48 (17%)
Income ≤$24 000/year	765 (90%)	172 (62%)
Ever smoker	815 (96%)	204 (74%)
Current alcohol consumption	419 (49%)	173 (62%)
Other injection drug use history	617 (73%)	26 (9%)
Chronic HCV infection	698 (82%)	237 (86%)
Median time since HCV infection, years (IQR)	21 (13, 29)	8 (2, 17)
Median current $CD4^+$ cell count, cells/μl (IQR)	394 (250, 577)	450 (293, 620)
Median nadir $CD4^+$ cell count, cells/μl (IQR)	170 (80, 299)	184 (70, 300)
Current ART use	692 (82%)	250 (90%)
Detectable HIV viral load >50 copies/ml	315 (37%)	68 (25%)
Tenofovir use	505 (60%)	167 (60%)
Atazanavir use	354 (42%)	72 (26%)
Lopinavir use	273 (32%)	104 (38%)
Clinical AIDS diagnosis	226 (27%)	80 (29%)
Hypertension	112 (13%)	50 (18%)
Diabetes	36 (4%)	12 (4%)
End-stage liver disease	67 (8%)	29 (10%)

Values are *n* (%), unless otherwise indicated. ART, antiretroviral therapy; HCV, hepatitis C virus; IQR, interquartile range.
[a]Five participants were missing data on injection cocaine use history.
[b]Missing data was as follows: income ($n = 1$); smoking ($n = 2$); chronic HCV ($n = 37$); nadir $CD4^+$ cell count ($n = 67$); HIV viral load ($n = 21$); hypertension ($n = 6$); diabetes ($n = 6$); and clinical AIDS diagnosis ($n = 5$).

Table 2. Crude and adjusted odds ratios for prevalent chronic renal impairment ($N = 1129$).

	Unadjusted OR (95% CI) [a]	Adjusted OR (95% CI)[a]
Past injection cocaine use	1.91 (1.04, 3.51)	2.03 (0.96, 4.32)
Chronic HCV infection	0.90 (0.48, 1.67)	1.05 (0.54, 2.06)
Age (per 5-year increase)	1.46 (1.28, 1.66)	1.69 (1.43, 1.99)
Women	2.77 (1.78, 4.31)	4.51 (2.70, 7.54)
Current income ≤$24 000/year	2.04 (0.97, 4.29)	1.56 (0.69, 3.52)
Time since HCV infection (per 5-year increase)	1.21 (1.10, 1.34)	1.03 (0.91, 1.16)
Detectable HIV viral load (>50 copies/ml)	0.81 (0.50, 1.31)	1.02 (0.60, 1.74)
Tenofovir use	2.10 (1.28, 3.46)	1.97 (1.13, 3.42)
Atazanavir use	2.01 (1.30, 3.13)	1.90 (1.17, 3.09)
Lopinavir use	1.96 (1.26, 3.05)	1.91 (1.17, 3.12)
Hypertension	2.04 (1.21, 3.45)	1.66 (0.92, 2.99)

CI, confidence interval; HCV, hepatitis C virus; OR, odds ratio.
[a]Multiple imputation used for missing data.

3.6 years [interquartile range (IQR) 1.6, 5.5] and the crude CRI incidence rate was 31 per 1000 person-years of follow-up (95% CI 26, 37). The median eGFR of those at the time of CRI was 63 ml/min per 1.73 m^2 (IQR 57, 67). The majority of patients with CRI (89%) never recovered eGFR above 70 ml/min per 1.73 m^2 and 42% progressed to eGFR below 60 ml/min per 1.73 m^2.

