Trends in cause-specific mortality in HIV–hepatitis C coinfection following hepatitis C treatment scale-up

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Objective: Hepatitis C virus (HCV) treatment may reduce liver-related mortality but with competing risks, other causes of mortality may undermine benefits. We examined changes in cause-specific mortality among HIV–HCV coinfected patients before and after scale-up of HCV treatment.

Design: Prospective multicentre HIV–HCV cohort study in Canada.

Methods: Cause-specific deaths, classified using a modified 'Coding of Cause of Death in HIV' protocol, were determined for two time periods, 2003–2012 and 2013–2017, stratified by age (20–49; 50–80 years). Comparison of trends between periods was performed using Poisson regression. To account for competing risks, multinomial regression was used to estimate the cause-specific hazard ratios of time and age on cause of death, from which end-stage liver disease (ESLD)-specific 5-year cumulative incidence functions were estimated.

Results: Overall, 1634 participants contributed 8248 person-years of follow-up; 273 (17%) died. Drug overdose was the most common cause of death overall, followed by ESLD and smoking-related deaths. In 2013–2017, ESLD was surpassed by drug overdose and smoking-related deaths among those aged 20–49 and 50–80, respectively. After accounting for competing risks, comparing 2003–2012 to 2013–2017, ESLD deaths declined (adjusted hazards ratio: 0.18, 95% confidence interval 0.05–0.62). However, both early and late period cumulative incidence functions demonstrated increased risk of death from ESLD for patients with poor HIV control and advanced fibrosis.

Conclusion: The gains made in overall mortality with HCV therapy may be thwarted if modifiable harms are not addressed. Although ESLD-related deaths have decreased over time, treatment should be further expanded, prioritizing those with advanced fibrosis.   Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

With the widespread use of combination antiretroviral therapy (cART), there has been substantial declines in AIDS-related mortality [1−4]. Consequently, people living with HIV have seen impressive gains in life expectancy resulting in the increasing importance of coinfections such as hepatitis C virus (HCV) as contributors to morbidity and mortality [5]. Due to shared routes of transmission, recent estimates are that 2.3 million (6.2%) of HIV-infected individuals are coinfected with HCV globally and 170 00 Canadians [6]. HCV−HIV coinfection is associated with a three-fold higher risk of death compared with HIV-mono-infection and a 12 times higher rate of mortality compared with the general population [7,8]. HIV hastens liver fibrosis progression, resulting in increased liver-associated morbidity and mortality, particularly in the setting of low $CD4^+$ T-cell counts [9].

Liver disease-related deaths secondary to cirrhosis, liver failure and hepatocellular carcinoma (HCC) have accounted for 20−25% of all causes of death in several studies of HIV−HCV coinfection [8,10,11]. Before widespread HCV treatment, end-stage liver disease (ESLD) was the primary cause of death in the Canadian Co-infection Cohort [8]. HCV treatment uptake has been primarily limited to individuals with advanced fibrosis and there is emerging evidence that deaths secondary to liver disease may be declining in recent calendar periods in some [12,13] but not all studies. This may be partly explained by the finding that achieving sustained virologic response (SVR) following treatment reduces rates of hepatic decompensation, HCC and death from liver-related and nonliver-related causes [9,14−18]. In addition to liver-related outcomes, HCV infection has been associated with increased cardiovascular morbidity, renal dysfunction, insulin resistance and cancers [19−23]. People infected with HCV also experience increased mortality due to substance abuse and drug overdose [25,26]. Determining which modifiable factors may be contributing to excess mortality in coinfected patients is necessary to address potentially preventable causes of death and to develop more effective interventions to reduce the excess mortality and maximize the benefits of HCV therapy in this population [24−26].

The primary objective of this study was to examine cause-specific mortality among HIV−HCV coinfected patients, with a particular focus on evaluating changes in mortality trends over time, before and after the scale-up of effective HCV treatments.

Methods

Study population and data collection

We used data from the Canadian Co-infection Cohort Study (CTN222), an open prospective multicentre study recruiting patients 16 years of age and older with documented HIV infection and with chronic HCV infection or evidence of HCV exposure (e.g. HCV seropositive by ELISA serologically false-negative, HCV RNA-positive). From April 2003 to December 2017, 1634 patients were enrolled from 18 sites across six Canadian provinces. Cohort design and protocol have been reported in detail elsewhere [27]. After written informed consent, patients underwent an initial evaluation followed by study visits approximately every 6 months. At each visit, sociodemographic and behavioral information (including smoking, alcohol and drug use) were self-reported in questionnaires, medical treatments and diagnoses were collected by research personnel, and laboratory analyses were performed. The study was approved by the community advisory committee of the Canadian Institutes of Health Research-Canadian HIV Trials Network and by all institutional ethics boards of participating centers.

All patients with at least one cohort visit between April 2003 and December 2017 were included. Patients were censored on the date of death or at their last clinic visit prior to December 2017. Deaths were reported by clinics. In addition, linkage to provincial vital statistics was available in three of the six provinces (Quebec, Alberta and British Columbia, representing 66.5% of participants) and was used to identify deaths and their causes among participants lost to follow-up (defined as no study visit for >1 year) throughout the study period. For all identified deaths, sites used a standardized case report form to capture information near the time of death and accurately describe the causes of death including primary and secondary causes, while giving a global assessment of the underlying cause of death using a modification of the Coding of Cause of Death in HIV Protocol [28]. Each site completed the form using death certificates, medical charts, discharge summaries, coroner reports or autopsy reports whenever available. Deaths were classified into five categories: ESLD, smoking-related, drug overdose, other and unknown causes. Deaths due to ESLD included liver cirrhosis, ascites, hepatic encephalopathy, bleeding esophageal varices, spontaneous bacterial peritonitis and HCC [29]. Smoking-related deaths included causes such as cardiovascular disease (CVD), esophageal and lung cancer, and pneumonia among smokers. Deaths due to other causes included AIDS, cancer (other than esophageal, lung and liver), infection (nonpulmonary), as well as suicide, trauma and accidents.

