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ORIGINAL RESEARCH

Hepatitis C virus coinfection and the risk of cardiovascular disease among HIV-infected patients

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Background

Among HIV-infected patients, hepatitis C virus (HCV) coinfection is associated with lower cholesterol levels, but it remains unclear how it affects cardiovascular outcomes.

Methods

We performed logistic regression to evaluate acute myocardial infarction (AMI) and cerebrovascular disease (CVD) events by HCV status among HIV-infected US veterans in the highly active antiretroviral therapy (HAART) era (1996–2004). We then performed survival analyses to evaluate incident AMI and CVD, exploring antiretroviral therapy (ART) as a time-dependent variable.

Results

A total of 19 424 HIV-infected patients [31.6% of whom were HCV-coinfected (HIV/HCV)] contributed 76 376 patient-years of follow-up. HCV coinfection was associated with lower rates of hypercholesterolaemia (18.0% in HIV/HCV *vs.* 30.7% in HIV-only patients; $P<0.001$), but higher rates of hypertension (43.8% *vs.* 35.6%; $P<0.0001$), type 2 diabetes mellitus (16.2% *vs.* 11.1%; $P<0.0001$) and smoking (36.7% *vs.* 24.7%; $P=0.009$). Rates of AMI and CVD were significantly higher among HIV/HCV than HIV-only patients: 4.19 *vs.* 3.36 events/1000 patient-years, respectively ($P<0.001$), for AMI; and 12.47 *vs.* 11.12 events/1000 patient-years, respectively ($P<0.001$), for CVD. When analyses were controlled for diabetes mellitus, hypertension, age and duration of ART, hazard ratios (HRs) among those with HIV/HCV (*vs.* HIV only) were 1.25 [95% confidence interval (CI) 0.98–1.61; $P=0.072$] for AMI and 1.20 (CI 1.04–1.38; $P=0.013$) for CVD. Hypertension (HR 2.05; $P<0.001$), greater age (HR 1.79; $P<0.001$) and longer duration (cumulative years) of antiretroviral use (HR 1.12; $P=0.0411$) were also associated with increased risk of AMI in the adjusted model.

Conclusions

In the HAART era, HCV coinfection was associated with a significantly increased risk of CVD and a trend towards an increased risk of AMI among HIV-infected patients.

Keywords: acute myocardial infarction, cerebrovascular disease, hepatitis C, highly active antiretroviral therapy, incidence

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Introduction

The increase in overall survival of HIV-infected patients has been associated with a shift in underlying cause of death, with decreased representation of AIDS-related causes and increased representation of non-AIDS-related deaths, which rose by 33% in one recent series [1]. The most prevalent non-AIDS-related causes of morbidity and mortality are chronic liver disease, metabolic complications including cardiovascular disease, and non-AIDS-defining malignancies [1–3].

It has been estimated that 15 to 30% of all HIV-infected persons are also infected with the hepatitis C virus (HCV) [4,5]. The percentage of HIV-infected patients coinfected with HCV was found to vary significantly in previous studies depending on risk factors, from as low as 4% among HIV-infected non-drug users to as high as 89% among HIV-infected injecting drug users (IDUs) [4–7]. It is now well established that there is a significantly elevated risk of severe liver disease in persons who are coinfected

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with HIV and HCV [8], but extrahepatic complications of HCV infection [9] are less well studied in the HIV-infected population.

Among HIV-infected patients, HCV coinfection has been shown to be associated with higher rates of several metabolic complications including lipodystrophy [10], hepatic steatosis and nonalcoholic fatty liver disease (NAFLD) [11], metabolic syndrome [12], glucose intolerance and diabetes [13,14]. Conversely, a growing body of literature shows that HCV infection has been associated with lower rates of HIV- and highly active antiretroviral therapy (HAART)-associated dyslipidaemias among HIV-infected patients, with lower mean total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) [10,15–21]. Also, patients with chronic HCV monoinfection have lower rates of lipid abnormalities than age- and sex-matched healthy subjects [22], and LDL-C concentrations were inversely correlated with the severity of liver disease [23]. Hepatitis C has also been associated with lower C-reactive protein (CRP) levels in both HIV-negative and HIV-positive subjects [24,25]. The beneficial impact of HCV coinfection on lipids and CRP – two independent predictors of cardiovascular disease – has led some to postulate that HCV coinfection may, to some extent, ameliorate the increased cardiovascular risk associated with HIV infection and HAART use [24].

