DOI: 10.1111/j.1468-1293.2012.01028.x

HIV Medicine (2013), **14**, 10–20

ORIGINAL RESEARCH

HIV and hepatitis C virus coinfection in Canada: challenges and opportunities for reducing preventable morbidity and mortality

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Objectives

Hepatitis C virus (HCV) has emerged as an important health problem in the era of effective HIV treatment. However, very few data exist on the health status and disease burden of HIV/HCV-coinfected Canadians.

Methods

HIV/HCV-coinfected patients were enrolled prospectively in a multicentre cohort from 16 centres across Canada between 2003 and 2010 and followed every 6 months. We determined rates of a first liver fibrosis or endstage liver disease (ESLD) event and all-cause mortality since cohort enrolment and calculated standardized mortality ratios compared with the general Canadian population.

Results

A total of 955 participants were enrolled in the study and followed for a median of 1.4 (interquartile range 0.5–2.3) years. Most were male (73%) with a median age of 44.5 years; 13% self-identified as aboriginal. There were high levels of current injecting drug and alcohol use and poverty. Observed event rates [per 100 person-years; 95% confidence interval (CI)] were: significant fibrosis (10.21; 8.49, 12.19), ESLD (3.16; 2.32, 4.20) and death (3.72; 2.86, 4.77). The overall standardized mortality ratio was 17.08 (95% CI 12.83, 21.34); 12.80 (95% CI 9.10, 16.50) for male patients and 28.74 (95% CI 14.66, 42.83) for female patients. The primary causes of death were ESLD (29%) and overdose (24%).

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*See Appendix.

Conclusions
We observed excessive morbidity and mortality in this HIV/HCV-coinfected population in care. Over 50% of observed deaths may have been preventable. Interventions aimed at improving social circumstances, reducing harm from drug and alcohol use and increasing the delivery of HCV treatment in particular will be necessary to reduce adverse health outcomes among HIV/HCV-coinfected persons.

Keywords: aboriginal health, epidemiology, hepatology, infectious diseases, public health

Accepted 10 April 2012

Introduction

In developed countries such as Canada, HIV infection has evolved from a uniformly deadly disease to become chronic and manageable as a result of effective antiretroviral therapies (ARTs) [1,2]. As fewer patients experience HIV-related morbidity and mortality, comorbidities and their associated consequences have consequently emerged as primary health concerns and are increasingly driving healthcare utilization and costs [3,4]. Coinfection with hepatitis C virus (HCV) is among the most important of these comorbidities. As a consequence of shared routes of transmission, over 30% of HIV-infected individuals are coinfected with HCV, with approximately 10 million dually infected [5] world-wide and an estimated 13 000–15 000 dually infected of the 65 000 HIV-infected persons in Canada [6]. The natural course of HCV infection is accelerated in HIV-coinfected individuals, with faster progression of liver fibrosis leading to a higher risk of cirrhosis, endstage liver diseases (ESLDs), and hepatocellular carcinoma [7,8]. Despite the potential burden of this important comorbidity, very few data exist on the health status of Canadians coinfected with HIV and HCV, disease progression rates, and the factors that are associated with adverse outcomes in this population. Indeed, good estimates of liver disease progression rates among coinfected persons in general are lacking in the recent ART era.

The Canadian Co-infection Cohort Study (CCC) was established to determine the effect of ART and HCV treatment on the progression to ESLD in HCV/HIV-coinfected individuals. The cohort provides a unique opportunity to evaluate the health status of coinfected patients receiving care and to assess regional variations in sociodemographic and clinical characteristics, as well as to document health outcomes in this population. Such information will be essential for developing and targeting therapeutic interventions and to meet the challenge of providing effective medical care to the growing number of persons living with HIV and HCV coinfection, not only in Canada, but in developed countries which are similarly facing epidemics of HIV/HCV coinfection.

Methods

Study design, population and setting

The CCC (CTN222) is a prospective multicentre study recruiting coinfected patients from existing HIV clinic populations at 16 centres across five Canadian provinces (Fig. 1). The cohort was initiated in 2003 in Montreal, Quebec, and then was expanded to other urban and semi-urban centres in 2007. As of October 2010, 955 patients were enrolled. Details on the cohort design and protocol are reported elsewhere [9]. Eligible patients were adults aged over 16 years with documented HIV infection [enzyme-linked immunosorbent assay (ELISA) with western blot confirmation] and with chronic HCV infection or evidence of HCV exposure (e.g. HCV-seropositive by ELISA with recombinant immunoblot assay version II (RIBA II) or encoded antigen/enzyme immuno assay (EIA) confirmation, and/or HCV RNA positive). All potentially eligible patients were invited to participate to avoid selection bias. Patients who initially refused were eligible to enrol in future. 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 centres. Patients received $15 per visit to compensate for out-of-pocket expenses.

