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Chronic Hepatitis C Virus Infection is Associated with All-Cause and Liver-Related Mortality in a Cohort of HIV-Infected Patients with Alcohol Problems

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Abstract

Aims—To assess the association between hepatitis C virus (HCV) infection and overall and liver-related death in human immunodeficiency virus (HIV)-infected patients with alcohol problems.

Design—We analyzed data from a cohort of HIV-infected adults with current or past alcohol problems enrolled between 2001 and 2003, searching for causes of death until 2010 using the National Death Index.

Setting and participants—Participants were HIV-infected adults with current or past alcohol problems, recruited in Boston, MA from HIV clinics at two hospitals, homeless shelters, drug treatment programs, subject referrals, flyers, and another cohort study with comparable recruitment sites.

Measurements—The primary and secondary outcomes were all-cause and liver-related mortality, respectively. The main independent variable was HCV RNA status (positive vs. negative). Mortality rates and Kaplan-Meier survival curves were calculated by HCV status for both overall and liver-related mortality. Cox proportional hazards models were used to assess the association between HCV infection and overall and liver-related death, adjusting for alcohol and drug use over time.

Findings—397 adults (50% HCV-infected) were included. As of December 31, 2009, 83 cohort participants had died (60 HCV-infected, 23 HCV-uninfected; log rank test $p < 0.001$), and 26 of those deaths were liver-related (21 HCV-infected, 5 HCV-uninfected; log rank test $p < 0.001$). All-

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cause and liver-related mortality rates were 4.68 and 1.64 deaths per 100 person-years for HCV-infected patients and 1.65 and 0.36 per 100 person-years for those without HCV, respectively. In the fully adjusted Cox model, HCV infection was associated with both overall [HR 2.55 (95%CI: 1.50–4.33), $p<0.01$], and liver-related mortality [HR 3.24 (95%CI:1.18–8.94), $p=0.02$].

Conclusion—Hepatitis C virus infection is independently associated with all-cause and liver-related mortality in human immunodeficiency virus-infected patients with alcohol problems, even when accounting for alcohol and other drug use.

Introduction

Chronic hepatitis C infection (HCV) is a known cause of cirrhosis and liver cancer and prior studies have confirmed that liver disease is a major cause of death among patients with HIV infection (1)(2). There is a growing appreciation for the adverse effects of chronic inflammation in the setting of HIV infection, and its contribution to premature mortality in the era of highly active antiretroviral therapy (HAART) (3). Co-infection with hepatitis C is associated with alterations in biomarkers of inflammation (4), which may ultimately lead to increased risk of death from non-liver causes (5). Hepatitis C has been associated with risk for cardiovascular disease (CVD) in some studies (6)(7), as well as all-cause and CVD-related death (8)(9). However, alcohol and other drug use can also lead to chronic inflammation and premature mortality from drug-related causes (10). Persons with HCV are more likely to use alcohol and other drugs compared to those who are uninfected (11). Prior studies that have examined mortality and associations between HCV and mortality have often lacked person-level data on these important confounders.

Therefore, we undertook this study to compare mortality (all-cause and liver-related) between persons with and without HCV infection in a cohort of HIV-infected patients with current or past alcohol problems and a range of use from abstinence to heavy drinking, adjusting for important confounders such as alcohol and other drug use.

Methods

Participants and methods

Study Design and objectives—This study utilized data from a prospective observational cohort study (HIV-Longitudinal Interrelationships of Viruses and Ethanol [HIV-LIVE]), in which assessments occurred at 6-month intervals over a maximum of 42 months (12). The study was initiated in August 2001 and the last study visit was performed in March 2006. Deaths were ascertained through the National Death Index (NDI) from 2001 to the end of 2009. Methods for establishing a match can be found on the NDI website (<http://www.csc.gov/nchs/ndi.htm>). In brief, each record is matched by first and last name, date of birth, sex, social security number and state of birth.

The primary objective of this study was to assess the association between chronic HCV infection and all-cause and liver-related mortality in a population of HIV-infected adults with current or past alcohol problems.

Participants—Recruitment for the HIV-LIVE cohort occurred from a previous cohort study; an intake clinic for HIV-infected patients; HIV primary care and specialty clinics at two hospitals; homeless shelters; drug treatment programs; subject referrals; and flyers (12). Enrollment occurred between August 2001 and July 2003. Eligibility criteria were the following: 1) documented HIV antibody test by ELISA and confirmed by Western blot; 2) two or more affirmative responses to the CAGE alcohol screening questionnaire (13), or physician investigator diagnosis of alcoholism; and 3) ability to speak English or Spanish.

