# Significant differences in clinical outcomes between HIV-hepatitis C virus coinfected individuals with and without injection drug use history

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**Objective:** Studies focusing on HIV-hepatitis C virus (HCV) coinfected individuals without a history of IDU are limited. It is plausible that poorer clinical outcomes in HIV-HCV coinfection are due to factors associated with IDU, not from HCV itself. This study compares HIV treatment outcomes and survival between HIV-HCV coinfected individuals with and without IDU history.

**Design:** Observational cohort study.

**Methods:** We analyzed data from a multisite Canadian cohort study of HIV-positive individuals initiating combination antiretroviral therapy (ART) after 1 January 2000. This analysis was restricted to 1254 participants with HCV coinfection and known IDU history. Cox proportional hazards regression was used to evaluate time from ART initiation to virologic suppression (two consecutive measures <250 copies/ml) and $CD4^+$ cell count recovery (+100 cells/μl). In order to account for loss to follow-up (LTFU), competing risk analysis was used to evaluate time to death.

**Results:** A total of 1254 participants (31% women) were included. During a median follow-up time of 3.8 years (interquartile range = 2.1–6.2), 217 deaths were reported and 148 participants were LTFU. In adjusted multivariable analysis, individuals with IDU history were significantly less likely to achieve virologic suppression [adjusted hazard ratio (AHR) = 0.78, 95% confidence interval (CI) = 0.64–0.95]; marginally less likely to have $CD4^+$ cell count recovery (AHR = 0.82, 95% CI = 0.66–1.00); and had a significantly higher risk of death (AHR = 2.15, 95% CI = 1.25–3.70).

**Conclusion:** IDU history independently elevates risk for poorer clinical outcomes, separate from HCV coinfection. HIV-HCV coinfected persons are not homogeneous in characteristics or outcomes, suggesting care should be taken during statistical analyses if attributing poorer HIV-specific outcomes solely to HCV coinfection.



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## Introduction

As the burden of AIDS-related complications and associated mortality has decreased significantly since the introduction of combination antiretroviral therapy (ART) [1,2], the burden of non-AIDS conditions such as liver disease is an increasing concern – with hepatitis C virus (HCV) contributing substantially [3,4]. Liver disease attributed to HCV infection is a leading cause of mortality among coinfected individuals [5]. In the United States, population-based data reveal that HCV has surpassed HIV as a cause of overall mortality [6].

Untreated HCV infection may progress at an accelerated rate among coinfected individuals [7–9]. However, the influence of HCV infection on HIV progression is less clear. Studies have documented hindered immune restoration and poorer clinical outcomes in coinfected patients [10–13], although it is plausible that poorer outcomes are due to factors associated with IDU, and not from HCV itself [14].

Due to variable collinearity, studies exploring treatment experiences and outcomes of coinfected patients may not differentiate between individuals with and without a history of IDU, despite significant variation in socio-demographic and other life circumstances between these groups. This approach may disregard individuals who acquired HCV through a non-IDU route and constitute a unique group of interest for HCV prevention, care, and treatment.

As in other settings, HCV coinfection is frequent among HIV-positive individuals in Canada [15,16]. Of the 71 300 Canadians living with HIV [17], an estimated 18–20% are coinfected with HCV [18,19]. There is a clear need to identify all HIV-positive individuals who may be at risk of HCV infection as well as to document the treatment experiences and outcomes of these patients. This study compares demographic and clinical characteristics, HIV treatment responses, and survival between HIV-HCV coinfected individuals with and without IDU history in Canada.

## Methods

### Cohort and inclusion criteria

The Canadian Observational Cohort (CANOC) collaboration is a multisite cohort study of antiretroviral-naive HIV-positive individuals initiating ART on or after 1 January 2000 [20]. Participants must be more than 18 years of age and have baseline (within 6 months of ART initiation) $CD4^+$ cell count and viral load testing results. Eight cohorts contribute data to CANOC from the country's three largest provinces: Ontario, British Columbia, and Quebec. Data extraction is performed locally at the participating sites and pooled at the coordinating center in Vancouver, British Columbia. All participating cohorts have received ethical approval from their institutional boards to contribute data to CANOC. The last date of follow-up for the current analysis was 11 March 2010 (total study $n = 6673$).

