Effect of serostatus for hepatitis C virus on mortality among antiretrovirally naive HIV-positive patients

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Abstract

Background: We examined the effect of hepatitis C virus (HCV) seropositivity on risk of death among people receiving their first antiretroviral treatment (ART) for HIV infection.

Methods: In British Columbia, the HIV/AIDS Drug Treatment Program is the only source of free ART. Patients who initiated a triple-drug ART regimen between July 31, 1996, and July 31, 2000, were included if they were ART-naive and had baseline HCV serological data. Outcomes of interest for survival analysis were deaths from natural and HIV-related causes, with a data cutoff of June 30, 2003.

Results: Of 1186 eligible subjects, 606 (51%) were HCV positive and 580, negative. Fewer HCV-positive people were male (78% v. 93%, $p < 0.001$) and had an AIDS diagnosis at baseline (11% v. 15%, $p = 0.028$). Their CD4 fraction was significantly higher at baseline (19% v. 16% of T lymphocytes, $p < 0.001$) but their absolute CD4 counts, log HIV viral load and the type of ART initiated were similar to those of HCV negative people. Of 163 deaths (from natural causes only) during the study period, 118 (19%) were in HCV positive and 45 (8%) in HCV negative patients ($p < 0.001$); of the 114 deaths attributed to HIV infection, these proportions were 79 (13%) versus 35 (6%; $p < 0.001$). After adjustment for potential confounders, HCV seropositivity remained predictive of death (adjusted hazard ratio [HR] 2.20, 95% confidence interval [CI] 1.50–3.21, $p < 0.001$), especially HIV-related death (adjusted HR 1.75, 95% CI 1.13–2.72, $p = 0.012$).

Interpretation: In this population-based HIV treatment program, we found HCV seropositivity to be an independent predictor of mortality, especially death related to HIV infection.

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Seropositivity for hepatitis C virus (HCV) is prevalent among people who are HIV-positive.[1] Although several authors have found that liver disease has become a leading cause of death among those infected with HIV,[2–4] debate continues as to the effect of HCV infection on HIV disease progression, as measured by new AIDS-defining illnesses, CD4 T-cell decline or HIV-related mortality.[4–9] Mortality in this population can be strongly confounded by factors such as adherence to a course of antiretroviral therapy (ART), illicit use of injected drugs and previous administration of ART.

During the 1990s, Vancouver experienced an explosive epidemic of HIV and HCV infection among the city's 10 000 users of injected drugs;[10] currently, more than 30% are coinfected with both viruses.[11] Here we report on the effect of HCV serostatus on the risk of death among participants in a population-based HIV and AIDS treatment program who had received no previous ART, adjusting for adherence to ART and history of injection drug use. Specifically, we describe the effect of HCV serostatus on risk of death, particularly HIV-related death.

Methods

The HIV/AIDS Drug Treatment Program, described in detail elsewhere,[12] is the only source of free antiretroviral drugs in British Columbia. The program follows therapeutic guidelines that are consistent with international standards.[13] Data for this analysis were drawn from all program clients who started their first ART between July 31, 1996 and July 31, 2000 and began it with a triple-drug regimen consisting of 2 nucleoside analogue reverse-transcriptase inhibitors (NRTIs) plus either a protease inhibitor (PI) or a non-nucleoside reverse-transcriptase inhibitor (NNRTI) ($n = 1388$). The analysis was further restricted to those for whom HCV serologic data were available ($n = 1186$). Our cutoff date for follow-up data was June 30, 2003.

Mortality data were obtained from British Columbia Vital Statistics. We used codes from the International Classification of Diseases, tenth revision,[14,15] to evaluate the underlying cause of death; the specific codes used[16] can be found in an online appendix (available at www.cmaj.ca/cgi/content/full/173/2/160/DC1). HCV serologic data were obtained from plasma samples stored within 6 months before the initiation of ART; details of the assay method can also be found in the online appendix.

Approval for this study was obtained from the research ethics board of the University of British Columbia.

