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ORIGINAL ARTICLE

Incidence and predictors of cardiovascular disease, chronic kidney disease, and diabetes in HIV/HCV-coinfected patients who achieved sustained virological response

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Abstract Data on the effects of sustained virologic response (SVR) to hepatitis C virus (HCV) therapy on the outcome of extrahepatic complications are scarce. We conducted this study to assess the impact of SVR on the occurrence of chronic kidney disease (CKD), diabetes mellitus (DM), and cardiovascular disease (CVD) in a cohort of human immunodeficiency virus (HIV)-infected patients. We analyzed coinfected HIV/HCV patients in the Management of Standardized Evaluation of Retroviral HIV Infection (MASTER) cohort. Only event-free patients with a serum HCV-RNA determination at baseline were included. Patients were divided into four groups: INF-exposed with SVR; INF-exposed without SVR; spontaneous HCV clearance; untreated viremic patients. We estimated the incidence of extrahepatic complications and employed Kaplan–Meier curves and Cox regression to assess the association of SVR/INF strata adjusted for a series of confounders. Data from 1676 patients were analyzed (20.29 % started an INF-based regimen). Overall, the incidence of CKD, DM, CVD, and death was 5.32 [95 % confidence interval (CI) 3.99–6.98], 10.13 (95 % CI 8.20–12.37), 6.79 (95 % CI 5.26–8.65), and 13.49 (95 % CI 11.29–16.0) per 1000 person-years of follow-up, respectively. In the Cox model for treated patients, SVR was not associated with a lower risk of CKD, DM, CVD, and death compared to non-SVR. Cirrhosis was significantly associated with a higher risk of CKD [hazard ratio (HR) 2.13; 95 % CI 1.06–4.31], DM (HR 3.48; 95 % CI 2.18–5.57), and death (HR 6.18; 95 % CI 4.1–9.31), but not of CVD (HR 1.14; 95 % CI 0.57–2.3). There are still many unknowns regarding the impact of SVR on the occurrence of extrahepatic complications in coinfected HIV/HCV patients. Further investigations are needed in order to elucidate the role of SVR as an independent prognostic factor for extrahepatic events.

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Introduction

The widespread use of combination antiretroviral therapy (cART) has substantially improved the prognosis of patients infected with human immunodeficiency virus (HIV) [1]. However, despite cART, HIV-infected patients are at greater risk of death compared to the general uninfected population. As a consequence of the increase in survival, non-acquired immune deficiency syndrome (AIDS)-related diseases now account for more than 50 % of all deaths [2]. Chronic hepatitis

C (CHC) is a leading cause of non-AIDS-related mortality and morbidity among HIV-infected patients. HIV/hepatitis C virus (HCV)-coinfected patients have accelerated progression of HCV-related liver disease and increased mortality rate compared to HCV- or HIV-monoinfected patients. There is increasing evidence that the achievement of sustained virologic response (SVR) after pegylated interferon (peg-IFN) plus ribavirin (RBV) treatment reduces the incidence of hepatocellular carcinoma (HCC), liver decompensation, and overall mortality in HIV/HCV-coinfected patients [3–6]. Although HCV coinfection is associated with an increased risk of cardiovascular disease (CVD), chronic kidney disease (CKD), and diabetes mellitus (DM) among HIV-infected patients, the impact of SVR on the risk of the development of extrahepatic complications has been little investigated [7–9]. Therefore, we conducted this study to assess the impact of SVR on the incidence of extrahepatic events in a cohort of HIV/HCV-coinfected patients.

Patients and methods

Study population and design

Patients were selected from the Italian Management of Standardized Evaluation of Retroviral HIV Infection (MASTER) cohort, which is a longitudinal multicenter study composed of a general HIV patient population followed up in referral centers throughout Italy [10]. The ten Italian centers composing the MASTER cohort use a common electronic health record (NetCare™ or Health&Notes™) employed for clinical purposes since 1997. The electronic health record is designed to manage the everyday activities of the outpatient HIV clinics in each center. MASTER is, therefore, an open cohort in which unselected patients are continuously enrolled. Demographics, medication, and disease history are recorded at enrolment and updated on a 3-monthly basis. Subjects gave written informed consent for participation in the observational cohort, and each site obtained approval by a local Ethics Committee. MASTER has a centralized database in MySQL (https://www.mysql.com/). The centralized database is on a server physically detached from the Internet and other local area networks. When data updates are needed, a cabled connection is enabled and operated via secure file transfer protocol. Upon arrival, the data are already anonymized from the participating centers. All event-free (without CKD, DM, and CVD at baseline) coinfected HIV/HCV patients enrolled in MASTER were considered in this study. Of these, only the patients positive for HCV-RNA at the baseline were eligible for the study. All treated patients received an IFN-based regimen (peg-IFN or standard thrice-weekly INF plus RBV). Patients were divided into four groups: (a) INF-exposed with SVR (patients who achieved an SVR); (b) INF-exposed without SVR (patients who did not achieve an SVR); (c) spontaneous HCV clearance (corresponding to spontaneous viral clearance: untreated [after the enrolment] HCV-Ab positive and HCV-RNA negative patients); (d) untreated viremic patients (untreated [after the enrollment] HCV-Ab positive and HCV-RNA positive patients).

