Criteria Grid
Hepatitis C Research Studies, Tools, and Surveillance Systems

Best Practice/Intervention:	Brunet L. et al. (2015) Opioid use and risk of liver fibrosis in HIV/hepatitis C virus-coinfected patients in Canada. *HIV Med,* 17: 36-45.
Date of Review:	March 6, 2016
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☒ **Social Science** ☐ **Programmatic Review** ☐
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☐ **Hepatitis C/HIV** ☒ **Other:** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **people co-infected with HCV/HIV using opioid** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **Canada** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	Primary research; to evaluate the use of both prescribed and illicit opioids in the HIV/HCV co-infected population and to assess the role of opioid use in the development of liver fibrosis.
Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?	☐	☒	☐	Data was not used for decision-making.
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	The cohort includes a large population that represents Canadians with HCV/HIV co-infection. Particular efforts were made

				to include marginalize populations such as Aboriginal people, women, and people who inject drugs.
Are the best practices/methodology/results described applicable in developed countries?	☐	☒	☐	
	YES	**NO**	**N/A**	**COMMENTS**
Are the best practices/methodology/results described applicable in developing countries?	☐	☒	☐	Results of this study are only applicable in Canada.
The research study/tool/data dictionary is easily accessed/available electronically	☒	☐	☐	Open access can be found on http://onlinelibrary.wiley.com/
Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	Cost effective analysis was not conducted.
Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?	☐	☒	☐	
How is the research study/tool funded? ***Please got to Comments section***	☐	☐	☐	This research was funded by the Fonds de recherche Santé-Québec, Réseau SIDA/maladies infectieuses, the Canadian Institutes of Health Research, and the CIHR Canadian HIV Trials Network.
Is the best practice/intervention dependent on external funds?	☐	☒	☐	
Other relevant criteria: _____	☐	☐	☐	- Over 40% of the population in the cohort study received opioid prescription, almost 30% used opioids illicitly and approximately 20% were prescribed opioids and also used them illicitly - Opioids use were not found to be associated with increase in

				median APRI score or with faster progression to advanced liver fibrosis - Findings of potential harmful effect of opioids are derived from cell culture or animal model experiments and may not reflect the reality of people using opioids
WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				
Are these data regularly collected?	☒	☐	☐	Study utilizes data from the Canadian Co-infection Cohort study which recruit patients from 18 HIV clinics across Canada since October 1, 2013.
Are these data regularly collected at and/or below a national level?	☒	☐	☐	
Are these data collected manually or electronically?	☐	☐	☐	Electronically
RESEARCH REPORTS				
Has this research been published in a juried journal?	☒	☐	☐	HIV Medicine
Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?	☐	☐	☐	New data/information

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ORIGINAL RESEARCH

Opioid use and risk of liver fibrosis in HIV/hepatitis C virus-coinfected patients in Canada

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Objectives

Opioid use and opioid-related mortality have increased dramatically since the 1990s in North America. The effect of opioids on the liver is incompletely understood. Some studies have suggested that opioids cause liver damage and others have failed to show any harm. HIV/hepatitis C virus (HCV)-coinfected persons may be particularly vulnerable to factors increasing liver fibrosis. We aimed to describe opioid use in an HIV/HCV-coinfected population in Canada and to estimate the association between opioid use and liver fibrosis.

Methods

We conducted a cross-sectional descriptive analysis of the Canadian Co-infection Cohort Study data to characterize opioid use. We then conducted a longitudinal analysis to assess the average change in aspartate aminotransferase-to-platelet ratio index (APRI) score associated with opioid use using a generalized estimating equation with linear regression. We assessed the progression to significant liver fibrosis (APRI ≥ 1.5) associated with opioid use with pooled logistic regression.

Results

In the 6 months preceding cohort entry, 32% of the participants had received an opioid prescription, 28% had used opioids illicitly and 18% had both received a prescription and used opioids illicitly. Neither prescribed nor illicit opioid use was associated with a change in the median APRI score [exp(β) 0.99 (95% confidence interval (CI) 0.82, 1.12) and exp(β) 0.95 (95% CI 0.81, 1.10), respectively] or with faster progression to liver fibrosis [hazard odds ratio (HOR) 1.20 (95% CI 0.73, 1.67) and HOR 1.09 (95% CI 0.63, 1.55), respectively].

