Clinical Outcomes in Persons Coinfected With Human Immunodeficiency Virus and Hepatitis C Virus: Impact of Hepatitis C Virus Treatment

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(See the Editorial Commentary by Cooper on pages 2141–2.)

Background. A hepatitis C (HCV) cure is associated with changes in lipids and inflammatory biomarkers, but its impact on clinical endpoints among treated human immunodeficiency virus (HIV)/HCV coinfected persons is unclear.

Methods. People living with HIV from EuroSIDA with a known HCV status after January 2001 were classified into strata based on time-updated HCV RNA measurements and HCV treatment, as either HCV antibody–negative; spontaneously resolved HCV; chronic, untreated HCV; cured HCV (HCV RNA–negative); or HCV treatment failures (HCV RNA–positive). Poisson regression was used to compare incidence rates between HCV groups for end-stage liver disease (ESLD; including hepatocellular carcinoma [HCC]), non–acquired immunodeficiency virus defining malignancy (NADM; excluding HCC), and cardiovascular disease (CVD).

Results. There were 16 618 persons included (median follow-up 8.3 years, interquartile range 3.1–13.7). There were 887 CVD, 902 NADM, and 436 ESLD events; crude incidence rates/1000 person-years follow-up were 6.4 (95% confidence interval [CI] 6.0–6.9) for CVD, 6.5 (95% CI 6.1–6.9) for NADM, and 3.1 (95% CI 2.8–3.4) for ESLD. After adjustment, there were no differences in incidence rates of NADM or CVD across the 5 groups. HCV-negative individuals (adjusted incidence rate ratio [aIRR] 0.22, 95% CI 0.14–0.34) and those with spontaneous clearance (aIRR 0.61, 95% CI 0.36–1.02) had reduced rates of ESLD compared to cured individuals. Persons with chronic, untreated HCV infections (aIRR 1.47, 95% CI 1.02–2.13) or treatment failure (aIRR 1.80, 95% CI 1.22–2.66) had significantly raised rates of ESLD, compared to those who were cured.

Conclusions. Incidences of NADM or CVD were independent of HCV group, whereas those cured had substantially lower incidences of ESLD, underlining the importance of successful HCV treatment for reducing ESLD.

Keywords. HIV; hepatitis C; cardiovascular disease; malignancies; end-stage liver disease.

Persons living with human immunodeficiency virus (HIV) have increased incidences of comorbidities associated with aging, such as cardiovascular disease (CVD), non–acquired immunodeficiency syndrome (AIDS) defining malignancies (NADM), and

end-stage liver disease (ESLD) [1–4]. The age of the patient, duration of HIV infection, and effects of the HIV infection, including immunosuppression, chronic immune activation, and persistent low-grade inflammation, as well as coinfection with hepatitis C infection (HCV), have been suggested as important contributing factors [5–11]. Of the 36.7 million people living with HIV globally, an estimated 2.3 million individuals have serological evidence of a past or present HCV infection [12]. HCV itself is associated with increased incidence of ESLDs, hepatocellular carcinomas, and some malignancies, including non-Hodgkins lymphoma, cholangiocarcinoma, and pancreatic cancers [13], possibly due to chronic immune activation [14]. There are fewer studies in

populations that are HIV/HCV coinfected, compared to those that are HIV mono-infected. Recent studies have suggested an increased risk of CVD in those with HCV [15–17], although data are more limited in those with both HIV and HCV [17].

The recent availability of direct-acting antivirals (DAAs) for the treatment of HCV has shown cure rates over 90% in both HCV mono-infected and HIV/HCV coinfected persons [18]. This raises the question of whether people living with HIV but cured of HCV have a lower rate of long-term, non–liver related clinical outcomes compared to those who are untreated or failing treatment, or compared to those who are HCV antibody–positive and HCV RNA–negative without treatment (spontaneous clearers). Berenguer et al [19] demonstrated no differences in NADM among those with a sustained virologic response (SVR), but a marginally significant increased risk of CVD in an analysis only including treated individuals, while Kovari et al [20] found no differences in CVD or NADM when comparing those who were HCV antibody–negative, spontaneous clearers, or chronically infected, as well as those treated with and without SVR. Previous studies in coinfected persons have been limited by small sizes, short durations of follow-up, poorly defined clinical endpoints, data collection in single countries, differences in methodologies or groups compared, and the inability to adjust for some important confounders.

The aim of this study was to investigate clinical outcomes in a large, European, multi-cohort study, according to HCV status in HIV-coinfected persons from across Europe, comparing persons who were HCV-negative, spontaneous clearers, with those who had chronic, untreated HCV, were cured, or were failing HCV treatment.