Data collection and definitions

After providing informed consent, each participant underwent an initial evaluation followed by study visits approximately every 6 months. Sociodemographic, behavioural, medical and treatment data were collected using a standardized questionnaire in either English or French. Questionnaires were self-completed or completed with the assistance of a research assistant/nurse. Standard instruments were used to measure quality of life (EQ-5D™) [10]. Additionally, charts were abstracted by research personnel to obtain historical data such as nadir CD4 T-cell count, HIV RNA and all prior HIV and HCV treatment histories and diagnoses. Treatment and diagnostic data were updated by research personnel at each follow-up visit. At baseline and each

Fig. 1 Geographical distribution of centres participating in the Canadian Co-infection Cohort Study.

subsequent visit, laboratory assessments were performed, including complete blood count, serum chemistry, liver profile, plasma HIV RNA, absolute and relative CD4 lymphocyte counts and plasma HCV RNA. The duration of HCV infection was determined using the date of HCV seroconversion, if known, or the year of first injecting drug use (IDU) or blood product exposure as a proxy of HCV infection [11]. ART was defined as taking at least three antiretrovirals concurrently.

Outcome measures

AIDS diagnoses were defined according to the Centers for Disease Control and Prevention classification (e.g. not by CD4 cell criteria alone) [12]. The aspartate aminotransferase (AST) to platelet ratio index (APRI) was used as a noninvasive surrogate for liver fibrosis and defined as: 100 × (AST/upper limit of normal)/platelet count (10^9/L) [13,14]. An APRI score > 1.5 was considered to indicate significant fibrosis (corresponding to a biopsy score > F2) [14]. ESLD included liver cirrhosis, ascites, hepatic encephalopathy, bleeding oesophageal varices, spontaneous bacterial peritonitis and hepatocellular carcinoma. Clinical endpoints of ESLD were verified against source documents using specific case report forms and reviewed centrally. Case report forms solicited detailed information on means by which diagnoses were obtained (e.g. radiological, endoscopic, electroencephalogram (EEG), laboratory and liver biopsy results) and their associated findings. We employed definitions for diagnoses similar to those described by Lo Re *et al.* [15] All reported deaths were verified and classified following the 'Coding of Death in HIV' (CoDe) system (www.cphiv.dk/CoDe/tabid/55/Default.aspx). Each time a participant was reported to have died, sites completed a detailed case report form which included all information related to the death (including death certificate information, autopsy reports if available and clinical diagnoses and events immediately preceding the death, including specific information related to ESLD). Linkage to provincial vital statistics reports (death certificates) was performed in British Columbia, Alberta and Quebec and used to supplement data obtained in the case report forms and to determine if any participants who had been lost to follow-up had died. Primary and secondary causes of death were collected using International Classification of Diseases, Ninth Revision (ICD-9) codes. The final determination of cause of death was made independently by two investigators (MBK and MP) and in the cases ($n = 2$) where there were discrepancies, resolved by a third investigator (JC).

Statistical analysis

We compared baseline characteristics of participants between each province using the Kruskal–Wallis test for continuous variables and Pearson's χ^2 or Fisher exact test for categorical variables where appropriate. All tests were two-tailed and with a significance level of $\alpha = 0.05$.

We estimated the rate of health outcomes (fibrosis, ESLD, AIDS and all-cause death) since cohort enrolment by dividing the number of participants developing the event for the first time by the number of person-years at risk. Poisson count models were used to calculate confidence intervals (CIs) for incidence rates. The Kaplan–Meier survival method was used to obtain cumulative incidences of the various health outcomes. Standardized mortality ratios were calculated using the indirect method of standardization by sex and age group for each province; the comparison group was the general population of each province for 2007. Comparative data were obtained through the Canadian Human Mortality Database [16]. Analyses were performed using R program for Windows Release 2.11.1 (R cran, Auckland, New Zealand).