Statistical analysis

To compare trends in mortality over time, we created a dichotomous time variable for early (1 April 2003 to 31 December 2012) and late (1 January 2013 to 31 December 2017) periods chosen to represent the time before and after which HCV treatment uptake began to increase in the cohort [after the approval in Canada of simeprevir, the first of the second-generation direct-acting antivirals (DAAs), in November 2013], with equal amounts of person-time in

each period [30]. As causes of death may vary greatly by age group, age was also dichotomized: 20–49 years and 50–80 years. All cause and cause-specific event rates per 1000 person years were estimated using Poisson regression for the early and late cohort periods stratified by time-updated age. Standard errors were obtained using a quasi-likelihood approach and 95% confidence intervals (CIs) were constructed using the normal approximation for the log rate ratio. A competing risks survival model [31] was used to estimate the cause-specific adjusted hazard ratios (aHR) and 95% CIs of time and age groups on ESLD, smoking-related, drug overdose, other and unknown deaths, adjusted for time-updated detectable HIV RNA (HIV RNA ≥ 50 copies/ml), $CD4^+$ cell count 350 cells/μl or less, aspartate aminotransferase to platelet ratio index (APRI) index more than 1.5 (as a measure of fibrosis), and HCV RNA positivity at last visit. As we were interested in mortality from ESLD, we computed ESLD-specific 5-year cumulative incidence functions (CIFs) from the estimated cause-specific hazards, stratified by age group (20–49 vs. 50–80) and HCV RNA status (positive vs. negative) for three reference groups: (A) individuals in whom HIV is well controlled and who have no evidence of liver fibrosis ($CD4^+$ cell count ≥ 350 cells/μl, HIV RNA ≤ 50 copies/ml, APRI ≤ 1.5); (B) individuals in whom HIV is well controlled but who have evidence of liver fibrosis ($CD4^+$ cell count ≥ 350 cells/μl, HIV RNA ≤ 50 copies/ml, APRI > 1.5); and (C) individuals in whom HIV is not well controlled and have evidence of liver fibrosis ($CD4^+$ cell count < 350 cells/μl, HIV RNA > 50 copies/ml,

APRI > 1.5). The incidence derived from CIFs is interpreted as the 'probability of experiencing the primary event conditioned upon not experiencing either event (primary or competing) until that time' [32]. Statistical analyses were performed using R version 3.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics
A total of 1634 HIV–HCV coinfected patients were included with a median follow-up time of 4.3 [interquartile range (IQR) 2.2–8.9] years, totaling 8248 person-years. Patient sociodemographic and clinical characteristics at cohort entry for each time period are presented in Table 1. Comparing 2013–2017 with 2003–2012, a higher percentage of patients were on cART and had an HIV RNA below 50 copies/ml, while a smaller proportion of patients had a prior diagnosis of AIDS or ESLD, were HCV treatment naïve and HCV RNA positive. Similar proportions of patients reported active (in the last 6 months) or a history of IDU, alcohol use or smoking in both time periods. More Indigenous people entered the cohort in the more recent time period; these participants were younger and had lower fibrosis scores.

Overall, 686 (42%) patients received at least one HCV treatment course between 2003 and 2017. A total of 760

Table 1. Characteristics of HIV-hepatitis C virus cohort participants at the beginning of each time period.

	2003–2012, $n = 1124$	2013–2017, $n = 1326$
Follow-up time, median (IQR) (years)	4.2 (3.6, 5.3)	3.2 (1.7, 4.5)
Age, median (IQR) (years)	45 (39, 50)	48 (42, 53)
Female, no. (%)	298 (27)	376 (28)
Indigenous, no. (%)	175 (16)	320 (24)
Greater than high school education, no. (%)	302 (27)	355 (27)
Gross monthly income <$1500, no. (%)	852 (76)	958 (72)
History of IDU, no. (%)	904 (80)	472 (82)
Active IDU, no. (%)	390 (35)	409 (31)
History of alcohol use, no. (%)	1029 (92)	978 (74)
Current alcohol use, no. (%)	583 (52)	754 (57)
Ever smoked cigarettes, no. (%)	1020 (91)	518 (89)
Current smoker, no. (%)	847 (75)	960 (72)
Time since HIV diagnosis, median (IQR) (years)	11 (6.1, 16)	14 (7.7, 20)
Prior AIDS diagnosis, no. (%)	314 (28)	117 (8.8)
Nadir $CD4^+$ cell count, median (IQR) (cells/μl)	169 (80, 280)	190 (84, 317)
$CD4^+$ cell count, median (IQR) (cells/μl)	380 (240, 545)	450 (280, 643)
HCV RNA positive, no. (%)	877 (78)	804 (61)
HIV RNA <50 copies/ml, no. (%)	653 (72)	950 (80)
On cART, no. (%)	912 (81)	1184 (89)
cART-naive, no. (%)	132 (12)	45 (3.4)
cART interruption, no. (%)	76 (6.8)	50 (3.8)
Duration HCV infection, median (IQR) (years)	18 (10, 25)	20.3 (12, 28)
HCV treatment naive, no. (%)	923 (82)	906 (68)
HCV genotype (1 and 4)[a], no. (%)	689 (80)	378 (79)
APRI > 1.5, no. (%)	225 (20)	229 (17)
Prior ESLD diagnosis, no. (%)	100 (8.9)	63 (4.8)

APRI, aspartate aminotransferase-to-platelet ratio; cART, combination antiretroviral therapy; ESLD, end-stage liver disease; HCV, hepatitis C virus; IQR, interquartile range.
[a]Only among participants with available genotypes (857 in 2003–2012 and 480 in 2013–2017).

HCV treatment courses were given with 261 (34%) between 2003 and 2012 and 499 (66%) between 2013 and 2017. In total, 516 (68%) treatment courses were with DAAs, all in the second time period. Between 2003 and 2012, SVR rates among those treated were low in both age groups; among HCV RNA+ patients, only 61% (120/197) aged 20−49 and 52% (28/54) aged greater than 50 cleared their HCV infection. Between 2013 and 2017, SVR rates increased in both age groups with 84% (192/229) of treated patients aged 20−49 and 85% (216/254) aged greater than 50 clearing their HCV infection. After accounting for treatment uptake, the proportion of HCV RNA+ patients who were cured increased from 14 to 39% between 2003−2012 and 2013−2017 overall. Comparing the two time periods, treatment uptake increased most among those with at least moderate fibrosis (APRI > 1.5), particularly for the older age group, suggesting that older patients with advanced fibrosis were being prioritized to receive therapy.

