

Hepatitis C Infection and the Risk of Non-Liver-Related Morbidity and Mortality in HIV-Infected Persons in the Swiss HIV Cohort Study

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(See the Editorial Commentary by Lo Re on pages 498–500.)

Background. Hepatitis C virus (HCV) infection has been associated with increased non-liver-related morbidity and mortality. However, studies have yielded inconsistent results.

Methods. The incidence of clinical events in human immunodeficiency virus (HIV)-infected HCV-seropositive and incidence density-matched HCV-seronegative participants of the Swiss HIV Cohort Study from August 1994 to December 2014 was studied. We compared (1) HCV-seropositive with HCV-seronegative participants and (2) HCV-viremic with successfully treated nonviremic patients. Poisson regression was used to assess differences between these groups.

Results. We included 2503 HCV-seropositive participants (540 with spontaneous HCV clearance, 1294 untreated HCV RNA positive, 345 treated with sustained virologic response [SVR], 43 during treatment, and 281 treated without SVR), and 2503 HCV-seronegative controls. After a mean follow-up of 8.2 years, we observed (HCV seropositive and HCV seronegative, respectively) 107 and 18 liver events, 41 and 14 kidney events, 230 and 121 osteoporosis/fractures, 82 and 94 diabetes mellitus, 114 and 129 cardiovascular events, 119 and 147 non-AIDS malignancies, 162 and 126 Centers for Disease Control and Prevention HIV category B/C events, 106 and 10 liver-related deaths, and 227 and 218 non-liver-related deaths. Compared with HCV-negative controls, HCV-seropositive participants had an increased risk of liver events (incidence rate ratio [IRR], 6.29 [95% confidence interval {CI}, 3.52–11.22]), liver-related death (IRR, 8.24 [95% CI, 3.61–18.83]), kidney events (IRR, 2.43 [95% CI, 1.11–5.33]), and osteoporosis/fracture (IRR, 1.43 [95% CI, 1.03–2.01]). Among HCV-seropositive individuals, treated participants without SVR vs those with SVR had a higher risk of liver events (IRR, 6.79 [95% CI, 2.33–19.81]), liver-related death (IRR, 3.29 [95% CI, 1.35–8.05]), and diabetes mellitus (IRR, 4.62 [95% CI, 1.53–13.96]). Similar but not statistically significant differences were found between untreated HCV RNA-positive patients and those with SVR.

Conclusions. While HCV exposure was associated with an increased risk of kidney disease and osteoporosis/fracture, this risk did not seem to be dependent of persistent HCV RNA. Successful HCV treatment was associated with a lower incidence of liver disease, liver-related death, and diabetes mellitus, whereas the other conditions studied were less affected.

Keywords. HCV; HIV; non-liver-related comorbidity; mortality; extrahepatic disease.

Prevalence of hepatitis C virus infection (HCV) is high among people living with human immunodeficiency virus (HIV), with rates of up to 30% in some regions [1]. It is a major health

issue as it often leads to end-stage liver disease and death [2]. In addition to the burden of liver disease, chronic HCV infection has been associated with a number of extrahepatic manifestations. HCV-related autoimmune and lymphoproliferative diseases, including cryoglobulinemia and lymphomas, were documented soon after HCV discovery [3]. More recently, reports on other non-liver-related HCV-associated manifestations have been published [4, 5]. The current literature supports the view that risk of metabolic alterations, including hypercholesterolemia, insulin resistance, and diabetes mellitus, is increased in HCV infection [6]. Associations between HCV and the development of chronic kidney disease and bone-related and cardiovascular events have been suggested,

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although large cohort studies have yielded conflicting results [4, 5]. A Spanish study found that HCV eradication after treatment in HIV/HCV-coinfected patients was associated not only with a reduction in liver-related but also with a reduction in non-liver-related mortality [7].

Multiple factors may mediate the association between HCV and non-liver-related comorbidities. In addition to the contribution of progressive liver disease and lifestyle-related risk factors associated with HCV exposure, including intravenous drug use, alcohol use, and poor nutrition, HCV itself has been postulated as a contributing cause by promoting immune activation, systemic inflammation, and oxidative stress.

