Hepatitis C infection and the risk of non-liver-related morbidity and mortality in HIV-positive persons in the Swiss HIV Cohort Study.

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40-word summary: We investigated the association between HCV-infection and non-liver-related morbidity and mortality in HIV-positive persons. While HCV-seropositivity was associated with an increased risk of kidney and bone-related events, replicating HCV-infection was associated with diabetes mellitus, but not with other non-liver-related conditions.

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ABSTRACT (250 words)

Background: 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 HIV-infected HCV-seropositive and incidence-density-matched HCV-seronegative participants of the Swiss HIV Cohort Study from 08/1994 to 12/2014 was studied. We compared firstly, HCV-seropositive with HCV-seronegative participants, and secondly, 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 SVR, 281 treated without SVR, and 2503 HCV-seronegative controls. After a mean follow-up of 8.2 years, we observed 107/18 (HCV-seropositive/HCV-seronegative) liver events, 41/14 kidney events, 230/121 osteoporosis/fractures, 82/94 diabetes mellitus, 114/129 cardiovascular events, 119/147 non-AIDS malignancies, 162/126 HIVCDC B/C events, 106/10 liver-related deaths, and 227/218 non-liver-related deaths. Compared to HCV-negative controls, HCV-seropositive participants had an increased risk of liver events (IRR 6.29[95% CI 3.52-11.22]), liver-related death (8.24[3.61-18.83]), kidney events (2.43[1.11-5.33]), and osteoporosis/fracture (1.43[1.03-2.01]). Among HCV-seropositive individuals, treated participants without SVR versus those with SVR had a higher risk of liver events (6.79[2.33-19.81]), liver-related death (3.29[1.35-8.05]), and diabetes mellitus (4.62[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 while the other conditions studied were less affected.

Key words: HCV, HIV, non-liver-related comorbidity, mortality, extrahepatic disease

INTRODUCTION

Prevalence of hepatitis C virus infection (HCV) is high among people living with 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]. 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, bone-related and cardiovascular events have been suggested, 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].

There are multiple factors that 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 (IDU), 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 (DAA) 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 evaluated the association between HCV-seropositivity and non-liver-related diseases. In order 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 i) 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 ii) to investigate whether successful HCV treatment reduces the risk of non-liver-related events and death by comparing HCV-viremic with successfully treated nonviremic persons, within the Swiss HIV Cohort Study.

PATIENTS AND METHODS

Swiss HIV Cohort Study (SHCS)

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 (IDU). In a previous study we assessed the longterm

epidemiological trends in treatment uptake, efficacy and mortality among HCV-coinfected SHCS participants [2]. This study focuses on assessing non-hepatic 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 was repeated every second year of follow-up in participants with previously negative results. In persons with risk factors (ongoing IDU, 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 chart 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-positive persons [11].

Patients' selection

All SHCS participants with at least one study visit between 08/1994 and 12/2014, with available HCV antibody test and, if seropositive, at least one 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 splitted 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 positive, 4) HCV-seropositive treated with sustained viral response (SVR), and 5) HCV-seropositive treated non-SVR.

Definitions

SVR was defined as at least one negative HCV-RNA test ≥12 weeks after the end of treatment as described previously [2] and according to standard definition [12]. The non-invasive biomarker of liver fibrosis FIB-4 was calculated as follows: (age x AST)/[platelet count (10^9 cells/L) x sqr(ALT)]. 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 was collected by a questionnaire on self-reported alcohol consumption. Severe alcohol abuse was defined according to the WHO definition (female >40g/d, male >60g/d).

Liver-related events included liver cirrhosis, bleeding from gastric or esophageal varices, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, portal hypertension, ascites, non-alcoholic 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. Classification of 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 uni- 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 IDU, and duration of HIV and HCV-infection. We also adjusted for HIV-1 RNA which is strongly correlated with antiretroviral treatment. However, modelling the large number of individual drugs and different regimens was not feasible and by incidence density sampling we selected HCV negative controls which likely had comparable ART exposure. All variables except sex and HIV acquisition category were time-updated. Since only 0.85% of semiannually scheduled follow-up visits had gaps of more than 1.5 years (i.e. 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 not presented because of low event numbers. We used Stata/SE 14.1 (StataCorp, College Station, Texas, USA) for all analyses.