Two outcome measures were important to our analysis: death from natural biological causes (i.e., not caused by an accident, overdose, suicide or murder; for the purposes of this study, death from such causes was classified as a non-event), and death specifically attributed to HIV infection. As stated, we analyzed data available up to June 30, 2003; participants who died of nonbiological causes in the first analysis, or of nonbiological or biological but HIV-unrelated causes in the second, stopped being counted in the analysis (i.e., were censored) from the last known date of contact with the HIV/AIDS Drug Treatment Program.

The variables considered in our analyses included clients' sex;

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age (in 10-year increments); history of injection drug use (used or not used); whether AIDS was diagnosed at baseline; adherence to HIV medication during the first year of therapy; changes over time from baseline in CD4 count (categorized into $\leq 0.09 \times 10^9$/L, $0.10–0.19 \times 10^9$/L, $0.20–0.35 \times 10^9$/L and $> 0.35 \times 10^9$/L [the reference category]); time-dependent $\log_{10}$ HIV viral load per log increase from the baseline measurement; and whether an NNRTI or a PI was part of the initial ART drug combination.

Adherence to ART has been validated as a strong predictor of both virologic response[17] and survival.[18,19] Our study subjects were considered adherent to treatment if the length of time their dispensed antiretroviral medication was expected to last was more than 95% of the patient's follow-up (or survival) time. Note that this calculation was restricted to each study patient's first year of ART in order to avoid the reverse causation that could occur among those who become too sick to take medication and therefore cease therapy.

Hypothesized interactions were tested a priori between HCV infection and any history of injection drug use, and between injection drug use and adherence to medication.

HCV treatment was not factored into the statistical model because effective HCV treatment was unavailable before June 2003, when Pegetron (peginterferon bundled with ribavirin) was approved for prescription use in British Columbia. Response rates to regular interferon treatment (with or without ribavirin) in patients coinfected with HIV and HCV are very low;[16] we therefore considered the effect of HCV treatment in this population to be negligible.

In our statistical analyses we used an "intention to continue treatment" approach whereby data were included for analysis according to when the eligible study subject was first dispensed ART, regardless of whether the treatment was later discontinued or modified.

We compared data for HCV-positive and -negative study subjects by means of parametric analyses as well as methods unaffected by distribution. We used Pearson's χ^2 test to analyze categorical data, Fisher's exact test for contingency tables in which one-quarter or more of the expected cell frequencies were less than 5, and the Wilcoxon rank-sum test for continuous variables. We estimated cumulative mortality rates using the Kaplan–Meier method and compared survival curves with the Wilcoxon log-rank test. Finally, we calculated unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) with Cox proportional-hazards methods. Potential confounding factors adjusted for in the analysis included age, sex, type of ART regimen, time-updated CD4 count and viral load, injection drug use and adherence to treatment. Time was measured in months from the start of antiretroviral treatment. We validated the assumption of proportional hazards by inspecting plots of the log of the cumulative hazard functions in the HCV positive and HCV negative study groups. Data were right-censored at the time of the event of interest, either at June 30, 2003, or at the date of the last preceding contact with the HIV/AIDS Drug Treatment Program.

Results

There were 1186 people whose data were included for analysis: 606 (51%) were HCV positive and 580 (49%) HCV negative. Their characteristics at baseline are summarized in Table 1. Compared with the HCV negative subjects, those who were HCV positive were less likely to be male (78% v. 93%, $p < 0.001$) and to have had an AIDS diagnosis at baseline (11% v. 15%, $p = 0.028$); they also had a lower median CD4 fraction (0.19 v. 0.16, $p < 0.001$). The 2 groups were statistically similar for absolute baseline CD4 count, baseline log HIV viral load and whether their ART was initiated with an NNRTI or a PI.

The median follow-up for all study subjects was 52.3 months (interquartile range [IQR] 39.5–66.7 mo). Among HCV positive clients, the median follow-up was 49.9 (IQR 36.8–63.9) months, compared with 54.8 (IQR 42.7–70.1) months among HCV negative subjects. Of 163 deaths from natural causes that occurred during our study, 118 (72%) were among HCV positive patients and 45 (28%), HCV negative patients ($p < 0.001$). There were also 45 deaths unrelated to physical health, including 38 HCV positive clients (6% of that population) and 7 HCV negative (1%).