Mortality

Overall, 273 (17%) patients died representing a death rate of 32.9 per 1000 person-years (95% CI 26.3−40.5). Of 198 deaths in the three provinces performing data linkage, 48 (24%) occurred among patients who were lost to follow-up and were captured through linkage. The median age at death was 47 [IQR 43−53] years. Unadjusted death rates were slightly lower among men (32.7 deaths per 1000 person-years) compared with women (34.1 deaths per 1000 person-years), as well as among Indigenous (31.5 deaths per 1000 person-years) compared with non-Indigenous persons (37.0 deaths per 1000 person-years). At cohort entry, compared with those alive, deceased patients were older, had longer durations of HCV infection, were more likely to have significant fibrosis (APRI > 1.5) and/or a history of ESLD, and were less likely to have HIV RNA below 50 copies/ml at last visit (Supplementary Table 1, http://links.lww.com/QAD/B440). Median CD4$^+$ cell counts were lower at last visit (330 cells/μl; IQR 175−530 cells/μl) among patients who died than among those who remained alive (480 cells/μl; IQR 283−689 cells/μl). Deceased patients more frequently reported smoking and active IDU at the time of last visit.

Drug overdose was the most common cause of death overall ($n = 49$; 18%), followed closely by ESLD ($n = 46$; 17%) and smoking-related deaths ($n = 41$; 15%, of which CVD and pneumonia accounted for 5.5% each, and esophageal and lung cancers for 4%). HCC accounted for 27 and 30% of ESLD-related deaths in the early and late time periods, respectively. Other important causes of death were infections ($n = 22$; 8%), other cancers ($n = 19$, 7%), and suicide, trauma and accidents ($n = 16$; 6%). AIDS-related deaths were rare ($n = 6$; 2%). Despite thorough record review, 54 deaths (20%) were unable to be classified and remained of unknown cause. Among individuals who died of ESLD, only two had achieved

Table 2. All cause and cause-specific event rates (95% confidence interval) per 1000 person-years by age group and time period.

Outcome	Age	2003−2012	2013−2017
All cause	20−49	23.08 (14.71, 36.21)	23.80 (14.02, 40.93)
	50−80	58.35 (38.86, 87.62)	38.30 (25.24, 58.11)
ESLD	20−49	4.55 (2.02, 10.21)	3.06 (0.93, 10.09)
	50−80	14.41 (7.50, 27.67)	3.48 (1.16, 10.49)
Smoking			
All	20−49	2.80 (0.94, 8.35)	2.55 (0.64, 10.18)
	50−80	10.81 (4.86, 24.01)	5.97 (2.44, 14.57)
CVD	20−49	0	1.02 (0.11, 9.27)
	50−80	5.04 (1.55, 16.40)	2.98 (0.83, 10.66)
Lung cancer	20−49	1.05 (0.22, 5.11)	0
	50−80	3.60 (1.06, 12.28)	1.49 (0.31, 7.27)
Pneumonia	20−49	1.75 (0.62, 4.90)	1.53 (0.41, 5.79)
	50−80	2.16 (0.57, 8.17)	1.49 (0.39, 5.64)
Drug overdose	20−49	6.99 (2.48, 19.70)	4.60 (0.98, 21.51)
	50−80	5.76 (1.12, 29.62)	5.97 (1.57, 22.71)
Other			
All	20−49	4.20 (1.77, 9.96)	7.66 (3.54, 16.60)
	50−80	15.85 (8.37, 30.00)	16.91 (10.12, 28.26)
AIDS	20−49	1.40 (0.62, 3.16)	0
	50−80	0.72 (0.14, 3.68)	0.50 (0.10, 2.54)
Suicide/Trauma/Accident	20−49	1.40 (0.31, 6.37)	2.04 (0.45, 9.30)
	50−80	2.16 (0.38, 12.43)	2.49 (0.64, 9.64)
Cancer (nonliver, non-HIV, nonesophageal/lung)	20−49	0.70 (0.06, 7.89)	1.02 (0.09, 11.52)
	50−80	5.76 (1.72, 19.36)	3.48 (0.95, 12.72)
Infection	20−49	0.35 (0.01, 13.12)	2.04 (0.33, 12.52)
	50−80	5.04 (1.28, 19.85)	4.97 (1.58, 15.65)
Unknown	20−49	4.55 (1.42, 14.57)	6.13 (1.82, 20.60)
	50−80	11.53 (4.03, 32.94)	5.97 (1.78, 20.06)