However, beyond atheroma formation (to which dyslipidaemia contributes), endothelial dysfunction and thrombosis are generally accepted as the proximate steps of atherogenesis, and knowledge of the role of biomarkers for these two processes is expanding [26]. HCV coinfection during HIV treatment (but not among antiretroviral-naïve subjects) is associated with higher values for some biomarkers of early atherosclerosis, suggesting, by extension, that coinfection in treated but not untreated patients raises patients' risk for cardiovascular disease [27].

Small epidemiological studies have yielded conflicting results on the association of HCV infection and cardiovascular disease in the general population [28] and HIV-infected patients [29]. We utilized the Department of Veterans Affairs HIV Clinical Case Registry to elucidate the impact of HIV/HCV coinfection on incident cardiovascular disease adjusting for traditional cardiac risk factors.

Methods

Sources of data

Our source of data was the HIV Clinical Case Registry (CCR) of the Veterans Affairs' (VA) Center for Quality Management for a study period of 1984–2004 [30]. This registry is created by aggregating data from patient with a diagnosis of HIV disease seen at each VA facility into a national database. ''Snapshots'' extracts of the CCR national database - such as the one used in this analysis - are created on an annual basis. The CCR is both a registry at every VA facility to support local care delivery and a national clinical database. The CCR database aggregates data from all facilities to the unique patient level. It compiles very detailed data on HIV-infected patients' demographics, diagnoses, laboratory tests, and clinic and drug utilization. For the current analysis, only patients who entered the registry in the HAART era (1996–2004) were included.

Exposure

We used diagnostic codes and HCV antibody tests to identify patients with HCV coinfection. We included the following International Classification of Diseases (ICD-9) codes when they appeared as one of the listed discharge diagnoses: 070.41, 'acute hepatitis C with hepatic coma'; 070.44, 'chronic hepatitis C with hepatic coma'; 070.51, 'acute hepatitis C without mention of hepatic coma'; 070.54, 'chronic hepatitis C without mention of hepatic coma'; V02.62, 'hepatitis C carrier'. A validation study previously showed that the presence of an HCV code was 94% predictive of a positive HCV laboratory test result, while the absence of a code was 90% predictive of the absence of a positive test result. Of all patients with HIV infection in the VHA CCR, 96% were tested for HCV [31].

Lipid profiles were extracted from each patient's records, including TC and TG levels. For patients with more than one measurement of the lipid profile during the study period, the measurement with the highest level of TC and TG was used, regardless of lipid-lowering therapy history. These laboratory measures were used to classify patients as having hypercholesterolaemia and/or hypertriglyceridaemia.

The proportion of patients with other known cardiovascular risk factors, including hypertension, type 2 diabetes mellitus and smoking status, was calculated in HIV/HCV-coinfected and HIV-monoinfected patients. Patients' records were reviewed for the presence of the following ICD-9 codes when they appeared as one of the listed discharge diagnoses: 401, 'essential hypertension'; 250.0, 'diabetes mellitus without mention of complication' (except when the fifth digit was 1 or 3, indicating 'type 1 diabetes mellitus'); 250.1 to 250.9, 'diabetes mellitus with complications'; 305.1, 'tobacco use disorder'; V15.82, 'history of tobacco use'.

Data on the use of antiretroviral and lipid-lowering medications were also extracted. We calculated the duration of use of medications by estimating the number of days covered by each prescription.