Participant characteristics at the index visit and at the end of follow-up stratified by whether they developed CRI are summarized in Table 3. Overall, most participants had initially healthy kidney function, with a median eGFR of 104 ml/min per 1.73 m^2 (IQR 94, 112). Two hundred and eighty-seven participants (27%) reported recent injection cocaine use in the past 6 months prior to the index visit. Of these, 61 participants (21%) reported using injection cocaine on average of at least 3 days/week. Four hundred and twenty participants (40%) reported using injection cocaine at least once during follow-up. Compared to those participants who did not develop CRI, those with CRI were older, more likely to be women, had a lower income and $CD4^+$ cell count, were more likely to be on atazanavir or lopinavir-based regimens, and were more likely to have hypertension and ESLD.

The discrete-time proportional-hazards models are shown in Table 4. After adjusting for time-updated confounders, current injection cocaine use increased the risk of CRI by 26%, though this effect was highly variable. Those who reported recently using injecting cocaine at least 3 days/week, however, had a more than two-fold greater risk of developing CRI, compared to those who did not report using injection cocaine since the last visit. Those who regularly reported using injection cocaine (i.e. ≥75% of follow-up visits) were also at greater

Table 3. Baseline participant characteristics and characteristics at end of follow-up by chronic renal impairment outcome in the incident cohort ($N = 1061$).

Characteristics	Index visit[a] [*n* (%)]	Status at end of follow-up[b]	
		CRI ($n = 126$) [*n* (%)]	No CRI ($n = 935$) [*n* (%)]
Median age, years (IQR)	45 (39, 50)	51 (46, 57)	48 (43, 53)
Female	266 (25%)	37 (29%)	229 (24%)
Income ≤$24 000/year	873 (82%)	107 (87%)	748 (81%)
Current smoker	781 (74%)	91 (72%)	663 (72%)
Current injection cocaine use	287 (27%)	26 (21%)	172 (19%)
Median eGFR, ml/min per 1.73 m^2 (IQR)	104 (94, 112)	63 (57, 67)	101 (91, 110)
Chronic HCV infection	886 (84%)	90 (73%)	649 (70%)
Median $CD4^+$ cell count, cells/μl (IQR)	400 (257, 574)	417 (230, 640)	478 (296, 664)
Detectable HIV viral load >50 copies/ml	393 (37%)	24 (20%)	214 (23%)
Tenofovir use	438 (41%)	68 (54%)	500 (53%)
Atazanavir use	253 (24%)	40 (32%)	226 (24%)
Lopinavir use	184 (17%)	23 (18%)	118 (13%)
AIDS diagnosis	283 (27%)	47 (37%)	287 (31%)
Hypertension	104 (10%)	34 (27%)	170 (18%)
Diabetes	43 (4%)	11 (9%)	52 (6%)
End-stage liver disease	88 (8%)	32 (25%)	150 (16%)

Values are *n* (%), unless otherwise indicated. CRI, chronic renal impairment; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; IQR, interquartile range.
[a]Missing data at the index visit was as follows: income ($n = 6$); current smoking ($n = 6$); injection cocaine ($n = 3$); chronic HCV ($n = 29$); $CD4^+$ cell count ($n = 7$); HIV viral load ($n = 10$); and clinical AIDS diagnosis ($n = 6$).
[b]Missing data at the end of follow-up was as follows: income ($n = 12$); current smoking ($n = 10$); injection cocaine ($n = 8$); chronic HCV ($n = 9$); $CD4^+$ cell count ($n = 27$); HIV viral load ($n = 30$); and clinical AIDS diagnosis ($n = 23$).

Table 4. Discrete-time proportional-hazards analysis for incident chronic renal impairment ($N = 1061$)[a].