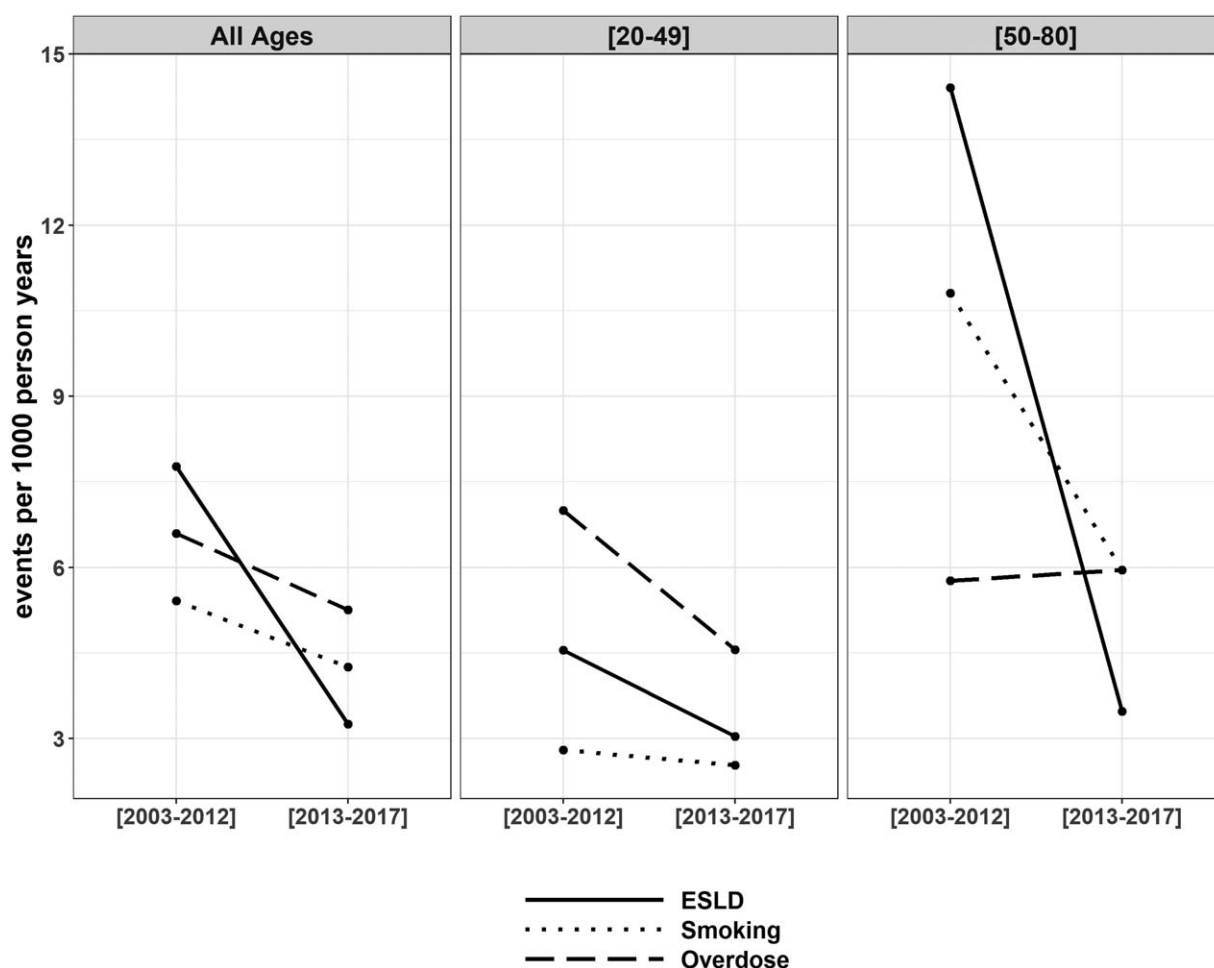CVD, cardiovascular disease; ESLD, end-stage liver disease.

Fig. 1. Unadjusted cause-specific event rates per 1000 person-years by age group and time period.

SVR (one in each of the 2003−2012 and 2013−2017 time periods).

Unadjusted, disease-specific mortality rates by time period and age group are shown in Table 2 and Fig. 1. All-cause mortality remained stable among those aged 20−49 but decreased among those aged 50−80 over time. Overall, deaths due to ESLD decreased over time with a notable decrease in these deaths among those aged 50−80 years. ESLD was no longer the most common cause of death in the 2013−2017 time period in either age group. Although deaths secondary to drug overdose decreased among those aged 20−49, they still accounted for the greatest proportion of deaths in this age group in the later time period. Drug overdose deaths remained stable among those aged 50−80. Similarly, smoking-related deaths decreased with time; however, among those aged 50−80, they accounted for the greatest proportion of deaths from 2013 to 2017.

Cause-specific aHR are shown in Fig. 2. After accounting for competing risks, from 2003−2012 to 2013−2017, there was a significantly decreased risk of death from

ESLD (aHR 0.18, 95% CI 0.05−0.62); deaths due to overdose and smoking also appeared to decrease but not as markedly (aHR 0.55, 95% CI 0.26−1.16 and aHR 0.60, 95% CI 0.27−1.37, respectively). The risk of death from all causes was higher in those with a positive HCV RNA at last visit. The risk of death from ESLD and smoking-related causes was significantly higher among individuals aged 50−80.