Outcomes

We report on two outcomes: incident acute myocardial infarction (AMI) and incident cerebrovascular disease (CVD; transient ischaemic attacks or strokes). We included the following ICD-9 codes when they appeared as one of the listed discharge diagnoses: 410, 'AMI,' except with a fifth digit of 2 (indicating a subsequent instead of initial episode of care); 433, 'occlusion and stenosis of precerebral arteries'; 434, 'occlusion of cerebral arteries'; 436, 'acute but ill-defined CVD'; 437.0, 'cerebral atherosclerosis'; 437.1, 'other generalized ischemic CVD'; 431, 'intracerebral haemorrhage'; and 435, 'transient cerebral ischemia'.

Statistical analysis

Our analysis was limited to the patients enrolled in the database from 1996 to 2004 (the HAART era). We defined the start of the follow-up period as the date of first receipt of care for HIV infection at a VA facility from the date of registration in the CCR, the date of the first HIV-related laboratory test, or the date of a clinic visit or hospital admission; whichever came first. We performed time-to-event modelling using the interval from the start of the follow-up period to 31 December 2004, or 6 months after care was last received at a VA facility.

The percentages of HIV-infected and HIV/HCV-coinfected patients with hypercholesterolaemia (defined as TC $\geq$ 240 mg/dL) and hypertriglyceridaemia (defined as serum TG $\geq$ 200 mg/dL) were calculated. To account for the fact that some previously dyslipidaemic patients could have normalized lipid profiles during the period of observation because they were receiving lipid-lowering medications, we calculated a composite endpoint combining patients with laboratory evidence of dyslipidaemia (hypercholesterolaemia and/or hypertriglyceridaemia) with those on lipid-lowering therapy.

Baseline characteristics were compared using the χ^2 test or the *t*-test as appropriate. Rates of AMI and CVD among HIV-monoinfected and HIV/HCV-coinfected patients were calculated. Logistic regression models were fitted to model whether or not a patient experienced an event (AMI or CVD separately). Cox proportional hazards models were fitted to model the time until an event (AMI or CVD separately). Univariate and multivariate models were fitted for the dichotomous (logistic regression) and time-to-event (Cox proportional hazards) analyses. The multivariate models included the traditional cardiovascular risk factors of age, diabetes mellitus, hypertension and smoking. Additionally, the Cox proportional hazards models included antiretroviral therapy (ART) as a time-varying covariate. All analyses were performed using SAS v9.13 (SAS Institute, Cary, NC, USA).

Results

Study population

We identified 19 424 patients who used VA services for HIV disease during the study period. The mean duration of follow-up was 3.93 years, and total follow-up was 76 376 patient-years. The mean age at registry entry was 46.2 years [standard deviation (SD) 10.2 years]. The proportion of males was 97.5%. The reported primary HIV risk factors were homosexual contact (19%), IDU (10%), heterosexual contact (9%), and multiple, unknown or unreported (62%). A total of 15 000 (77%) patients have received any ART for at least 30 days during the follow-up period. Mean treatment duration was 1.93 (SD 2.07) years.

During the entire period of observation, 26.5 and 53.7% of the patient population met our definition for hypercholesterolaemia and hypertriglyceridaemia, respectively. A higher proportion (62.2%) had either hypercholesterolaemia or hypertriglyceridaemia, or were on lipid-lowering therapy. The proportions of patients with hypertension, type 2 diabetes mellitus and current or past smoking history were 38.2, 12.7 and 28.5%, respectively.

Correlates of HCV coinfection

A total of 6136 patients (31.6%) were coinfected with HIV and HCV (HIV/HCV). Table 1 summarizes the characteristics of our patients with HIV infection only and with HIV/HCV coinfection.

HCV coinfection, dyslipidaemia and other cardiovascular risk factors

In univariate analysis, HCV coinfection was associated with a significantly reduced prevalence of hypercholesterolaemia (18.0% in HIV/HCV *vs.* 30.7% in HIV-only patients; $P<0.001$) and hypertriglyceridaemia (49.6% *vs.* 55.7%; $P<0.001$). Coinfected patients were also less likely to meet the composite endpoint of laboratory-defined dyslipidaemia or being on lipid-lowering therapy (55.6% *vs.* 65.4%; $P<0.001$).