METHODS

The EuroSIDA Study
Persons were included from the EuroSIDA study, a large, prospective, observational cohort of almost 23 000 patients living with HIV-1 who were followed in 100 hospitals in 35 European countries, plus Israel and Argentina. Individuals were enrolled into 10 cohorts from 1994 onward. In Cohort 10, all patients living with HIV were also required to be positive for anti-HCV antibodies (HCV RNA–positive or –negative or with an unknown status). At recruitment, in addition to demographic and clinical data, a complete antiretroviral therapy history was obtained, together with the most recent CD4 cell counts and HIV RNA measurements, as well as all HCV tests, HCV RNA, HCV genotype, hepatitis B surface antigen (HBsAg), and hepatitis B virus DNA. Data were collected prospectively at clinical sites and sent to the coordinating center at yearly intervals. At each follow-up visit, all CD4 cell counts, HIV RNA, HCV tests, HCV RNA, genotype, and HBsAg results measured since the last follow-up were collected, together with start and stop dates for antiretroviral drugs and HCV and hepatitis B virus drugs. Detailed information about the data collected in EuroSIDA can be found at http://www.chip.dk/Ongoing-Studies/EuroSIDA/About.

Inclusion and Exclusion Criterion
All persons with a known HCV serostatus and a prospective follow-up after 1 January 2001 (start of standardized collection of NADM) were eligible for inclusion. The baseline was defined as the latest of 1 January 2001, enrollment in EuroSIDA, known HCV serostatus, or, for those HCV positive, known HCV RNA status. Persons aged <16 years at baseline or without a CD4 count and viral load in the 12 months before or 1 month after baseline were excluded.

Based on time-updated HCV antibody tests, HCV RNA, and HCV treatment, we defined 5 HCV groups:

1. HCV antibody–negative;
2. HCV antibody–positive, HCV RNA–negative, and untreated (spontaneous clearers);
3. HCV antibody–positive, HCV RNA–positive, and untreated (chronic infections);
4. HCV antibody–positive, HCV RNA–negative, and treated (successfully treated with any licensed HCV therapy; cured); and
5. HCV antibody–positive, HCV RNA–positive, and treated (treatment failure).

Persons were followed until their last visit (median June 2017), date of death, or a clinical event, whichever occurred first. Person-years of follow-up (PYFU) and clinical events were accrued according to the current HCV strata using the latest information carried forward. Fatal and nonfatal CVD (myocardial infarction [MI], stroke, and invasive coronary procedures [angioplasty, coronary bypass, or carotid endarterectomy]), NADM (excluding hepatocellular carcinoma), and ESLD (ascites, hepatorenal syndrome, grade III/IV hepatic encephalopathy, unspecified liver decompensation, oesophageal variceal bleeding, spontaneous bacterial peritonitis, liver transplantation, and hepatocellular carcinoma) were included as clinical events (further information about these events is available at https://www.chip.dk/Studies/EuroSIDA/Study-documents). An extensive data monitoring and quality assurance program is in place within EuroSIDA; all clinical events were monitored and reviewed by study personnel, as well as via a random selection of information from persons without clinical events.

Statistical Analysis
We performed 3 separate analyses with each of the clinical events (CVD, NADM, and ESLD) as endpoints. Persons with a diagnosis before baseline were included with a follow-up to the next unique event; that is, recurrences of the same event were excluded from analyses. Characteristics of patients were compared across strata using simple summary statistics. Incidence rates per 1000 PYFU of each clinical event were calculated within HCV groups, and Poisson regression was used to compare these rates, after adjustment for relevant confounding

variables. Models were adjusted for gender, HIV transmission category, ethnic origin, region of Europe (North, Central West, South, Central East, East, and Argentina [21]), nadir CD4, age, liver fibrosis stage (as previously described [22]; this was included as measured at baseline, as it could lie on the causal pathway for the endpoints considered), baseline date (as fixed value at baseline), hepatitis B status, HIV viral load, AIDS status, NADM, ESLD, CVD, history of smoking (never smoked, current smoker, past smoker, or unknown smoking status), hypertension, diabetes, and chronic kidney disease (defined as 2 consecutive estimated glomerular filtration rate < 60 mg/dl at least 3 months apart, calculated using the chronic kidney disease-EPI formula [23]) as time-updated variables.

Sensitivity analyses were performed using the last observation carried forward for a maximum of 12 months, in addition to excluding those from Central East and Eastern Europe and those aged <50 years. The latter 2 sensitivity analyses address the extent to which the results were driven by people more recently infected with HCV. Among those HCV-positive, the role of liver fibrosis stage [24] was investigated. Given the recent introduction of DAAs and the improved response rates compared to the pre-DAA treatments, an exploratory analysis considered the different HCV treatments (interferon plus ribavirin and DAA with or without interferon) in those cured (Group 4) and those with treatment failure (Group 5). Power was very limited in this analysis and, therefore, the crude incidence rate (IR) ratios were only adjusted for age, which was the strongest predictor of both CVD and NADM.

All analyses were performed in SAS version 9.4 (Statistical Analysis Software, Cary, NC).