RESULTS

Study population

Of 2625 HCV-seropositive and 14,876 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, 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 to HCV-seronegative patients were more often female (33.7 vs. 21.6%), acquired HIV infection more likely by IDU (68.3 vs. 2.3%), were longer HIV infected (median duration 18.5 vs. 16.2 years), had lower ART use (95.8 vs. 97.8%), were more likely to be current smokers (74.1 vs. 37.2%), and active IDUs (12.7 vs. 0.4%), and consumed more often severely alcohol (13.7 vs. 6.2%) (p=<0.001 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/HCV-seronegative patients: 107/18 liver events, 41/14 kidney events,

230/121 osteoporosis/fractures, 82/94 diabetes mellitus, 114/129 cardiovascular diseases, 119/147 non-AIDS malignancies, 162/126 HIV CDC B/C events, 106/10 liver-related deaths, and 227/218 non-liver-related deaths. Incidence rates (IRs) per 1000 person-years stratified by HCV status are shown in supplementary Table 2. Mean follow-up for untreated patients with spontaneous clearance/with HCV-RNA positive was 8.0 (range 0.01-16.6) years, 9.2 (0.005-19.1) years; for treated with/without SVR was 5.7 (0.003-12.7) years, 6.1 (0.008-12.4) years, and for HIV-monoinfected patients 8.3 (0.02-21.7) years.

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; 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 IRR 6.29 [95% CI 3.52-11.22]), liver-related death (8.24 [3.61-18.83]), kidney disease (2.43 [1.11-5.33]), and osteoporosis/fracture (1.43 [1.03-2.01]), compared to HCV-seronegative controls. No evidence for an increased risk in HCV-seropositive persons was found for diabetes mellitus (1.27 [0.83-1.93]), cardiovascular disease (0.90 [0.60-1.34]), non-AIDS malignancy (1.07 [0.75-1.52]), HIV CDC stage B/C events (1.12 [0.79-1.60]), and non-liver-related death (0.90 [0.68-1.21]).

Comparing each of the four HCV-seropositive groups to HCV-seronegative controls

The adjusted incidence rate ratios (IRR) 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 HIV CDC B/C events compared to 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 clearer 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 to HIV-monoinfected controls.

Comparing HCV-viremic patients (untreated HCV-RNA positive and treated non-SVR) to those with SVR

Treated non-SVR versus 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 elevated incidence of

kidney disease, cardiovascular events, and non-AIDS malignancies but without reaching statistical significance. (Figure 3, Table S1).

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 seven-fold reduction of liver-related events and a three-fold reduction in liver-related deaths.

We noted that diabetes 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, the EuroSIDA cohort collaboration [19] and the INSIGHT SMART and ESPRIT study groups [20] found an increased risk in replicating but not cleared HCV infection compared to HIV-monoinfected participants. In a similar US and Canadian cohort study results were contradictory, maybe 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 to 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 to HIV-monoinfected and HCV- and HIV-uninfected persons [22, 23]. Hansen et al demonstrated that fracture risk did not differ between viremic versus non-viremic 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 antiretroviral treatment, 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 non-responders compared with successfully treated patients. In the current literature

reports regarding the association between chronic HCV infection and cardiovascular disease are conflicting. While 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 who found an increased frequency of new AIDS-defining events and death in HCV treatment nonresponders vs. responders [7], we noted an increased risk of HIV CDC B/C events in non-SVR compared to HIV-monoinfected patients. Non-SVR compared to those with SVR had a higher incidence of HIV/AIDS events, but without reaching statistical significance. Since CD4 cell levels and suppression of HIV replication were similar between non-SVR and HIV-monoinfected participants at time of HIV/AIDS events, respectively 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 immune deficiency 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, 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 not only of liver-related but 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 contributer 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 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 troughout the various endpoints. 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/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-positive individuals have an increased risk of kidney disease and bone-related events which 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 DAA's on non-liver-related morbidity and mortality.

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CONFLICT OF INTEREST

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Figure 1: Patient Flowchart

*results of analyses not presented because of low event numbers.
Abbreviations: HCV: Hepatitis C virus; SVR: sustained viral response

Figure 2: Incidence rate ratios and 95% confidence intervals for the development of clinical events and deaths in multivariable analysis according to 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 injection drug use, duration of HIV and HCV-infection.
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Figure 3: Incidence rate ratios and 95% confidence intervals for the development of clinical events and deaths in multivariable analysis according to HCV viremia in treated patients during a follow-up time period of 8.2 years (mean). On the left side: multivariable analysis adjusted for HIV acquisition category, age, HIV-1 RNA, smoking, alcohol use, active injection drug use, duration of HIV and HCV-infection. On the right side: additionally adjusted for liver fibrosis stage measured by FIB-4 score.

Abbreviations: SVR, sustained viral response; Tx, treatment.