Results

A total of 955 participants were enrolled and followed for a median of 1.4 years [interquartile range (IQR) 0.5–2.3 years]; 175 had only one baseline visit, of whom 66 were enrolled within 6 months of the analyses. Of those with more than one visit, 9% were lost to follow-up. Baseline demographic characteristics of the study population by province are shown in Table 1. The majority of participants were male (73%) with a median age of 44.5 years (IQR 39.5–49.6 years). One hundred and twenty persons (13%) self-identified as being of aboriginal ethnicity (First Nations or Metis). The proportion of aboriginal participants varied regionally and was much higher in British Columbia (33%), Alberta (21%) and Ontario (14%) compared with Quebec (1.5%). Aboriginals were more likely to be female compared with non-aboriginals (52% *vs*. 22%, respectively; $P < 0.001$). Most participants were living below the poverty line (76% with a gross monthly income < CDN$1500) and only 13% had achieved greater than high school education. Participants living in British Columbia and Quebec were the most socially disadvantaged. Overall, 458 (57%) had been previously incarcerated (78% of aboriginals *vs*. 53% of non-aboriginals; $P < 0.001$), 422 (44%) reported a psychiatric diagnosis, 25 (3%) were homeless and 67 (7%) lived in shelters at cohort entry. There were very high rates of past and current (past 6 months) substance use among participants, with 81% reporting a history of IDU (38% were currently injecting; 23% sharing needles); 50% were current alcohol drinkers (31% reported binge/hazardous drinking, defined as >6 drinks/day) and 77% currently smoked cigarettes.

Clinical characteristics

Baseline clinical characteristics are shown in Table 2. The majority of participants were receiving ART (82%), of whom 71% had an undetectable HIV RNA with a median CD4 cell count of 364 cells/μL (IQR 230, 530 cells/μL). The median CD4 cell count of those not on ART was 373 cells/μL (IQR 259, 550 cells/μL).

One hundred and thirteen participants (12%) were HCV RNA negative without having received prior treatment for HCV, indicating spontaneous clearance of their infection. One hundred and fifty-eight (17%) had received treatment for HCV prior to cohort entry. Of the remaining 797 patients never treated for HCV, 102 (13%) initiated treatment during follow-up (6.6/100 person-years; 95% CI 5.3 to 7.9). Thus, 70% of the cohort had never received HCV treatment.

Morbidity and mortality

Table 3 shows the incidence rates for health outcomes among participants since enrolment in the cohort. The cumulative incidences of liver fibrosis, ESLD, AIDS and death are shown in Figure 2. None of the participants with ESLD underwent liver transplantation. Death rates in the cohort were much higher than overall Canadian population death rates at all ages; see Figure 3. The overall standardized mortality ratio was 17.08 (95% CI 12.83, 21.34); the estimates were 12.80 (95% CI 9.10, 16.50) for male patients and 28.74 (95% CI 14.66, 42.83) for female patients. Causes of death were: ESLD ($n = 18$; 29%), drug overdose ($n = 15$; 24%), cancer ($n = 6$; 10%), AIDS-defining illnesses (5%), and others (18%) including trauma, respiratory failure, bacterial infection and septic shock. The cause for the remaining 11 could not be determined.

Discussion

The CCC comprises nearly 10% of the estimated number of HIV/HCV-coinfected persons in Canada. Good estimates for the number of coinfected persons actually accessing care are not available. The only available data relate to the Province of Ontario, where approximately 65% of persons diagnosed with HIV have accessed care at least once (defined as having at least one HIV viral load measurement after diagnosis), whereas only 51% can be said to be in regular medical follow-up [17]. Thus, the 955 cohort participants probably represent close to 20% of all coinfected patients receiving treatment in Canada.

We have provided a comprehensive picture of the extent of vulnerabilities that present challenges to effective care and prevention of serious morbidity and mortality in this population. There are extremely high rates of social instability, poverty, mental illness and alcohol and drug use. Aboriginals are disproportionately represented in our cohort. Whereas they comprised 3.8% of the Canadian population in 2006 and 8% of prevalent HIV infections [18], 15% of our cohort overall and 33% in British Columbia

Table 1 Baseline sociobehavioural characteristics among HIV/hepatitis C virus (HCV)-coinfected patients across Canada