People coinfected with HIV and HCV were significantly more likely to die of HIV-related causes than were those infected with HIV alone (13% v. 6%, $p < 0.001$). Of those who died of liver-related causes, 7 (1%) were HCV positive and 1 (< 1%) HCV negative; cancer-related causes, 3 HCV positive and 2 HCV negative (both < 1%); and other causes, 20 (3%) HCV positive and 7 (1%) HCV negative. Cause of death was unknown for 9 HCV positive (1.5% v. 0 HCV negative) subjects.

Fig. 1 displays the results of Kaplan–Meier analysis, in which HCV serostatus was strongly associated with time to death ($p < 0.001$), even after restricting the analysis to people who were more than 95% adherent to their antiretroviral medication in the first year of treatment ($p < 0.001$). Cumulative survival at 1, 3 and 5 years after ART initiation was as follows: HCV positive at 1 year 0.97 (95% CI 0.96–0.98), at 3 years 0.92 (95% CI 0.90–0.94) and at 5 years 0.85 (95% CI 0.82–0.88); HCV negative at 1 year 0.98 (95% CI 0.97–0.99), at 3 years 0.96 (95% CI 0.94–0.98) and at 5 years 0.94 (95% CI 0.92–0.96).

Table 1: Characteristics of HIV-positive subjects at initiation of their first ART, by hepatitis C virus (HCV) serostatus

Characteristic	No. (and % or interquartile range) HCV seropositive *n = 606*	HCV seronegative *n = 580*	*p* value
Sex, male	473 (78)	541 (93)	< 0.001
Age, median, yr	37.8 (32.2–44.0)	36.8 (32.0–43.8)	0.50
Any injection drug use	285 (47)	36 (6)	< 0.001
Diagnosed with AIDS at start of ART	65 (11)	87 (15)	0.028
CD4 cell count, median			
Cells $\times 10^9$/L	0.28 (0.13–0.43)	0.27 (0.13–0.42)	0.56
% of T lymphocytes	0.19 (0.11–0.27)	0.16 (0.09–0.24)	< 0.001
HIV RNA, median, log	5.0 (4.6–5.0)	5.0 (4.6–5.0)	0.99
ART begun with PI	417 (69)	388 (67)	0.48
Begun with NNRTI	189 (31)	192 (33)	

Note: ART = antiretroviral therapy, PI = protease inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor.

Table 2 summarizes the unadjusted and adjusted hazards of death from natural causes and HIV-related death. After controlling for sex, age at baseline, having a history of injection drug use, adherence to ART, having an AIDS diagnosis at baseline, time-updated CD4 count and log HIV viral load, HCV serostatus remained strongly predictive of death in this population (adjusted HR 2.20, 95% CI 1.50–3.21, $p < 0.001$). Adjusting for the same factors, HCV coinfection remained independently predictive of an HIV-related death (adjusted HR 1.75, 95% CI 1.13–2.72, $p = 0.012$).

Injection drug use was examined for interaction with HCV seropositivity and with treatment adherence. Because no evidence was found of an interaction in either case, neither was included in the final models.