Definitions

SVR was defined as a confirmed (twice over 3 months) undetectable serum HCV-RNA level 24 weeks after the discontinuation of therapy. Patients not fulfilling the SVR definition criteria, including those who relapsed after achieving end-of-treatment response, were classified as non-SVR. CKD and DM were defined as estimated glomerular filtration rate (eGFR) and fasting glucose plasma levels <60 mL/min/1.73 m^2 and >126 mg/dL in two consecutive time points within 3 to 9 months, respectively. The eGFR was calculated using the modification of diet in renal disease (MDRD) formula. All major CVD, including coronary heart disease, cerebrovascular disease, chronic heart failure, and peripheral vascular disease, were evaluated. Liver fibrosis was defined using the FIB-4 score, and was calculated by Sterling's formula: age (years) × AST [U/l]/(platelets [10^9/l] × (ALT [U/l])$^{1/2}$). Cirrhosis was defined by a FIB-4 score >3.25 [11]. The presence of an AIDS-defining illness was defined using the 1993 Centers for Disease Control and Prevention (CDC) criteria [12]. The body mass index (BMI) was calculated according to a standardized definition as weight in kilograms divided by height in meters squared. The result of the BMI calculation was categorized as obese (BMI ≥30 kg/m^2), overweight (BMI 25–29.9 kg/m^2), and normal weight (BMI 18.5–24.9 kg/m^2). Hypertension was defined as a systolic blood pressure (SBP) of ≥140 mmHg and/or a diastolic blood pressure (DBP) of ≥90 mmHg.

Statistical analysis

Descriptive results are presented as medians with interquartile range (IQR) and percentages with 95 % confidence intervals (CI). The person-years of follow-up (PYFU) were calculated for each participant as the time from the enrollment date to either an event date (death, CKD, DM, CVD) or 31 December 2012 for those who were still alive (and on active follow-up) then. The incidence of extrahepatic events and death was expressed per 1000 PYFU. The cumulative risk of events was estimated by the Kaplan–Meier method and the statistical significance of the difference was assessed by a log-rank test. Cox proportional hazard regression models were used to explore factors predictive of extrahepatic events and deaths, using both baseline (calendar year, age, mode of HIV transmission, HCV genotype, HBsAg) and time-updated covariates (BMI, SBP, DBP, cirrhosis, high-density lipoprotein

[HDL], low-density lipoprotein [LDL], triglycerides [TGL], CD4+ T-cell count, HIV-RNA load, number of AIDS events, abacavir [ABC], tenofovir [TDF], other nucleoside/-tide reverse transcriptase inhibitors [NRTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs], ritonavir-boosted atazanavir [ATV/r], ritonavir-boosted lopinavir [LPV/r], ritonavir-boosted indinavir [IDV/r], other protease inhibitors [PIs], other ART classes, INF-exposed, SVR). Also, we used time-updated variables recording the occurrence of an end-point event when analyzing a different end-point; for instance, we adjusted the Cox models for DM and CVD when analyzing the CKD end-point. According to common rule, we set the threshold for statistical significance at a p-value of 0.05.

Results

Patients' characteristics

A total of 1676 persons met the inclusion criteria and were included in this analysis. The patients' characteristics are shown in Table 1. In brief, the median age was 40.22 years (IQR 36.01–44.88); 1218 (72.67 %) patients were men; 879 (52.45 %) patients became HIV-infected through injection drug use (IDU), 361 (21.54 %) patients were infected through heterosexual contact, and 160 (9.55 %) through homosexual contact; 48 (2.86 %) patients had prior AIDS-defining conditions; 285 (17.0 %) had a CD4+ T-cell count <200/mmc. Cirrhosis was present in 16.11 % of the cases and 29.42 % were infected by HCV genotype 1. A total of 340 (20.29 %) patients started an INF-based regimen during the observation period. Among these, 54 (15,88 %) patients had a cirrhosis and 36.76 and 35.29 % were infected by genotypes 1 and 3, respectively. One hundred and two (30.0 %) of the INF-exposed patients achieved an SVR in the period study. Among the untreated population, spontaneous HCV clearance was observed in 58 (4.34 %) out of 1336 patients.

Outcomes

Overall, the incidences of CKD, DM, CVD, and death were 5.32 (95 % CI 3.99–6.98), 10.13 (95 % CI 8.20–12.37), 6.79 (95 % CI 5.26–8.65), and 13.49 (95 % CI 11.29–16.0) per 1000 PYFU, respectively. Kaplan–Meier curves showing the occurrence of extrahepatic events and deaths according to the study groups are reported in Fig. 1. Patients who achieved an SVR after treatment were associated with a lowest probability of occurrence of DM and death by Kaplan–Meier survival analysis (log-rank $p=0.033$ and $p<0.0001$, respectively), while CKD and CVD were not (log-rank $p=0.120$ and $p=0.097$, respectively). The pooled probability of DM, CVD, and death (log-rank $p=0.0059$, $p=0.04$, and $p<0.0001$, respectively) but not CKD (log-rank $p=0.150$) was significantly lower in patients achieving SVR with INF-based regimens or spontaneous clearance than in treated or untreated viremic patients. Overall, the probability of occurrence of DM and death (log-rank $p=0.046$ and $p<0.0001$, respectively) but not CKD and CVD (log-rank $p=0.86$ and $p=0.2$, respectively) was significantly lower in INF-exposed patients than in non-exposed patients (Fig. 2). The Kaplan–Meier estimated survival rates were 99 % (95 % CI 98–100 %) at 5 years and 95 % (95 % CI 92–98 %) at 10 years in the INF-exposed patients; for the INF-unexposed patients, the survival rates were 92 % (95 % CI 90–93 %) at 5 years and 84 % (95 % CI 81–87 %) at 10 years.