For this analysis, participants must have documented HCV coinfection ($n = 3831$ excluded because HCV-negative; $n = 1453$ because they were never tested) and nonmissing IDU history ($n = 135$ excluded). Participants were classified as 'ever HCV coinfected' if identified as HCV-positive through physician reports, antibody test results, or PCR test results.

### Outcomes and statistical methods

Demographic and clinical variables were compared by IDU history, defined as a documented HIV risk factor of injection drug use (ascertained from a combination of surveys, medical record data, and physician interviews). Variables of interest included age, sex, province, other HIV risk factors, baseline AIDS-defining illnesses, baseline $CD4^+$ cell count and viral load, initial ART regimen, year of ART initiation, viral load monitoring rate, and follow-up time. Categorical demographic and clinical characteristics were compared by IDU history using the Pearson $\chi^2$ or Fisher's exact test. Continuous variables were compared using the Wilcoxon rank-sum test.

The primary outcomes of interest included responses to ART and all-cause mortality. Response to ART was examined using two measures: time to virologic suppression and time to $CD4^+$ cell count recovery. Virologic suppression was defined as two consecutive plasma HIV-RNA measurements less than 250 copies/ml. The viral load level of less than 250 copies/ml was selected to accommodate potential differences in assay sensitivities between provinces [21,22]. $CD4^+$ cell count recovery was defined as an increase of at least 100 cells/μl after starting ART. Cox proportional hazards regression was used to estimate the hazard ratio associated with IDU history for both outcomes. In order to account for loss to follow-up (LTFU), competing risk analysis was used to evaluate time to death (all-cause). Mortality data were obtained through physician reporting or linkage to provincial vital statistics registries. LTFU was defined as no contact for at least 1 year.

Participants without outcomes of interest during follow-up were censored as of the date of their last viral load (virologic suppression analysis), $CD4^+$ cell count test ($CD4^+$ cell recovery analysis), or last contact (mortality). Statistical analyses were performed using SAS software (version 9.3; SAS Institute, Cary, North Carolina, USA).

## Results

### Demographic and clinical characteristics

A total of 1254 individuals (31% women) met the eligibility criteria. The median age of participants at baseline was 41 years (interquartile range, IQR = 35–47) and 79% were from British Columbia. Overall, 88% of participants ($n = 1106$) had a documented history of IDU. The majority of participants initiated ART on nonnucleoside reverse transcriptase inhibitor (NNRTI)-based (44%) or boosted protease inhibitor-based (43%) regimens. Over a median follow-up time of 3.8 years (IQR = 2.1–6.2), 217 deaths ($n = 203$ among IDU, $n = 14$ among non-IDU) were reported and 148 participants ($n = 116$ IDU, $n = 32$ non-IDU) were lost to follow-up.

Table 1 compares demographic and clinical characteristics by IDU history status. At baseline, individuals with IDU history were younger (median 41 vs. 43 years) and had lower $CD4^+$ cell counts (median 170 vs. 200 cells/μl; both $P < 0.01$). Participants also differed significantly by IDU history in terms of sex, province, other HIV risk factors, viral load monitoring rate, and baseline ART regimens. Of the 148 coinfected individuals without IDU history, the majority were men ($n = 118$, 80%), with 67% ($n = 79$) having a documented HIV risk factor of sex with other men.

### Clinical outcomes

Using Kaplan–Meier methods, the estimated probability of virologic suppression was 0.76 [95% confidence interval (CI) = 0.68–0.82] and 0.88 (95% CI = 0.81–0.92) for