Conclusions

Although opioids were commonly used both legally and illegally in our cohort, we were unable to demonstrate a negative impact on liver fibrosis progression.

Keywords: hepatitis C, HIV, liver fibrosis, opioids

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*See Appendix.

Introduction

Since the 1990s, opioid use has increased dramatically in North America and opioid-related overdose and mortality have increased in parallel [1]. Many behavioural and drug-related factors, such as the type and doses of opioids prescribed and poly-substance use, appear to contribute to

the observed increase in opioid-related deaths [2]. Liver-related deaths are frequent among opioid users. In Australia, among 841 cases of fatal opioid toxicity, significant liver damage was the most frequent pathology revealed at autopsy [3]. Opioid-dependent individuals were reported to be about 17 times more likely to die of any liver-related cause and far more likely to die of chronic liver disease and liver cancer compared with the general population [4,5]. The increased risk of liver disease in opioid users is largely explained by chronic hepatitis C virus (HCV) infection, which is common in this population [6]. It is, however, unclear whether opioids directly contribute to liver fibrosis progression, which is a prerequisite for cirrhosis and is associated with morbidity and mortality.

Opioid analgesics and methadone substitution therapy are frequently prescribed both to HIV- and HCV-infected persons [7] who might be at greater risk of opioid-related liver morbidity because coinfection is associated with an accelerated progression of liver fibrosis [8]. Morphine has also been shown to enhance expression of HCV mRNA in cell culture [9], suggesting the potential for a direct effect of opioids on liver morbidity in a coinfected population.

Current literature on the effect of opioids on the liver is conflicting. In experimental studies, administration of opioid-receptor agonists to animals or in cell cultures leads to increased levels of transaminases [10,11], hepatic glutathione s-transferase [12], histopathological abnormalities [11], liver inflammation [13], fatty accumulation [13], and fibrosis [13]. Supporting evidence from observational studies is weak. Cross-sectional studies demonstrate that heroin users have higher transaminase levels compared with users of other drugs or alcohol [14] and increased collagen deposition compared with non-drug users [15]. Other experimental studies have identified only a moderate effect of opioids on elevation of transaminase levels [16], glutathione levels [17] and fibrosis [18]. A cross-sectional study of HCV-infected male veterans failed to show an association between methadone use and liver fibrosis [19]. Although studies have suggested that opioid receptor antagonists may prevent opioid-related liver damage [20–24], two randomized controlled trials comparing use of methadone (an agonist) to buprenorphine (a mixed agonist-antagonist) demonstrated similar transaminase levels in the two groups [25,26]. The effect of opioid use and abuse on liver-related outcomes in HIV/HCV-coinfected persons remains unknown.

The first objective of this study was to evaluate the use of both prescribed and illicit opioids by the participants of the Canadian Co-infection Cohort Study. As a second objective, we assessed the role of prescribed and/or illicit opioid use in the development of liver fibrosis in HIV/HCV-coinfected persons.

Methods

The Canadian co-infection cohort study

The Canadian Co-infection Cohort Study is a multicentre longitudinal study of HIV/HCV-coinfected persons from 18 HIV clinics across Canada. The cohort's eligibility criteria are the following: (a) to be ≥16 years old; (b) to have documented HIV infection (HIV positive by enzyme-linked immunosorbant assay with western blot confirmation); and (c) to show evidence of HCV infection (HCV seropositive by enzyme-linked immunosorbent assay with recombinant immunoblot assay II or enzyme immunoassay confirmation, or, if serologically false negative, HCV RNA positive). After providing informed consent, participants are followed every 6 months, completing questionnaires regarding sociodemographic factors and drug exposures, and also providing blood samples. Clinical events are recorded by research coordinators through chart review. The cohort design and protocol have previously been described [27]. As of 1 October 2013, 1238 patients had been recruited.

Approval has been obtained from the relevant ethics committee for each study site and the Canadian Co-infection Cohort Study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Exposure to opioids

Prescribed opioid use (natural, semi-synthetic or synthetic opioid receptor agonists or mixed agonist-antagonist) was assessed through participant self-report. This information was supplemented by review of the patient's clinical file. Illicit opioid use and route of administration (injection or not) were assessed through participant self-report at each study visit.