	Total ($n=955$)	Quebec ($n=382$)	British Columbia ($n=266$)	Alberta ($n=47$)	Ontario ($n=249$)	Nova Scotia ($n=11$)	P-value
Sociodemographic							
Gender							<0.001
Male	695 (73%)	301 (79%)	155 (58%)	32 (68%)	198 (80%0	9 (82%)	
Female	251 (26%)	77 (20%)	107 (40%)	14 (30%)	51 (20%)	2 (18%)	
Transgender	9 (1%)	4 (1%)	4 (2%)	1 (2%)	0 (0%)	0 (0%)	
Age (years)	44.5 (39.5, 49.6)	43.7 (39.0, 48.4)	44.3 (38.9, 49.8)	43.6 (37.9, 49.1)	46.6 (41.2, 52.0)	49.2 (43.2, 54.8)	<0.001
Born in Canada	759 (90%)	343 (92%)	216 (93%)	36 (92%)	153 (83%)	11 (100%)	<0.01
Ethnicity							<0.001
White	762 (80%)	370 (97%)	161 (61%)	34 (72%)	186 (75%)	11 (100%)	
Asian	24 (3%)	3 (1%)	5 (2%)	2 (4%)	14 (6%)	0 (0%)	
Black	15 (2%)	2 (0.5%)	4 (2%)	1 (2%)	8 (3%)	0 (0%)	
Hispanic	10 (1%)	2 (0.5%)	3 (1%)	0.00	4 (2%)	0 (0%)	
Aboriginal	141 (15%)	5 (1%)	92 (35%)	10 (21%)	34 (14%)	0 (0%)	
Greater than high school education	125 (13%)	43 (11%)	9 (3%)	8 (17%)	48 (19%)	2 (18%)	<0.01
Gross monthly income >$1500	223 (24%)	54 (14%)	62 (23%)	17 (40%)	84 (34%)	6 (55%)	<0.001
Marital status							<0.001
Single	620 (66%)	285 (75%)	155 (59%)	26 (57%)	149 (60%)	5 (45%)	
Married/common-law	184 (20%)	44 (12%)	58 (22%)	12 (26%)	65 (26%)	5 (45%)	
Widowed	40 (4%)	12 (3%)	14 (5%)	2 (4%)	11 (4%)	1 (9%)	
Divorced	91 (10%)	27 (7%)	34 (13%)	6 (13%)	24 (10%)	0 (0%)	
Sexual orientation							<0.01
Heterosexual	711 (75%)	292 (83%)	211 (81%)	35 (76%)	164 (66%)	9 (82%)	
Homosexual	172 (18%)	60 (16%)	33 (13%)	7 (15%)	70 (28%)	2 (18%)	
Bisexual	64 (7%)	28 (7%)	18 (7%)	4 (9%)	14 (6%)	0 (0%)	
Risk behaviours							
History of IDU	771 (81%)	318 (83%)	237 (90%)	41 (87%)	167 (67%)	8 (73%)	<0.001
IDU duration at baseline (years)	20 (13, 27)	19 (11, 26)	20 (14, 29)	19 (13, 27)	21 (13, 29)	30 (19, 34)	<0.05
Active IDU within 6 months	324 (34%)	147 (39%)	119 (45%)	4 (9%)	52 (21%)	2 (18%)	<0.001
Needle sharing ever†	580 (76%)	264 (84%)	171 (73%)	25 (63%)	113 (67%)	7 (88%)	<0.001
Equipment sharing ever†	567 (74%)	225 (72%)	184 (77%)	26 (67%)	125 (73%)	8 (88%)	0.516
Used clean needles services ever†	606 (79%)	262 (85%)	193 (82%)	35 (85%)	111 (64%)	5 (63%)	<0.001
Ever used therapy programmes for drug addiction	553 (59%)	224 (60%)	179 (68%)	28 (61%)	115 (48%)	7 (70%)	<0.001
Current alcohol use	475 (50%)	225 (59%)	95 (36%)	16 (34%)	132 (53%)	7 (64%)	<0.001
Binge drinking >6 drinks/day‡	131 (31%)	61 (35%)	28 (30%)	3 (19%)	39 (30%)	0 (0%)	0.268
Cigarette smoking ever	869 (92%)	350 (93%)	250 (95%)	43 (92%)	216 (87%)	10 (91%)	<0.05
Current marijuana smoking	501 (53%)	210 (56%)	130 (49%)	15 (32%)	139 (57%)	7 (64%)	<0.05
History of sexwork or use	451 (47%)	196 (51%)	145 (55%)	24 (51%)	81 (33%)	5 (45%)	<0.001
Ever been incarcerated	458 (57%)	130 (42%)	171 (72%)	31 (78%)	120 (58%)	6 (55%)	<0.001

Values are *n* (%) or median (interquartile range). Descriptive statistics were compared using the χ^2 test, Fisher's *t*-test, and the Kruskal–Wallis test.
IDU, injecting drug use.
†Based on number of IDUs ($n=324$).
‡Based on number of patients drinking ($n=475$).