HCV-coinfected patients were significantly more likely than HIV-monoinfected patients to have a diagnosis of hypertension (43.8% *vs.* 35.6%, respectively; $P<0.0001$) or type 2 diabetes mellitus (16.2% *vs.* 11.1%; $P<0.0001$) or to have a past or current smoking history (36.7% *vs.* 24.7%; $P<0.0001$). The proportions of HIV-monoinfected and HIV/HCV-coinfected patients with antiretroviral exposure were virtually identical (80.0 and 79.9%, respectively). The mean duration of ART exposure was slightly lower in HIV/HCV-coinfected than in HIV-monoinfected patients (1.87 years *vs.* 1.96 years, respectively; $P=0.006$).

AMI and CVD rates and risk factors among HIV-monoinfected and HIV/HCV-coinfected patients

During the observation period, representing 76 376 patient-years, a total of 278 AMIs were diagnosed; 171 among HIV-monoinfected and 107 among HIV/HCV-coinfected patients. Rates of AMI were significantly higher among HIV/HCV-coinfected patients than HIV-monoinfected patients: 4.19 *vs.* 3.36 events/1000 patient-years, respectively ($P<0.001$). During the same period, 868 CVDs were diagnosed; 555 in HIV-monoinfected and 313 in HIV/HCV-coinfected patients. Rates of CVD were also significantly higher among HIV/HCV-coinfected patients: 12.47 *vs.* 11.12 events/1000 patient-years for HIV/HCV-coinfected and HIV-monoinfected patients, respectively ($P<0.001$).

Unadjusted hazard ratios (HRs) for AMI and CVD associated with HCV coinfection (*vs.* HIV monoinfection) were 1.25 [95% confidence interval (CI) 0.98–1.59; $P=0.075$] and 1.12 (95% CI 0.98–1.29; $P=0.105$), respectively (Table 2). In multivariate Cox proportional hazards analysis controlling for hypertension, type 2 diabetes mellitus, age, tobacco use and duration of antiretroviral use, HCV coinfection was independently associated with CVD (adjusted HR 1.20; 95% CI 1.04–1.38; $P=0.013$). Its association with AMI was not statistically significant (HR 1.25; 95% CI 0.98–1.61; $P=0.072$).

Other factors associated with AMI in the multivariate model included greater age (HR 1.79 for each 10-year increment; 95% CI 1.60–2.01; $P<0.001$), hypertension (HR 2.05; 95% CI 1.57–2.67; $P<0.001$), and longer duration of ART (HR 1.12 for each year of use; 95% CI 1.01–1.25; $P=0.0411$). Type 2 diabetes mellitus was associated with increased risk of AMI in unadjusted analysis (HR 1.75; 95% CI 1.32–2.32) but not in the adjusted model (HR 1.01; 95% CI 0.76–1.35). Smoking was also not associated with increased risk of AMI (HR 1.01; 95% CI 0.78–1.30).

Table 1 Patient characteristics

	HIV-monoinfected ($n=13\,288$)	HIV/HCV-coinfected ($n=6136$)	*P*-value
Demographics			
Age (years) [mean (SD)]	45.82 (11.25)	47.00 (7.31)	0.50
Race/ethnicity (%)			<0.001
White	47.59	27.50	
Black	42.76	61.34	
Other	9.65	11.16	
Male (%)	97.28	97.98	0.004
*Mean laboratory values (SD)**			
Highest serum cholesterol (mg/dL)	218.03 (70.60)	195.12 (59.63)	<0.0001
Highest triglyceride (mg/dL)	331.06 (352.99)	275.53 (274.15)	<0.0001
Highest LDL cholesterol (mg/dL)	130.82 (45.18)	111.39 (44.25)	<0.0001
Highest HbA1C	6.44 (2.24)	6.78 (2.54)	<0.0001
Lowest CD4 count during follow-up period (cells/μL)	229.78 (234.96)	213.32 (221.87)	<0.0001
Highest viral load (copies/mL)	170 228 (267 356)	160 678 (285 285)	0.0878
Prevalence of comorbidities (cardiovascular risk factors)			
ART exposure (%)	79.99	79.91	0.903
Time on ART (years) [mean (SD)]	1.96 (2.10)	1.87 (2.00)	0.006
Hypercholesterolaemia (%)	30.70	17.95	<0.0001
Hypertriglyceridaemia (%)	55.68	49.59	<0.0001
Dyslipidaemia or on lipid-lowering drugs (%)	65.41	55.63	<0.0001
Hypertension (%)	35.60	43.82	<0.0001
Diabetes (%)	11.13	16.17	<0.0001
Smokers (former and current) (%)	24.74	36.69	<0.0001