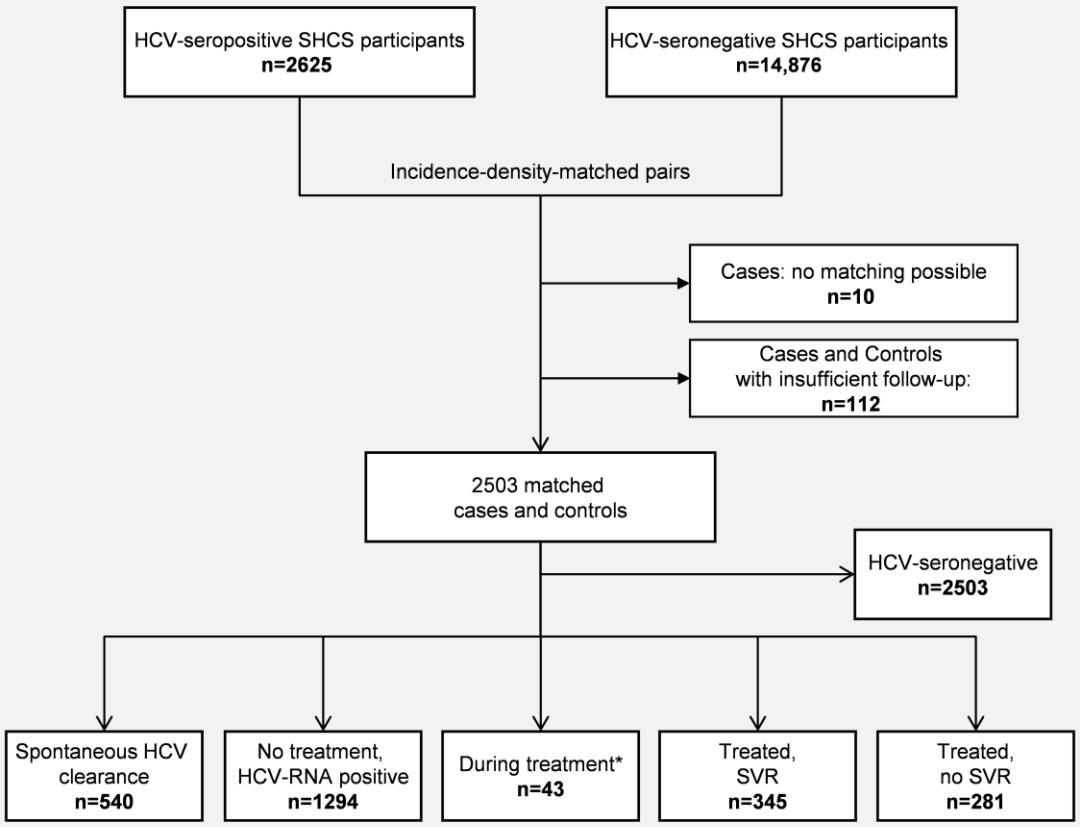
Table 1: Patient characteristics of HCV-positive SHCS participants grouped by HCV status and HCV-negative controls at last follow-up.

		HCV-positive untreated		HCV-positive treated		HCV-negative
		HCV-RNA neg.	HCV-RNA pos.	SVR	no SVR	
No. of patients, n		540	1294	345	281	2503
Male gender, n (%)		318 (58.9)	850 (65.7)	250 (72.5)	212 (75.4)	1961 (78.4)
Median age, years (IQR)		48 (42-52)	46 (41-52)	49 (43-53)	50 (45-55)	50 (44-58)
HIV acquisition, n (%)	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	n (%)	120 (22.2)	302 (23.3)	71 (20.6)	56 (19.9)	553 (22.1)
CD4 cells/µl	median (IQR)	549 (368-759)	451 (280-678)	592 (443-805)	523 (360-746)	543 (371-753)
	<200 cells/µ	46 (8.5)	204 (15.8)	10 (2.9)	19 (6.8)	208 (8.3)
On antiretroviral therapy	n (%)	510 (94.4)	1236 (95.5)	337 (97.7)	275 (97.9)	2448 (97.8)
With HIV RNA undetectable	n (%)	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*	available, n (%)	525 (97.2)	1132 (90.6)	299 (86.7)	228 (81.1)	-

	>800'000 IU/ml	20 (3.8)	535 (47.3)	150 (43.5)	124 (54.4)	-
FIB-4 liver fibrosis score	available, n (%)	500 (92.6)	1121 (86.6)	340 (98.6)	270 (96.1)	2231 (89.1)
	>3.25**, n (%)	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	n (%)	56 (10.4)	217 (16.8)	19 (5.5)	21 (7.5)	9 (0.4)
Severe alcohol consumption	n (%)	70 (13.0)	198 (15.3)	40 (11.6)	29 (10.3)	155 (6.2)

* HCV-RNA highest value ever measured (in cases without HCV-RNA values, only qualitative measurements available).
**A FIB-4 score >3.25 is indicative for advanced fibrosis/cirrhosis [13].
Abbreviations: CDC, Centers for Disease Control and Prevention; HBV, hepatitis B virus; HCV hepatitis C virus; IDU, intravenous drug user; MSM, men who have sex with men; SVR, sustained viral response.