RESULTS

Of 22 826 persons enrolled in EuroSIDA, 18 736 persons had known HCV antibody and RNA statuses and were eligible for inclusion into this analysis. We excluded 1918 persons (1456 with no prospective follow-up after baseline, 462 with unknown CD4 count and/or HIV viral load); thus, 16 818 (89.8%) persons were included. Those excluded were less likely to have had a prior AIDS diagnosis, had a higher CD4 count nadir, were enrolled in EuroSIDA later in calendar time, and were more likely to be on antiretroviral therapy. Baseline characteristics are shown in Table 1; the largest group was those HCV antibody–negative (n = 10 433, 62.0%). Overall, most were male (74%), of White ethnic origin (85.2%), ever exposed to combination antiretroviral therapy (83.9%), and current smokers (54.3%) with a median age of 41 (interquartile range [IQR] 35–49) and CD4 cell count of 438 (IQR 281–630 cells/μl). As expected, on average those treated for HCV (Groups 4 and 5) were older, had higher CD4 counts, and were from Northern, Central, or Southern Europe. At baseline, the previous HCV treatment was predominantly interferon plus ribavirin in both those cured

(Group 4; 74.6%) and those with treatment failure (Group 5; 84.6%).

Clinical Events and Hepatitis C Virus Strata

During a median follow-up of 8.3 years (IQR 3.1–13.7), we observed 887 CVD, 902 NADM, and 436 ESLD events. Figure 1 summarizes the clinical events within each of these categories. The most common CVD events were invasive coronary procedures (351; 39.6%), and stroke (249; 28.1%), with few differences between hepatitis strata (P = .25). The most common NADM event was anal cancer (143; 15.9%), followed by lung cancer (96; 10.6%). Almost all cases of prostate cancer were seen in HCV-negative persons (Group 1). The majority of ESLD events were end-stage hepatic encephalopathy (110; 25.2%) and death from ESLD (103; 23.6%). There were some differences in the strata according to type of ESLD (P = 0.0029), with a much higher proportion of ESLD events in those who were HCV-positive (Groups 3–5). Although there were 100 events in those HCV antibody–negative (Group 1), this included 37 events in those HBsAg-positive.

Incidence Rates and Adjusted Incidence Rate Ratios of Clinical Events in Hepatitis C Virus Strata

The crude IRs per 1000 PYFU of CVD, NADM, and ESLD were 6.4 (95% confidence interval [CI] 6.0–6.9), 6.5 (95% CI 6.1–6.9), and 3.1 (95% CI 2.8–3.4), respectively (Figure 2). For CVD, there was some evidence of a difference in the IRs between the 5 strata (global P = .0005). The lowest IR was seen for those with chronic, untreated HCV (Group 3; 4.6, 95% CI 3.7–5.6 per 1000 PYFU) and the highest was in spontaneous clearers (Group 2; 7.9, 95% CI 5.8–10.1 per 1000 PYFU). There were no significant differences between the 5 strata for NADM (global P = 0.32), with rates in all strata between 5 and 7 per 1000 PYFU. Although there were a number of ESLD events in those HCV-negative (Group 1), there was a low incidence of ESLD in those with chronic, untreated infections (Group 3), while those with treatment failure (Group 5) had the highest rates of ESLD (9.6 [95% CI 8.2–10.9] and 9.9 [95% CI 7.7–12.1] per 1000 PYFU, respectively; global P < .0001).

Compared to those cured (Group 4), there were few differences in the adjusted IR ratios for CVD or NADM across the 5 groups (Figure 3). Consistent results and no differences between the groups were seen when considering MI or stroke individually. Unsurprisingly, those who were HCV-negative (Group 1) had significantly reduced rates of ESLD (adjusted IR ratio [aIRR] 0.22, 95% CI 0.14–0.34), while persons with chronic, untreated infections (Group 3; aIRR 1.47, 95% CI 1.02–2.13; P = .041) or treatment failure (Group 5; aIRR 1.80, 95% CI 1.22–2.66; P = .0033) had significantly higher IRs of ESLD compared to those cured (Group 4). Spontaneous clearers (Group 3) had a marginally significantly lower IR of ESLD, compared to those cured (Group 4; aIRR 0.61, 95% CI 0.36–1.02 ; p = .058). There