Aspartate aminotransferase-to-platelet ratio index (APRI) score and liver-related morbidity and mortality

At each visit, we calculated the APRI score as: $100 \times$ (aspartate aminotransferase/upper limit of normal)/platelet count (10^9 cells/L). An APRI score ≥ 1.5 indicates significant liver fibrosis (equivalent to a score of ≥2 on the Metavir scale) [28]. We chose to use this validated biomarker because, while liver biopsies are considered the gold standard to detect fibrosis, they are expensive, prone to sampling error, unethical to perform every 6 months for research purposes, and often unacceptable for patients unless a treatment decision is being considered.

End-stage liver disease (ESLD) was defined as a diagnosis of liver cirrhosis, ascites, portal hypertension, spontaneous bacterial peritonitis, encephalopathy, oesophageal varices or hepatocellular carcinoma. Participants were categorized

as having experienced a hepatic event if they had a diagnosis of ESLD or experienced ESLD-related death. Study site coordinators completed dedicated case report forms in the event of death or ESLD diagnosis. Two investigators independently classified causes of death using the Coding of Death in HIV (CoDe) system [29]. Participants in British Columbia, Alberta and Quebec (74% of the cohort) were linked to provincial vital statistics to capture deaths among patients lost to follow-up.

Statistical analyses

Two analytical cohorts were selected. The *prevalence cohort* consisted of all participants with at least two study visits and with active HCV viral replication at baseline. This cohort allowed us to evaluate the effect of opioid use regardless of the baseline disease stage. We created the *incidence cohort* by restricting the population to patients without significant fibrosis or ESLD events at baseline in order to study the effect of opioid use on progression to these outcomes in follow-up. All participants were censored at initiation of HCV treatment because it can affect the APRI measure. Missing data were handled using multiple imputation with chained equations.

We performed descriptive statistics for prescribed and illicit opioid use at cohort entry in both cohorts. In the prevalence cohort, we estimated the average response in the natural log of the continuous APRI score corresponding with prescribed and/or illicit opioid use by fitting a linear regression with generalized estimating equations (GEEs). Different correlation structures were used to find the best fitting model using the quasi-likelihood under the independence model criterion (QIC). In the incidence cohort, we performed a survival analysis using pooled logistic regression with a polynomial representation of time to assess the association of prescribed and/or illicit opioid use, compared with no use, with progression to significant fibrosis (defined as APRI $\geq$ 1.5).

All statistical models were adjusted for baseline age, sex and estimated time since HCV infection in addition to the previous visit's time-updated alcohol use, other illicit drug use, antiretroviral therapy, CD4 cell count and presence of detectable HIV viral load. The linear regression model was further adjusted for years of follow-up. Two indicators of opioid use during the previous study interval were included in each model: an indicator for prescribed opioid use and one for illicit opioid use. STATA, version 13 (StataCorp, College Station, TX) was used to perform all analyses.

Sensitivity analyses

Four planned sensitivity analyses were performed with both the prevalence and the incidence cohort by replacing the exposure variables in the models described above. The first sensitivity analysis consisted of replacing the indicators for prescribed and illicit opioid use by an indicator for any opioid use. With the second, we explored the effect of the number of different opioids prescribed or taken illicitly during a study interval. In the third, we used the cumulative number of intervals during which opioids were used with or without a prescription. Finally, we introduced an indicator for opioid injection and one for other routes of opioid administration instead of the indicator for illicit use in general.

Two further sensitivity analyses were performed with the incidence cohort data only. First, we repeated the survival analysis using hepatic events as the outcome. We also performed a Monte Carlo sensitivity analysis with record-level correction of the measurement error in prescribed opioid use to assess the progression to liver fibrosis while accounting for potential measurement error of the exposure to prescribed opioids [30]. We used trapezoidal probability distributions for sensitivity (0.45, 0.5, 0.6 and 0.99) and specificity (0.7, 0.8, 0.9 and 1) selected based on published validation studies [31–33].

Results

Prevalence cohort: opioid use and changes in median APRI score

Selection of participants in the prevalence and incidence cohorts is described in Fig. 1. The prevalence cohort comprised 800 participants who contributed a median of 39 months of follow-up for a total of 3058 person-years. The majority were male with low income. Approximately 50% had been using alcohol and the majority were on antiretroviral therapy with controlled HIV infection. Further details regarding baseline demographic and clinical characteristics are summarized in Table 1.