Factors predictive of extrahepatic events and deaths

The results from the Cox regression analysis are shown in Table 2. In brief, overweight and obese patients were associated with a 2.0- to 3.8-fold higher risk of DM than those with normal BMI. A CD4+ cell count less than 200 cells/mmc was significantly associated with a high risk of extrahepatic events and deaths, whereas an HIV-RNA level less than 500 copies/mL resulted in a decreased CVD risk and mortality. AIDS-defining conditions were significantly associated with the risk of CKD (hazard ratio [HR] 1.24; 95 % CI 1–1.54, $p=0.05$) and death (HR 1.42; 95 % CI 1.2–1.68, $p<0.0001$), but not DM (HR 0.92; 95 % CI 0.54–1.56, $p=0.751$) and CVD (HR 1.11; 95 % CI 0.74–1.67, $p=0.617$). Cirrhosis was significantly associated with the risk of CKD (HR 2.13; 95 % CI 1.06–4.31, $p=0.034$), DM (HR 3.48; 95 % CI 2.18–5.57, $p<0.0001$), and death (HR 6.18; 95 % CI 4.1–9.31, $p<0.0001$), but not of CVD (HR 1.14; 95 % CI 0.57–2.3, $p=0.708$). Finally, in the Cox regression model for treated patients, SVR was not associated with a lower risk of CKD (HR 1.05; 95 % CI 0.29–3.9, $p=0.936$), DM (HR 0.95; 95 % CI 0.27–3.37, $p=0.931$), CVD (HR 0.76; 95 % CI 0.38–1.52, $p=0.44$), and death (HR 1.17; 95 % CI 0.21–6.35, $p=0.858$) compared to non-SVR.

Sensitivity analyses

We performed an alternative analysis for the CKD end-point by considering a generalized estimating equation model where the eGFR was regressed as a continuous variable using multiple observations per patient every 3 months. The directions of relative risks obtained from this analysis were consistent with the results obtained by Cox regression. Also, we further selected the subpopulation of patients who started INF therapy at some point and repeated analyses by shifting the baseline time to the date of the first INF cycle. The incidences of CKD, DM, CVD, and death were 8.62 (95 % CI 5.13–13.67), 11.03 (95 % CI 6.95–16.70), 8.15 (95 % CI 4.76–13.11), and 5.25 (95 % CI 2.69–9.31) per 1000 PYFU, respectively. The univariate log-rank tests made upon the Kaplan–Meier analysis

Table 1 Patients' characteristics

		All patients ($n = 1676$)	Treated patients ($n = 340$)
Age, years, [median (IQR)]		40.22 (36.01–44.88)	39.8 (35.85–43.51)
Male gender [*n* (%)]		1218 (72.67)	262 (77.06)
Italian-born [*n* (%)]		1520 (90.69)	319 (93.82)
Risk for HIV transmission [*n* (%)]	IDU	879 (52.45)	212 (62.35)
	Homosexual contacts	160 (9.55)	22 (6.47)
	Heterosexual contacts	361 (21.54)	64 (18.82)
	Other/unknown	276 (16.47)	42 (12.35)
BMI [*n* (%)]	Normal	374 (22.32)	90 (26.47)
	Obese	44 (2.63)	4 (1.18)
	Overweight	135 (8.05)	49 (14.41)
	Unknown	1123 (67.0)	197 (57.94)
DBP [*n* (%)]	Elevated	100 (5.97)	21 (6.18)
	Normal	321 (19.15)	94 (27.65)
	Unknown	1255 (74.88)	225 (66.18)
SBP [*n* (%)]	Elevated	168 (10.02)	45 (13.24)
	Normal	254 (15.16)	71 (20.88)
	Unknown	1254 (74.82)	224 (65.88)
HBsAg [*n* (%)]	Negative	1125 (67.12)	114 (33.53)
	Positive	118 (7.04)	175 (51.47)
	Unknown	433 (25.84)	51 (15.0)
HCV genotype [*n* (%)]	1a	277 (16.53)	62 (18.24)
	1	68 (4.06)	21 (6.18)
	1b	148 (8.83)	42 (12.35)
	2	34 (2.03)	7 (2.06)
	3	36 (2.15)	10 (2.94)
	3a	264 (15.75)	110 (32.35)
	4	111 (6.62)	29 (8.53)
	Other/unknown	738 (44.03)	59 (17.35)
Cirrhosis [*n* (%)]		270 (16.11)	54 (15.88)
Cholesterol [*n* (%)]	<200 mg/dl	1192 (71.12)	287 (84.41)
	200–239 mg/dl	226 (13.48)	34 (10.0)
	≥240 mg/dl	87 (5.19)	11 (3.24)
	Unknown	171 (10.20)	8 (2.35)
HDL [*n* (%)]	<45 mg/dl	647 (38.60)	181 (53.24)
	45–59 mg/dl	315 (18.79)	74 (21.76)
	≥60 mg/dl	151 (9.01)	38 (11.18)
	Unknown	563 (33.59)	47 (13.82)
LDL [*n* (%)]	<100 mg/dl	509 (30.37)	157 (46.18)
	100–129 mg/dl	255 (15.21)	71 (20.88)
	≥130 mg/dl	173 (10.32)	38 (11.18)
	Unknown	739 (44.09)	74 (21.76)
TGL [*n* (%)]	<150 mg/dl	945 (56.38)	201 (59.12)
	150–199 mg/dl	267 (15.93)	50 (14.71)
	≥200 mg/dl	306 (18.26)	51 (15.0)
	Unknown	158 (9.43)	38 (11.18)
CD4+ T-cell count [*n* (%)]	<200/mmc	285 (17.00)	16 (4.71)
	200–499/mmc	755 (45.05)	146 (42.94)
	≥500/mmc	576 (34.37)	169 (49.71)
	Unknown	60 (3.58)	9 (2.65)