With the advent of direct-acting antivirals (DAAs) offering high cure rates within 12–24 weeks, the landscape of HCV treatment has changed dramatically. In most countries, access to these drugs is restricted to persons with advanced liver fibrosis due to their high costs. In this context, it is of major importance to determine whether therapeutic HCV eradication has an effect on non-liver-related morbidity and mortality in addition to the benefit on the liver and to conceive whether HIV/HCV-coinfected patients may benefit from HCV treatment independent of liver disease.

Many studies have evaluated the association between HCV seropositivity and non-liver-related diseases. To assess the role of ongoing viral replication independent of behavioral and social characteristics associated with HCV exposure, it is important to investigate the contribution of HCV viremia on extrahepatic morbidity and mortality.

The aims of the study were (1) to explore the contribution of HCV exposure to non-liver-related morbidity and mortality by comparing HCV-seropositive with HCV-seronegative HIV-infected persons, and (2) to investigate whether successful HCV treatment reduces the risk of non-liver-related events and death by comparing HCV-viremic with successfully treated non-viremic persons, within the Swiss HIV Cohort Study (SHCS).

PATIENTS AND METHODS

Swiss HIV Cohort Study

The SHCS is an ongoing, prospective cohort study that continuously enrolls and observes HIV-infected adults at 5 university outpatient clinics, 2 large district hospitals, affiliated regional hospitals, and private practices, since 1988. This nationwide cohort covers 69% of all patients living with AIDS, and 75% of persons receiving antiretroviral therapy (ART) in Switzerland [8, 9]. Demographic, clinical, and laboratory data are collected at registration and every 6 months thereafter using a standard protocol. This includes detailed structured information on nicotine, alcohol, and intravenous drug use. In a previous study, we assessed the long-term epidemiological trends in treatment uptake, efficacy, and mortality among HCV-coinfected SHCS participants [2]. This study focuses on assessing nonhepatic events among this patient group. The protocol was approved by

local ethical review boards, and written informed consent was obtained from all participants.

Laboratory Measurements and Data Collection

All SHCS participants are routinely screened for HCV antibodies at study entry. Since 1998, serology is repeated every second year of follow-up in participants with previously negative results. In persons with risk factors (ongoing intravenous drug use, sexually active men who have sex with men) HCV serology is done every year. Starting routinely in 2002, quantitative HCV RNA measurements and HCV genotype determination were undertaken in HCV-seropositive persons. The information on treatment history and outcomes of HCV infection, retrieved from the SHCS database, was ascertained and completed by a retrospective medical record review using a structured questionnaire.

Within the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cohort collaboration cardiovascular end points, diabetes mellitus, renal disease, liver disease, and non-AIDS-defining malignancies are prospectively collected, regularly monitored, and centrally adjudicated [10]. Within the SHCS, HIV-associated opportunistic infections and bone-related events are documented. Information on causes of death have been prospectively collected using the Cause of Death (CoDe) in HIV protocol, which is specifically designed for classifying causes of death in HIV-infected persons [11].

Selection of Patients

All SHCS participants with at least 1 study visit between August 1994 and December 2014, with available HCV antibody test and, if seropositive, at least 1 HCV RNA test, were included in the analyses. HCV-seronegative control patients were matched 1:1 to seropositive participants by incidence density matching based on cohort inclusion (± 2 years) and last visits (± 2 years). We split follow-up time for each participant as follows: (1) HIV monoinfected; (2) HCV seropositive, untreated with spontaneous clearance; (3) HCV seropositive untreated with HCV RNA positivity; (4) HCV seropositive treated with sustained virologic response (SVR); and (5) HCV seropositive treated without SVR (hereafter, “non-SVR”).

Definitions

SVR was defined as at least 1 negative HCV RNA test ≥ 12 weeks after the end of treatment as described previously [2] and according to standard definition [12]. The noninvasive biomarker of liver fibrosis, FIB-4, was calculated as follows: $(\text{age} \times \text{aspartate aminotransferase}) / [\text{platelet count} (10^9 \text{ cells/L}) \times \text{sqr}(\text{alanine aminotransferase})]$. Advanced fibrosis/cirrhosis was defined as FIB-4 > 3.25 [13]. Undetectable HIV RNA was defined by values < 50 copies/mL. Data on alcohol use were collected by a questionnaire on self-reported alcohol consumption. Severe alcohol abuse was defined according to the World Health Organization definition (female > 40 g/day, male > 60 g/day).