Prescribed and illicit opioid use is presented in Table 2. At cohort entry, 43% of the participants in the prevalence cohort were using prescribed and/or illicit opioids. Almost a third had received at least one prescription for opioids in the previous 6 months and the majority were prescribed only one type of opioid. Opioids were used illicitly by 28% of the participants, among whom 29% injected only, 45% used other routes of administration only and 26% used opioids by both injection and alternate routes.

Figure 2a shows that methadone was the type of opioid most often prescribed at baseline (62% of users). The most frequently injected opioids reported were heroin (84%), morphine (64%), speedball (heroin and cocaine injected together) (60%) and hydromorphone (56%), as presented in Fig. 2b. Methadone (42%) and codeine combined with

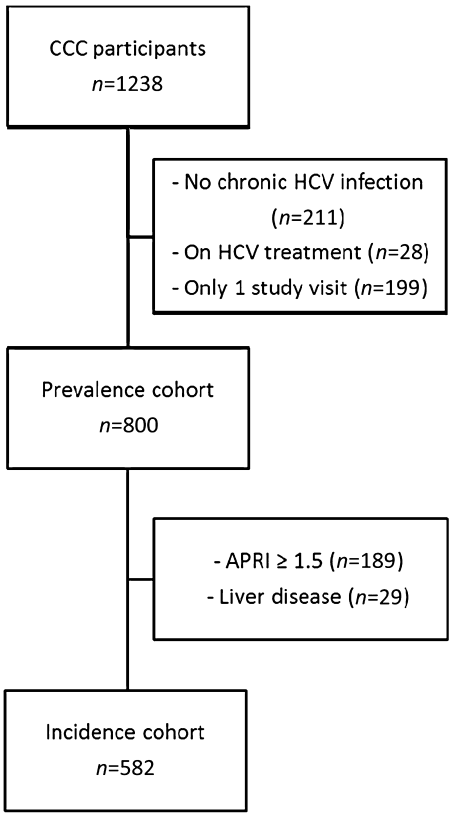

Fig. 1 Study population flow chart. APRI, aspartate aminotransferase-to-platelet ratio index; CCC, Canadian Co-infection Cohort Study; HCV, hepatitis C virus.

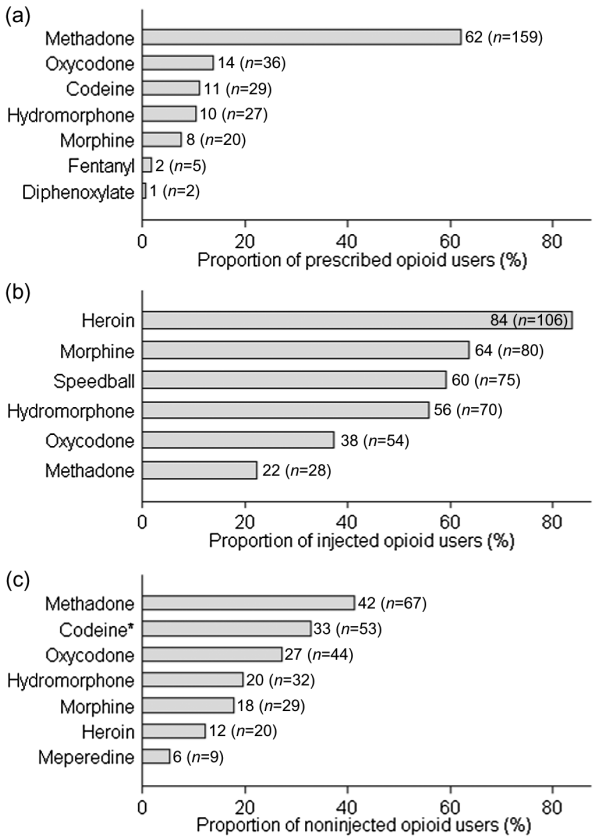

Fig. 2 Types of opioids used in the prevalence cohort. (a) Prescribed opioids; (b) illicit opioids, injected; (c) illicit opioids, other routes of administration. *Codeine in combination with acetaminophen.