Table 1 (continued)

		All patients ($n = 1676$)	Treated patients ($n = 340$)
HIV-RNA load [*n* (%)]	<500 copies/mL	890 (53.10)	265 (77.94)
	500–4999 copies/mL	253 (15.10)	24 (7.06)
	≥5000 copies/mL	472 (28.16)	44 (12.94)
	Unknown	61 (3.64)	7 (2.06)
AIDS events [*n* (%)]		48 (2.86)	13 (3.82)
ABC [*n* (%)]		196 (11.69)	58 (17.06)
TDF [*n* (%)]		483 (28.82)	140 (41.18)
Other NRTI [*n* (%)]		1165 (69.51)	84 (24.71)
NNRTI [*n* (%)]		391 (23.33)	85 (25.0)
ATV/r [*n* (%)]		169 (10.08)	49 (14.41)
LPV/r [*n* (%)]		253 (15.10)	42 (12.35)
IDV/r [*n* (%)]		94 (5.61)	4 (1.18)
Other PIs [*n* (%)]		477 (28.46)	112 (32.94)
Other classes [*n* (%)]		159 (9.49)	27 (7.94)
INF-exposed with SVR at last follow-up [*n* (%)]		102 (6.09)	102 (30.0)
INF-exposed without SVR at last follow-up [*n* (%)]		238 (14.20)	238 (70.0)
Spontaneous HCV clearance last follow-up [*n* (%)]		58 (3.46)	–
Untreated viremic patients at last follow-up [*n* (%)]		1278 (76.25)	–

IDU injection drug use, *BMI* body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *TGL* triglycerides, *ABC* abacavir, *TDF* tenofovir, *NRTI* nucleoside/-tide reverse transcriptase inhibitors, *NNRTI* non-nucleoside reverse transcriptase inhibitors, *ATV/r* ritonavir-boosted atazanavir, *LPV/r* ritonavir-boosted lopinavir, *IDV/r* ritonavir-boosted indinavir, *PIs* protease inhibitors, *SVR* sustained virologic response

did not show any appreciable difference in hazard below the 0.05 level, except for a lower survival of the unknown BMI group vs. the normal BMI group when looking at the CKD end-point. Among INF-exposed patients, HBV co-infection (HR 18.08; 95 % CI 1.39–235.66, $p = 0.027$) and AIDS-defining conditions (HR 3.61; 95 % CI 1.31–9.97, $p = 0.013$) were significantly associated with the risk of CKD, whereas high triglyceride levels (≥200 mg/dl) were independently associated with the development of CVD events (HR 5.28; 95 % CI 1.17–23.73, $p = 0.030$). Moreover, BMI ≥30 kg/m^2 (HR 132.79; 95 % CI 4.84–3644.72, $p = 0.003$), unknown BMI (HR 6.95; 95 % CI 1.17–41.17, $p = 0.032$), cirrhosis (HR 7.65; 95 % CI 1.95–29.98, $p = 0.003$), TDF (HR 6.77; 95 % CI 1.42–32.18, $p = 0.016$), and LPV/r (HR 0.07; 95 % CI 0.01–0.96, $p = 0.046$) were the only independent predictors of DM in treated patients. Finally, there were not enough death events for a reliable Cox regression analysis.