Exclusion criteria were: 1) scoring <21 on the 30-item Mini-Mental State Examination (i.e., cognitive impairment) (14)(15); and 2) inability to provide informed consent (12). For the current analysis we excluded participants who lacked data to determine the presence or absence of HCV infection (see below). The Institutional Review Boards of Boston Medical Center and Beth Israel Deaconess Medical Center approved this study.

Measures

Dependent variable: The primary dependent variable was all-cause mortality. Causes of death were obtained from NDI-plus, a service from the National Death that includes causes of death as registered on death certificates. The underlying cause of death was based on the International Classification of Diseases (ICD), Tenth Revision.

Liver-related death was the secondary outcome. Death was classified as liver-related, based on mortality codes described by Manos et al.(16) if the primary cause of death or any of the first four underlying conditions included any of the following ICD-10 codes: B16 (acute hepatitis B), B17 (other acute viral hepatitis), B18 (chronic viral hepatitis), B19 (unspecified viral hepatitis), B94.2 (sequelae of viral hepatitis), C22 (malignant neoplasm of the liver), I85 (esophageal varices), K70 (alcoholic liver disease), K71 (toxic liver disease), K73 (chronic liver disease), K74 (fibrosis or cirrhosis of the liver), K75 (other inflammatory diseases of the liver), K76 (other diseases of the liver [e.g. portal hypertension, hepatorenal syndrome and hepatic failure]), K77 (liver disorders in diseases classified elsewhere).

Independent variables: The primary independent variable was HCV infection defined as a positive HCV antibody result by ELISA confirmed with the presence of detectable HCV RNA by polymerase chain reaction (PCR). HCV uninfected people were those who had a negative HCV antibody result or a positive HCV antibody result but no detectable HCV RNA on PCR testing. Additional sensitivity analyses were performed excluding the participants who were HCV antibody positive but HCV RNA negative (i.e. cleared infection) from the analyses.

Covariates: Potential confounders controlled for in the analyses were age, sex, race/ethnicity, CD4 count/mm³ [categorized as <200 and ≥200], current (past month) smoking, current heavy alcohol use, lifetime alcohol consumption, injection drug use (IDU) (prior 6 months), homelessness (prior 6 months) and cocaine and/or heroin use (prior 12 months for baseline visit and prior 6 months for follow-up visits). The composite variable current cocaine/heroin use was chosen because it was associated with short-term mortality in a prior study of this cohort (17), and because it avoided strong correlations with IDU. Current heavy alcohol use (last 30 days) was defined according to National Institute on Alcohol Abuse and Alcoholism guidelines for “at-risk” drinking: >14 drinks/week or ≥5 drinks on one occasion for men <65 years of age, and >7 drinks/week or ≥4 drinks on one occasion for all women and for men ≥65 years of age and was assessed using a validated calendar method (18). Lifetime alcohol consumption was calculated and expressed in kg. of alcohol, multiplying the number of lifetime alcohol units x 14 grams of alcohol/unit. Number of lifetime alcohol units was captured by Lifetime Drinking History (19).

Statistical analysis—Baseline characteristics were compared across groups (HCV infected v. uninfected) using Chi-square or Fisher’s exact test for categorical values and ANOVA for continuous variables. Mortality rates were calculated using person-years (p-y) of observation for descriptive purposes. Person-year rates were obtained by dividing the number of deaths observed during the study period by the total time of follow-up. Mortality rates were calculated separately for overall and liver-related mortality. Using the HCV uninfected (i.e. those who had a negative HCV antibody result or a positive HCV antibody

result but no detectable HCV RNA) as the reference category, mortality ratios were calculated for the association between HCV infection and overall and liver-related mortality.