Table 1 Baseline characteristics of the study populations

Characteristic	Prevalence cohort	Incidence cohort
Number of participants	800	582
Person-visits	4865	3652
Number of study visits [median (IQR)]	7 (4–10)	8 (4–11)
Months of follow-up [median (IQR)]	39 (19–56)	42 (19–58)
Age (years) [median (IQR)]	44 (39–50)	43.8 (38–49)
Male [*n* (%)]	582 (73)	408 (70)
Monthly income of $1500 CAD or less [*n* (%)]	615 (77)	455 (78)
Homeless [*n* (%)]	101 (13)	70 (12)
Alcohol use in past 6 months [*n* (%)]	415 (52)	293 (50)
Used injection drugs in past 6 months [*n* (%)]	294 (37)	228 (39)
Other drug use (not injected) in past 6 months [*n* (%)]	364 (46)	269 (46)
Duration of HCV infection (years) [median (IQR)]	18 (10–25)	18 (10–25)
Time since HIV diagnosis (years) [median (IQR)]	11 (6–17)	11 (6–16)
CD4 cell count (cells/μL) [median (IQR)]	374 (240–540)	388 (258–551)
Undetectable HIV viral load (<50 copies/mL) [*n* (%)]	438 (55)	319 (55)
HIV viral load if detectable (copies/mL) [median (IQR)]	2047 (111–30065)	2344 (117–30231)
Baseline APRI score [median (IQR)]	0.70 (0.43–1.46)	0.53 (0.38–0.80)
Prevalent cases of APRI ≥ 1.5 [*n* (%)]	189 (24)	NA
Prevalent cases of ESLD [*n* (%)]	84 (11)	NA

IQR, interquartile range; APRI, aspartate aminotransferase-to-platelet ratio index; CAD, Canadian dollars; ESLD, end-stage liver disease; HCV, hepatitis C virus; NA, not applicable.

acetaminophen (33%) were the illicit opioids most often used without injection (Fig. 2c).

At cohort entry, participants in the prevalence cohort had a median APRI score of 0.7, 24% had already reached the cut-off for significant fibrosis and 11% had experienced an ESLD event (Table 1). In follow-up, ESLD caused or contributed to the death of 19 persons (21% of deaths). Figure 3 presents the types of opioids reported at the visit prior to their last by persons who finished follow-up without liver fibrosis, those who developed liver fibrosis and those who were diagnosed with or died of ESLD.

Table 2 Prescribed and illicit opioid use in the study population at cohort entry

Opioid use	Prevalence cohort (n = 800) n (%)	Incidence cohort (n = 582) n (%)
Any opioid use	344 (43)	260 (45)
Prescribed opioid use	255 (32)	198 (34)
Number of different opioids prescribed*		
0	545 (68)	384 (66)
1	234 (29)	180 (31)
2	19 (2)	16 (3)
3	2 (0)	2 (0)
Illicit opioid use	228 (28)	176 (30)
Injected only (among illicit opioid users)	67 (29)	50 (28)
Not injected only (among illicit opioid users)	102 (45)	79 (45)
Both (among illicit opioid users)	59 (26)	47 (27)
Both prescribed and illicit opioid use	144 (18)	116 (20)

*Prescribed opioids included the following: codeine, morphine, hydromorphone, oxycodone, diphenoxylate, fentanyl, meperedine, methadone and tramadol.

After accounting for age, sex, time since HCV infection, alcohol use, antiretroviral therapy use, CD4 cell count, undetectable HIV viral load and years of follow-up, neither prescribed nor illicit opioids were associated with a statistically significant change in the median APRI score, as presented in Table 3. Changes in the median APRI score were modest. For example, use of prescribed opioids was associated with a 1% decrease in the median APRI score [exp(β) 0.99; 95% confidence interval (CI) 0.85, 1.12] and illicit use was associated with a 5% decrease in the median APRI score (exp(β) 0.95; 95% CI 0.81, 1.10). Alcohol use, however, was associated with a 20% increase in the median APRI score and a higher CD4 cell count was protective.

Incidence cohort: opioid use and progression to significant liver fibrosis

The incidence cohort consisted of 582 participants, contributing a median of 42 months of follow-up for a total of 2293 person-years, as shown in Fig. 1. There were no important differences between the prevalence and the incidence cohorts either with respect to baseline demographic and clinical characteristics or pertaining to opioid use (Tables 1 and 2).