Variables	Unadjusted HR (95% CI)	Adjusted HR (95% CI)		
		Any recent use model	Frequency of recent use model	Cumulative use model
Current injection cocaine use	0.96 (0.62, 1.48)	1.26 (0.80, 2.00)	–*	–*
Frequency of use				
Nonuser	1 (Reference)	–*	1 (Reference)	–*
Occasional	0.67 (0.36, 1.25)	–*	0.83 (0.44, 1.58)	–*
Regular	1.22 (0.50, 3.00)	–*	1.73 (0.69, 4.34)	–*
Heavy	1.74 (0.91, 3.34)	–*	2.65 (1.35, 5.21)	–*
Proportion of follow-up time				
Nonuser	1 (Reference)	–*	–*	1 (Reference)
≥1% to <33%	0.66 (0.38, 1.13)	–*	–*	0.73 (0.41, 1.28)
≥33% to <75%	0.76 (0.43, 1.35)	–*	–*	1.05 (0.57, 1.94)
≥75%	1.33 (0.82, 2.14)	–*	–*	1.82 (1.07, 3.07)
Chronic HCV infection	1.06 (0.72, 1.58)	0.93 (0.62, 1.40)	0.94 (0.62, 1.40)	0.93 (0.62, 1.39)
Age (per 5-year increase)	1.49 (1.33, 1.66)	1.53 (1.36, 1.72)	1.54 (1.37, 1.74)	1.53 (1.36, 1.72)
Women	1.34 (0.91, 1.97)	1.75 (1.17, 2.62)	1.75 (1.17, 2.62)	1.79 (1.19, 2.70)
Income ≤$24 000/year	1.35 (0.80, 2.27)	1.65 (0.95, 2.87)	1.67 (0.96, 2.89)	1.63 (0.93, 2.86)
$CD4^+$ cell count (per 100 cells/μl increase)	0.98 (0.92, 1.04)	0.99 (0.93, 1.06)	0.99 (0.93, 1.06)	0.99 (0.93, 1.05)
Detectable HIV viral load >50 copies/ml	0.82 (0.52, 1.30)	0.80 (0.50, 1.29)	0.80 (0.50, 1.29)	0.77 (0.48, 1.25)
Tenofovir use	1.12 (0.78, 1.59)	1.24 (0.87, 1.79)	1.24 (0.86, 1.78)	1.25 (0.87, 1.80)
Atazanavir use	1.30 (0.89, 1.89)	1.51 (1.01, 2.26)	1.53 (1.02, 2.29)	1.51 (1.01, 2.27)
Lopinavir use	1.03 (0.65, 1.62)	1.25 (0.77, 2.03)	1.22 (0.75, 1.99)	1.23 (0.75, 2.00)
Incident AIDS diagnosis	2.71 (1.19, 6.18)	3.21 (1.38, 7.45)	3.31 (1.43, 7.70)	3.44 (1.48, 8.03)
Hypertension	1.79 (1.20, 2.67)	1.31 (0.86, 1.99)	1.29 (0.85, 1.96)	1.32 (0.87, 2.00)
End-stage liver disease	2.54 (1.70, 3.80)	2.10 (1.37, 3.22)	2.10 (1.38, 3.22)	2.11 (1.37, 3.23)

The symbol '–' indicates that the covariate excluded from multivariate model. CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio.
[a]Multiple imputation used for missing data.

risk of developing CRI, compared to those who never reported using the drug. In all adjusted models, increasing age, female sex, atazanavir use, incident AIDS diagnosis, and prevalent ESLD were associated with CRI. As with the prevalent analysis, chronic HCV was not associated with incident CRI. There was no evidence of interaction between any of the injection cocaine exposures and other covariates in all models (all $P > 0.05$). Further adjustment for smoking, diabetes, and time since HCV infection did not appreciably change the results.

Supplemental analyses

First, we compared annual rates of change in eGFR between injection cocaine users and nonusers using a longitudinal model (Suppl Table 1, http://links.lww.com/QAD/A887). The overall annual rate of change in eGFR was 1.1 ml/min per 1.73 m^2. Relative to nonusers, current injection cocaine users experienced a decline in eGFR that was 0.27 ml/min per 1.73 m^2 per year faster (95% CI −0.01, 0.55). Heavy users and those who regularly reported using injection cocaine experienced declines that were 0.49 ml/min per 1.73 m^2 per year (95% CI −0.07, 1.06) and 0.48 ml/min per 1.73 m^2 per year faster (95% CI 0.11, 0.86), respectively, compared to nonusers. Second, we compared the association between cocaine used through noninjection routes of administration and CRI. Current and cumulative exposure to noninjection cocaine demonstrated a similar association with CRI as injection cocaine (Suppl Table 2, http://links.lww.com/QAD/A887). Current users of noninjection crack/cocaine had a 54% greater risk of CRI (hazard ratio 1.54, 95% CI 0.98, 2.41) and heavy users had a two-fold greater risk of CRI (hazard ratio 2.03, 95% CI 1.22, 3.39).