Table 1. Characteristics at Baseline

		All		HCV Antibody Negative Group 1		Group 2 Spontaneous Clearers		Group 3 Chronic Untreated Infection		Group 4 Cured		Group 5 Treatment Failure	
		N	%	n	%	n	%	n	%	n	%	n	%
All		16 818	100.0	10 433	62.0	919	5.5	3756	22.3	828	4.9	882	5.2
Gender	M	12 451	74.0	7945	76.2	606	65.9	2641	70.3	613	74.0	646	73.2
	F	4367	26.0	2488	23.8	313	34.1	1115	29.7	215	26.0	236	26.8
HIV risk	MSM	6415	38.1	5495	52.7	118	12.8	415	11.0	211	25.5	176	20.0
	IDU	4320	25.7	287	2.8	548	59.6	2508	66.8	454	54.8	523	59.3
	Het	4818	28.6	3891	37.3	168	18.3	530	14.1	107	12.9	122	13.8
	Other	1265	7.5	760	7.3	85	9.2	303	8.1	56	6.8	61	6.9
Ethnic origin	White	14 327	85.2	8765	84.0	760	82.7	3367	89.6	660	79.7	775	87.9
	Other	2491	14.8	1668	16.0	159	17.3	389	10.4	168	20.3	107	12.1
Region	South	4227	25.1	2309	22.1	208	22.6	1027	27.3	292	35.3	391	44.3
	Central	4611	27.4	3027	29.0	271	29.5	854	22.7	263	31.8	196	22.2
	North	3537	21.0	2570	24.6	156	17.0	611	16.3	109	13.2	91	10.3
	Central East	2161	12.8	1345	12.9	140	15.2	552	14.7	38	4.6	86	9.8
	East	1775	10.6	753	7.2	134	14.6	663	17.7	118	14.3	107	12.1
	Argentina	507	3.0	429	4.1	10	1.1	49	1.3	8	1.0	11	1.2
HBV status	Negative	14 177	84.3	9099	87.2	674	73.3	3016	80.3	680	82.1	708	80.3
	Positive	1261	7.5	736	7.1	153	16.6	262	7.0	54	6.5	56	6.3
	Unknown	1380	8.2	598	5.7	92	10.0	478	12.7	94	11.4	118	13.4
Ever cART	No	2710	16.1	1825	17.5	128	13.9	564	15.0	88	10.6	105	11.9
	Yes	14 108	83.9	8608	82.5	791	86.1	3192	85.0	740	89.4	777	88.1
HIV VL	< 500	11 399	67.8	6714	64.4	658	71.6	2540	67.6	748	90.3	739	83.8
	> 500	5419	32.2	3719	35.6	261	28.4	1216	32.4	80	9.7	143	16.2
Comorbidities	AIDS	4296	25.5	2823	27.1	245	26.7	899	23.9	151	18.2	178	20.2
	CVD	337	2.0	228	2.2	13	1.4	55	1.5	24	2.9	17	1.9
	NADM	318	1.9	184	1.8	21	2.3	71	1.9	19	2.3	23	2.6
	ESLD	189	1.1	41	0.4	14	1.5	67	1.8	30	3.6	37	4.2
	Hypertension	3676	21.9	2358	22.6	194	21.1	713	19.0	210	25.4	201	22.8
	Diabetes	671	4.0	423	4.1	29	3.2	109	2.9	57	6.9	53	6.0
	CKD[a]	98	0.6	30	0.3	8	0.9	26	0.7	22	2.7	12	1.4
Smoking status	Never	4554	27.1	3569	34.2	142	15.5	475	12.6	194	23.4	174	19.7
	Current	9133	54.3	4933	47.3	633	68.9	2644	70.4	441	53.3	482	54.6
	Previous	1570	9.3	919	8.8	89	9.7	341	9.1	101	12.2	120	13.6
	Unknown	1561	9.3	1012	9.7	55	6.0	296	7.9	92	11.1	106	12.0
Fibrosis	0/1	6585	39.2	3379	32.4	498	54.2	1737	46.2	511	61.7	460	52.2
	2	484	2.9	37	0.4	24	2.6	228	6.1	76	9.2	119	13.5
	3	238	1.4	14	0.1	8	0.9	96	2.6	70	8.5	50	5.7
	4	468	2.8	33	0.3	35	3.8	203	5.4	87	10.5	110	12.5
	Unknown	9043	53.8	6970	66.8	354	38.5	1492	39.7	84	10.1	143	16.2
Prior HCV treatment	INTF + RIBA	1364	79.8	…	…	…	…	…	…	618	74.6	746	84.6
	DAA + INTF	182	10.6	…	…	…	…	…	…	96	11.6	86	9.8
	DAA only	284	16.6	…	…	…	…	…	…	208	25.1	76	8.6
Age (y), median (IQR)		41	(35–49)	41	(34–49)	41	(35–48)	40	(34–46)	48	(40–54)	46	(38–52)
CD4 (mm³), median (IQR)		438	(281–630)	430	(280–613)	442	(277–662)	420	(265–620)	525	(347–762)	531	(360–748)
Nadir CD4 (mm³), median (IQR)		180	(72–293)	180	(70–296)	162	(58–291)	172	(77–285)	190	(61–296)	197	(102–302)
Baseline (mm/yy), median (IQR)		06/06	(01/01–03/12)	12/03	(01/01–07/08)	5/09	(02/02–12/14)	12/06	(11/01–10/14)	03/15	(09/14–10/15)	10/14	(4/10–4/15)

Baseline was defined as latest of 1 January 2001, enrollment to EuroSIDA, known HCV antibody status, or, for those HCV antibody–positive, known HCV RNA status. Spontaneous clearers shows data for those HCV antibody–positive, HCV RNA–negative, and untreated; chronic untreated infection shows data for those HCV antibody–positive, HCV RNA–positive, and untreated; cured shows data for those HCV antibody–positive, HCV RNA–negative, and treated; and treatment failure shows data for those HCV antibody–positive, HCV RNA–positive, and treated. All $P < .0001$ except prior NADM ($P = .3$), prior CVD ($P = .015$), nadir CD4 ($P = .0011$), and HCV treatment with DAA + INTF ($P = .22$).