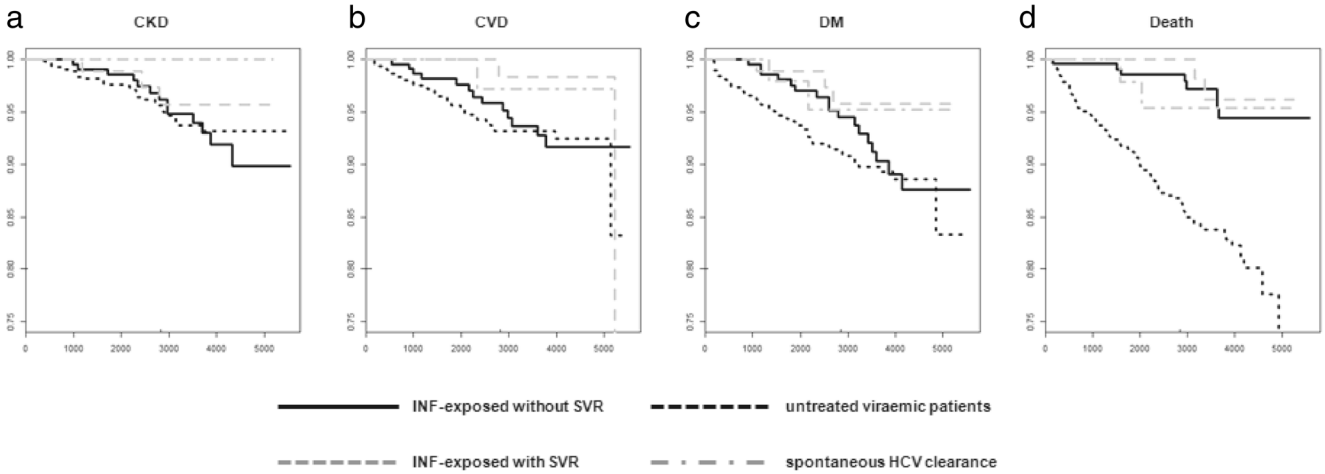

Fig. 1 Kaplan–Meier curves showing the occurrence of events according to the study groups. **a** *CKD* chronic kidney disease (log-rank $p = 0.120$). **b** *CVD* cardiovascular disease (log-rank $p = 0.097$). **c** *DM* diabetes mellitus (log-rank $p = 0.033$). **d** Death (log-rank $p < 0.0001$); *SVR* sustained virologic response

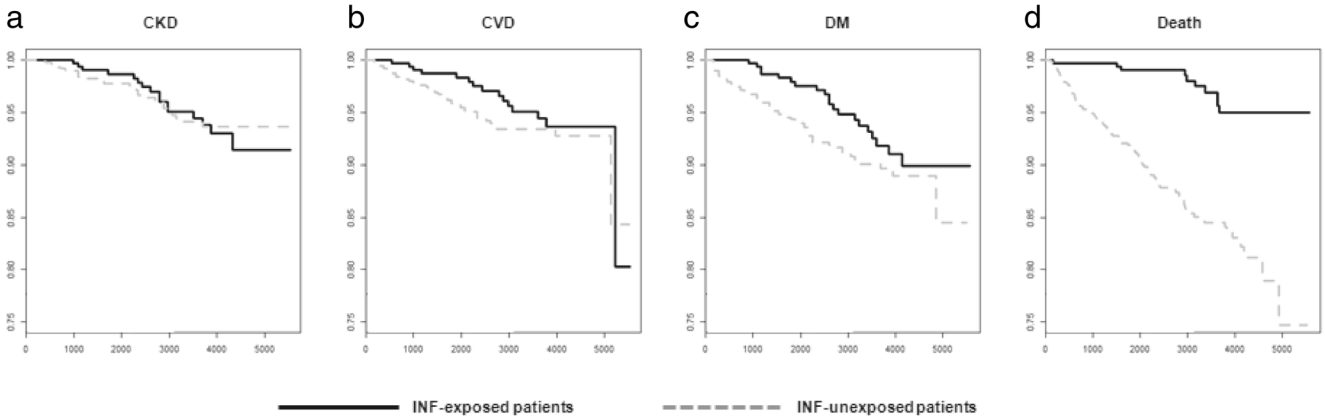

Fig. 2 Kaplan–Meier curves showing the occurrence of events according to the anti-HCV therapy status. **a** *CKD* chronic kidney disease (log-rank $p = 0.86$.; **b** *CVD* cardiovascular disease (log-rank $p = 0.2$.; **c** *DM* diabetes mellitus (log-rank $p = 0.046$). **d** Death (log-rank $p < 0.0001$); *SVR* sustained virologic response

Discussion

In this work, using Kaplan–Meier curves, we found that patients who achieved an SVR had a lower risk of occurrence of DM and death but not of other extrahepatic events. However, in the Cox regression model, we did not find any significant difference between patients who achieved an SVR and those who did not. Particularly, in contrast to the observations of other studies, the achievement of SVR following INF therapy was not significantly associated with a reduction in the risk of death [3, 4]. Our results can be partly explained by the sample size of treated patients (20 % out of all enrolled patients) and different INF-based regimens (peg-IFN or standard thrice-weekly INF plus RBV) that have been used in the 15-year period of enrolment in the cohort. However, we observed that untreated viremic patients had a 2.84-fold higher risk of death than those treated who did not achieve an SVR. The much more likely explanation is a bias toward treatment in different populations than those not treated with respect to medical compliance. Again these findings can be related, in part, to the influence of INF-based therapy on liver fibrosis progression. Although this effect is most prominent in patients who achieved a virologic response in both HCV-monoinfected and HCV/HIV-coinfected patients, even patients without viral response can show an improvement [13–16].

In our cohort, advanced liver disease was independently associated with CKD ($p = 0.034$) and DM ($p < 0.0001$), but not CVD ($p = 0.708$). Indeed, CKD and DM are among the most common complications found in cirrhotic patients [17, 18]. Furthermore, we found that mortality was significantly higher in cirrhotic patients compared to non-cirrhotic patients ($p < 0.0001$). These findings are consistent with previously published data showing that HIV/HCV-coinfected patients had a marked reduction in survival compared with HIV-monoinfected patients and HIV-coinfected patients without cirrhosis [19]. Recently, in the EuroSIDA cohort, Grint et al. showed a crude death rate for overall death and liver-related death of 103.8 (95 % CI 86.6–121.0) and 42.4 (95 % CI 31.0–53.7) per 1000 PYFU in cirrhotic patients, respectively, and of 18.7 (95 % CI 16.0–21.5) and 1.2 (95 % 0.5–1.9) per 1000 PYFU in patients with absent/minimal liver fibrosis, respectively [20].