**Table 1. Demographic and clinical characteristics among HIV-hepatitis C virus coinfected persons in the Canadian Observational Cohort by IDU history status ($n = 1254$).**

| | Total | IDU history | | |
|---|---|---|---|---|
| Variable | $n = 1254$ | No ($n = 148$) | Yes ($n = 1106$) | *P* value |
| Baseline age | 1254 | 43 (37–50) | 41 (34–46) | <0.001 |
| Sex | | | | |
| Female | 387 | 30 (20.3) | 357 (32.3) | 0.003 |
| Male | 867 | 118 (79.7) | 749 (67.7) | |
| Province | | | | |
| British Columbia | 989 | 70 (47.3) | 919 (83.1) | <0.001 |
| Ontario | 77 | 21 (14.2) | 56 (5.1) | |
| Quebec | 188 | 57 (38.5) | 131 (11.8) | |
| HIV risk factors | | | | |
| MSM | | | | |
| No | 1079 | 59 (42.8) | 1020 (92.3) | <0.001 |
| Yes | 164 | 79 (57.2) | 85 (7.7) | |
| Heterosexual sex | | | | |
| No | 731 | 96 (69.6) | 635 (57.5) | 0.008 |
| Yes | 512 | 42 (30.4) | 470 (42.5) | |
| Baseline ADI | | | | |
| No | 1020 | 106 (79.7) | 914 (86.8) | 0.033 |
| Yes | 166 | 27 (20.3) | 139 (13.2) | |
| Initial third ARV class | | | | |
| NNRTI | 555 | 58 (39.2) | 497 (44.9) | <0.001 |
| Single PI | 131 | 24 (16.2) | 107 (9.7) | |
| Boosted PI | 544 | 57 (38.5) | 487 (44) | |
| NRTI | 24 | 9 (6.1) | 15 (1.4) | |
| Initial third ARV | | | | |
| Nevirapine | 215 | 18 (12.2) | 197 (17.8) | 0.031 |
| Efavirenz | 338 | 40 (27) | 298 (26.9) | |
| Lopinavir | 234 | 28 (18.9) | 206 (18.6) | |
| Atazanavir | 294 | 30 (20.3) | 264 (23.9) | |
| Other | 173 | 32 (21.6) | 141 (12.7) | |
| Year of ART initiation | 1254 | 2004 (2002–2007) | 2005 (2002–2007) | 0.187 |
| Baseline $CD4^+$ cell count (cells/μl) | 1254 | 198 (115–280) | 170 (90–250) | 0.007 |
| Baseline viral load ($log_{10}$) | 1254 | 4.9 (4.4–5.0) | 4.9 (4.4–5.0) | 0.239 |
| VL testing rate (/year) | | | | |
| <3 | 280 | 20 (14) | 260 (24.1) | <0.001 |
| 3–4 | 277 | 19 (13.3) | 258 (23.9) | |
| 5–6 | 415 | 59 (41.3) | 356 (33) | |
| >6 | 251 | 45 (31.5) | 206 (19.1) | |
| Follow-up time (years) | 1254 | 3.6 (2.3–6.9) | 3.8 (2.1–6.2) | 0.735 |
| Lost to follow-up | 1254 | 32 (21.6) | 116 (10.5) | <0.001 |
| Died during follow-up | 1254 | 14 (9.5) | 203 (18.4) | 0.005 |

Results presented as median (interquartile range, IQR) or frequency (%). ADI, AIDS-defining illness; ART, antiretroviral therapy; ARV, antiretroviral agent; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VL, plasma viral load.

non-IDU and 0.57 95% CI = 0.54–0.60 and 0.67 (95% CI = 0.64–0.69) for IDU, at 6 and 12 months post-ART initiation, respectively. For $CD4^+$ cell recovery, probabilities were 0.57 (95% CI = 0.48–0.64) and 0.69 (95% CI = 0.60–0.76) for non-IDU and 0.46 (95% CI = 0.43–0.49) and 0.62 (95% CI = 0.58–0.65) for IDU, at 6 and 12 months, respectively. Based on the competing risk cumulative incidence function, among non-IDU, mortality rates at 12 and 24 months after ART initiation were 0.01 (95% CI = 0.00–0.04) and 0.02 (95% CI = 0.01–0.06). For IDU, mortality rates at the same time points were 0.05 (95% CI = 0.04–0.06) and 0.07 (95% CI = 0.06–0.09).