Kaplan-Meier survival curves and log-rank tests were used to compare overall and liver-related mortality for those with and without HCV infection. A censor date of 12/31/2009 was used for participants who were still alive at the end of the period in which NDI data was available. For liver-related mortality analyses, those who died from causes other than liver-related were censored on their date of death. Cox proportional hazard models with age as the time-scale were fit to evaluate associations between HCV infection and overall and liver-related mortality adjusting for potential confounders. For overall mortality, the fully adjusted model controlled for gender, race (black versus non-black), baseline lifetime alcohol consumption and the following time dependent covariates: CD4 count, smoking, heavy alcohol use, injection drug use, homelessness and cocaine/ heroin use. The adjusted model for liver-related mortality controlled for only gender, race-ethnicity, CD4 cell count, heavy alcohol use, and cocaine/ heroin use given the more limited number of events. Time dependent covariates were recorded during the course of the HIV-LIVE study period (up to 2006). Adjusted hazard ratios (HR) and 95% confidence intervals (CI) are reported for each model. Schoenfeld residuals (20) were used to identify violations in the proportional hazards assumption of the Cox model. For each model, covariate-wise residuals were plotted against time to identify trends, which would indicate poor model fit. Residuals did not show any strong patterns over time, suggesting acceptable model fit. Spearman correlations were used to evaluate potential collinearity between independent variables and covariates. No pair of variables included in the same regression model was highly correlated ($r > 0.40$). All analyses were conducted using two-sided tests and a significance level of 0.05. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Inc., NC, USA). Additional sensitivity analyses were performed excluding the participants who were HCV antibody positive but HCV RNA negative from the referent HCV uninfected group.

Results

Between 2001 and the end of 2003, 400 participants were enrolled in the HIV-LIVE cohort. Of those, all but 3 participants had available information documenting HCV infection. Therefore, the study population was 397 adults (200 of them infected with HCV).

Table 1 shows the baseline characteristics of the 397 participants stratified by HCV infection. Participants with HCV infection were significantly older and more likely to report injection drug use, current cocaine/ heroin use and recent homelessness. One third of the participants had current heavy alcohol use and most of them were current smokers. No differences were observed in the prevalence of heavy alcohol use or smoking according to the presence of HCV co-infection. However, HCV infected participants had a significantly higher lifetime alcohol consumption at baseline ($p=0.03$).

As of December 31st, 2009, 83 participants had died (60 HCV-infected, 23 HCV-uninfected; log-rank test $p < 0.001$), and 26 deaths were liver-related (21 HCV-infected, 5 HCV-uninfected; log-rank test $p < 0.001$). For the three participants whose cause of death was unlisted, death was not classified as liver-related. The median follow-up was 6.7 years and included 2688.5 person-years. Table 2 shows the mortality rates overall and stratified by HCV infection status. Using HCV uninfected patients as the reference category; the mortality ratios (95%CI) for the association between HCV infection and overall and liver-related mortality were 2.57 (1.66–3.98) and 4.14 (1.59–10.75), respectively.

The Kaplan-Meier survival curves for all-cause and for liver-related death are shown in Figure 1 and Figure 2. Based on the log-rank test, HCV infection was significantly

associated with poorer all-cause and liver-related survival, $p<0.0001$ and $p=0.0009$, respectively.

In the unadjusted Cox model, HCV infection was significantly associated with all-cause mortality (hazard ratio [HR] (95%CI) 2.84 (1.73–4.68; $p<0.01$). HCV infection remained associated with all-cause mortality (HR 2.55, 95%CI: 1.50–4.33; $p<0.01$) in the fully adjusted model. Of note, CD4 count was significantly associated with all-cause mortality [HR (95%CI) 2.97 (1.89–4.67) $p<0.01$ for $CD4<200$ cells/mm³]. Cocaine/ heroin use was also associated with a higher risk of mortality, though results did not reach statistical significance [HR 1.58 (0.98–2.55) $p=0.06$]. Table 3 shows the fully adjusted model for the association between HCV infection and all-cause mortality.

In the unadjusted Cox model, HCV infection was significantly associated with liver-related mortality (HR [95%CI] 4.14 [1.54–11.12]; $p<0.01$). HCV remained associated with liver-related mortality (HR [95%CI] 3.24 [1.18–8.94]; $p=0.02$) in the multivariable adjusted model (Table 4). Among covariates, baseline CD4 count <200 cells/mm³ and cocaine/ heroin use were also associated with liver-related death (HR [95%CI] 2.79 [1.27–6.15]; $p=0.01$ and 2.29 [1.01–5.18]; $p<0.05$, respectively), while current heavy alcohol use was not.