Discussion

In this prospective study of HIV–HCV coinfected patients, past injection cocaine increased the risk of CRI, independent of chronic HCV infection, ART use, and other traditional kidney disease risk factors. Furthermore, frequent injection cocaine use of three or more times per week was associated with rapid progression to CRI. We also found that regular use of injection cocaine was associated with CRI progression. Relative effect estimates for cocaine use in this analysis were large. For example, past injection cocaine use was associated with an approximately two-fold greater risk of prevalent CRI. Similar associations were also observed for frequent and cumulative injection and noninjection cocaine in the incident cohort. We also found important clinical differences in annual rates of change in eGFR between injection cocaine users and nonusers. Given that the prevalence of injection drug use in this population is high, cocaine use may be an important modifiable risk factor for CKD among coinfected patients [22]. These results support that screening guidelines for CKD among HIV-infected populations should be expanded to include cocaine users as a high-risk group for kidney disease, as has previously been suggested [34,35].

This is the first cohort study to examine the effect of injection cocaine use, a known nephropathic drug [23,24,36], on renal function among HIV or coinfected populations. Previous research in non-HIV-infected populations has been limited by small sample sizes, poor exposure ascertainment, and the use of nonlongitudinal study designs, which have led to inconsistent results. For example, in a case-control study of recreational drug use and ESRD, cocaine use was not associated with being on dialysis; however, the effect estimate lacked precision as the population controls reported no past illicit drug use [37]. In a cohort of 647 hypertensive men, past cocaine use was strongly associated with mild increases in SCr concentrations [38]. However, because of the retrospective cohort design, drug use may have occurred after follow-up time in the analysis began for many participants. Results from this study are similar to results from a longitudinal analysis of acute kidney disease among a cohort of 367 HCV-infected patients, which have characteristics comparable to our coinfected cohort [39]. Garg *et al.* [39] reported that recent injection or noninjection cocaine use was associated with a two-fold greater risk of a concomitant rise in SCr, which may be a marker for future chronic disease. Our study supports that elevations in creatinine associated with cocaine use are not transient, but rather lead to chronic kidney dysfunction because the vast majority of those developing CRI never returned to normal renal function.

Results from this study are consistent with clinical studies that demonstrate pathogenic effects of cocaine on the kidney [40]. Cocaine is known to have strong vasoconstrictive effects on smooth muscle tissue, which may accelerate hypertensive nephrosclerosis. Furthermore, kidney epithelial cells exposed to cocaine experienced a reduction in intracellular glutathione, an antioxidant and important component of cellular homeostasis, increasing oxidative stress, and may reduce normal kidney function [24]. Results of our analysis were appreciably similar for noninjection cocaine use, suggesting the nephropathic potential of cocaine is drug-specific and not related to route of administration.