Abbreviations: cART, combination antiretroviral therapy; CVD, cardiovascular disease; DAA, direct-acting antivirals; ESLD, end-stage liver disease; F, female; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, intravenous drug user and heterosexual; INTF, interferon; IQR, interquartile range; M, male; mm/yy, month/year; MSM, men who have sex with men; NADM, non–AIDS defining malignancy; RIBA, ribavirin; VL, viral load.

aCKD status could be calculated for 14861 at baseline; 9264, 800, 3259, 748, 790 in groups 1-5 respectively. P-value excluding those with unknown CKD status <.0001.
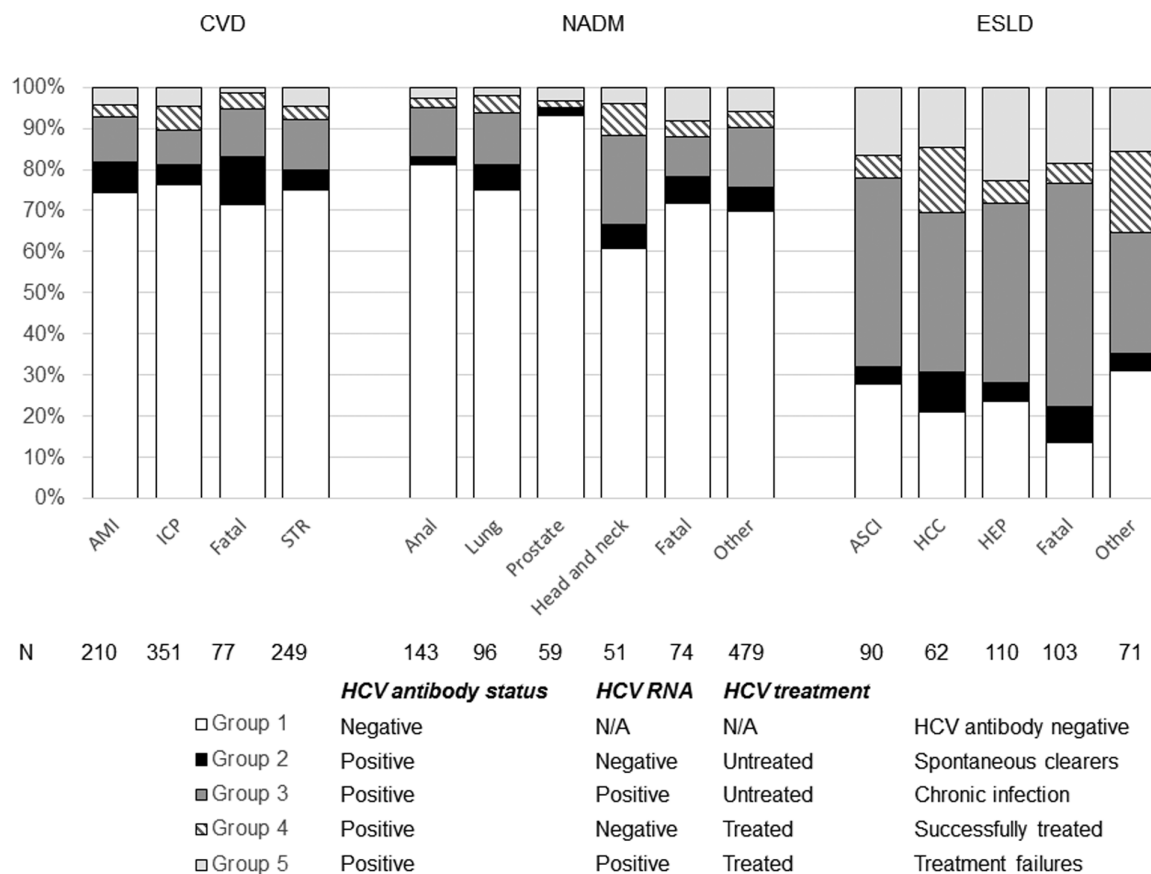
Figure 1. Type of clinical events by hepatitis C strata. Abbreviations: AMI, acute myocardial infarction; ASCI, ascites; CVD, cardiovascular disease; ESLD, end-stage liver disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HEP, end-stage hepatis encephalopathy; ICP, invasive coronary procedure; NADM, non–acquired immunodeficiency syndrome defining malignancy; STR, stroke.

was no evidence that the associations between HCV strata and each of the clinical events differed according to age (above or below 50, all P interactions > 0.15).

Baseline fibrosis stage was not associated with CVD or NADM (global Ps = .33 and .53, respectively), although it should be noted that this information was missing for half the participants. As expected, the baseline fibrosis stage was strongly associated with an increased IR of ESLD (global P < .0001). Compared to those with F0/F1 fibrosis, those with F2 fibrosis had a 2.5-fold increased IR of ESLD (aIRR 2.51, 95% CI 1.66–3.80; p <.0001) increasing to a >5-fold increase in those with F4 fibrosis (aIRR 5.80, 95% CI 4.12–8.19; p <.0001). Analyses were repeated including fibrosis as time-updated, with consistent results (data not shown).