Table 2 Baseline clinical characteristics among HIV/hepatitis C virus (HCV)-coinfected patients across Canada

	Total ($n = 955$)	Quebec ($n = 382$)	British Columbia ($n = 266$)	Alberta ($n = 47$)	Ontario ($n = 249$)	Nova Scotia ($n = 11$)	P-value
HIV infection							
Time since HIV diagnosis (years)	12 (7, 17)	12 (7, 17)	11 (7, 15)	12 (8, 16)	12 (6, 20)	14 (11, 22)	0.082
Nadir CD4 count (cells/μL)	160 (72, 280)	180 (80, 300)	150 (80, 230)	175.0 (86, 310)	158 (58, 270)	193 (76, 311)	0.258
CD4 count (cells/μL)	372 (242, 540)	357 (220, 530)	350 (250, 500)	429 (298, 594)	426 (273, 593)	629 (225, 481)	<0.01
CD8 count (cells/μL)	690 (460, 990)	680 (470, 997)	680 (470, 957)	637 (417, 1050)	734 (457, 1002)	626 (403, 1020)	0.921
Highest HIV RNA load ($\log_{10}$ copies/mL)	5.0 (4.3, 5.3)	4.9 (4.3, 5.3)	5.0 (4.6, 5.3)	5.1 (4.3, 5.5)	4.8 (4.2, 5.4)	5.2 (4.3, 5.6)	<0.05
HIV RNA load ($\log_{10}$ copies/mL)	1.7 (1.7, 3.0)	1.7 (1.7, 3.8)	1.6 (1.6, 2.6)	1.4 (1.4, 1.8)	1.7 (1.7, 1.9)	1.7 (1.6, 2.6)	<0.001
HIV RNA load $\leq$ 50 copies/mL	566 (60%)	195 (52%)	155 (59%)	34 (72%)	177 (73%)	5 (45%)	<0.001
On ART	780 (82%)	290 (76%)	224 (84%)	42 (89%)	214 (86%)	10 (91%)	<0.01
ART-naïve	113 (12%)	57 (15%)	28 (11%)	2 (4%)	25 (10%)	1 (9%)	0.121
ARV treatment interruption	71 (7%)	37 (10%)	18 (7%)	3 (6%)	13 (5%)	0 (0%)	0.285
AIDS diagnoses	297 (31%)	88 (24%)	106 (40%)	14 (30%)	88 (35%)	1 (9%)	<0.001
HCV infection							
Duration of HCV infection (years)	19 (11, 25)	18 (9, 24)	19 (12, 27)	19 (12, 25)	19 (9, 26)	20 (12, 31)	<0.05
Ever treated for HCV	158 (17%)	34 (9%)	34 (13%)	9 (19%)	74 (30%)	7 (64%)	<0.001
HCV RNA[†] positive	650 (85%)	308 (88%)	157 (78%)	30 (81%)	151 (90%)	4 (57%)	<0.001
HCV genotype[‡]							<0.05
1	521 (73%)	171 (67%)	165 (77%)	23 (64%)	153 (76%)	9 (90%)	
2	38 (5%)	9 (4%)	13 (6%)	4 (11%)	11 (5%)	1 (10%)	
3	141 (20%)	63 (25%)	35 (16%)	9 (25%)	34 (17%)	0 (0%)	
4	18 (3%)	12 (5%)	2 (1%)	0 (0%)	4 (2%)	0 (0%)	
APRI	0.6 (0.4, 1.2)	0.6 (0.4, 1.2)	0.6 (0.4, 1.1)	0.7 (0.3, 1.5)	0.6 (0.4, 1.2)	0.6 (0.3, 1.1)	0.797
APRI $\geq$ 1.5	182 (20%)	74 (21%)	49 (19%)	10 (27%)	47 (19%)	2 (20%)	0.768
ESLD	92 (11%)	29 (10%)	19 (7%)	3 (7%)	41 (17%)	0 (0%)	<0.01

Values are *n* (%) or median (interquartile range). Descriptive statistics were compared using the χ^2 test, Fisher's *t*-test, and the Kruskal–Wallis test.
ART, antiretroviral therapy; ARV, antiretroviral; APRI, aspartate aminotransferase to platelet ratio; ESLD, endstage liver disease.
[†]Based on number of HCV RNA tests ($n = 763$).
[‡]Based on number of HCV genotype tests ($n = 718$).