It is notable that in our analysis, chronic HCV infection was not associated with an increased risk of CRI. As HCV has been associated with specific glomerular diseases, such as MPGN, it has been hypothesized that patients with a chronic HCV infection may be at a greater risk for CKD, compared to those who have spontaneously cleared the virus or developed a sustained virologic response to HCV treatment [41]. Indeed, in studies of patients enrolled in the Strategies for Management of Antiretroviral Therapy (SMART) and Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) trials, and the EuroSIDA cohort, the coinfected patients with HCV viral loads at least 800 000 and 500 000 IU/ml, respectively, had larger CKD incidence rates compared to those with resolved HCV infections [42,43]. In the larger North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) cohort, however, rates of incident CKD did not differ between coinfected patients with any quantifiable or undetectable HCV viral load [21]. None of these studies accounted for cocaine use. It is therefore possible that some or much of the effect attributed to HCV may instead be related to cocaine abuse rather than to HCV itself. Due to the lack of quantitative measures for all participants, we were unable to determine if HCV RNA levels may impact risk of renal impairment at higher thresholds. Among the subset of participants with available quantitative HCV RNA measures, the median HCV RNA was high (median 1.3 million IU/ml) and there was no evidence that cocaine use was associated with level of HCV RNA, suggesting our findings were not confounded by HCV viremia.

As reported previously, past exposure to tenofovir was associated with prevalent CRI [13,44]. Consistent with findings from an assessment of the effect of cumulative ART exposure, past use of lopinavir and atazanavir, two protease inhibitors, and current atazanavir use were also associated with CRI in this study [26]. We found no evidence of interaction between any of these nephrotoxic ART agents and injection cocaine use, suggesting that renal safety of these medications is not affected by cocaine use.

The study has several important strengths. First, the cohort collected detailed, time-updated information on the use of specific illicit drugs, and their frequency of use. This information is typically not recorded in clinical databases used for other HIV cohort studies on CKD. Previous studies have also ascertained drug exposure retrospectively or at only one time point. Second, with regular HCV RNA testing, this study isolated the effect of HCV viremia from the effect of specific injection drug use, which has not previously been done in HIV-infected cohorts. Finally, we used a validated kidney function equation to measure eGFR and required two consecutive measurements, at least 3 months apart, to confirm incident CRI and rule out acute kidney injury.

Our study has also several potential limitations. First, although data were obtained from a large cohort of coinfected patients, study power was limited to detect smaller effect sizes and interactions between exposure and covariates. Therefore, we only considered CRI as our outcome rather than traditional CKD (eGFR <60 ml/min per $1.73\,m^2$), as there were few CKD events. Whereas it is possible that risk factors for CRI may differ from CKD, there is increasing interest in identifying patients at earlier risk for CKD, so interventions and modifications of treatment can be implemented [26]. Our analysis of CRI may help to achieve this aim. Second, drug history was measured by self-report and may result in misclassification if some patients failed to report drug use. We do not expect the degree of misclassification to be biased, however, as drug use history was collected

independently of objective serum creatinine measures. Third, as only 3% of the study participants were black, we were unable to adequately evaluate race as a confounder or effect modifier. Finally, HCV viremia was measured using a combination of qualitative and quantitative molecular assays. As a result, we were unable to assess a dose–response relationship between viremia and CRI as we classified all those with any detectable HCV viral load as being viremic.

In conclusion, we found evidence to suggest that cumulative exposure and frequent cocaine use are associated with CRI progression among HIV–HCV coinfected patients. The role of substance use in contributing to renal disease in coinfection has been underappreciated and should be taken into consideration when evaluating impaired renal function in this setting.