Figure 1



*results of analyses not presented because of low event numbers.
Abbreviations: HCV, hepatitis C virus; SVR, sustained viral response.

Figure 2

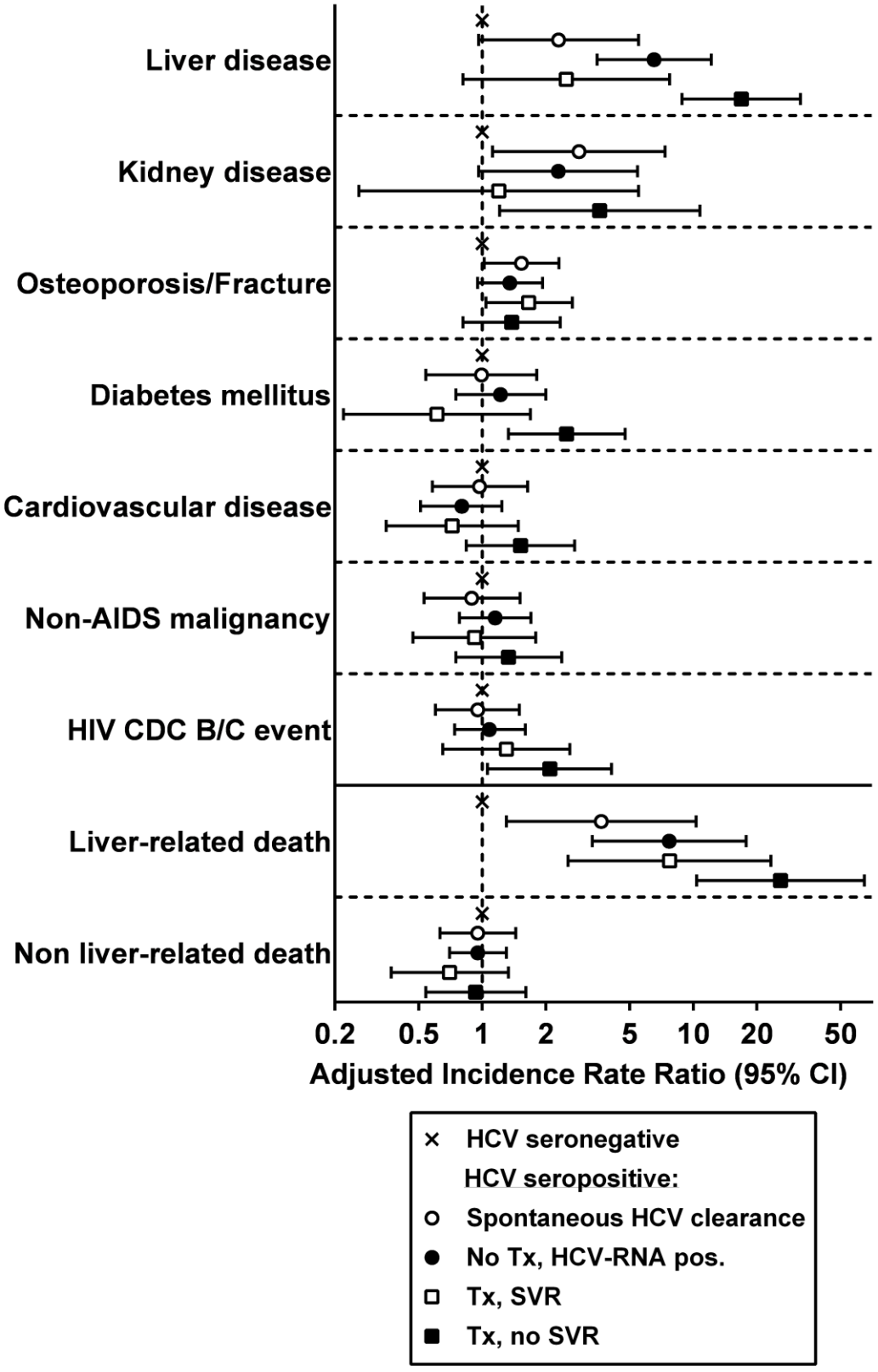


Figure 3