The early and late period ESLD-specific CIFs are shown in Fig. 3. Among patients in whom HIV was well controlled and without liver fibrosis (reference group A), the estimated risk of death due to ESLD was very low even in the presence of a positive HCV RNA, regardless of age or time period. In contrast, for similar patients with advanced liver fibrosis, the risk of death from ESLD was higher (reference group B); however, this risk was reduced in recent years, particularly among those with a positive HCV RNA. Finally, patients with poorly controlled HIV and advanced fibrosis (group C) had the highest risk of death from ESLD. However, even this group experienced marked reductions in risk of ESLD over time, including among those whose HCV RNA was positive.
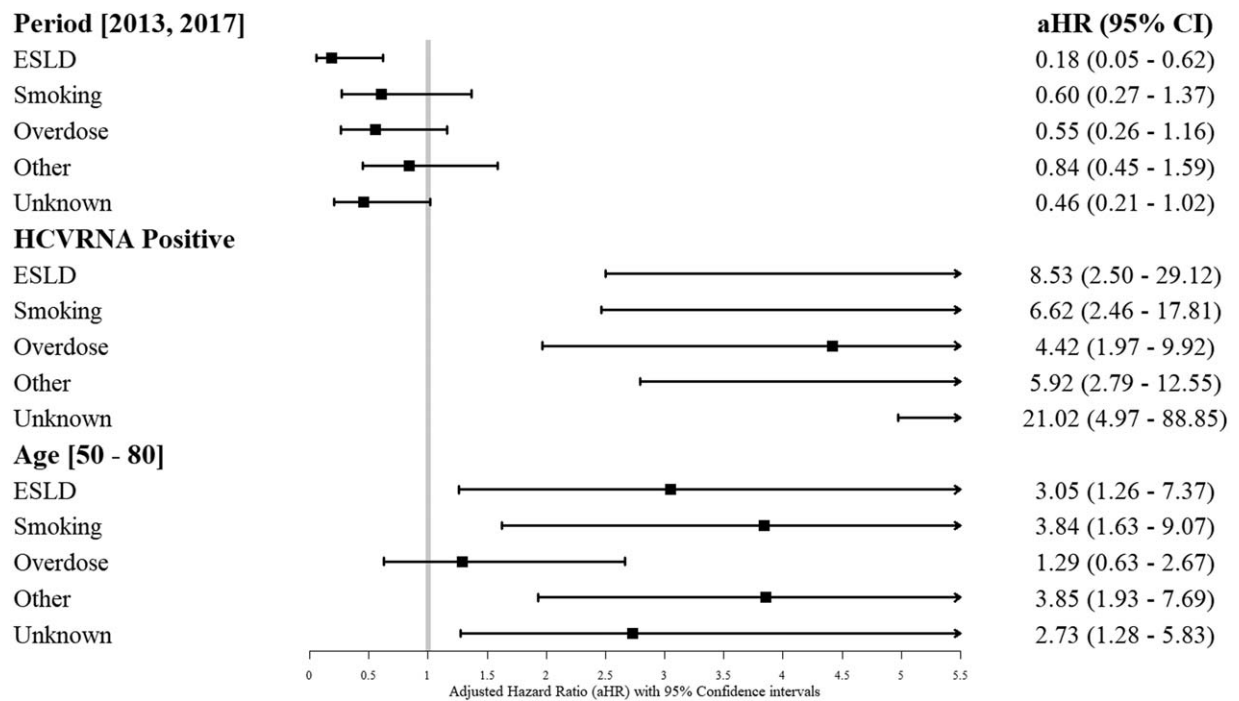
Fig. 2. Cause-specific adjusted hazard ratios (95% confidence intervals) for time period, hepatitis C virus RNA and age on end-stage liver disease, smoking-related, overdose, other and unknown causes of death. The reference categories for each grouping are: time period 2003–2012; hepatitis C virus RNA negative and age 20–49. ESLD, end-stage liver disease.
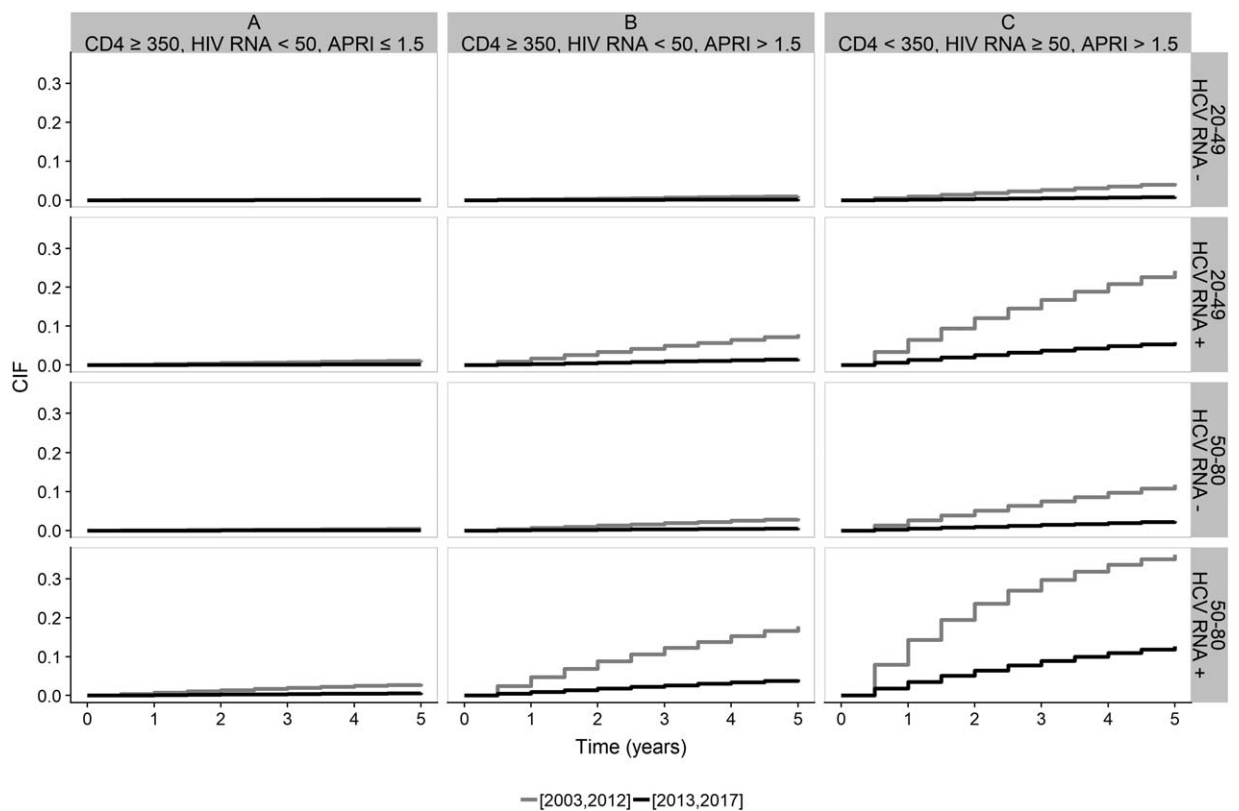

Fig. 3. Early and late period 5-year end-stage liver disease-specific cumulative incidence functions by reference group (a, b and c) stratified by age group (20–49 and 50–80) and hepatitis C virus RNA status [positive (+) and negative (−)]. Grey lines represent the early time period (2003–2012) and black lines represent the late time period (2013–2017).

Discussion

Our study prospectively identified trends in cause-specific mortality in a large cohort of HIV–HCV coinfected patients receiving care in a universal Canadian healthcare system before and after wider uptake of HCV therapy. We observed a very high overall death rate of 32.9 deaths per 1000 person-years (17% of our cohort died between 2003 and 2017) with the majority of deaths occurring prematurely (median age at death of 47 years). The observed death rate among Indigenous persons (31.5 deaths per 1000 person-years) was somewhat lower than expected. This was likely due to the recent entry of younger Indigenous participants with lower fibrosis scores in the late time period. All-cause mortality remained stable among those aged 20–49 and decreased among those aged 50–80 over time, but still remains high. Declining death rates were explained by a reduction in mortality from a variety of causes, emphasizing the need to appropriately account for competing risks of death when evaluating the role of HCV therapy on mortality. Deaths due to ESLD have declined over time and were no longer the leading cause of death in our cohort in the more recent time period. Instead, overdose accounted for the greatest proportion of deaths overall and among individuals aged 20–49 years while smoking-related deaths were the leading cause of death in those aged 50–80.