Acknowledgements

The Site Investigators of the Canadian Co-Infection Cohort (CTN222) are: Drs Lisa Barrett, MD, QEII Health Science Center for Clinical Research, Halifax, NS; Jeff Cohen, MD, Windsor Regional Hospital Metropolitan Campus, Windsor, ON; Brian Conway, MD, PENDER Downtown Infectious Diseases Clinic, Vancouver, BC; Curtis Cooper, MD, The Ottawa Hospital Research Institute, Ottawa, ON; Pierre Côté, MD, Clinique du Quartier Latin, Montréal, QC; Joseph Cox, MD, MSc, MUHC IDTC-Montréal General Hospital, Montréal, QC; John Gill, MD, Southern Alberta HIV Clinic, Calgary, AB; Shariq Haider, MD, McMaster University Medical Centre – SIS Clinic, Hamilton, ON; Mark Hull, MD, MHSc, BC Centre for Excellence in HIV/AIDS, Vancouver, BC; Marina Klein, MD, MSc, McGill University Health Centre, Division of Infectious Diseases and Chronic Viral Illness Service, Montreal, QC; Julio Montaner, MD, BC Centre for Excellence in HIV/AIDS and the University of British Columbia, Vancouver, BC; Neora Pick, MD, Oak Tree Clinic, Children's and Women's Health Centre of British Columbia, University of British Columbia, Vancouver, BC; Anita Rachlis, MD, Sunnybrook &Women's College Health Sciences Centre, Toronto, ON; Danielle Rouleau, MD, Centre Hospitalier de l'Université de Montréal, Montréal, QC; Roger Sandre, MD, Health Sciences North - The HAVEN/Hemophilia Program, Sudbury, ON; Aida Sadr, MD, Native BC Health Center, St-Paul's Hospital, Vancouver, BC; Mark Tyndall, MD, ScD, Department of Medicine, Infectious Diseases Division, University of Ottawa, Ottawa, ON; Marie-Louise Vachon, MD, Centre Hospitalier Universitaire de Québec, Québec, QC; Steve Sanche, MD, SHARE University of Saskatchewan, Saskatoon, SK; Sharon Walmsley, MD, MSc, University Health Network, Toronto, ON; Alex Wong, MD, Regina Qu'Appelle Health Region, Regina General Hospital, Regina, SK.

We thank all study coordinators and nurses for their assistance with study coordination, participant recruitment, and care.

Author contributions: As corresponding author, M.B.K. helped design and supervised the study and had full access to all the data and took responsibility for the integrity of the data and the accuracy of the data analysis. C.R. was responsible for managing the data and conducted all the analyses with critical input from E.E.M.M. and R.S.-P. C.R. and M.B.K. drafted the manuscript. J.C., C.C., V.M.-L., S.W., and J.G. recruited and followed participants. All of the authors participated in critical revision and have seen and approved the final manuscript and have participated sufficiently in the work to take public responsibility for its content.

Financial support: The study was supported through grant support from the Fonds de recherche en santé-Québec, Réseau SIDA/maladies infectieuses (FRQ-S); the Canadian Institutes of Health Research (CIHR MOP-79529); and the Canadian Institutes of Health Research Canadian HIV Trials Network (CTN222).

Conflicts of interest

Salary awards were obtained from the FRQ-S (Chercheur National career award to M.B.K.) and CIHR Doctoral Research Award (C.R.).

References

1. Roling J, Schmid H, Fischereder M, Draenert R, Goebel FD. **HIV-associated renal diseases and highly active antiretroviral therapy-induced nephropathy.** *Clin Infect Dis* 2006; **42**:1488–1495.
2. Winston J, Deray G, Hawkins T, Szczech L, Wyatt C, Young B. **Kidney disease in patients with HIV infection and AIDS.** *Clin Infect Dis* 2008; **47**:1449–1457.
3. Mocroft A, Kirk O, Gatell J, Reiss P, Gargalianos P, Zilmer K, *et al*. **Chronic renal failure among HIV-1-infected patients.** *AIDS* 2007; **21**:1119–1127.
4. Wyatt CM, Winston JA, Malvestutto CD, Fishbein DA, Barash I, Cohen AJ, *et al*. **Chronic kidney disease in HIV infection: an urban epidemic.** *AIDS* 2007; **21**:2101–2103.
5. Overton ET, Nurutdinova D, Freeman J, Seyfried W, Mondy KE. **Factors associated with renal dysfunction within an urban HIV-infected cohort in the era of highly active antiretroviral therapy.** *HIV Med* 2009; **10**:343–350.
6. 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**:1380–1387.
7. George E, Lucas GM, Nadkarni GN, Fine DM, Moore R, Atta MG. **Kidney function and the risk of cardiovascular events in HIV-1-infected patients.** *AIDS* 2010; **24**:387–394.
8. Winston JA, Klotman PE. **Are we missing an epidemic of HIV-associated nephropathy?** *J Am Soc Nephrol* 1996; **7**:1–7.
9. 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**:541–546.
10. Atta MG, Gallant JE, Rahman MH, Nagajothi N, Racusen LC, Scheel PJ, *et al*. **Antiretroviral therapy in the treatment of HIV-associated nephropathy.** *Nephrol Dial Transplant* 2006; **21**:2809–2813.
11. Ryom L, Mocroft A, Lundgren JD. **Antiretroviral therapy, immune suppression and renal impairment in HIV-positive persons.** *Curr Opin HIV AIDS* 2014; **9**:41–47.