The most frequent cause of death among those with HCV infection was liver-related death with 21 deaths, accounting for 35% of the total in that group; while among the HCV negative participants the most frequent cause of death was “Other cause of death” with 8 deaths (3 deaths of pulmonary cause, 2 cardiovascular deaths and 3 deaths of unknown cause) corresponding to 35% of the total (see Table S1). There were 5 liver-related deaths in patients without chronic HCV infection. Two of those represented a resolved HCV infection and were positive for hepatitis B surface antigen (HBsAg), another had a resolved HCV infection and one had a positive HBsAg alone. The HCV antibody negative and HBsAg negative participant who died from a liver-related death died from GI bleeding. We also calculated mortality rates stratifying the study sample in three groups: chronic HCV infection (HCV antibody positive and detectable HCV RNA), resolved infection (HCV antibody positive and HCV RNA undetectable) and no prior infection (HCV antibody negative). The overall mortality rate appeared highest among those with chronic HCV infection for overall mortality [4.68 per 100 p-y (3.64–6.03)], while those with resolved HCV infection [1.82 per 100 p-y (0.68–4.84)] and those without prior HCV infection [1.62 per 100 p-y (1.03–2.53)] had similar mortality rates. The liver-related mortality rate was 1.64 per 100 p-y (1.07–2.51) in the chronic HCV infection group, 1.36 per 100 p-y (0.44–4.23) in the resolved HCV infection group, and 0.17 per 100 p-y (0.04–0.68) in those without prior HCV infection. When we performed additional sensitivity analyses excluding those 32 patients who had a resolved HCV infection (HCV antibody positive and undetectable HCV RNA) the conclusions were consistent with original analysis, namely that chronic hepatitis C was significantly associated with overall and liver-related mortality (adjusted HR [95%CI] 2.72 [1.52–4.85]; $p<0.01$ and 7.49 [1.68–33.30]; $p<0.01$, respectively).

Discussion

We found that HCV infection was independently associated with both all-cause and liver-related mortality in a cohort of HIV-infected adults with current or past alcohol problems. Results were consistent in analyses adjusted for smoking, alcohol use and other drug use (injection drug use and use of cocaine and/or heroin). Furthermore, mortality rates in this cohort were higher than those reported in previous studies of HIV-infected persons (21)(22)

(23)(24), which reinforce the observation that HCV infection is an important risk factor for mortality in HIV-infected people with alcohol problems (25).

It is notable that the overall mortality rates in this cohort were higher than what has been reported by some recent cohort studies of HIV-infected people (0.65–1.17 deaths per 100 py in other cohorts v. 3.16 per 100 p y in our cohort); this observation merits speculation as to its basis (21)(22)(23)(24). There are several possible explanations for this study's higher observed mortality. First, this cohort was comprised of HIV-infected persons with current or past alcohol problems. Alcohol problems are associated with a multitude of co-morbidities (26) as well as risk for accelerated liver disease in the setting of HCV (27)(28). As such, our results may reflect that HIV-infected patients with alcohol problems may be at greater risk for early death compared to those who do not have alcohol problems. In addition, there was a high prevalence of illicit drug use in this study cohort, which was associated with liver-related death. Our findings are more in line with research on cohorts of HIV-infected injection drug users, for which all-cause mortality rates range between 6.5 and 12.2 per 100 p-y (29)(30).

Participants in our cohort had other predictors of poor prognosis, specifically that antiretroviral treatment receipt was not universal, and the receipt of HCV antiviral therapy was very low (31). Among covariates, a CD4 count <200 cells/mm³ was associated with both all-cause and liver-related mortality. Access to antiretroviral treatment and HCV antiviral treatment, has been shown to improve clinical outcomes (32)(33), even mortality (34) in similar cohorts of HIV-infected patients with substance use problems.

Our finding that HCV was associated with all-cause mortality, as well as liver-related mortality, is consistent with prior research. Several large studies (not specifically focused on HIV-infected populations) have suggested that HCV infection is associated with death from causes other than liver disease. A study of blood donors found a threefold increase in all-cause mortality associated with being seropositive for HCV, including significantly increased mortality from cardiovascular causes (8). Likewise, a study using National Health and Nutrition Examination Survey data found that all-cause mortality was twice as high for those with HCV infection (35). Furthermore a large study from Taiwan found that HCV infection was associated with an increased risk for death from a number of non-hepatic diseases (36). Other studies have demonstrated significant associations between HCV and cardiovascular disease (37)(38), end-stage renal disease (39) and hematological malignancies (40), thus it is plausible that HCV could increase risk of death from non-hepatic causes.