After adjustments for age, province, baseline viral load, viral load testing rate, initial third antiretroviral agent, and year of ART initiation, individuals with IDU history were less likely to virologically suppress after ART initiation [adjusted hazard ratio (AHR) = 0.78, 95% CI = 0.64–0.95; $P = 0.012$; Table 2)]. Controlling for the same confounders, a marginal difference was observed between individuals with and without IDU history in time to $CD4^+$ cell count recovery (AHR = 0.82, 95% CI = 0.66–1.00; $P = 0.055$; Table 2).

When adjusting for age, province, year of ART initiation, and baseline $CD4^+$ cell count, significant differences were observed between individuals with and without IDU history in the time to death analysis using proportional hazards models (AHR = 2.10, 95% CI = 1.21–3.65; $P = 0.009$; data not shown). Accounting for LTFU in the competing risk analysis (adjusted for the same confounders in addition to baseline viral load), significant differences remained (AHR = 2.15, 95% CI = 1.25–3.70; $P = 0.006$; Table 2).

## Discussion

Our results demonstrate that significant differences exist in characteristics, HIV treatment responses, and survival between HIV-HCV coinfected individuals with and without IDU history in a multisite Canadian cohort study, contributing a number of novel findings on coinfection for this region. Of note, this study was conducted in a setting with universal healthcare access in which ART and related care are subsidized.

Our study identified 148 HIV-HCV coinfected persons in CANOC without a history of IDU. The majority of these individuals were men (80%), with 67% having a documented HIV risk factor of sex with other men. Although biologically less efficient, sexual transmission of HCV is increasingly reported in the literature, especially among HIV-positive MSM [23–25]. Individuals with IDU history and MSM have different characteristics and healthcare needs that influence their therapeutic outcomes. Pantalone *et al.* [26] reported that despite more consistent engagement in care and higher rates of medication adherence, coinfected MSM are more likely to also report mental health concerns that are unique to

**Table 2. Adjusted multivariable results for HIV virologic suppression, $CD4^+$ cell count recovery, and mortality (competing risk with loss to follow-up) after antiretroviral therapy initiation.**

| | Virologic suppression ($n = 1223$) | | $CD4^+$ cell count recovery ($n = 1186$) | | Mortality ($n = 1254$) | |
|---|---|---|---|---|---|---|
| Variable | Adjusted hazard ratio (95% CI) | *P* value | Adjusted hazard ratio (95% CI) | *P* value | Adjusted hazard ratio (95% CI) | *P* value |
| Age (per decade) | 1.15 (1.07–1.24) | <0.001 | 1.10 (1.02–1.19) | 0.014 | 1.39 (1.18–1.63) | <0.001 |
| Province | | | | | | |
| British Columbia | 1.00 | | 1.00 | | 1.00 | |
| Ontario | 0.98 (0.72–1.34) | 0.901 | 0.94 (0.69–1.30) | 0.722 | 0.43 (0.20–0.90) | 0.026 |
| Quebec | 1.27 (1.05–1.53) | 0.013 | 1.17 (0.96–1.42) | 0.110 | 0.78 (0.51–1.18) | 0.240 |
| IDU history | 0.78 (0.64–0.95) | 0.012 | 0.82 (0.66–1.00) | 0.055 | 2.15 (1.25–3.70) | 0.006 |
| Initial third ARV | | | | | | |
| Nevirapine | 1.00 | | 1.00 | | – | – |
| Efavirenz | 1.30 (1.04–1.61) | 0.019 | 1.13 (0.90–1.41) | 0.296 | | |
| Lopinavir | 1.23 (0.98–1.55) | 0.073 | 1.02 (0.80–1.31) | 0.858 | | |
| Atazanavir | 1.39 (1.10–1.76) | 0.006 | 1.43 (1.11–1.83) | 0.005 | | |
| Other | 0.97 (0.77–1.22) | 0.801 | 1.04 (0.82–1.32) | 0.746 | | |
| VL testing rate (/year) | | | | | | |
| <3 | 1.00 | | 1.00 | | – | – |
| 3–4 | 1.75 (1.45–2.12) | <0.001 | 1.60 (1.31–1.95) | <0.001 | | |
| 5–6 | 2.06 (1.73–2.46) | <0.001 | 1.56 (1.29–1.88) | <0.001 | | |
| >6 | 2.41 (1.96–2.97) | <0.001 | 2.37 (1.91–2.94) | <0.001 | | |
| Year of ART initiation[a] | 1.01 (0.98–1.05) | 0.361 | 1.01 (0.98–1.04) | 0.610 | 1.03 (0.97–1.08) | 0.360 |
| Baseline $CD4^+$ cell count (/100 cells) | – | – | 0.95 (0.91–0.99) | 0.027 | 0.93 (0.83–1.04) | 0.220 |
| Baseline viral load ($log_{10}$) | 0.78 (0.71–0.86) | <0.001 | – | – | 1.14 (0.84–1.54) | 0.400 |