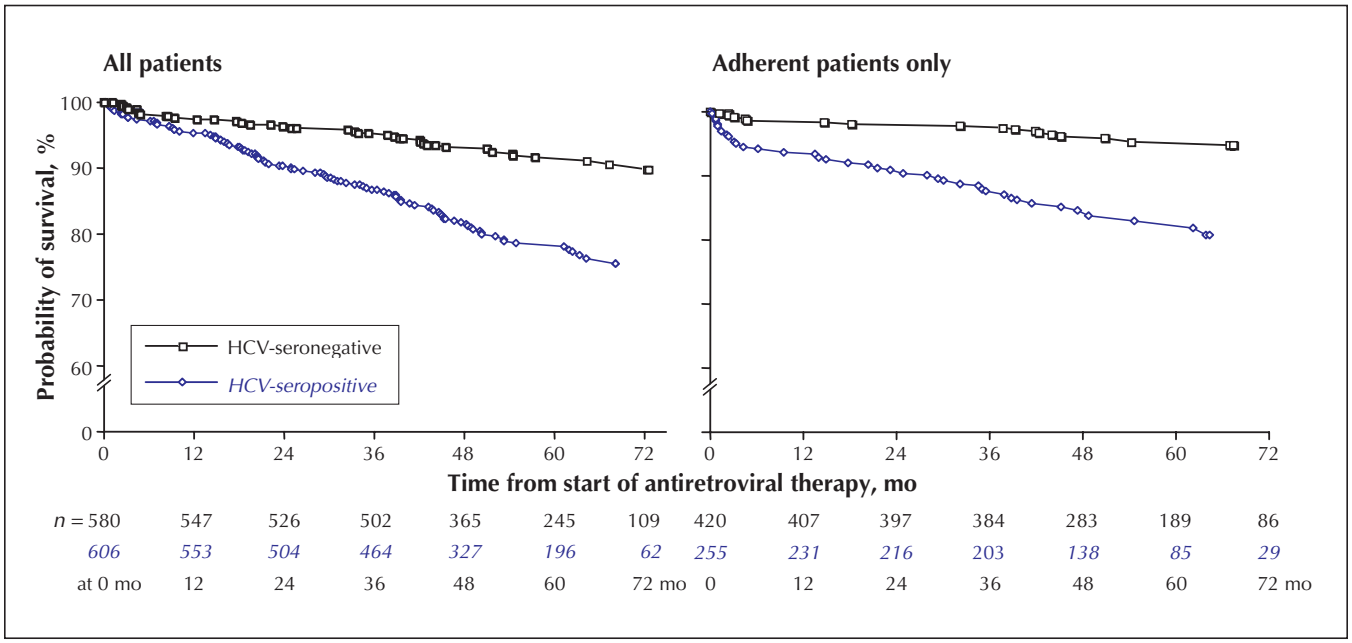

Fig. 1: Probability of survival by hepatitis C virus (HCV) serostatus among HIV-infected subjects initiating their first antiretroviral therapy, showing deaths from natural causes only (excluding, for example, drug-overdose and traffic fatalities, suicides and homicides). The graph on the right includes data from only those subjects who were at least 95% adherent to their therapy regimen.

Table 2: Predictors of death among HIV-positive study subjects

	Hazard ratio (95% confidence interval)			
	Death from natural causes ($n = 168$)		HIV-related death ($n = 114$)	
Factor	Unadjusted	Adjusted	Unadjusted	Adjusted
Sex, male	0.77 (0.51–1.16)	1.05 (0.69–1.60)	0.74 (0.46–1.21)	1.08 (0.65–1.78)
Age at baseline, per 10-yr interval	1.37 (1.17–1.59)	1.47 (1.24–1.74)	1.23 (1.02–1.49)	1.33 (1.08–1.63)
Seropositive for hepatitis C virus	2.81 (1.99–3.96)	2.20 (1.50–3.21)	2.43 (1.63–3.62)	1.75 (1.13–2.72)
Injection drug use	0.96 (0.68–1.36)	0.62 (0.43–0.89)	0.86 (0.56–1.32)	0.57 (0.36–0.88)
Adherence to treatment ≥ 95%	0.39 (0.29–0.54)	0.84 (0.59–1.20)	0.31 (0.21–0.46)	0.72 (0.47–1.12)
AIDS diagnosed at baseline	1.66 (1.12–2.45)	1.19 (0.78–1.82)	1.88 (1.20–2.94)	1.41 (0.87–2.30)
CD4 counts, BL+, time-updated				
$\leq 0.09 \times 10^9$/L	33.53 (20.44–54.31)	19.45 (11.49–32.94)	79.50 (36.43–173.49)	42.21 (18.30–93.00)
$0.10–0.19 \times 10^9$/L	7.00 (3.91–12.56)	4.86 (2.69–8.79)	13.54 (5.65–32.46)	9.04 (3.72–21.95)
$0.20–0.35 \times 10^9$/L	3.52 (2.01–6.23)	2.81 (1.58–5.00)	6.29 (2.63–15.10)	4.81 (2.00–11.60)
$> 0.35 \times 10^9$/L	1.00	1.00	1.00	1.00
Log HIV viral load per log BL+, time-updated	2.22 (1.89–2.61)	1.48 (1.24–1.77)	2.72 (2.21–3.35)	1.67 (1.34–2.09)
Antiretroviral treatment including NNRTI rather than PI at start	0.89 (0.63–1.27)	—	0.75 (0.48–1.16)	—