Liver-related events included liver cirrhosis, bleeding from gastric or esophageal varices, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, portal hypertension, ascites, nonalcoholic steatosis hepatitis, and liver transplantation. Kidney disease included permanent dialysis and kidney transplantation. Cardiovascular events included myocardial infarction, cerebral infarction, cerebral hemorrhage, coronary angioplasty, and procedure on other arteries. Deaths were classified as liver related (including acute events complicating cirrhosis and liver cancer), and non-liver related. Events involving other organs than the liver but clearly associated with liver cirrhosis, including variceal hemorrhage and hepatorenal syndrome, were classified as liver related.

Statistical Analysis

A case-cohort study design within the SHCS was chosen. Trends between HCV-seropositive and HCV-seronegative and among the different HCV-seropositive groups were analyzed using nonparametric tests for trend. Follow-up was counted from the beginning of each HCV stage to the date of first diagnosis of a clinical event, the end of the respective HCV stage, or the patient's last cohort visit, whichever occurred first. Thus, HCV-positive patients could contribute follow-up time in different HCV stages. Associations of HCV status and the different clinical events were investigated using univariable and multivariable Poisson regression. Standard errors of Poisson models were calculated using clustered sandwich estimators allowing for intragroup correlation of the matched pairs. Multivariable models were adjusted for HIV acquisition category, age, smoking, alcohol use, active intravenous drug use, and duration of HIV and HCV infection. We

also adjusted for HIV type 1 RNA, which is strongly correlated with ART. However, modeling the large number of individual drugs and different regimens was not feasible, and by incidence density sampling we selected HCV-negative controls who likely had comparable ART exposure. All variables except sex and HIV acquisition category were time-updated. Because only 0.85% of semiannually scheduled follow-up visits had gaps of >1.5 years (ie, 2 missed visits) we did not impute interim data but carried last values of time-updated variables forward. Periods during HCV treatment were also included but are not presented because of low event numbers. We used Stata/SE software version 14.1 (StataCorp, College Station, Texas) for all analyses.

RESULTS

Study Population

Of 2625 HCV-seropositive and 14876 HCV-seronegative SHCS participants followed between August 1994 and December 2014, 2503 HCV-seropositive cases and 2503 matched HCV-seronegative controls were included in the analyses. The HCV-seropositive group included 540 patients with spontaneous clearance, 1294 untreated HCV RNA positive, 345 treated with SVR, 43 during treatment, and 281 treated non-SVR participants (Figure 1). HCV treatment consisted in 90.1% of pegylated interferon plus ribavirin, and in 9.9% of a regimen containing DAAs (87% interferon based).

Characteristics of participants stratified by HCV status at last follow-up visit are displayed in Table 1. HCV-seropositive patients compared with HCV-seronegative patients were more often female (33.7% vs 21.6%), acquired HIV infection more likely by intravenous drug use (68.3% vs 2.3%), were longer HIV infected (median duration, 18.5 vs 16.2 years), had lower

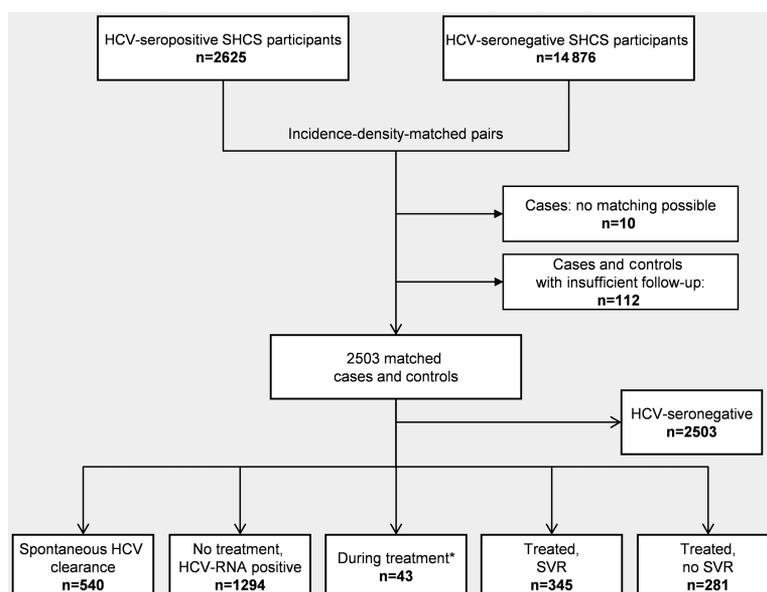


Figure 1. Patient flowchart. *Results of analyses not presented because of low event numbers. Abbreviations: HCV, hepatitis C virus; SHCS, Swiss HIV Cohort Study; SVR, sustained virologic response.