ART, antiretroviral therapy; HCV, hepatitis C virus; LDL, low-density lipoprotein; SD, standard deviation; HbA1C, glycosylated haemoglobin.
*Mean values during the period of observation.

Table 2 Acute myocardial infarction (AMI) and cerebrovascular disease (CVD) risk by hepatitis C virus (HCV) status

Event	Patient group	Number of events	Patient-years (×1000)	Event rate	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
AMI	HIV	171	50.86	3.36	1.25 (0.98–1.59) $P=0.075$	1.25 (0.98–1.61) $P=0.072$
	HIV/HCV	107	25.54	4.19		
CVD	HIV	555	49.90	11.12	1.12 (0.98–1.29) $P=0.105$	1.20 (1.04–1.38) $P=0.013$
	HIV/HCV	313	25.10	12.47		

HIV, HIV-monoinfected patients; HIV/HCV, HIV/HCV-coinfected patients.
*Adjusted for hypertension, age, type 2 diabetes and tobacco use.

In addition to HCV, factors associated with CVD in multivariate analysis were greater age (HR: 1.65; 95% CI 1.54–1.76; $P<0.001$) and hypertension (HR 1.48; 95% CI 1.28–1.75; $P<0.001$). Type 2 diabetes mellitus again was associated with increased risk of CVD in unadjusted analysis (HR 1.56; 95% CI 1.32–1.85) but not in the adjusted model (HR 1.05; 95% CI 0.88–1.25). Duration of ART was not associated with CVD in the adjusted or unadjusted models.

Discussion

Our data show that, in the HAART era, HCV coinfection is independently associated with a significantly increased risk of CVD and a trend towards an increased risk of AMI among HIV-infected patients. In the general population, Kalantar-Zadeh *et al.* [32] found HCV infection to be associated with higher all-cause and cardiovascular mortality among dialysis patients. Conversely, Arcari *et al.* found no association between HCV infection and AMI in young military recruits [33]. The finding is, however, hardly reassuring given the presumed level of physical fitness of the cohort.

Our data are consistent with a recently published analysis comparing a large cohort of 82 083 HCV-monoinfected veterans with 89 582 HCV-negative control subjects. Despite a favourable risk profile – younger age, lower lipid levels and lower prevalence of hypertension – HCV infection was associated with a higher risk of coronary artery disease after adjustment for traditional risk factors (HR 1.25; 95% CI 1.20–1.30) [34]. The current study suggests that these findings regarding HCV infection and cardiovascular disease also extend to patients with HIV infection.

To date, there have been limited and contradictory findings on the role of HCV coinfection on the cardiovascular risk of HIV-infected patients. Analysis of the D:A:D cohort data recently found similar rates of AMI between HIV/HCV-coinfected and HIV-monoinfected patients, as in our cohort: 3.32 (95% CI 2.96–3.69) and 2.73 (95% CI 2.17–3.29) per 1000 patient-years, respectively; the difference was not statistically significant [14].