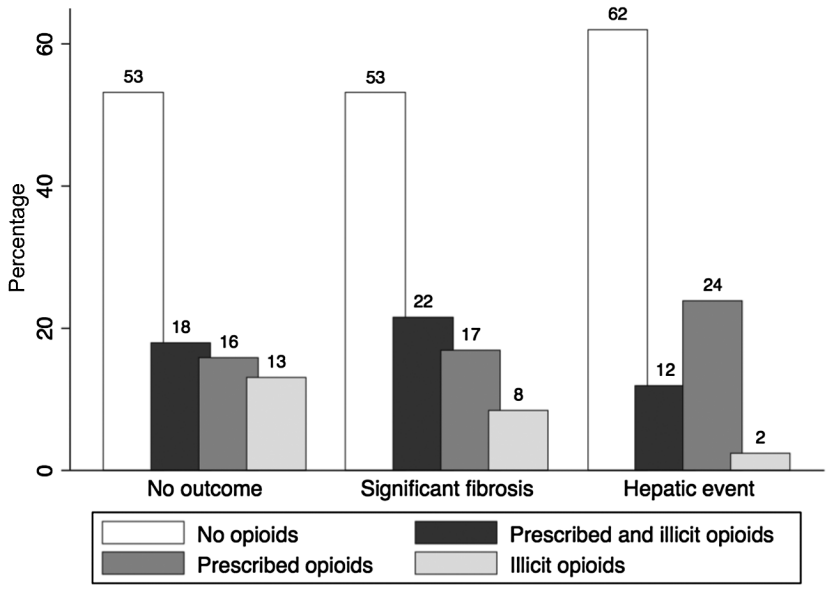

Fig. 3 Opioid use by liver outcome at the visit before last (if no outcome) or at the visit before a liver outcome was reported in the prevalence cohort. Significant fibrosis: aspartate aminotransferase-to-platelet ratio index (APRI) ≥ 1.5; hepatic event: diagnosis of end-stage liver disease (ESLD) or ESLD-related death. The same participant can contribute to more than one category if the different liver outcomes occurred at different study visits. If outcomes were reported at the same visit, then they were attributed to the most severe category.

Table 3 Relationship between opioid use and change in median aspartate aminotransferase-to-platelet ratio index (APRI) score in the prevalence cohort or development significant liver fibrosis in the incidence cohort

	Prevalence cohort (GEE) Ln(APRI score)* Exp(β) (95% CI)	Incidence cohort (Pooled logistic regression) Significant fibrosis† HOR (95% CI)
Prescribed opioid use‡	0.99 (0.85, 1.12)	1.20 (0.73, 1.67)
Illicit opioid use‡	0.95 (0.81, 1.10)	1.09 (0.63, 1.55)
Baseline		
Age (5-year increments)	1.03 (0.99, 1.07)	1.01 (0.90, 1.12)
HCV duration (5-year increments)	1.02 (0.99, 1.05)	1.00 (0.91, 1.09)
Female	0.98 (0.84, 1.11)	1.40 (0.89, 1.94)
Updated		
Alcohol use‡	1.20 (1.08, 1.32)	1.42 (0.89, 1.94)
Other illicit drug use‡	0.91 (0.81, 1.00)	1.22 (0.71, 1.74)
Antiretroviral use‡	0.94 (0.81, 1.07)	0.84 (0.42, 1.26)
CD4 cell count (per 100 cells/μl)‡	0.96 (0.94, 0.98)	0.99 (0.92, 1.06)
Undetectable HIV RNA‡	0.97 (0.87, 1.08)	0.94 (0.52, 1.37)
Time since cohort entry (years)	1.02 (1.00, 1.05)	NA§
Intercept	0.62 (0.47, 0.95)	0.06 (0.01, 0.31)

*Ln(APRI score) was used as the outcome. We show exp(β), which represents the change in the median APRI score associated with a one unit increase in the continuous dependent variables, or the presence of the characteristic recorded using dichotomous variables.
†Significant fibrosis: APRI ≥ 1.5.
‡Last visit before outcome assessment.
§Models were adjusted for time using a polynomial function of the visit number (visit, visit^2, visit^3 and visit^4).
CI, confidence interval; GEE, generalized estimating equation; HCV, hepatitis C virus; HOR, hazard odds ratio; NA, not applicable.

