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

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Abstract

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 co-infected patients.

Methods: Data from 1,129 participants in the Canadian Co-Infection Cohort with baseline and follow-up serum creatinine measurements between 2003-2014 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 <70 mL/min/1.73m^2. Multivariate logistic regression was used to calculate odds ratios (ORs) and discrete-time proportional hazards models were used to calculate hazard ratios (HRs) 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 [OR 2.03, 95% confidence interval (CI): 0.96, 4.32]. During follow-up, 126 of 1,061 participants (12%) developed incident CRI (31 per 1,000 person-years). Compared to non-users, heavy (≥ 3 days/week) and frequent injection cocaine users (≥ 75% of follow-up time) experienced more rapid progression to CRI [HR 2.65, 95% CI: 1.35, 5.21 and HR 1.82, 95% CI: 1.07, 3.07, respectively]. There was no association between chronic HCV and CRI in either cohort.

Conclusions: After accounting for HCV RNA, frequent and cumulative injection cocaine abuse were associated with CRI progression and should be taken into consideration when evaluating impaired renal function in HIV-HCV co-infection.

MeSH Keywords:

Cocaine; Substance Abuse, Intravenous; Renal Insufficiency; HIV; Hepatitis C, Chronic; Coinfection.

Introduction

Chronic kidney disease (CKD) is a prevalent comorbidity among HIV-infected persons [1, 2]. It is estimated that 5% to 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) co-infection has also been implicated as an important risk factor for CKD and ESRD among HIV patients [12-16]. Due to shared routes of transmission, approximately 25% of people living with HIV are also co-infected with HCV [17]. Membranoproliferative glomerulonephritis (MPGN) is more common in HCV co-infected compared to HIV mono-infected 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 co-infected 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 co-infected 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 ≥ 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, as well as 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 1,366 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 (Figure 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) < 70 mL/min/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 < 70 mL/min/1.73 m^2 [26]. We calculated eGFR using the 2009 SCr-based CKD-EPI equation [27]. This equation has been validated in HIV-infected populations [28, 29]. A confirmed eGFR decline to < 70 mL/min/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 last six months. Frequency of injection cocaine use was categorized as: no use in the last month (referent), occasional use (< 1 day/week), regular use (1 or 2 days/week), or heavy use (≥ 3 days/week). Cumulative exposure to injection cocaine was defined using the proportion of total follow-up time where 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.

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

Based on low-income cut-offs from Statistics Canada, annual income was dichotomized at $24,000 CAD [31]. Hypertension was defined by clinical diagnosis, systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg, or the use of any anti-hypertensive 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 October 1st, 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 (HR) 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 last six 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, TX) was used for all analyses.

Supplemental analyses

In a supplemental analysis, we modeled continuous eGFR using generalized estimating equations (GEE) to compare longitudinal rates of change in eGFR per year between injection cocaine users and non-users. 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 non-injection cocaine and CRI using discrete-time proportional hazards models.

Results

Prevalent Cohort

Of the 1,366 participants included, 1,129 (83%) met the inclusion criteria (Figure 1). Overall, most participants were male, aged over 45 years and 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 female, 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 co-infected 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 $CD4^+$ count, AIDS, diabetes and ESLD (OR 2.06, 95% CI: 0.96, 4.43), and when eGFR < 60 mL/min/1.73 m^2 was used to define prevalent CRI (OR 1.92, 95% CI: 0.75, 4.91).

Incident Cohort

Among the 1,366 participants with available eGFR measurements, 1,061 (78%) did not have prevalent CRI at the index visit and were followed for at least two study visits (Figure 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 3.6 years (IQR: 1.6, 5.5) and the crude CRI incidence rate was 31 per 1,000 person-years of follow-up (95% CI: 26, 37). The median eGFR of those at the time of CRI was 63 mL/min/1.73 m^2 (IQR: 57, 67). The majority of patients with CRI (89%) never recovered eGFR > 70 mL/min/1.73 m^2 and 42% progressed to eGFR < 60 mL/min/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/1.73 m^2 (IQR: 94, 112). Two hundred and eighty-seven participants (27%) reported recent injection cocaine use in the

last six months prior to the index visit. Of these, 61 participants (21%) reported using injection cocaine on average ≥ 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 female, had a lower income and $CD4^+$ count, were more likely to be on atazanavir or lopinavir-based regimens and were more likely to have hypertension and end-stage liver disease.