12. 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.
13. Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M, *et al*. **Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients.** *AIDS* 2010; **24**:1667–1678.
14. Fischer MJ, Wyatt CM, Gordon K, Gibert CL, Brown ST, Rimland D, *et al*. **Hepatitis C and the risk of kidney disease and mortality in veterans with HIV.** *J Acquir Immune Defic Syndr* 2010; **53**:222–226.
15. Jotwani V, Li Y, Grunfeld C, Choi AI, Shlipak MG. **Risk factors for ESRD in HIV-infected individuals: traditional and HIV-related factors.** *Am J Kidney Dis* 2012; **59**:628–635.
16. Kalayjian RC, Lau B, Mechekano RN, Crane HM, Rodriguez B, Salata RA, *et al*. **Risk factors for chronic kidney disease in a large cohort of HIV-1 infected individuals initiating antiretroviral therapy in routine care.** *AIDS* 2012; **26**:1907–1915.
17. Alter MJ. **Epidemiology of viral hepatitis and HIV co-infection.** *J Hepatol* 2006; **44**:S6–S9.
18. George E, Nadkarni GN, Estrella MM, Lucas GM, Sperati CJ, Atta MG, *et al*. **The impact of hepatitis C coinfection on kidney disease related to human immunodeficiency virus (HIV): a biopsy study.** *Medicine (Baltimore)* 2011; **90**:289–295.
19. Izzedine H, Sene D, Cacoub P, Jansen H, Camous L, Brocheriou I, *et al*. **Kidney diseases in HIV/HCV-co-infected patients.** *AIDS* 2009; **23**:1219–1226.
20. Pipili C, Ilonidis G, Cholongitas E. **Hepatitis C virus and kidney: a strong association with different clinical aspects.** *Liver Int* 2011; **31**:1071–1080.
21. Lucas GM, Jing Y, Sulkowski M, Abraham AG, Estrella MM, Atta MG, *et al*. **Hepatitis C viremia and the risk of chronic kidney disease in HIV-infected individuals.** *J Infect Dis* 2013; **208**:1240–1249.
22. Klein MB, Rollet KC, Saeed S, Cox J, Potter M, Cohen J, *et al*. **HIV and hepatitis C virus coinfection in Canada: challenges and opportunities for reducing preventable morbidity and mortality.** *HIV Med* 2013; **14**:10–20.
23. Gitman MD, Singhal PC. **Cocaine-induced renal disease.** *Expert Opin Drug Saf* 2004; **3**:441–448.
24. Jaffe JA, Kimmel PL. **Chronic nephropathies of cocaine and heroin abuse: a critical review.** *Clin J Am Soc Nephrol* 2006; **1**:655–667.
25. Klein MB, Saeed S, Yang H, Cohen J, Conway B, Cooper C, *et al*. **Cohort profile: the Canadian HIV-hepatitis C co-infection cohort study.** *Int J Epidemiol* 2010; **39**:1162–1169.
26. Ryom L, Mocroft A, Kirk O, Worm SW, Kamara DA, Reiss P, *et al*. **Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study.** *J Infect Dis* 2013; **207**:1359–1369.
27. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al*. **A new equation to estimate glomerular filtration rate.** *Ann Intern Med* 2009; **150**:604–612.
28. Inker LA, Wyatt C, Creamer R, Hellinger J, Hotta M, Leppo M, *et al*. **Performance of creatinine and cystatin C GFR estimating equations in an HIV-positive population on antiretrovirals.** *J Acquir Immune Defic Syndr* 2012; **61**:302–309.