Among HIV-infected populations, there is mixed evidence for the impact of chronic HCV infection on AIDS-related mortality (41)(42)(43). Several cohort studies have found that the increased mortality observed in HIV and HCV co-infected patients is mainly driven by liver disease (2)(23)(28). However, there is growing evidence that HCV might also have a role in causing non-liver related deaths among persons with HIV (21)(44)(45). In a meta-analysis of 27 studies in the HAART era, HCV conferred a risk ratio of all-cause mortality of 1.35 (95%CI 1.11–1.63) (43). Two more recent studies have confirmed those findings. In the D:A:D cohort, the relative rate of all-cause mortality among co-infected persons was 1.21 (95%CI 1.06–1.39) (46). Another cohort study of 2,025 adults with HIV infection found that the relative risk for all-cause mortality in patients with HCV infection was 1.5 (95%CI 1.2–1.9) (23). Besides the effects on the liver, HCV is associated with inflammation (47), especially in the context of HIV (4); such increased inflammation from co-infection may explain the increased incidence of cardiovascular (7)(48) and renal disease (49)(50), and may partially account for the increased mortality.

Substance use is also an important cause of mortality that might have confounded results in prior studies (41)(43), but our study is unique in that we adjusted for individuals' use. According to our results, HCV infection was associated with all-cause mortality even after adjustment for substance use that itself can lead to poorer outcomes (e.g., injection drug use, current cocaine/ heroin use, and smoking). These results suggest that current cocaine/ heroin use may be a risk factor for death (even though borderline significant), which is consistent with a prior study of short-term mortality in the same cohort (17). Substance use-related deaths are common among persons with HIV infection (25) and/ or HCV infection (51). Moreover, current use of cocaine/ heroin use was associated with liver-related death, independently of the effect of HCV infection. This data raises the possibility that drug use is particularly harmful in HIV-infected patients with chronic liver disease.

Of note, we found that 3 of the 32 participants with a serologic pattern consistent with resolved HCV infection died of a liver-related death. Given the limited number of subjects and events among those with resolved HCV infection, we did not perform a regression analysis with a three-level HCV variable and instead performed a sensitivity analysis excluding patients with resolved HCV infection to confirm the main findings. The point estimate of the hazard ratio for overall mortality (2.72; 95%CI 1.71–5.04) was similar to our primary analysis (2.55; 95%CI 1.50–4.33), but the hazard ratio for liver-related death (7.49; 95%CI 1.68–33.30) was higher than our primary analysis (3.24; 95%CI 1.18–8.94). These exploratory results may support other prior research suggesting that patients with resolved HCV infection are still at greater risk of liver-related morbidity compared to individuals who have never been infected (52).

The present study has several limitations. First, we used NDI data (based on death certificates) to classify deaths as liver-related, therefore there may have been misclassification of the cause of deaths (16)(53). We expect that this misclassification would be non-differential with regards to HCV status, though it is possible that the person coding the death certificate might be more likely to select a liver-related cause given a range of possible contributing causes of death, which would bias in favor of the observed association. However, such misclassification of cause of death cannot impact our finding of an association between HCV infection and all-cause mortality. Although our median follow-up time (6.7 years) was considerable, we were still limited by a modest number of death outcomes, which did not allow us to look at additional specific causes of death (such as cardiovascular or drug-related deaths). As mentioned previously, because of small outcomes we were unable to compare outcomes between patients with chronic HCV and those who had resolved infection, groups that might have a similar profile for other risks (substance use). Prior studies of opioid dependent patients that have compared mortality among HCV infected versus those with resolved infection have not observed differences (54)(55). However, we attempted to adjust for individual-level differences in substance use, which may differ among individuals who have and have not been exposed to HCV. In addition, we had no information regarding antiretroviral therapy during follow-up, so we were not able to include it as a covariate in the regression analysis, and we did not include a measure of lifetime smoking. Finally, although we adjusted for current smoking, heavy alcohol or other substance use during the course of the study (median follow-up 3.3 years) we did not have data to update these covariates past the follow-up period of the study despite being able to collect mortality data for an additional three years through the National Death Index. This may have introduced bias into the study however the direction and magnitude of the potential confounding is unclear.

In conclusion, HCV infection was independently associated with both all-cause and liver-related mortality in a cohort of HIV-infected adults with alcohol problems at great risk for

premature death, even with adjustment for potential confounders such as alcohol, smoking and other drug use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Kaplan Meier survival curve for all-cause mortality in persons with HIV infection with and without HCV infection
 $p < 0.001$ by log-rank test.

Figure 2.

Kaplan Meier survival curve for liver-related mortality in persons with HIV infection with and without HCV infection
 $p < 0.001$ by log-rank test.