Sensitivity and Exploratory Analyses

Analyses excluding those from Central East and Eastern Europe showed consistent results, as well as an analysis limited to those aged >50 years. A sensitivity analysis where the last HCV RNA measurement was carried forward for a maximum of 12 months also showed similar results.

In an exploratory analysis, we compared the IRs of CVD and NADM in those cured (Group 4) and with treatment failure

(Group 5), according to whether the HCV treatment was interferon plus ribavirin or DAA-based (with or without interferon; Table 2). There was limited power for this analysis and we were only able to adjust for age, which was the strongest factor associated with both CVD and NADM. Those cured with DAA had a similar incidence of NADM (aIRR 0.82, 95% CI 0.40–1.69; p = .59) to those cured with interferon plus ribavirin (comparison within Group 4). Similarly, those with treatment failure following treatment with DAA had a very similar IR of NADM (aIRR 1.01, 95% CI 0.45–2.44; p = .98), compared to those failing treatment following interferon plus ribavarin (comparison within group 5). There were few differences when comparing CVD outcomes in those treated with either interferon plus ribavirin or DAAs in those cured (Group 4) or failing treatment (Group 5). Despite the limited power and wide CIs, all the estimates comparing those cured or unsuccessfully treated with DAAs for NADM and CVD were close to 1, suggesting only small differences.

DISCUSSION

In this large study of more than 16 000 people living with HIV, with a median follow-up of over 8 years, we found no differences

HCV antibody status	HCV RNA	HCV treatment	
Negative	N/A	N/A	HCV antibody negative
Positive	Negative	Untreated	Spontaneous clearers
Positive	Positive	Untreated	Chronic infection
Positive	Negative	Treated	Successfully treated
Positive	Positive	Treated	Treatment failures
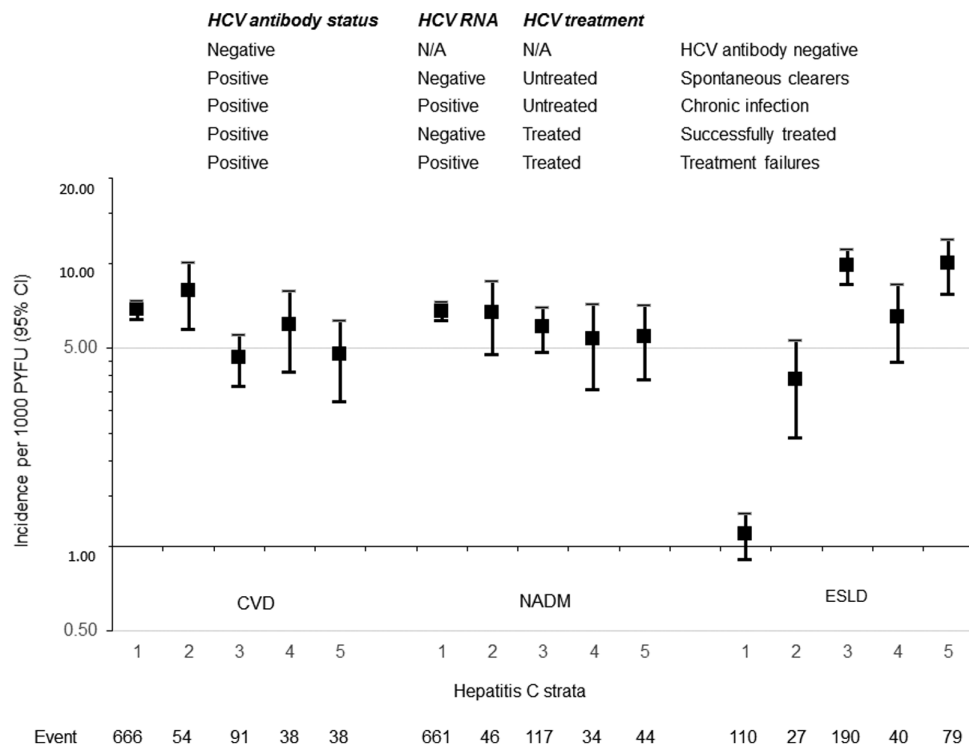
Figure 2. Crude incidence rates of cardiovascular disease, non–AIDS defining malignancy, and end-stage liver disease. Abbreviations: CI, confidence interval; CVD, cardiovascular disease; ESLD, end-stage liver disease; HCV, hepatitis C virus; NADM, non–AIDS defining malignancy; PYFU, person-years of follow-up.