Note: BL+ = increase from baseline, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor.

Interpretation

In this previously ART-naive HIV-infected population receiving highly active antiretroviral therapy, our findings strongly supported the hypothesis that HCV seropositivity is an independent predictor of death, particularly HIV-related death. Our data are consistent with findings from other studies[4,5,20] that have shown that HCV coinfection has an adverse impact on HIV disease progression and HIV-related mortality.

HCV infection could affect HIV-related survival and mortality in several ways. Liver injury and increased ART toxicity may preclude patients coinfected with HIV and HCV from tolerating antiretroviral therapy.[21,22] Because the progression of HCV disease is exacerbated in the setting of HIV infection,[16] cause of death may be noted as being only HIV-related.

This analysis had 4 key strengths. Because the data were drawn from an HIV population–based cohort, our findings are more generalizeable than those from other studies. By adjusting for adherence to antiretroviral medications and a history of injection drug use, we were able to at least partially account for 2 potentially important confounding factors. Because the study was restricted to people who initiated ART since 1996, this analysis was not subject to the kind of survivorship bias inherent in studies that analyzed the survival of coinfected individuals before and after 1996.[9,20] And by removing data for deaths without a natural cause and (in the HIV subanalysis) non–HIV-related events, we have conservatively biased our estimates.

This analysis also had 5 potential limitations. First, the HCV data were based on serologic testing alone and not confirmed with polymerase chain reaction testing. Roughly 5% of seronegative people will have detectable HCV RNA,[23] and 5%–10% of HIV-infected patients who are HCV seropositive will nevertheless have undetectable HCV RNA;[24] this suggests that the potential for misclassification bias is minimal. Second, our measure of adherence was restricted to the first year of therapy; this was done explicitly to avoid the possible reverse-causation that may result from patients who become less adherent to their ART because they are too sick to take the medications. Furthermore, this measure may be limited because it is a proxy for actually swallowing pills, but it has been strongly validated with both surrogate and clinical outcomes.[17,19] Third, although we have been able to adjust for the confounding effect of any history of injection drug use, this variable is not a marker of current use, and residual confounding may therefore be present. Our finding that any injection drug use in adjusted analyses was associated with about a 40% reduced risk of mortality may be related to residual confounding. Fourth, we were unable to account for the duration of HIV infection. Finally, because our centre has previously shown that 30% of people in British Columbia dying of HIV-related causes have never received antiretroviral therapy,[25] and because the sociodemographic profile of these patients is consistent with people expected to be infected with both HIV and HCV in British Columbia, it is reasonable to suggest that the findings of our present study may be underestimates.

In summary, in this population-based study of HIV-infected people receiving their initial antiretroviral therapy, these data have suggested that HCV seropositivity is independently predictive of increased mortality, particularly HIV-related death, even after controlling for lack of adherence to antiretroviral drug therapy and history of injection drug use. Further work is needed to fully characterize the mechanisms responsible for the increased mortality observed among patients infected with both the human immunodeficiency and hepatitis C viruses.

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Contributors: Paula Braitstein conceived the idea and methods for the analysis and was primarily responsible for the analysis and writing of the manuscript. Benita Yip was the data manager and senior statistician on the project. Robert Hogg was responsible for the data set. Valentina Montessori, David Moore and Julio Montaner were consultant physicians throughout the development of the manuscript.

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