We found that CKD was independently associated with an increased risk of death according to the findings of other authors [21]. Of note, in our cohort, it was found that CKD was significantly associated with a high risk of CVD ($p = 0.042$). By using a large national registry of HIV-infected patients, Choi et al. found that a reduced eGFR was an independent risk marker for adverse cardiovascular outcomes [22]. Similarly, in the Icona cohort, it was found that the incidences of CVD events among patients with severely impaired (defined as eGFR CKD-epi <60 mL/min), mildly impaired (defined as eGFR 60–89 mL/min), and normal renal function (defined as eGFR >90 mL/min) were 11.9 (95 % CI 6.19–22.85), 4.63 (95 % CI 3.51–6.11), and 2.91 (95 % CI 2.30–3.67) per 1000 PYFU, respectively [23].

An association between HCV infection and DM has been reported by various authors [24, 25]. Among HIV-infected patients, HCV coinfection is associated with a higher risk of DM occurrence in the highly active antiretroviral therapy (HAART) era but not in the pre-HAART era [26]. Furthermore, DM is a stronger predictor of death in HIV/HCV-coinfected patients. In our study, DM was significantly associated with a 2-fold increased risk of death. Similarly, in a multivariable Poisson regression model of the D:A:D study, patients with DM were at an increased risk of death from all-cause (adjusted relative rate [ARR] 1.77; 95 % CI 1.54–2.03), AIDS-related (ARR 1.48; 95 % CI 1.11–1.97), liver-related (ARR 2.37; 95 % CI 1.68–3.35), CVD-related (ARR 1.83; 95 % CI 1.29–2.59), and other/unknown causes (ARR 1.88; 95 % CI 1.49–2.38), but not non-AIDS malignancies (ARR 1.22; 95 % CI 0.80–1.85) [27]. More recently, in a French cohort