ART use (95.8% vs 97.8%), were more likely to be current smokers (74.1% vs 37.2%) and active intravenous drug users (12.7% vs 0.4%), and more often severely consumed alcohol (13.7% vs 6.2%) ($P < .001$ for all comparisons, not shown in Table 1).

Incidence Rates of Clinical Events and Deaths

After a mean follow-up of 8.2 years, we observed the following events for HCV-seropositive and HCV-seronegative patients, respectively: 107 and 18 liver events, 41 and 14 kidney events, 230 and 121 osteoporosis/fractures, 82 and

94 diabetes mellitus, 114 and 129 cardiovascular diseases, 119 and 147 non-AIDS malignancies, 162 and 126 Centers for Disease Control and Prevention (CDC) HIV category B/C events, 106 and 10 liver-related deaths, and 227 and 218 non-liver-related deaths. Incidence rates (IRs) per 1000 person-years stratified by HCV status are shown in Supplementary Table 2. Mean follow-up was as follows: 8.0 (range, 0.01–16.6) years for untreated patients with spontaneous clearance; 9.2 (range, 0.005–19.1) years for untreated patients with HCV RNA positivity; 5.7 (range, 0.003–12.7) years for those treated with SVR; 6.1 (range, 0.008–12.4)

Table 1. Patient Characteristics of Hepatitis C Virus (HCV)-Infected Swiss HIV Cohort Study Participants Grouped by HCV Status and HCV-Uninfected Controls at Last Follow-up

Characteristic	HCV Positive, Untreated		HCV Positive, Treated		HCV Negative
	HCV RNA Negative	HCV RNA Positive	SVR	No SVR	
No. of patients	540	1294	345	281	2503
Male sex	318 (58.9)	850 (65.7)	250 (72.5)	212 (75.4)	1961 (78.4)
Age, y, median (IQR)	48 (42–52)	46 (41–52)	49 (43–53)	50 (45–55)	50 (44–58)
HIV acquisition					
MSM	65 (12.0)	114 (8.8)	65 (18.8)	44 (15.7)	1511 (60.4)
IDU	362 (67.0)	930 (71.9)	204 (59.1)	185 (65.8)	58 (2.3)
Heterosexual	99 (18.3)	218 (16.9)	60 (17.4)	44 (15.7)	857 (34.2)
Other	14 (2.6)	32 (2.5)	16 (4.6)	8 (2.9)	77 (3.1)
Years HIV infected, median (IQR)	18.4 (10.4–25.0)	17.4 (9.8–23.8)	20.9 (12.3–26.8)	21.2 (13.2–26.0)	16.2 (9.9–21.5)
Prior AIDS	120 (22.2)	302 (23.3)	71 (20.6)	56 (19.9)	553 (22.1)
CD4 count, cells/ μ L, median (IQR)	549 (368–759)	451 (280–678)	592 (443–805)	523 (360–746)	543 (371–753)
CD4 count <200 cells/ μ L	46 (8.5)	204 (15.8)	10 (2.9)	19 (6.8)	208 (8.3)
On antiretroviral therapy	510 (94.4)	1236 (95.5)	337 (97.7)	275 (97.9)	2448 (97.8)
With HIV RNA undetectable	436 (80.7)	983 (76.0)	316 (91.6)	248 (88.3)	2099 (83.9)
Years HCV infected, median (IQR)	13.9 (7.7–20.0)	13.0 (7.4–18.4)	15.6 (9.9–20.6)	16.0 (10.9–20.9)	...
HCV genotype					
1	21 (3.9)	465 (35.9)	86 (24.9)	118 (42.0)	...
2	0	29 (2.2)	9 (2.6)	4 (1.4)	...
3	21 (3.9)	203 (15.7)	126 (36.5)	47 (16.7)	...
4	6 (1.1)	193 (14.9)	17 (4.9)	30 (10.7)	...
Other/unknown	492 (91.1)	404 (31.2)	107 (31.0)	82 (29.2)	...
HCV RNA ^a					
Available	525 (97.2)	1132 (90.6)	299 (86.7)	228 (81.1)	...
>800000 IU/mL	20 (3.8)	535 (47.3)	150 (43.5)	124 (54.4)	...
FIB-4 liver fibrosis score					
Available	500 (92.6)	1121 (86.6)	340 (98.6)	270 (96.1)	2231 (89.1)
>3.25 ^b	35 (6.5)	221 (17.1)	22 (6.4)	99 (35.2)	97 (3.9)
Active HBV	59 (10.9)	60 (4.6)	21 (6.1)	13 (4.6)	164 (6.6)
Body mass index, kg/m ² , median (IQR)	22.5 (20.2–25.6)	22.1 (19.8–25.1)	22.7 (20.4–25.2)	23.3 (20.8–26.5)	23.7 (21.4–26.4)
Smoking					
Current	393 (72.8)	1029 (79.5)	216 (62.6)	185 (65.8)	930 (37.2)
Former	107 (19.9)	187 (14.5)	87 (25.2)	65 (23.1)	762 (30.4)
Never	40 (7.4)	78 (6.0)	42 (12.2)	31 (11.0)	811 (32.4)
Active intravenous drug use	56 (10.4)	217 (16.8)	19 (5.5)	21 (7.5)	9 (0.4)
Severe alcohol consumption	70 (13.0)	198 (15.3)	40 (11.6)	29 (10.3)	155 (6.2)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, intravenous drug user; IQR, interquartile range; MSM, men who have sex with men; SVR, sustained virologic response.