Table 3 Rates of health outcomes among HIV/hepatitis C virus (HCV)-coinfected patients since cohort entry

	n (%)	Denominator*	Rate per 100 PY (95% CI)
Progression to significant fibrosis (APRI ≥ 1.5)	123 (15.91%)	773	10.27 (8.45 to 12.08)
ESLD	47 (5.45%)	863	3.14 (2.24 to 4.04)
AIDS	26 (3.95%)	658	2.24 (1.38 to 3.09)
Deaths			
Overall	62 (6.49%)	955	3.73 (2.80 to 4.66)
Female	16 (6.37%)	251	4.16 (2.12 to 6.20)
Male	46 (6.62%)	695	3.59 (2.56 to 4.63)

CI, confidence interval; ESLD, end-stage liver disease; APRI, aspartate aminotransferase to platelet ratio; PY, person-years.
*Participants without outcome of interest at baseline.

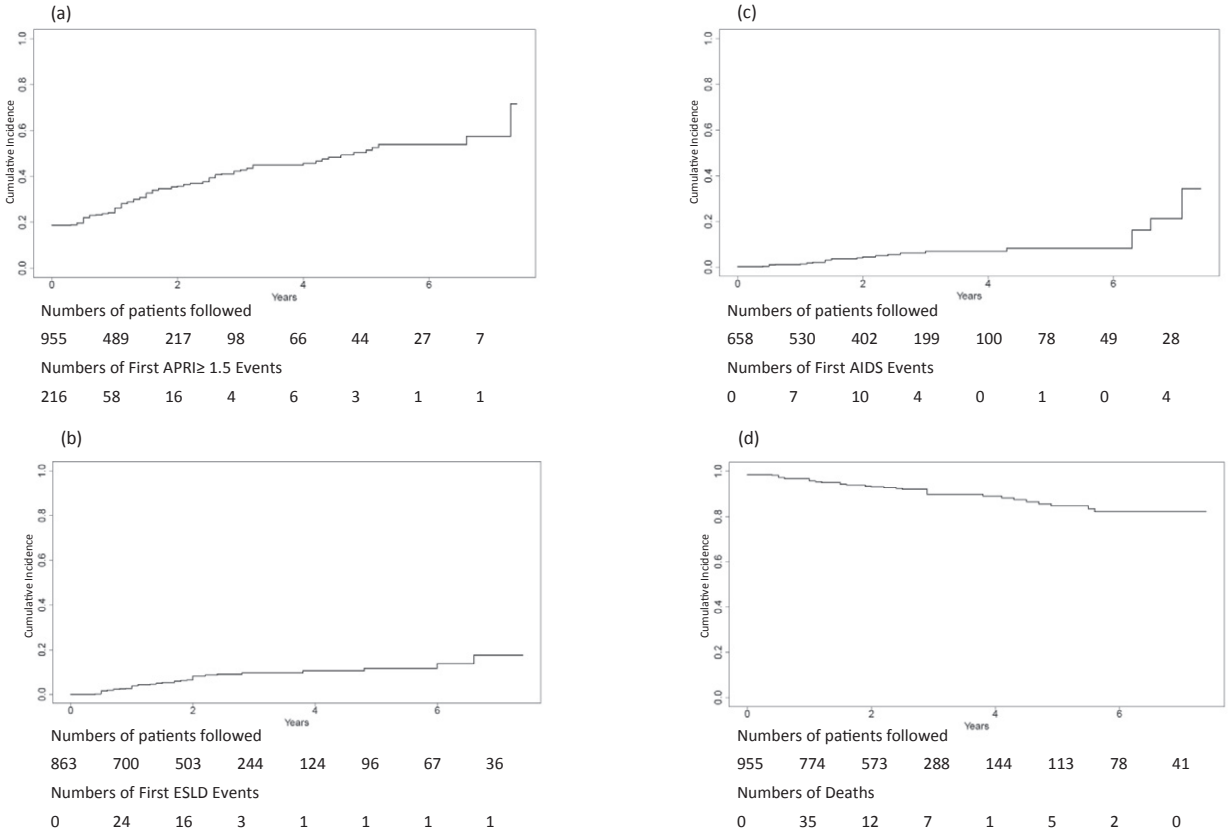

Fig. 2 The cumulative incidences of a first liver fibrosis, endstage liver disease or AIDS event and time to all-cause death among participants in the Canadian Co-infection Cohort Study since enrolment. (a) First aspartate aminotransferase to platelet ratio index (APRI) ≥ 1.5; (b) first endstage liver disease (ESLD) event; (c) first AIDS event; (d) death.

self-identified as aboriginal and a very high proportion of these were women (62%).