With the introduction of all oral DAAs resulting in more than 95% of coinfected persons achieving SVR in clinical trials, opportunities to halt liver fibrosis and decrease liver-related sequelae and mortality rates have increased substantially [33,34]. We were interested in evaluating the impact of the wider availability and effectiveness of HCV treatment on causes of death in coinfected patients in the real world. Unlike in HIV, when the introduction of cART led to very rapid reductions in AIDS-related mortality, studying the effects of HCV treatment is more complex. The impact of HCV therapy would be expected to be considerably slower given the time it takes for HCV to result in advanced liver disease. Furthermore, the coinfected population is at particularly high risk for competing causes of deaths from lifestyle exposures primarily related to risks associated with substance use. Finally, in developed countries, the demographics of the coinfected population are shifting over time; age-related comorbidities are becoming more prevalent, further impacting the causes of mortality.

Despite this, we observed a reduction in ESLD deaths over time, with a notable decrease in such deaths among those aged 50–80. The decline in ESLD deaths is likely multifactorial and related to the expansion of treatment in the cohort after 2013, the recent availability of highly effective DAA therapy, the prioritization of older individuals with advanced fibrosis/cirrhosis for treatment, and early deaths amongst those with very advanced cirrhosis. When examining the CIFs, it becomes apparent that ESLD deaths are rare among patients without liver fibrosis and with well controlled HIV, and the impact of HCV treatment in this subgroup will likely be difficult to demonstrate even after a long period of time. In contrast, increased rates of HCV treatment uptake appear to be having an impact even among those with poor HIV control and advanced fibrosis − those who are at the highest risk of ESLD-related deaths − highlighting the need to prioritize treatment for these patients. Our finding that nearly all ESLD deaths occurred in patients who did not achieve SVR further reinforces this. Within our cohort, as of December 2017, 46% of patients with significant fibrosis had not yet achieved SVR. Among cirrhotics who achieved SVR, continued monitoring for HCC will be important to prevent a resurgence of ESLD deaths in the future [22,23]. Finally, the observed decline in ESLD deaths among those who remained HCV RNA positive in this group is likely explained by the early deaths (in 2003−2012) amongst those with very advanced cirrhosis.

Several recent studies have shown declining liver-specific mortality over time [10,17,18,35]. However, most studies did not account for competing risks [17,18,35] and censored competing events [18], thereby upwardly biasing the incidence [31]. Grint *et al.* [10] accounted for competing risks, but their study was done in the pre-DAA era, making ours the first in the DAA era to examine trends in cause-specific mortality in coinfected patients, while simultaneously accounting for competing causes of death.

For those not at high risk for death from ESLD, it is clear that other behavioral risk factors will need to be addressed to reduce the high mortality rate among coinfected persons. The opioid epidemic sweeping across North America, particularly among young adults is of great concern [36,37]. In our cohort, drug overdose was the most common cause of death. Significantly, even in the face of this epidemic, deaths due to overdose among those aged 20−49 have actually decreased, suggesting that improved linkage and access to harm reduction services may be occurring concurrently with HIV and HCV treatment. We previously observed that the number of patients reporting active IDU declined by approximately 10% following HCV treatment [38], implying that there may be indirect benefits associated with treatment centered around accessing harm reduction programs. However, such programs must be sustained after treatment to reduce reinfection and the harms of IDU among high risk people who inject drugs [39].

Smoking emerged as one of the most important modifiable risk factors associated with increased mortality in our cohort, particularly in the older age group. The prevalence of smoking was extraordinarily high in cohort participants, with over 90% reporting smoking in their

lifetime and 75% currently – smoking rates that are over five times the Canadian average in 2017 (13%) [40]. Similarly, we did observe a reduction in deaths due to smoking-related causes that coincided with modest reductions in smoking between the two time periods, which may be in part explained by prolonged engagement in care, with associated health promotion and availability of smoking cessation services for cohort participants. Multidisciplinary care settings represent ideal models in which to broaden interventions offered alongside HCV therapy to maximize health outcomes [41]. Given that treatment for HCV requires a high degree of motivation and relatively frequent contact with the healthcare system, this may in fact be the most opportune time to address these modifiable risk factors.

In fact, while we must continue to advocate for universal access to HCV treatment, failing to address the structural, social and economic determinants of health that continue to drive the epidemic may undermine the advances made in ESLD mortality with treatment [42]. Although great efforts have been made to scale up access to HCV treatment in most countries, efforts to address addiction, mental health, homelessness, poverty and discrimination have paled in comparison. It is exactly these types of interventions – access to harm reduction services, regulated opioid distribution programs [36], drug treatment centers, easy access to naloxone and supportive housing programs – that will be required to reduce mortality in this population going forward. Our findings are in keeping with recent studies that have demonstrated that behavioral risk factors account for approximately 50% of excess mortality in chronic hepatitis C infection [25,26], further reinforcing the importance of integrated services. There are individual-level and population-level benefits to HCV treatment beyond mortality such as improved quality of life and the reduced risk of transmission, respectively; however, providing HCV treatment alone while neglecting to concurrently address the social determinants of health will do little to improve the health outcomes of the majority of individuals with chronic HCV as our data have shown [42].

The Canadian Co-infection Cohort comprises a diverse patient population followed at various primary and tertiary care clinics in urban and semiurban areas in Canada and is thus representative of the coinfected Canadian population [26]. Our study has limitations. Our results are not generalizable to HIV–HCV coinfected individuals who do not access care, for whom mortality rates are expected to be even higher. Despite the use of standardized case report forms to qualify causes of death as accurately as possible, the cause of death in 20% of persons remained unknown – a percentage that is comparable with previous studies [10]. Unknown deaths were often those found dead outside healthcare settings and may have represented overdose or sudden cardiac deaths. The proportion of deaths that were unknown diminished over

time, suggesting determination of causes of death may have improved. Furthermore, as linkage to vital statistics was not complete, we may have missed deaths among patients lost to follow-up.