^aHCV RNA highest value ever measured (in cases without HCV RNA values, only qualitative measurements available).

^bA FIB-4 score >3.25 is indicative for advanced fibrosis/cirrhosis [13].

years for those treated without SVR; and 8.3 (range, 0.02–21.7) years for HIV-monoinfected patients.

Among the HCV-seropositive participants, 412 of 2460 patients (16.7%) died. Main causes of death were liver related (31.8%), sepsis (15.9%), substance abuse (15.4%), HIV/AIDS (14.1%), and non-AIDS malignancies (14.1%), in 333 participants with known causes of death. In the HCV-seronegative group, 283 (11.3%) patients died; the main causes were non-AIDS malignancies (23.4%), HIV/AIDS (16.1%), and cardiovascular diseases (12.4%), in 228 patients with known causes of death.

HCV-Associated Risks of Comorbidities and Death

Comparing HCV-Seropositive Groups Combined to HCV-Seronegative Controls

HCV-seropositive persons had an increased risk of liver disease (adjusted incidence rate ratio [IRR], 6.29 [95% confidence interval {CI}, 3.52–11.22]), liver-related death (IRR, 8.24 [95% CI, 3.61–18.83]), kidney disease (IRR, 2.43 [95% CI, 1.11–5.33]), and osteoporosis/fracture (IRR, 1.43 [95% CI, 1.03–2.01]), compared with HCV-seronegative controls. No evidence for an increased risk in HCV-seropositive persons was found for diabetes mellitus (IRR, 1.27 [95% CI, .83–1.93]), cardiovascular disease (IRR, 0.90 [95% CI, .60–1.34]), non-AIDS malignancy (IRR, 1.07 [95% CI, .75–1.52]), CDC HIV category B/C events (IRR, 1.12 [95% CI, .79–1.60]), and non-liver-related death (IRR, 0.90 [95% CI, .68–1.21]).

Comparing Each of the 4 HCV-Seropositive Groups to HCV-Seronegative Controls

The adjusted IRRs for the development of comorbidities and death for the different HCV-seropositive groups compared to HCV-seronegative controls are shown in Figure 2. HCV-treated non-SVR patients had the highest incidence of liver disease, liver-related death, kidney disease, diabetes mellitus, and CDC HIV category B/C events compared with HCV-seronegative controls. They also had the highest risk of cardiovascular events and non-AIDS malignancies but without reaching statistical significance.

The risk of osteoporosis/fracture was significantly increased in HCV spontaneous clearers and patients with SVR compared to HIV-monoinfected controls. The incidence of non-liver-related death was similar in all of the HCV-seropositive groups compared with HIV-monoinfected controls.