Table 2 Predictors of extrahepatic events and deaths

	CKD, HR (95 % CI)	CVD, HR (95 % CI)	DM, HR (95 % CI)	Death, HR (95 % CI)
Year of baseline	1 (0.88–1.15)	1.01 (0.9–1.13)	0.91 (0.83–1.01)	0.94 (0.87–1.02)
Male vs. female	2.26 (0.89–5.72)	1.06 (0.53–2.11)	1.14 (0.64–2.04)	0.77 (0.5–1.19)
Age of baseline	***1.05 (1–1.1)***	***1.08 (1.03–1.13)***	***1.06 (1.03–1.1)***	***1.05 (1.01–1.08)***
Non-Italian- vs. Italian-born	1.35 (0.39–4.64)	0.85 (0.2–3.61)	1.63 (0.71–3.74)	1.56 (0.76–3.19)
Homosexual vs. heterosexual	0.98 (0.25–3.87)	1.34 (0.41–4.39)	0.92 (0.35–2.44)	***0.06 (0–0.76)***
Risky IDU vs. heterosexual	0.92 (0.37–2.26)	1.73 (0.76–3.95)	0.88 (0.47–1.65)	1.6 (0.89–2.89)
Other/unknown vs. heterosexual	1.7 (0.57–5.06)	0.95 (0.28–3.23)	0.98 (0.42–2.29)	1.48 (0.64–3.42)
BMI obese vs. normal	1.4 (0.3–6.62)	1.14 (0.25–5.14)	***3.58 (1.16–11.05)***	1.05 (0.35–3.14)
BMI overweight vs. normal	0.35 (0.1–1.23)	0.57 (0.22–1.46)	2 (0.95–4.24)	0.7 (0.32–1.53)
BMI unknown vs. normal	0.96 (0.47–1.94)	0.91 (0.48–1.74)	1.42 (0.78–2.59)	***0.57 (0.36–0.89)***
DBP normal/unknown vs. elevated	0.72 (0.25–2.06)	0.73 (0.32–1.66)	0.9 (0.32–2.47)	2.02 (0.83–4.92)
SBP normal/unknown vs. elevated	0.98 (0.38–2.55)	***0.44 (0.21–0.95)***	1.33 (0.56–3.16)	0.63 (0.35–1.17)
HCV genotype 1 vs. 1a	Pooled into other/unknown	0.73 (0.16–3.37)	0.89 (0.29–2.69)	0.83 (0.33–2.07)
HCV genotype 1b vs. 1a	0.97 (0.33–2.86)	1.47 (0.6–3.64)	1 (0.47–2.1)	***0.42 (0.19–0.95)***
HCV genotype 2 vs. 1a	2.24 (0.55–9.12)	1.94 (0.53–7.03)	1.33 (0.37–4.71)	0.21 (0.03–1.76)
HCV genotype 3a vs. 1a	0.79 (0.3–2.08)	1.72 (0.79–3.74)	0.87 (0.45–1.71)	0.86 (0.49–1.51)
HCV genotype 4 vs. 1a	1.36 (0.47–3.92)	0.62 (0.19–2.01)	1.47 (0.69–3.11)	0.46 (0.19–1.14)
HCV genotype other/unknown vs. 1a	0.87 (0.35–2.15)	0.68 (0.28–1.68)	0.65 (0.32–1.3)	1.31 (0.79–2.17)
HBsAg positive vs. negative	1.91 (0.87–4.2)	1.24 (0.68–2.28)	1.01 (0.59–1.72)	1.21 (0.78–1.88)
HBsAg unknown vs. negative	2.35 (0.79–6.97)	0.74 (0.24–2.26)	1.64 (0.86–3.13)	0.6 (0.31–1.15)
Cirrhosis	***2.13 (1.06–4.31)***	1.14 (0.57–2.3)	***3.48 (2.18–5.57)***	***6.18 (4.1–9.31)***
HDL 45–59 mg/dl vs. <45 mg/dl	1.03 (0.48–2.2)	0.67 (0.32–1.39)	0.7 (0.38–1.29)	***0.47 (0.26–0.86)***
HDL ≥60 mg/dl vs. <45 mg/dl	1.27 (0.46–3.52)	1.01 (0.4–2.57)	0.87 (0.38–2.02)	***0.31 (0.11–0.88)***
HDL unknown vs. <45 mg/dl	0.69 (0.1–4.64)	1.43 (0.31–6.58)	0.57 (0.21–1.56)	0.99 (0.42–2.37)
LDL 100–129 mg/dl vs. <45 mg/dl	0.9 (0.44–1.87)	1.23 (0.63–2.41)	0.7 (0.38–1.3)	0.72 (0.39–1.34)
LDL ≥130 mg/dl vs. <100 mg/dl	0.81 (0.29–2.21)	1.85 (0.88–3.88)	0.5 (0.21–1.19)	1.06 (0.49–2.3)
LDL unknown vs. <100 mg/dl	0.46 (0.13–1.7)	0.59 (0.17–2.04)	0.76 (0.36–1.6)	0.98 (0.49–1.96)
TGL 150–199 mg/dl vs. <150 mg/dl	1.54 (0.7–3.39)	1.17 (0.56–2.43)	***1.9 (1.09–3.31)***	0.88 (0.49–1.58)
TGL ≥200 mg/dl vs. <150 mg/dl	1.46 (0.65–3.27)	1.84 (0.96–3.54)	1.6 (0.93–2.78)	1.32 (0.82–2.13)
TGL unknown vs. <150 mg/dl	***2.53 (1.01–6.34)***	1.1 (0.39–3.09)	0.86 (0.37–1.98)	***0.4 (0.2–0.8)***
CD4+ T-cell count 200–499/mmc vs. <200/mmc	0.57 (0.26–1.26)	***0.5 (0.25–1)***	***0.5 (0.29–0.88)***	***0.38 (0.25–0.58)***
CD4+ T-cell count >500/mmc vs. <200/mmc	***0.38 (0.16–0.94)***	***0.38 (0.17–0.83)***	0.61 (0.33–1.14)	***0.25 (0.14–0.45)***
HIV-RNA load 500–4999 copies/mL vs. >5000 copies/mL	0.74 (0.08–6.83)	0.63 (0.2–1.95)	0.74 (0.29–1.87)	0.51 (0.24–1.1)
HIV-RNA load <500 copies/mL vs. >5000 copies/mL	2.19 (0.71–6.79)	***0.46 (0.22–0.95)***	0.8 (0.44–1.44)	***0.63 (0.4–0.97)***
AIDS events	***1.24 (1–1.54)***	1.11 (0.74–1.67)	0.92 (0.54–1.56)	***1.42 (1.2–1.68)***
ABC	1.35 (0.62–2.95)	***2.37 (1.25–4.5)***	1.54 (0.85–2.8)	1.09 (0.6–1.96)
TDF	1.05 (0.51–2.17)	0.91 (0.47–1.74)	1.26 (0.73–2.17)	0.99 (0.6–1.64)
Other NRTIs	0.88 (0.36–2.15)	1.44 (0.63–3.3)	1.1 (0.6–1.99)	0.73 (0.43–1.23)
NNRTIs	0.49 (0.17–1.46)	0.83 (0.36–1.9)	0.82 (0.45–1.49)	0.72 (0.4–1.31)
ATV/r	1.4 (0.65–2.99)	2.02 (0.95–4.3)	0.55 (0.25–1.2)	0.82 (0.44–1.53)
LPV/r	0.66 (0.22–1.96)	1.34 (0.62–2.9)	0.7 (0.35–1.41)	0.88 (0.47–1.64)
IDV/r	***4.32 (1.08–17.3)***	0.69 (0.34–1.44)	1.77 (0.66–4.78)	0.49 (0.11–2.12)
Other PIs	1.64 (0.75–3.59)	0.41 (0.1–1.76)	0.95 (0.54–1.67)	0.96 (0.58–1.61)
Other classes	0.81 (0.25–2.63)	0.56 (0.12–2.57)	***1.89 (1–3.59)***	0.97 (0.51–1.85)
INF-exposed with SVR vs. INF-exposed without SVR	1.05 (0.29–3.9)	0.76 (0.38–1.52)	0.95 (0.27–3.37)	1.17 (0.21–6.35)
Spontaneous HCV clearance vs. INF-exposed without SVR	0.65 (0.31–1.34)	0.66 (0.08–5.26)	0.83 (0.46–1.5)	***2.84 (1.33–6.07)***
Untreated viremic patients vs. INF-exposed without SVR	Inf.	0.91 (0.26–3.14)	1.14 (0.25–5.21)	2.03 (0.37–11.02)