The impact of these combined vulnerabilities on the health of the coinfected population appears to be appreciable. Despite 82% of participants in the cohort receiving ART, only 71% were virologically suppressed. Another 6% had interrupted treatment at baseline. While these results are not dissimilar from those of other studies in IDU populations, these viral suppression rates are lower than those reported generally in HIV-infected persons [19–21]. Together, our results highlight that a significant proportion of participants have difficulty with treatment adherence and consequently are at risk for developing viral resistance and experiencing HIV-related disease progression. Indeed, the rate of AIDS was very high, at twice the reported rate in a US HIV-infected population for the period 2003–2007

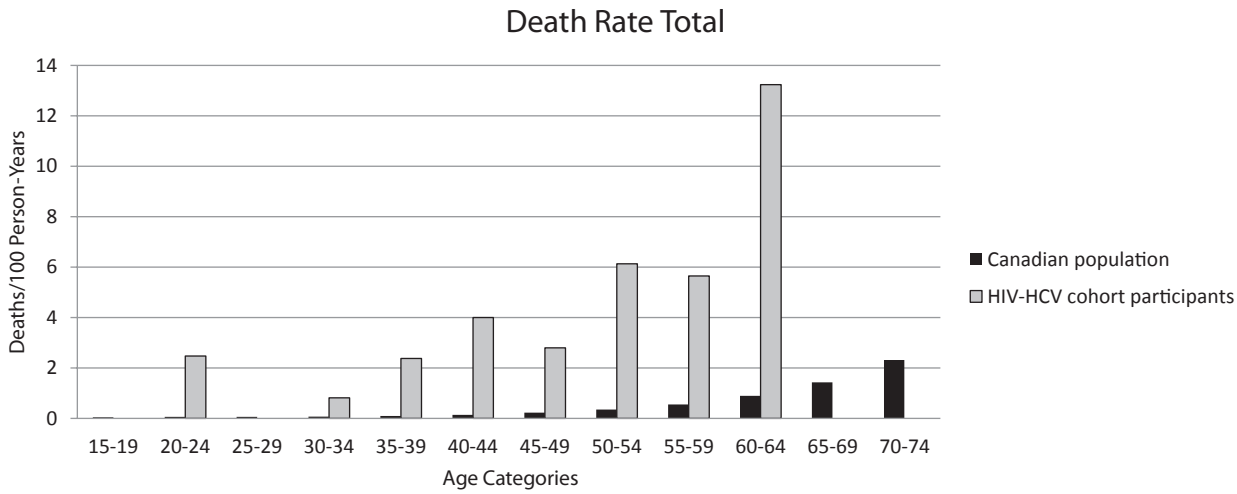

Fig. 3 Mortality rates by age comparing participants in the Canadian Co-infection Cohort Study with the general Canadian population (2007). Source for Canadian population data: Canadian Human Mortality Database [14].

[22]. Incomplete HIV suppression may also have implications for HIV transmission, especially given the high percentage of participants that report sharing injection equipment and risky sexual behaviours. Finally, treatment interruptions have also been associated with increased risk for non-AIDS-related adverse outcomes, including liver disease progression and death, particularly among coinfected persons [23,24].

HCV infection is a chronic infection which if left untreated follows a slow clinical course progressing to ESLD and hepatocellular carcinoma [25]. HIV increases chronicity and accelerates the natural history of HCV [7,26]. This impact is mirrored in our cohort: the median age of the population and time since HCV infection suggest that we are poised for a peak of chronic liver disease and its consequences. Indeed, at baseline many participants already had significant fibrosis and ESLD. Even over the short duration of follow-up, we observed very high progression rates of fibrosis and the occurrence of clinical ESLD events; rates approximately six times higher than those reported in HCV-monoinfected populations infected for a similar duration (0.53/100 person-years), though similar to rates reported among HIV/HCV-coinfected persons in other studies (2.63/100 person-years) [27]. Indeed, ESLD has emerged as the primary cause of death among cohort participants.

There is mounting and consistent evidence that successful treatment for HCV infection is the most effective means of preventing liver-related outcomes in coinfection [28]. Despite this, uptake of HCV treatment was low, with 70% of the cohort remaining untreated. While low, this treatment rate is consistent with those reported in the literature [29,30]. Numerous barriers to accessing HCV treatment have been described, including active drug use, poor adherence, and psychiatric and other medical comorbidities [31], all of which were present at high levels among cohort participants. Furthermore, HCV treatment itself is complex and associated with a number of important toxicities that limit its acceptance and impact successful treatment completion [32].