In conclusion, teasing out the potential benefits of HCV therapy will take time to demonstrate and is complex in the setting of HIV/HCV coinfection where there are multiple competing health and behavioral risks and. The immediate mortality benefits of HCV therapy will be concentrated among those with advanced fibrosis and efforts to expand treatment should prioritize this group. For those at lower risk of ESLD, while HCV treatment may have other benefits such as reducing transmission, focusing on interventions that target modifiable risk factors such as substance abuse and tobacco smoking will have the greatest impact on mortality in the short term and should therefore be integrated into routine HIV and HCV care.

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Conflicts of interest

None of the authors feels in conflict of interest with regards to this study and there was no pharmaceutical industry support to conduct this study. N.K. received grants and consulting fees from ViiV Healthcare and Gilead. M.W.H. has received honoraria for speaking engagements and/or consulting fees from AbbVie, Bristol Myers Squibb, Gilead, Merck, Ortho-Janssen and ViiV Healthcare. S.W. received grants, consulting fees, lecture fees, nonfinancial support and fees for the development of educational presentations from Merck, ViiV Healthcare, GlaxoSmithKline, Gilead, Abbvie, Bristol–Myers Squibb and Janssen. J.G. received personal fees for being a member of the national advisory boards of Gilead, Merck and ViiV Healthcare. C.C. reports consulting fees from AbbVie, Gilead and Merck; and grants from AbbVie and Gilead. Valérie Martel-Laferrière reports consulting fees from Merck and Gilead; grant from Gilead; and lecture fees from AbbVie, Merck and Gilead. N.P. received personal fees for being a member of advisory boards from Gilead, ViiV Healthcare and Merck. J.C. received consulting fees from Bristol-Meyers Squibb; grants from ViiV Healthcare and Gilead; and payment for lectures from Merck. M.B.K. received research grants for investigator-initiated trials from Merck and ViiV Healthcare; consulting fees from ViiV Healthcare, Bristol-Meyers Squibb, Merck, Gilead and AbbVie. All other authors report no potential conflicts.

References

1. Egger M, Hirschel B, Francioli P, Sudre P, Wirz M, Flepp M, et al. **Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. Swiss HIV Cohort Study.** BMJ 1997; **315**:1194–1199.
2. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. **Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators.** N Engl J Med 1998; **338**:853–860.
3. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, et al. **Decline in the AIDS and death rates in the EuroSIDA study: an observational study.** Lancet 2003; **362**:22–29.
4. Hogg RS, Yip B, Kully C, Craib K, O'Shaughnessy MV, Schechter MT, et al. **Improved survival among HIV-infected patients after initiation of triple-drug antiretroviral regimens.** CMAJ 1999; **160**:659–665.
5. Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, Buchacz K, et al. **Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada.** PLoS One 2013; **8**:e81355.
6. Platt L, Easterbrook P, Gower E, McDonald B, Sabin K, McGowan C, et al. **Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis.** Lancet Infect Dis 2016; **16**:797–808.
7. Kovari H, Ledergerber B, Cavassini M, Ambrosioni J, Bregenzer A, Stockle M, et al. **High hepatic and extrahepatic mortality and low treatment uptake in HCV-coinfected persons in the Swiss HIV cohort study between 2001 and 2013.** J Hepatol 2015; **63**:573–580.
8. Klein MB, Rollet-Kurhajec KC, Moodie EE, Yaphe S, Tyndall M, Walmsley S, et al. **Mortality in HIV-hepatitis C co-infected patients in Canada compared to the general Canadian population (2003–2013).** AIDS 2014; **28**:1957–1965.
9. Berenguer J, Alejos B, Hernando V, Viciana P, Salavert M, Santos I, et al. **Trends in mortality according to hepatitis C virus serostatus in the era of combination antiretroviral therapy.** AIDS 2012; **26**:2241–2246.
10. Grint D, Peters L, Rockstroh JK, Rakmanova A, Trofimova T, Lacombe K, et al. **Liver-related death among HIV/hepatitis C virus-co-infected individuals: implications for the era of directly acting antivirals.** AIDS 2015; **29**:1205–1215.
11. Morlat P, Roussillon C, Henard S, Salmon D, Bonnet F, Cacoub P, et al. **Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000.** AIDS 2014; **28**:1181–1191.
12. Branch AD, Van Natta ML, Vachon ML, Dieterich DT, Meinert CL, Jabs DA, et al. **Mortality in hepatitis C virus-infected patients with a diagnosis of AIDS in the era of combination antiretroviral therapy.** Clin Infect Dis 2012; **55**:137–144.
13. Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, et al. **Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration.** Lancet 2014; **384**:241–248.
14. Limketkai BN, Mehta SH, Sutcliffe CG, Higgins YM, Torbenson MS, Brinkley SC, et al. **Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/HCV.** JAMA 2012; **308**:370–378.
15. Berenguer J, Rodriguez E, Miralles P, Von Wichmann MA, Lopez-Aldeguer J, Mallolas J, et al. **Sustained virological response to interferon plus ribavirin reduces nonliver-related mortality in patients coinfected with HIV and hepatitis C virus.** Clin Infect Dis 2012; **55**:728–736.
16. Kovari H, Rauch A, Kouvos R, Rougemont M, Cavassini M, Schmid P, et al. **Hepatitis C infection and the risk of nonliver-related morbidity and mortality in HIV-infected persons in the Swiss HIV Cohort Study.** Clin Infect Dis 2017; **64**:490–497.
17. Van der Meer AJ, Feld JJ, Hofer H, Almasio PL, Valvaruso V, Fernandez-Rodriguez CM, et al. **Risk of cirrhosis related complications in patients with advanced fibrosis following hepatitis C virus eradication.** J Hepatol 2017; **66**:485–493.
18. Janjua NZ, Chong M, Kuo M, Woods R, Wong J, Yoshida EM, et al. **Long-term effect of sustained virological response on hepatocellular carcinoma in patients with hepatitis C in Canada.** J Hepatol 2017; **66**:504–513.
19. Fernández-Montero J, Barreiro P, Mendoza C, Labarga P, Soriano V. **Hepatitis C virus coinfection independently increases the risk of cardiovascular disease in HIV-positive patients.** J Viral Hepat 2016; **23**:47–52.
20. Allison RD, Tong X, Moorman AC, Ly KN, Rupp L, Xu F, et al. **Increased incidence of cancer and cancer-related mortality among persons with chronic hepatitis C infection, 2006–2010.** J Hepatol 2015; **63**:822–828.
21. Chen TY, Ding EL, Seage Iii GR, Kim AY. **Meta-analysis: increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression.** Clin Infect Dis 2009; **49**:1605–1615.
22. Tyndall MW, Craib KJ, Currie S, Li K, O'Shaughnessy MV, Schechter MT. **Impact of HIV infection on mortality in a cohort of injection drug users.** J Acquir Immune Defic Syndr 2001; **28**:351–357.
23. Deans GD, Raffa JD, Lai C, Fischer B, Krajden M, Amin J, et al. **Mortality in a large community-based cohort of inner-city residents in Vancouver, Canada.** Can Med Assoc Open Access J 2013; **1**:E68–E76.
24. Innes H, Hutchinson SJ, Obel N, Christensen PB, Aspinall EJ, Goldberg D, et al. **Liver mortality attributable to chronic hepatitis C virus infection in Denmark and Scotland – using spontaneous resolvers as the benchmark comparator.** Hepatology 2016; **63**:1506–1516.