Table 2 (continued)

	CKD, HR (95 % CI)	CVD, HR (95 % CI)	DM, HR (95 % CI)	Death, HR (95 % CI)
DM	0.98 (0.32–2.99)	***3.15 (1.04–9.53)***	NA	***2.03 (1.11–3.73)***
CVD	2.4 (0.79–7.27)	NA	1.94 (0.68–5.56)	***2.35 (1.07–5.16)***
CKD	NA	***3.15 (1.04–9.53)***	1.06 (0.24–4.65)	***2.42 (1.03–5.64)***

HR hazard ratio, *95 % CI* 95 % confidence interval, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *DM* diabetes mellitus, *IDU* injection drug use, *BMI* body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *TGL* triglycerides, *ABC* abacavir, *TDF* tenofovir, *NRTIs* nucleoside/-tide reverse transcriptase inhibitors, *NNRTIs* non-nucleoside reverse transcriptase inhibitors, *ATV/r* ritonavir-boosted atazanavir, *LPV/r* ritonavir-boosted lopinavir, *IDV/r* ritonavir-boosted indinavir, *PIs* protease inhibitors, *SVR* sustained virologic response, *NA* not applicable

study of 348 patients with cirrhosis due to HCV (6 % with HIV coinfection), Elkrief et al. found that DM is an independent prognostic factor for major liver-related outcomes in patients with cirrhosis and CHC. Particularly, baseline DM was independently associated with death or transplantation-free survival ($p = 0.027$), ascites ($p = 0.05$), bacterial infections ($p = 0.001$), and encephalopathy ($p < 0.001$) at inclusion. Furthermore, baseline DM was independently associated with the development of ascites ($p = 0.057$), renal dysfunction ($p = 0.004$), bacterial infections ($p = 0.007$), and hepatocellular carcinoma ($p = 0.016$) during the follow-up [28].

We found that CVD is an independent risk factor for death among HIV/HCV-coinfected patients. Overall, CVD is a leading cause of death among non-AIDS-related diseases [29]. On the other hand, the role of HCV infection as a predictor of CVD needs further validation for definitive conclusions [30]. Of note, in a large HIV registry, Bedimo et al. found that the rate of acute myocardial infarction and cerebrovascular disease were significantly higher among HIV/HCV-coinfected patients than in those with HIV monoinfection ($p < 0.001$). In the adjusted analysis, HCV coinfection was independently associated with cerebrovascular disease (HR 1.20; 95 % CI 1.04–1.38, $p = 0.013$), but not with acute myocardial infarction (HR 1.25; 95 % CI 0.98–1.61, $p = 0.072$) [7].

In our cohort, no effect of SVR was seen for CVD risk. It is noted that data for many of the key confounders were missing in a substantial proportion of patients. BMI, SBP, and DBP were missing in almost 70 % of patients across the groups. Moreover, smoking status was not available for this analysis. These are likely the key factors in the lack of significant findings in the regression analysis. Of note, in contrast to our data, in a retrospective case–control study in HIV/HCV-coinfected patients, Chew et al. showed that SVR-achieving patients had a significant decrease of serum markers of endothelial dysfunction compared to those not achieving an SVR [31].

In conclusion, aviremic patients (spontaneously or after INF-based treatments) had a lower probability of occurrence of DM and death. Moreover, INF-exposed patients had a lower probability of occurrence of DM and death than non-exposed patients. For INF-treated patients, achieving SVR showed no benefit in the reduction of extrahepatic complications or death. INF-treated patients, despite not achieving SVR, had a lower risk of death than non-treated patients who had active HCV replication. Finally, patients with cirrhosis have an increased risk of CKD, DM, and death. These results warrant further investigations to better characterize the role of SVR as an independent prognostic factor for extrahepatic events in HIV/HCV-coinfected patients.

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Compliance with ethical standards

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Conflict of interest SL received speaker grants from Janssen-Cilag, Pfizer, and travel grants from Gilead, Janssen-Cilag, Pfizer. SC received speaker grants from Abbvie, BMS, Gilead, MSD, Viiv, and travel grants from BMS, Gilead, ViiV, is a member of the advisory boards of Abbvie, scientific debrief for Gilead, employee of Gilead from August 2012 to July 2013; PN received speaker grants and advisory board honoraria from BMS, MSD, Viiv; AS received payment for the development of educational presentations from BMS, Gilead, MSD, ViiV; MDP received speaker grants from Abbvie, BMS, Gilead, MSD, Viiv, is a member of the advisory boards of Abbvie; AG received grants/research supports from Abbvie, Astellas, BMS, Boehringer, Gilead, Janssen, MSD, Novartis, Pfizer, Roche, ViiV, ANLAIDS Sezione Lombarda, honoraria or consultation fees from BMS, Gilead, Janssen, MSD, Novartis, ViiV, travel grant/supports from BMS, Gilead, Jansen, ViiV, and participation in a company-sponsored speakers' bureau of Gilead. The other authors declare no conflict of interests.

Ethical approval Each site obtained approval by a local Ethics Committee.

Informed consent Informed consent was obtained from all individual participants included in the study.

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