Comparing HCV-Viremic Patients (Untreated HCV RNA Positive and Treated Non-SVR) to Those With SVR

Treated patients with non-SVR vs those with SVR had a higher risk of liver events, liver-related death, and diabetes mellitus. To investigate whether the increased risks in non-SVR participants could be related to advanced liver fibrosis, we additionally adjusted for FIB-4 score. As expected, the risk of liver-related death in non-SVR patients did not remain increased. The difference in incidence of liver events and diabetes remained. HCV-viremic patients (both untreated HCV RNA positive and non-SVR) compared to those with SVR had a trend for an

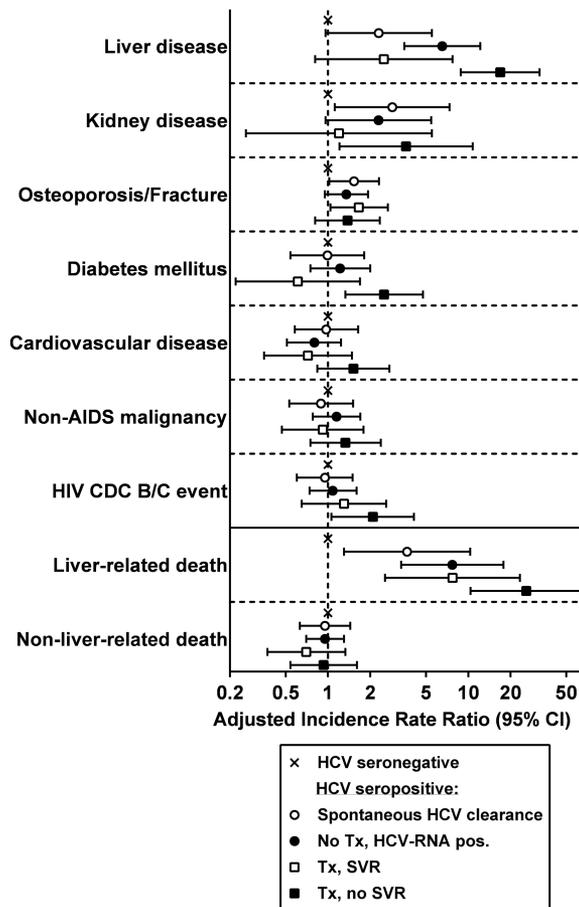


Figure 2. Incidence rate ratios and 95% confidence intervals for the development of clinical events and deaths in multivariable analysis according to hepatitis C virus (HCV) serostatus and HCV stage during a follow-up time period of 8.2 years (mean). Multivariable analysis adjusted for HIV acquisition category, age, HIV-1 RNA, smoking, alcohol use, active intravenous drug use, and duration of HIV and HCV infection. Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR, sustained virologic response; Tx, treatment.

elevated incidence of kidney disease, cardiovascular events, and non-AIDS malignancies but without reaching statistical significance (Figure 3; Supplementary Table 1).

DISCUSSION

In this large nationwide community-based HIV cohort study, HCV exposure was associated with an increased risk of kidney disease and osteoporosis. This risk did not seem to be related to persistent HCV replication. Compared with those with SVR, non-SVR participants had an increased risk of diabetes mellitus. Replicating HCV infection was not associated with other non-liver-related diseases and death. As expected, the risk of liver disease and liver-related death was increased in both HCV-exposed and HCV-viremic patients. SVR caused a 7-fold reduction of liver-related events and a 3-fold reduction in liver-related deaths.