HCV antibody status	HCV RNA	HCV treatment	
Negative	N/A	N/A	HCV antibody negative
Positive	Negative	Untreated	Spontaneous clearers
Positive	Positive	Untreated	Chronic infection
Positive	Negative	Treated	Successfully treated
Positive	Positive	Treated	Treatment failures
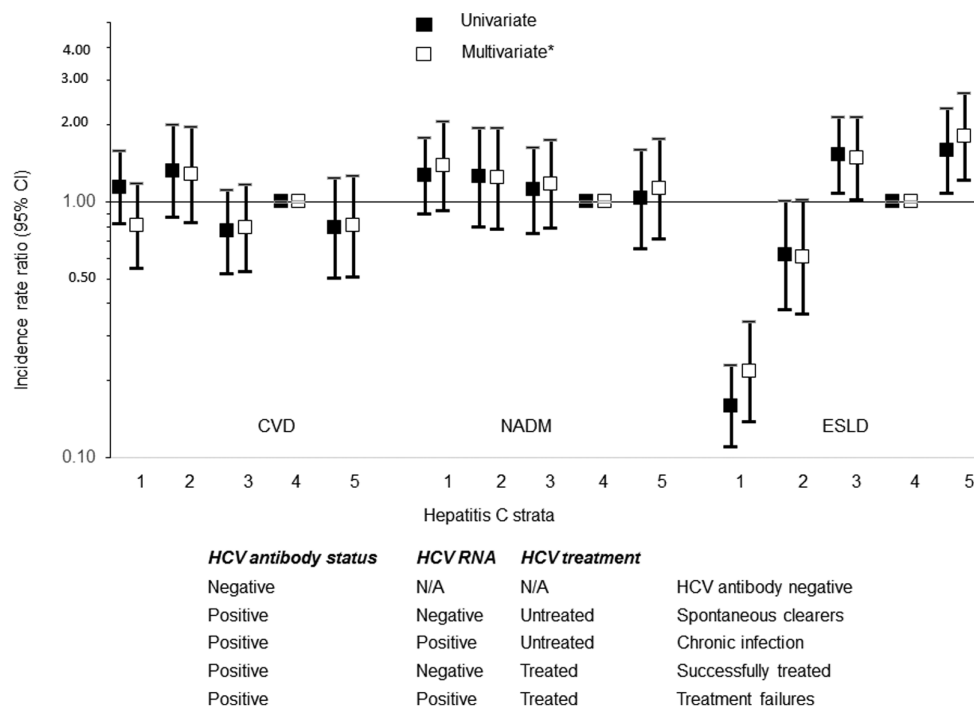
Figure 3. Univariate and multivariate incidence rate ratios of cardiovascular disease (CVD), non–AIDS defining malignancy (NADM), and end-stage liver disease (ESLD). *Adjusted for gender, HIV exposure category, ethnic origin, region of Europe, nadir CD4, age, fibrosis stage, and baseline date as fixed values at baseline; adjusted for hepatitis B status, HIV viral load, AIDS, smoking, hypertension, diabetes, use of statins, and CKD as time-updated variables. For CVD, CVD status at baseline was included, and ESLD and NADM were included as time-updated. For NADM, NADM status at baseline was included, and ESLD and CVD were included as time-updated. For ESLD, ESLD status at baseline was included, and CVD and NADM were included as time-updated. Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; ESLD, end-stage liver disease; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NADM, non–AIDS defining malignancy.

Table 2. Cardiovascular Disease, Non-acquired Immunodeficiency Syndrome Defining Malignancy, and Type of Hepatitis C Virus Treatment

		All	Interferon + Ribavirin	DAA-Based Treatment
Group 4: Cure				
CVD	Events	38	22	16
	PYFU	6292.6	4226.1	2066.4
	Incidence rate/1000 PYFU (95% CI)	6.0 (4.1–8.0)	5.2 (3.0–7.4)	7.7 (4.4–12.6)
	Unadjusted IRR (95% CI)	…	1.00 (ref)	1.49 (0.78–2.83)
				P = .23
	Adjusted for age (95% CI)	…	1.00 (ref)	1.08 (0.56–2.10)
				P = .82
NADM	Events	34	22	12
	PYFU	6348.6	4252.4	2096.2
	Incidence rate/1000 PYFU (95% CI)	5.4 (3.6–7.2)	5.2 (3.0–7.3)	5.7 (3.0–10.0)
	Unadjusted IRR (95% CI)	…	1.00 (ref)	1.11 (0.55–2.24)
				P = .78
	Adjusted for age (95% CI)	…	1.00 (ref)	0.82 (0.40–1.69)
				P = .59
Group 5; treatment failure				
CVD	Events	38	32	6
	PYFU	7978.1	7250.7	727.3
	Incidence rate/1000 PYFU (95% CI)	4.8 (3.3–6.3)	4.4 (2.9–5.9)	8.3 (3.0–18.0)
	Unadjusted IRR (95% CI)	…	1.00 (ref)	1.87 (0.78–4.47)
				P = .16
	Adjusted for age (95% CI)	…	1.00 (ref)	1.39 (0.57–3.42)
				P = .47
NADM	Events	44	38	6
	PYFU	8027.3	7284.2	743.1
	Incidence rate/1000 PYFU (95% CI)	5.5 (3.9–7.1)	5.2 (3.6–6.9)	8.1 (3.0–17.6)
	Unadjusted IRR (95% CI)	…	1.00 (ref)	1.55 (0.65–3.66)
				P = .32
	Adjusted for age (95% CI)	…	1.00 (ref)	1.01 (0.45–2.44)
				P = .98