At cohort entry, participants in the incidence cohort had a median APRI score of 0.5. Over the course of follow-up, 163 participants (28%) developed significant fibrosis and 27 (5%) experienced a clinical hepatic event. There was no ESLD-related death during follow-up in the incidence cohort. Neither prescribed (HOR 1.20; 95% CI 0.73, 1.67) nor illicit (HOR 1.09; 95% CI 0.63, 1.55) opioid use was significantly associated with faster progression to significant liver fibrosis. Similar associations between alcohol use or CD4 cell count and progression to liver fibrosis were observed as in the prevalence cohort; however, the 95% CI included 1.00. Results are summarized in Table 3.

Sensitivity analyses

Using different exposure definitions (any opioids *vs.* no opioid use, number of different opioids used, cumulative number of periods of use, separating injected and not injected illicit use), the results obtained were not appreciably different from those presented in Table 3 (data not shown). Using hepatic events as the outcome in the incidence cohort produced results comparable to those shown above for prescribed opioids but they were far more imprecise (HOR 2.26; 95% CI 0.78, 6.50). The results for illicit use pointed in the opposite direction, although the CI was also very wide (HOR 0.81; 95% CI 0.22, 2.90).

Accounting for potential measurement error in prescribed opioid use with the Monte Carlo sensitivity analysis did not change the results appreciably for the progression to significant liver fibrosis associated with prescribed opioid use (HOR 1.11; 95% simulation interval 0.62, 1.98).

Discussion

This study is the first description of illicit and prescribed opioid use and assessment of their association with liver fibrosis in an HIV/HCV-coinfected population. A high proportion of the Canadian Co-infection Cohort Study participants reported opioid use. Over 40% of the participants received opioid prescriptions, almost 30% used opioids illicitly and close to 20% who were prescribed opioids also used them illicitly during the same period. The rate of prescribed opioid use is similar to that recently described among HIV-infected veterans [7] and among patients being treated for noncancer pain conditions covered by two American commercial health plans [34]. The high rates of concurrent prescribed and illicit opioid use as well as the large proportion of prescription opioids used illicitly, however, suggest that opioid misuse is common in our population and similar to misuse rates recently reported among indigent HIV-infected persons [35]. A study of chronic noncancer pain opioid users also revealed that between 24 and 31% exhibited prescription opioid abuse behaviours [36].

Methadone was the most frequently prescribed opioid in the Canadian Co-infection Cohort. Opiate substitution therapy with methadone is an important component of harm reduction strategies. In addition to reducing injecting drug use, it decreases the risk of HIV transmission [37] and is associated with favourable health outcomes, including longer survival [38]. However, methadone has been associated with a substantial proportion of opioid-related deaths [2]. Therefore, it is important to investigate potential harmful clinical effects of prescribing methadone and other opioids in this population, such as liver outcomes.

The high prevalence of nonmethadone opioid use in this coinfection cohort and other cohorts of HIV-infected individuals could partly be explained by the need for pain management. Pain is a common problem for HIV-infected individuals [39,40]. HCV-infected persons may also experience pain caused by mixed cryoglobulinaemia, HCV-associated arthritis, peripheral neuropathy or fibromyalgia [41]. A high prevalence of pain could have explained some opioid misuse if patients attempt to control inadequately managed pain on their own.

In our coinfected population, neither prescribed opioids nor illicitly used opioids were associated with an increase in median APRI score or with a faster progression to advanced liver fibrosis. Our results were consistent between the prevalence and the incidence cohorts, and across a range of sensitivity analyses using different approaches to model opioid exposure (any opioids *vs*. no opioid use, number of different opioids used, cumulative number of periods of use, separating injected and not injected illicit use) or correcting for measurement error.