ART, antiretroviral therapy; ARV, antiretroviral agent; CI, confidence interval; VL, plasma viral load.
[a]Hazard ratio per incremental year in calendar time.

MSM and irrespective of IDU history. The high proportion of MSM among our non-IDU sample suggests the importance of individualized clinical assessments in patients identified as HIV-HCV coinfected.

While the incidence of HCV attributable to sexual transmission remains unknown in Canada, targeted public health messaging that communicates information on non-IDU HCV transmission risk, in addition to scale-up of HCV testing among HIV-positive MSM [27], may prove beneficial.

Similarly to findings presented here, significant differences between IDU and non-IDU have been reported in other studies that have investigated immunologic outcomes [28], virologic outcomes [29], and mortality [1,30,31]. However, to our knowledge, this is the first to report on such differences exclusively among HIV-HCV coinfected persons. Our findings demonstrate that IDU history independently elevates risk for poorer clinical outcomes, separate from HCV coinfection. We hypothesize that the observed differences between IDU and non-IDU may be an artefact of the IDU variable serving as a marker (i.e., a confounder by indication) for poor adherence to ART. ART adherence, a well established correlate of successful long-term HIV treatment outcomes [32,33], may be influenced among IDU by an interplay of competing circumstances and social-structural factors that include active addiction, housing instability, poverty and food insecurity, periods of incarceration, coexistent mental health disorders, and other concurrent conditions [14,34–36]. There are some data suggesting that certain drugs themselves may also negatively influence HIV treatment outcomes such as immune recovery [37–39].

Our findings allude to the importance of integrative, low-threshold services that aim to alleviate barriers to ART adherence for IDU. Such evidence-based services may include harm reduction strategies, directly observed therapy programs, and addiction services such as methadone maintenance [40–43]. As elucidated previously [14], provider/clinic-based characteristics that have been associated with improved ART adherence among IDU include the offering of ART delivery models that are highly flexible, incorporating features such as same day appointments, on-site pharmacies, drop-in services, and case management strategies.

Possible limitations should be considered when interpreting this analysis. Data were obtained from only three provinces, and our results are, therefore, not generalizable to all HIV-HCV coinfected persons in Canada. However, the 1254 included participants comprise over 10% of the estimated number of HIV-HCV coinfected persons in Canada, and a much higher proportion of coinfected persons accessing care. A further limitation is the potential for missing data, as by definition of our research question individuals in CANOC with missing IDU status or who were not tested for HCV were removed from the analysis.

We also acknowledge the potential for misclassification of HIV risk factors and particularly, an underreporting of IDU. This is possibly reflective of socially desirable risk reporting. Finally, the CANOC database does not contain information on current IDU, HCV viremia, or social determinants of health such as income and social supports, which may also significantly impact the outcomes examined.

In conclusion, we identified significant differences in clinical outcomes between HIV-HCV coinfected individuals with and without IDU history in Canada. Individuals living with both HIV and HCV are not a homogenous group; treatment and care should, thus, take into account these differences. Care should also be taken during statistical analyses if attributing poorer HIV-specific outcomes solely to HCV coinfection. These analyses are an important first step toward attempting to quantify HCV-specific impacts on clinical outcomes among HIV-HCV coinfected persons.

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C.C., A.C., K.C., and J.R. conceived of and designed the study. K.C. performed all statistical analyses. All authors contributed to the interpretation of the data. A.C. drafted the article. C.C. advised on all aspects of the study. All authors reviewed the article critically for important intellectual content and approved the final version submitted for publication.

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## Conflicts of interest

There are no conflicts of interest.

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