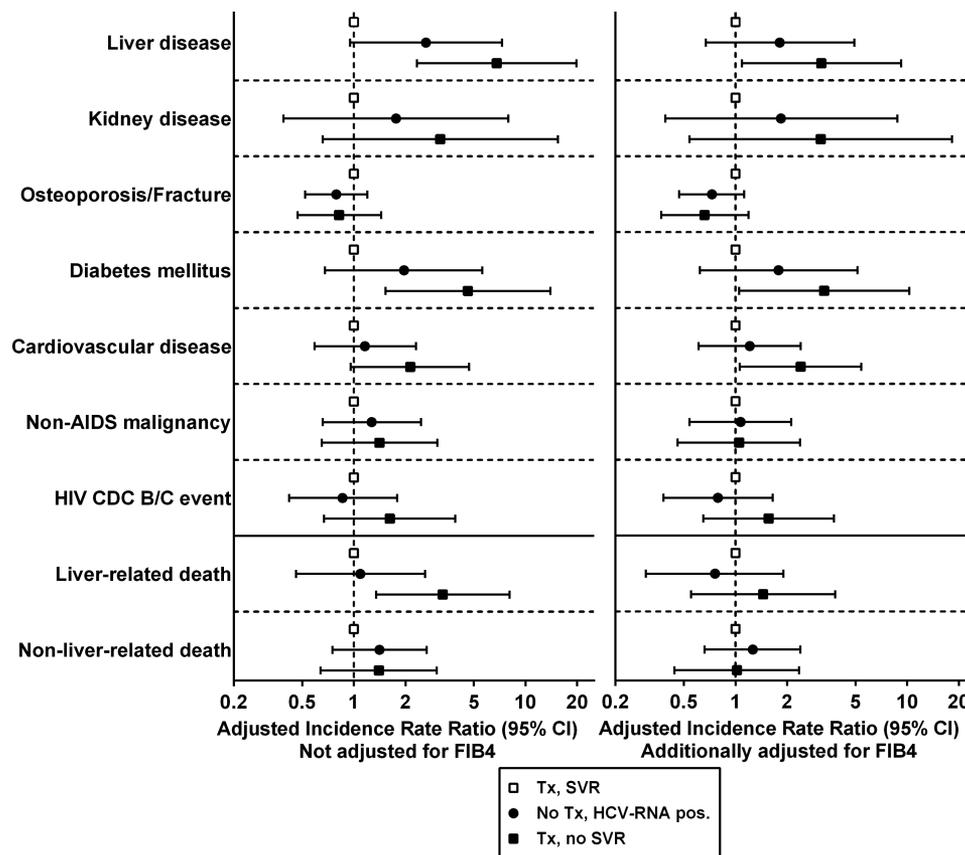


Figure 3. Incidence rate ratios and 95% confidence intervals for the development of clinical events and deaths in multivariable analysis according to hepatitis C virus (HCV) viremia in treated patients during a follow-up time period of 8.2 years (mean). Left: Multivariable analysis adjusted for HIV acquisition category, age, HIV-1 RNA, smoking, alcohol use, active intravenous drug use, and duration of HIV and HCV infection. Right: Additionally adjusted for liver fibrosis stage measured by FIB-4 score. Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR, sustained virologic response; Tx, treatment.

We noted that diabetes mellitus was the only non-liver-related disease associated with replicating HCV infection. In a recently published metaanalysis, diabetes mellitus was the most common extrahepatic manifestation of HCV infection, in addition to depression [14]. In line with our finding, in a Japanese study, achieving viral cure was associated with a significant reduction of developing diabetes [15]. Moreover, HCV eradication has been shown to ameliorate insulin resistance in hepatic tissues and whole body [16, 17]. HCV is considered to be a metabolic virus and is pathophysiologically linked to insulin resistance and type 2 diabetes [6]. Liver cirrhosis aggravates metabolic disorders [6]. Our results, however, indicate that the increased risk of diabetes in HCV-treated nonresponders cannot be solely explained by advanced liver fibrosis.

We found that HCV seropositivity was associated with increased risk of chronic kidney disease in accordance with others [18]. HCV-treated non-SVR participants, but not those with SVR, had an increased risk of kidney events compared with HIV-monoinfected patients. When we compared non-SVR participants with those with SVR, the incidence in kidney disease was elevated but did not reach statistical significance.

In accordance with our findings, two large cohort collaboration groups [19, 20] found an increased risk in replicating but not cleared HCV infection compared with HIV-monoinfected participants. In a similar US and Canadian cohort study, results were contradictory, perhaps due to considerable differences between cohorts regarding patient characteristics [21]. Taken together, these results suggest that in HIV/HCV-coinfected persons, HCV exposure is associated with increased kidney disease risk, most probably due to a high prevalence of traditional renal risk factors in this patient group.