Table 1

Baseline characteristics of HIV-LIVE cohort study participants – HIV-infected persons with current or past alcohol problems

	Total	HCV infected (n= 200)	HCV uninfected (n= 197)	p-value
Male [n (%)]	297 (75)	146 (73)	151 (77)	0.40
Age (mean ± SD)	42 (7.4)	44 (7.0)	41 (7.5)	<0.01
Race (black) [n (%)]	163 (41)	76 (38)	87 (44)	0.21
CD4 cell count [cells/mm ³]				
▪ <200 [n (%)]	74 (20)	41 (22)	33 (18)	0.29
▪ 200 [n (%)]	301 (80)	146 (78)	155 (82)	
HIV RNA viral load [copies/ mL]				
▪ >500 [n (%)]	194 (54)	95 (53)	99 (55)	0.71
Antiretroviral use [n (%)]	247 (62)	129 (65)	118 (60)	0.34
Heavy alcohol use [n (%)] [#]	124 (31)	58 (29)	66 (34)	0.32
Lifetime alcohol consumption (n=361)				
1 st tertile <240 kg [n (%)]	119 (33)	50 (28)	69 (38)	0.03
2 nd tertile [n (%)]	119 (33)	56 (31)	63 (35)	
3 rd tertile >828 kg [n (%)]	123 (34)	74 (41)	49 (27)	
Current smoking [n (%)]	303 (76)	158 (79)	145 (74)	0.20
Injection drug use (ever) [n (%)]	226 (57)	178 (89)	40 (20)	<0.01
Injection drug use (prior 6 months) [n (%)]	56 (14)	47 (24)	9 (5)	<0.01
Cocaine/ heroin use ⁺ [n (%)]	197 (50)	110 (55)	87 (44)	0.03
Homelessness (prior 6 months) [n (%)]	98 (25)	58 (29)	40 (20)	0.04

SD: standard deviation; IQR: interquartile range;

[#] last 30 days;

⁺ past 12 months at baseline.

Table 2

Mortality rates among HIV-infected persons with current or past alcohol problems during median follow-up of 6.7 years, stratified by HCV infection.

	All-cause mortality		Liver-related mortality	
	Mortality rate [per 100 py] (95% CI)	Mortality Ratio (95% CI)	Mortality rate [per 100 py] (95% CI)	Mortality Ratio (95% CI)
Total	3.16 (2.56, 3.91)		1.00 (0.69, 1.46)	
HCV Uninfected	1.65 (1.10, 2.48)	1	0.36 (0.15, 0.86)	1
HCV Infected	4.68 (3.64, 6.03)	2.57 (1.66, 3.98)	1.64 (1.07, 2.51)	4.14 (1.59, 10.75)

CI= Confidence interval.

Table 3

Multivariable analysis of the association between HCV infection and all-cause mortality in HIV-infected adults with current or past alcohol problems

	HR (95% CI)	p-value
HCV infection	2.55 (1.50 – 4.33)	<0.01
Female gender	1.10 (0.65 – 1.86)	0.72
Black race	1.17 (0.72 – 1.88)	0.53
CD4 cell count ^{&}	2.97 (1.89 – 4.67)	<0.01
Current smoking	1.39 (0.77 – 2.52)	0.28
Heavy alcohol use [*]	1.07 (0.64 – 1.78)	0.79
Lifetime alcohol consumption		
▪ 1 st tertile	1	
▪ 2 nd tertile	0.90 (0.49 – 1.65)	0.73
▪ 3 rd tertile	0.75 (0.41 – 1.37)	0.35
Injection drug use [#]	0.79 (0.42 – 1.49)	0.46
Homelessness [#]	1.04 (0.63 – 1.72)	0.87
Cocaine/ heroin use ⁺	1.58 (0.98 – 2.55)	0.06

HR (95% CI): Hazard ratio (95% Confidence Interval);

[&] <200 cells/ mm³;

^{*} last 30 days;

[#] past 6 months,

⁺ past 12 months at baseline and past 6 months at each follow-up visit.

Table 4

Multivariable analysis of the association between HCV infection and liver-related mortality in HIV-infected adults with current or past alcohol problems

	HR (95% CI)	p-value
HCV infection	3.24 (1.18 – 8.94)	0.02
Female gender	1.58 (0.69 – 3.62)	0.28
Black race	1.04 (0.46 – 2.34)	0.92
CD4 cell count ^{&}	2.79 (1.27 – 6.15)	0.01
Heavy alcohol use [*]	0.81 (0.33 – 2.00)	0.65
Cocaine/ heroin use ⁺	2.29 (1.01 – 5.18)	<0.05

HR (95% CI): Hazard ratio (95% Confidence Interval);

[&] <200 cells/ mm³;

^{*} last 30 days;

⁺ past 12 months at baseline and past 6 months at each follow-up visit.