29. Gagneux-Brunon A, Delanaye P, Maillard N, Fresard A, Basset T, Alamartine E, *et al*. **Performance of creatinine and cystatin C-based glomerular filtration rate estimating equations in a European HIV-positive cohort.** *AIDS* 2013; **27**:1573–1581.
30. Yombi JC, Jones R, Pozniak A, Hougardy JM, Post FA. **Monitoring of kidney function in HIV-positive patients.** *HIV Med* 2015; **16**:457–467.
31. Statistics Canada. Income Research Paper Series. Low Income Lines, 2011–2012. Catalogue no. 75F0002m. http://www.statcan.gc.ca/pub/75f0002m/75f0002m2013002-eng.pdf [Accessed 1 May 2015].
32. White IR, Royston P, Wood AM. **Multiple imputation using chained equations: issues and guidance for practice.** *Stat Med* 2011; **30**:377–399.
33. Allison PD. **Discrete-time methods for the analysis of event histories.** In: Leinhardt S. editor. *Sociological methodology* San Francisco: Jossey-Bass Publishers; 1982. pp. 61–97.
34. Gupta SK, Eustace JA, Winston JA, Boydstun II, Ahuja TS, Rodriguez RA, *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**:1559–1585.
35. Estrella MM, Fine DM. **Screening for chronic kidney disease in HIV-infected patients.** *Adv Chronic Kidney Dis* 2010; **17**:26–35.
36. Goel N, Pullman JM, Coco M. **Cocaine and kidney injury: a kaleidoscope of pathology.** *Clin Kidney J* 2014; **7**:513–517.
37. Perneger TV, Klag MJ, Whelton PK. **Recreational drug use: a neglected risk factor for end-stage renal disease.** *Am J Kidney Dis* 2001; **38**:49–56.
38. Vupputuri S, Batuman V, Muntner P, Bazzano LA, Lefante JJ, Whelton PK, *et al*. **The risk for mild kidney function decline associated with illicit drug use among hypertensive men.** *Am J Kidney Dis* 2004; **43**:629–635.
39. Garg S, Hoenig M, Edwards EM, Bliss C, Heeren T, Tumilty S, *et al*. **Incidence and predictors of acute kidney injury in an urban cohort of subjects with HIV and hepatitis C virus coinfection.** *AIDS Patient Care STDS* 2011; **25**:135–141.
40. Nzerue CM, Hewan-Lowe K, Riley LJ Jr. **Cocaine and the kidney: a synthesis of pathophysiologic and clinical perspectives.** *Am J Kidney Dis* 2000; **35**:783–795.
41. Fabrizi F, Plaisier E, Saadoun D, Martin P, Messa P, Cacoub P. **Hepatitis C virus infection, mixed cryoglobulinemia, and kidney disease.** *Am J Kidney Dis* 2013; **61**:623–637.
42. Mocroft A, Neuhaus J, Peters L, Ryom L, Bickel M, Grint D, *et al*. **Hepatitis B and C co-infection are independent predictors of progressive kidney disease in HIV-positive, antiretroviral-treated adults.** *PLoS One* 2012; **7**:e40245.
43. Peters L, Grint D, Lundgren JD, Rockstroh JK, Soriano V, Reiss P, *et al*. **Hepatitis C virus viremia increases the incidence of chronic kidney disease in HIV-infected patients.** *AIDS* 2012; **26**:1917–1926.
44. Horberg M, Tang B, Towner W, Silverberg M, Bersoff-Matcha S, Hurley L, *et al*. **Impact of tenofovir on renal function in HIV-infected, antiretroviral-naive patients.** *J Acquir Immune Defic Syndr* 2010; **53**:62–69.