Conversely, in a cross-sectional analysis of a cohort of 395 HIV-infected patients with current or past alcohol abuse, Freiberg *et al.* [29] found that coinfection with HCV was associated with self-reported history of cardiovascular disease. This study was limited by the small sample size and had other limitations, including self-report of the outcome variable and several other covariates, and the fact that all study subjects had alcohol problems, reducing the generalizability of the study findings. Accordingly, the current study addresses a knowledge gap and provides important data germane to HIV treatment in the light of the high prevalence of HCV coinfection.

With the longer survival of HIV-infected patients and the higher representation of non-AIDS events – including cardiovascular disease – as causes of morbidity and mortality among these patients, studies have mainly focused on the impact of ART and HIV infection itself as potential cardiovascular risk factors. The mechanisms underlying the association of HCV and cardiovascular diseases remain to be elucidated. HCV infection might be associated with a higher prevalence of traditional cardiovascular risk factors.

Our results also confirm previous observations that HCV coinfection is associated with lower rates of both hypercholesterolaemia and hypertriglyceridaemia. HCV appears to protect against the HAART-associated risk of developing hypercholesterolaemia. However, HCV coinfection was also associated with higher rates of other traditional cardiovascular risk factors, including hypertension and type 2 diabetes mellitus. As mentioned above, the association of HCV coinfection with AMI remained after controlling for these risk factors, suggesting another potential mechanism.

Recent evidence suggests that HCV coinfection might contribute to atherogenesis. In the general population, HCV infection has been found to be a risk factor for carotid atherosclerosis [35]. Vassalle *et al.* [36] reported that HCV seropositivity represented an independent predictor of coronary artery disease after adjusting for confounding risk factors [odds ratio (OR) 4.2; 95% CI 1.4–13.0]. Also, Ishizaka *et al.* [37] reported an independent association between HCV seropositivity and the presence of carotid artery plaque (OR 2.21; 95% CI 1.80–2.72) and thickening of the intima media (OR 4.18; 95% CI 3.39–5.14). HIV/HCV-coinfected patients receiving ART were found to have significant pro-atherogenic changes in endothelial status compared with HIV-monoinfected patients [27].

As expected, traditional risk factors such as greater age, diabetes, and high blood pressure predicted an increased risk of AMI or stroke. Unexpectedly, smoking was not associated with an elevated risk of cardiovascular disease. This surprising lack of association may be attributable to the incomplete and/or inaccurate data on present and past smoking in the database. Unlike our endpoint and the other covariates (including HCV, diabetes and hypertension), smoking status is not automatically recorded as a discharge diagnosis. It mainly tends to be recorded when counselling for smoking cessation was provided, and the recorded rate of former and current smokers (20.83%) is very likely to be a significant underreporting. Crothers *et al.* [38] found (through a self-administered questionnaire) over three times this rate of current or past smoking history (75%) in HIV-infected veterans. Incompleteness of smoking

information (a major cardiovascular risk) is therefore a major limitation of our study.

Beyond the above-mentioned likelihood of incompleteness or inaccuracies in the diagnostic codes, the retrospective nature of the study also precludes thorough control for potential unmeasured confounders, and the determination of causation. Further, as the population is almost exclusively male, it is unclear whether the findings will apply to female patients.

Strengths of our study include the large sample size from a well-defined cohort for which there is uniform data collection. The completeness of the data from the CCR, including laboratory values, drug dispensation and diagnoses (the accuracy of which has been validated, as mentioned above), allows a very thorough investigation of HIV-related outcomes.

In conclusion, we identified an independent association of HCV infection and cerebrovascular events, and a trend towards an association of HCV and AMI in HIV-infected VA patients when the analyses were controlled for traditional cardiac risk factors. With the very high prevalence of HCV coinfection, should it be confirmed as an independent predictor of cardiovascular events in other cohorts, it would be prudent to control for HCV infection in future studies of cardiovascular events among HIV-infected patients. Future research is needed to better elucidate the mechanisms by which HCV increases cardiovascular risk, particularly among those with HIV coinfection. Our findings also suggest that it is reasonable to consider HCV coinfection, among other comorbidities, in management decisions, including decisions on the timing and choice of antiretrovirals, and when monitoring for complications.

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