The majority of findings suggesting a potential harmful effect of opioids on the liver are derived from experiments conducted in cell culture or animal models and may not accurately reflect the reality of people regularly using opioids. Often, the doses used in animal experiments are much higher than those prescribed and the purity of the opioids used is generally greater than that of the opioids that can be purchased on the street. The observational studies suggesting a link between opioid use and liver diseases are predominantly case studies [15,42,43] or cross-sectional studies [3,14,19]. Results from these types of study should be interpreted carefully because it is not possible to ascribe temporality of exposure and events. There was no evidence of an association between methadone use and advanced fibrosis [odds ratio (OR) 1.29; 95% CI 0.56, 3.01] in a cross-sectional analysis of 571 male veterans with HCV infection [19]. Another cross-sectional study concluded that opioids had only a reversible effect on the liver, because current heroin users without HIV or HBV infection (but uncertain HCV status) exhibited microvasular alterations that were not present in liver biopsies of ex-heroin users [44]. The participant selection in cross-sectional studies of opioid use and liver disease may also introduce potential bias. For example, one study only included information on people who died from opioid overdose, among whom 37% of the individuals had steatosis, 11% had fibrosis and 7% had cirrhosis [3]. Another study grouped users of various drugs together and did not attempt to isolate the effect of opioids from the effect of other types of drugs in their analyses [14]. Randomized controlled trials have shown that groups who received an opioid agonist did not experience greater elevations in liver enzymes than groups who received a mixed agonist-antagonist [25,26], or groups who received no opioids [45]. In fact, it seems that use of opioids is not a determining factor for elevated liver enzymes or other liver outcomes, as opposed to a diagnosis of viral hepatitis [26,46].

This study was conducted with data from a large, multicentre Canadian cohort study. The population studied is representative of Canadians with coinfection who access care and particular efforts have been made to reach vulnerable populations such as Aboriginal people, women and people who inject drugs. Multiple sensitivity analyses were conducted to confirm the robustness of our findings. The quality of exposure measurement can have a substantial impact on the effects estimated. The validity of self-reported use of prescribed opioids, narcotics or pain killers has been assessed in various populations and showed low to moderate sensitivity but high specificity compared with administrative database, urine toxicology or medical records [31–33]. Considering the likelihood that the validity of the prescribed opioids measure is poor, we conducted a sensitivity analysis to account for this potential misclassification and confirmed the results obtained without correction. However, the Monte Carlo sensitivity analysis could not be performed for the analysis of continuous APRI score because of the complexity of applying this method of bias correction to a continuous outcome. We did not attempt to correct potential misclassification of illicit opioid use because validation studies suggest that self-report of these types of drugs is overall a valid measure [47]. We were unable to perform a dose – response analysis because information on prescribed doses and quantification of amount of illicit opioids used was not available. However, we were able to perform sensitivity analyses investigating the effect of the intensity and consistency of use.

It is possible that we lacked the power to detect an effect in the incidence cohort, as suggested by the wide CIs around the estimates for the effects of alcohol use or lower CD4 cell counts, which are both established risk factors for progression to significant liver fibrosis. However, sufficient

statistical power was present to identify an association between alcohol use or CD4 cell count and change in median APRI score in the prevalence cohort. This suggests that sufficient power was present to detect a clinically meaningful effect of opioids in the prevalence cohort.

Liver diseases progress slowly and the duration of follow-up in this cohort was relatively short, which limits the possibility of observing liver disease-related clinical outcomes. It is for this reason that we selected liver fibrosis progression as the outcome for the main analyses, as liver fibrosis is a precursor of liver disease. Longer follow-up would, however, be useful to confirm the results of this study and assess whether a longer exposure to opioids could be harmful.

We chose to use the APRI score as a marker for liver fibrosis because the invasiveness of liver biopsy precludes its use in a longitudinal research setting. Moreover, transient elastography was not performed in all study sites and repeated measures are currently limited in our cohort. Although the specificity of the APRI score cut-off for significant fibrosis is excellent, it has a low sensitivity [28], which could lead to some degree of outcome misclassification. However, most noninvasive markers of liver fibrosis available have been shown to perform with similar accuracy [48]. The APRI score has been validated in HIV/HCV-coinfected populations [28]. This marker has been shown to predict all-cause mortality [49] and occurrence of liver complications [50]. The results reported here are therefore clinically pertinent despite the lack of power to study ESLD as an outcome.

In conclusion, opioids are widely used in this Canadian HIV/HCV-coinfected population. A large proportion of patients received one or more prescriptions for an opioid and many also used opioids without a prescription in the same period of time. However, opioid users were not at increased risk of developing liver fibrosis compared with nonusers. While opioid use may have other negative consequences, aggravating liver disease does not seem to be a major concern when managing addiction or pain in HIV/HCV-coinfected patients.

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Appendix

The Canadian Coinfection Cohort Study involves 18 sites across Canada who recruit and follow HIV/HCV-coinfected patients. The following co-investigators have all taken part in the data collection pertaining to the present paper, and have reviewed its content. However, they did not partake in the analysis, writing or editing of this paper, nor has anyone received compensation for any contributions.

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