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

Discussion

In this prospective study of HIV-HCV co-infected 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 non-injection cocaine in the incident cohort. We also found important clinical differences in annual rates of change in eGFR between injection cocaine users and non-users. 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 co-infected 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 co-infected populations. Previous research in non-HIV-infected populations has been limited by small sample sizes, poor exposure ascertainment and the use of non-longitudinal 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 co-infected cohort [39]. Garg *et al.* reported that recent injection or non-injection

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 [39]. Our study supports that elevations in creatinine associated with cocaine use are not transient but rather lead to chronic kidney dysfunction as 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 non-injection 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 SMART and ESPRIT trials, as well as the EuroSIDA cohort, co-infected patients with HCV viral loads ≥ 800,000 IU/mL and 500,000 IU/mL, respectively, had larger CKD incidence rates compared to those with resolved HCV infections [42, 43].

In the larger NA-ACCORD cohort, however, rates of incident CKD did not differ between co-infected 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.

This study has several important strengths. First, the cohort collected detailed, time-updated information on the use of specific illicit drugs, as well as 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 three 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 co-infected 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/1.73 m^2), as there were few CKD events. While 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 is associated with CRI progression among HIV-HCV co-infected patients. The role of substance use in contributing to renal disease in co-infection has been underappreciated and should be taken into consideration when evaluating impaired renal function in this setting.

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Table 1: Baseline characteristics of 1,129 Canadian Co-Infection Cohort participants by history of injection cocaine use [a]

Characteristic [b]	History of Injection Cocaine Use (n=847)	No History of Injection Cocaine Use (n=277)
	n (%)	n (%)
Median age, years (IQR)	45 (39, 50)	47 (41, 53)
Female	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 $CD4^+$ count, cells/μL (IQR)	394 (250, 577)	450 (293, 620)
Median nadir $CD4^+$ 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. IQR = inter-quartile range; HCV = hepatitis C virus; ART = antiretroviral therapy.

[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 $CD4^+$ count n=67; HIV viral load n=21; hypertension n=6; diabetes n=6; clinical AIDS diagnosis n=5.

Table 2: Crude and adjusted odds ratios for prevalent chronic renal impairment (n=1,129)

	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 five year increase)	1.46 (1.28, 1.66)	1.69 (1.43, 1.99)
Female	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 five 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)

OR=odds ratio; HCV=hepatitis C virus; CI=confidence interval.

[a] Multiple imputation used for missing data.

Table 3: Baseline participant characteristics and characteristics at end of follow-up by chronic renal impairment (CRI) outcome in the incident cohort (n=1,061)

Characteristic	Index Visit [a]	Status at End of Follow-Up [b]	
	n (%)	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/1.73 m^2 (IQR)	104 (94, 112)	63 (57, 67)	101 (91, 110)
Chronic HCV Infection	886 (84%)	90 (73%)	649 (70%)
Median $CD4^+$ 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.

IQR = inter-quartile range; HCV = hepatitis C virus; eGFR = estimated glomerular filtration rate; CRI = chronic renal impairment.

[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; $CD4^+$ count n=7; HIV viral load n=10; 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; $CD4^+$ count n=27; HIV viral load n=30; clinical AIDS diagnosis n=23.

Table 4: Discrete-time proportional hazards analysis for incident chronic renal impairment (n=1,061) [a]

Variable	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				
Non-User	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				
Non-User	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 five 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)
Female	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)
$CD4^+$ 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)

HR = hazard ratio; CI = confidence interval; HCV = hepatitis C virus

[a] Multiple imputation used for missing data.

—–* : covariate excluded from multivariate model.

Figure Captions

Figure 1. Study participant flow chart for prevalent and incident cohorts. CRI= Chronic renal impairment; SCr= Serum creatinine.

Figure