HCV exposure was an independent risk factor for osteoporosis and fracture. However, replicating compared with resolved HCV infection was not associated with bone-related events. Accordingly, several observational studies have shown that HIV/HCV-coinfected patients have an increased fracture incidence compared with HIV-monoinfected and HCV- and HIV-uninfected persons [22, 23]. Hansen et al demonstrated that fracture risk did not differ between viremic vs nonviremic HCV infection [24]. This suggests that osteoporosis and fracture risk in HIV/HCV-coinfected patients is multifactorial and mainly determined by lifestyle-related risk factors associated with HCV

exposure, including illicit drug and alcohol abuse, poor nutrition, increased risk of trauma, and HIV and ART, rather than by HCV itself, and that achieving viral cure of chronic HCV infection will not significantly improve bone health.

We detected a trend of an increased risk of cardiovascular events in HCV nonresponders compared with successfully treated patients. In the current literature, reports regarding the association between chronic HCV infection and cardiovascular disease are conflicting. Although there is evidence that HCV should be considered a risk factor for carotid atherosclerosis, stroke, and heart failure (reviewed in [5, 25]), the association between HCV infection and coronary artery disease remains unclear (reviewed in [26]).

In line with a Spanish HIV/HCV cohort that found an increased frequency of new AIDS-defining events and deaths in HCV treatment nonresponders vs responders [7], we noted an increased risk of CDC HIV category B/C events in non-SVR compared with HIV-monoinfected patients. Non-SVR compared to those with SVR had a higher incidence of HIV/AIDS events, but without reaching statistical significance. As CD4 cell levels and suppression of HIV replication were similar between non-SVR and HIV-monoinfected participants at time of HIV/AIDS events, respectively, at last follow-up (Table 1), this finding cannot be explained by CD4 cell recovery, splenic sequestration in cirrhotic non-SVR patients [27], or control of HIV infection. One might speculate whether failure to achieve SVR might be due to an immunodeficiency predisposing also for HIV/AIDS-related opportunistic conditions.

Extrahepatic mortality was high in HCV-coinfected persons, consistent with our previous observations [2]. In HCV-seropositive participants, only one-third of deaths were liver related. Main causes of extrahepatic death were sepsis, substance abuse, and HIV/AIDS, indicating the important contribution of social and behavioral factors to mortality in this patient group. However, the risk of non-liver-related death in HCV-seropositive vs HCV-seronegative, and HCV-viremic vs nonviremic patients, was similar in adjusted analysis.

The treated non-SVR participants had the highest risk of liver-related and also of non-liver-related events. The prevalence of advanced liver fibrosis was by far the highest in this group (Table 1). When we adjusted for advanced fibrosis, most IRRs decreased, indicating that liver fibrosis is an important contributor to non-liver-related morbidity and mortality.

The strengths of our study include the use of a population-based, nationwide HIV/HCV cohort with a large number of patient-years with prospectively collected laboratory and clinical data, including regular HCV screening and coverage of incident events with use of structured event reporting forms. We were able to compare incidences of diseases and death between HCV-seropositive and demographically

similar HCV-seronegative SHCS participants, and between HCV-viremic and nonviremic patients. Furthermore, to analyze viremia as a time-updated variable allowed us to assess longitudinal effects of spontaneous and treatment-related viral clearance.

Our study has some limitations. Although we adjusted for several potential confounders, we cannot exclude unmeasured confounding. Even with multiple adjustments, there may remain differences between the groups, including socioeconomic status and education. We did not adjust for multiple outcomes and therefore cannot rule out false-positive findings. However, the observed patterns are consistent and pathophysiologically plausible throughout the various end points. The prevalence of less extensive renal disease is likely to be higher as kidney disease was defined by end-stage events, including dialysis and transplantation. As most SHCS participants were of normal weight, in cohorts with more overweight patients, the risk for diabetes and cardiovascular disease may be higher. Finally, in our study most of the HCV therapies consisted of pegylated interferon plus ribavirin. Future studies are expected to show whether the HCV clearance effect achieved by DAAs differs from that of the older regimen.

We conclude that HCV-exposed, HIV-infected individuals have an increased risk of kidney disease and bone-related events that does not seem to be related to persistent viral replication. In addition to a significant decrease of liver-related disease and death, therapeutic viral eradication leads to a reduction of diabetes mellitus. Prospective large-scale cohort collaborations are needed to further describe the impact of HCV eradication with DAAs on non-liver-related morbidity and mortality.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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