25. Schwarzinger M, Baillot S, Yazdanpanah Y, Rehm J, Mallet V. **Contribution of alcohol use disorders on the burden of chronic hepatitis C in France, 2008-2013: a nationwide retrospective cohort study.** *J Hepatol* 2017; **67**:454–461.

26. Innes H, McAuley A, Alavi M, Valerio H, Goldberg D, Hutchinson SJ. **The contribution of health risk behaviors to excess mortality in American adults with chronic hepatitis C: a population cohort-study.** *Hepatology* 2018; **67**:97–107.

27. 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* 2009; **39**:1162–1169.

28. Kowalska JD, Friis-Møller N, Kirk O, Bannister W, Mocroft A, Sabin C, *et al.* **The Coding Causes of Death in HIV (CoDe) Project: initial results and evaluation of methodology.** *Epidemiology* 2011; **22**:516–523.

29. Lo Re V 3rd, Lim JK, Goetz MB, Tate J, Bathulapalli H, Klein MB, Rimland D, *et al.* **Validity of diagnostic codes and liver-related laboratory abnormalities to identify hepatic decompensation events in the Veterans Aging Cohort Study.** *Pharmacoepidemiol Drug Saf* 2011; **20**:689–699.

30. Saeed S, Strumpf EC, Moodie EE, Young J, Nitulescu R, Cox J, *et al.* **Disparities in direct acting antivirals uptake in HIV hepatitis C co-infected populations in Canada.** *J Int AIDS Soc* 2017; **20**:1–10.

31. Jewell NP. **Correspondences between regression models for complex binary outcomes and those for structured multivariate survival analyses. Advances in statistical modeling and inference.** *Ser Biostat* 2007; **3**:45–64.

32. Manzoor BS, Adimadhyam S, Walton SM. *An introduction to competing risks.*2017, Available at: https://www.ispor.org/docs/default-source/publications/value-outcomes-spotlight/march-april-2017/vos-introduction-to-competing-risks.pdf?sfvrsn=df640ab6_2. [Accessed 17 August 2018].

33. Simmons B, Saleem J, Heath K, Cooke GS, Hill A. **Long-term treatment outcomes of patients infected with hepatitis C virus: a systematic review and meta-analysis of the survival benefit of achieving a sustained virological response.** *Clin Infect Dis* 2015; **61**:730–740.

34. Peters L. **EuroCoord. Is response to anti-HCV treatment predictive of mortality in HCV/HIV co-infected patients? [Abstract].** *15th European AIDS Conference.* Barcelona, Spain; 2015.

35. Rosenthal E, Roussillon C, Salmon-Céron D, Georget A, Hénard S, Huleux T, *et al.* **Liver-related deaths in HIV-infected patients between 1995 and 2010 in France: the Mortavic 2010 study in collaboration with the Agence Nationale de Recherche sur le SIDA (ANRS) EN 20 Mortalité 2010 survey.** *HIV Med* 2015; **16**:230–239.

36. Tyndall M. **An emergency response to the opioid overdose crisis in Canada: a regulated opioid distribution program.** *CMAJ* 2018; **192**:E36–E136.

37. U.S. Department of Health and Human Services. Results from the 2016 national survey on drug use and health. 2017. Available at: https://www.samhsa.gov/data/report/results-2016-national-survey-drug-use-and-health-detailed-tables. [Accessed 14 July 2018].

38. Yeung MW, Young J, Moodie E, Rollet-Kurhajec KC, Schwartzman K, Greenaway C, *et al.* **Changes in quality of life, healthcare use, and substance use in HIV/hepatitis C coinfected patients after hepatitis C therapy: a prospective cohort study.** *HIV Clin Trials* 2015; **16**:100–110.

39. Young J, Rossi C, Gill J, Walmsley S, Cooper C, Cox J, *et al.* **Risk factors for hepatitis C virus reinfection after sustained virologic response in patients coinfected with HIV.** *Clin Infect Dis* 2017; **64**:1154–1162.

40. Reid JL, Hammond D, Rynard VL, Burkhalter R. Tobacco use in Canada: patterns and trends, 2017 Edition. Waterloo, ON: Propel Centre for Population Health Impact, University of Waterloo. 2017. Available at: https://uwaterloo.ca/tobacco-use-canada/sites/ca.tobacco-use-canada/files/uploads/files/2017_tobaccouseincanada_final_0.pdf. [Accessed 17 August 2018].

41. Tait J, McIntyre P, McLeod S, Nathwani D, Dillon J. **The impact of a managed care network on attendance, follow-up and treatment at a hepatitis C specialist centre.** *J Vir Hepat* 2010; **17**:698–704.

42. Tyndall M. **Misplaced advocacy: what does better hepatitis C treatment really mean?** *CMAJ* 2015; **187**:1111–1112.