Finally, we observed very high rates mortality, particularly secondary to ESLD and drug overdose. Indeed, over 50% of deaths observed were attributable to these potentially preventable causes. Standardized mortality rates were particularly high among women, who were nearly 30 times more likely to die than Canadian women of the same age in the general population. In part this may be attributable to lower death rates among young and middle-aged women in the general population compared with men. Other potential reasons may include the over-representation of aboriginals and high levels of current IDU among women enrolled in the cohort. Although small numbers and the lack of standardized data available for aboriginals precluded obtaining standardized mortality ratios adjusted for ethnicity, it is notable that the death rates and standardized mortality ratios we observed for the coinfected population also far exceed reported age-adjusted death rates among aboriginals and Metis in Canada (e.g. standardized mortality ratios of 1.38 for men and 1.72 for women, for 1999–2001) [33].

Overall, mortality rates were high even when compared with other similar populations. For example, among HIV-infected patients starting ART in 13 cohorts in Europe, the USA and Canada, the overall crude death rate was 0.95/100

person-years with a standardized mortality ratio of 3.36 (95% CI 3.16–3.56) [34]. In the subgroup of IDUs, mortality was higher, at 1.95/100 person-years, although still almost two-fold lower than what we observed.

There is clearly an urgent need to address these potentially preventable causes of morbidity and mortality. In addition to improving HIV treatment adherence and increasing the numbers of patients receiving HCV therapies, it will be important to enhance existing harm reduction practices, including access to sterile injection equipment through syringe exchange programmes [35,36], supervised injection sites [37,38] and opiate substitution therapy [39,40], all of which have been demonstrated to be beneficial in preventing death from drug overdose, preventing HIV progression and reducing transmission risks for HIV and HCV. Increasing access to multidisciplinary teams to support entry and adherence to HIV and HCV treatment will be essential to tackle the health needs of this population. This will be increasingly important as newer, more effective direct-acting HCV therapies become available.

Strengths of our study include the very large number of diverse participants who are broadly representative of the Canadian coinfected population in care, careful outcome ascertainment and relatively low numbers lost to follow-up. Better ascertainment of deaths through linkage to administrative databases and careful data verification may partly explain the higher death rates we observed compared with previous studies. Even so, we may have actually underestimated true mortality rates as we were unable to fully determine whether those lost to follow-up had died. Our study was, however, restricted to patients engaged in care in urban and semi-urban settings. Thus, the rates of risk behaviours and treatment and health outcomes may not fully represent the experience of the wider coinfected population who may not be accessing medical care regularly. Therefore, our findings, while alarming, may actually represent an underestimate of the true disease burden experienced by HIV/HCV-coinfected patients. Self-report may also underestimate the degree and extent of risk behaviours.

Our findings highlight that interventions aimed at improving social circumstances, reducing harm from drug and alcohol use and increasing the delivery of HCV treatment in particular will be necessary to reduce adverse health outcomes and limit the looming epidemic of ESLD among HIV/HCV-coinfected persons and consequent mortality. Continued research is needed to evaluate the impact of therapies on disease progression, health service utilization and costs and how to better target preventive measures and treatment services for coinfected persons with the aim of reducing the individual and population burden of this important comorbidity.

Acknowledgements

This study was funded by the Fonds de recherche en santé du Québec, Réseau SIDA/maladies infectieuses (FRSQ), the Canadian Institutes of Health Research (CIHR MOP-79529) and the CIHR Canadian HIV Trials Network (CTN222). EM is supported by a University Faculty Award from the Natural Sciences and Engineering Research Council of Canada. MBK is supported by a Chercheur-Boursier clinicien senior career award from the FRSQ. CC is supported by an Ontario HIV Treatment Network for Career Scientist Award. We thank Alex Schnubb, Chantale Beauvais, Elaine Fernandez, Mitra Motamedi, Brenda Beckthold, Heather Haldane, Marcela Gil, Nancy McFarland, Claude Gagne, Warmond Chan, Linda Moran, Judy Latendre-Paquette, Evelyn Mann, Alison Ion, Despina Tzemis, Annemarie Wolff, and Manon Desmarais for their assistance with study coordination, participant recruitment and care.

Author contributions: As the corresponding author, MBK has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. She supervised the study design, conduct and reporting and participated in revising the manuscript. All of the authors have seen and approved the final manuscript and have participated sufficiently in the work to take public responsibility for its content.

Appendix

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