Group 4 data are for those cured, meaning HCV antibody–positive, HCV RNA–negative, and treated; Group 5 data are for those with treatment failure, meaning HCV antibody–positive, HCV RNA–positive, and treated. Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DAA, direct-acting antivirals; HCV, hepatitis C virus; IRR, incidence rate ratio; NADM, non–acquired immunodeficiency syndrome defining malignancy; PYFU, person-years of follow-up; ref, reference.

in CVD or NADM between those without HCV; spontaneous HCV clearers; those with chronic, untreated HCV infections; those cured; or treatment failures. As expected, we found large differences in ESLD depending on HCV serostatus and HCV RNA replication. To our knowledge, this is among the largest studies to date including HIV and HCV coinfected persons with clinical endpoints and comparing outcomes to persons who have been cured of HCV.

Biomarkers of cardiometabolic disease are elevated in both HIV- and HCV- infected individuals [25]. In contrast, chronic HCV infection is associated with lower LDL and total cholesterol levels, and studies have shown a reversal to a less favorable lipid profile after SVR [26, 27] and an increase in Framingham risk scores, driven by increases in low-density lipoprotein (LDL) cholesterol [26]. While biomarker studies are important, surrogate markers for clinical events can be limited and, therefore, large studies with adequate follow-ups and well-defined clinical events are crucial to confirm results from biomarker studies. Studies on the impact of SVR on the risk of CVD events in HCV mono-infected persons have shown conflicting results [28–32].

It is possible that lifestyle factors, such as continued injection drug use and alcohol use, as well as differences in demographics clinical events included, methodologies, and unmeasured confounding factors all contribute to different findings. Our study and results from other prospective, cohort studies of HIV/HCV-coinfected persons have all found no reduced risk of CVD events in those with an HCV cure [19, 20, 33]. Our study is significantly larger than previously published studies in HIV/HCV coinfected persons, is more heterogeneous, included persons from >30 European countries, was able to adjust for a wide range of potential confounders, and has well-validated endpoints.

Some studies have suggested that persons with chronic HCV have higher rates of some malignancies, including non-Hodgkins lymphoma, cholangiocarcinoma, and pancreatic cancer, compared to the general population [13]. HCV replication is associated with chronic immune activation that is seen in both T and B lymphocytes [34], while cirrhosis has been associated with a decrease in monocyte function and altered natural killer activity of T lymphocytes [35]. Despite these known associations, we found no association between NADM and our

well-defined HCV groups, which is also in agreement with previous, smaller studies of HIV/HCV-coinfected persons [19, 20]. Importantly, we were able to adjust for a number of important confounders, including smoking status (and whether persons were past or current smokers).

We found similar IRs of CVD and NADM when comparing interferon and ribavirin with DAAs (+/- interferon) in both those cured (Group 4) and those with treatment failure (Group 5). Although we had limited power, illustrated by the wide CIs, the point estimates were all close to 1, suggesting that any differences between HCV treatments and CVD and NADM outcomes were small. This is reassuring for persons starting HCV treatment with DAAs with a contemporary regimen, although further data is required. We cannot rule out confounding by indication in this exploratory analysis, as those treated with interferon and ribavirin may have been selected as those with more favorable prognoses. Finally, when stratifying by age and region of Europe, we found no differences in NADM and CVD in our HCV groups, suggesting our lack of findings for CVD and NADM were not driven by the duration of HCV infection. Further follow-ups of those treated with DAAs in large cohort studies are essential to confirm our results of no differences in CVD or NADM among persons exposed to DAAs.

There are a number of limitations to our study. We chose not to define SVR according to treatment guidelines [36], largely due to heterogeneity in measurements of HCV RNA across Europe. Instead, we used the last HCV RNA measurement, carried forward. For those where this was negative after HCV treatment, we assumed SVR. Sensitivity analyses limiting the time the HCV RNA data were carried forward showed consistent results. Furthermore, liver fibrosis stage and HCV genotype were missing for a number of persons. In order to increase power, we used a composite endpoint for NADM and CVD. Our results were similar for both MI and stroke, but the study was not sufficiently powered to consider whether our results differed across NADM. EuroSIDA has not consistently collected information on alcohol use, and we were not able to adjust for this important confounder. The strength of our study is that it is among the largest of coinfected persons reported to date, with well-validated clinical endpoints and an extensive quality assurance and data monitoring program. Our findings for ESLD were as expected, lending weight to the quality of the data and methods used.

Although an HCV cure has been shown to perturb levels of lipid and inflammatory biomarkers, studies of HIV/HCV-coinfected persons have lacked the power to focus on clinical events. Our study shows similar IRs of CVD and NADM across 5 well-defined HCV strata and underlines the importance of early treatment and HCV cures for reducing ESLD.

Notes

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APPENDIX

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