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Clinical Outcomes in Persons Coinfected with HIV and HCV: Impact of HCV Treatment

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INTRODUCTION

- Chronic HCV infection causes hepatic and systemic inflammation which can lead to fibrosis and liver disease, but could potentially also have detrimental effect on extra-hepatic organs[1].
- In contrast, chronic HCV infection is associated with lower levels of LDL cholesterol and levels have been shown to increase after HCV cure[2].
- Whereas HCV cure has been shown to reduce the risk of liver-related outcomes in HIV/HCV coinfected persons, there are few data on its impact on extra-hepatic clinical endpoints.

AIMS

- To investigate the impact of HCV coinfection and HCV treatment outcome on risk of cardiovascular disease (CVD), non-AIDS defining malignancies (NAMD) and end-stage liver disease (ESLD) in HIV-1 infected individuals.

METHODS

- Persons from the pan-European HIV cohort study EuroSIDA with known anti-HCV and HCV-RNA status after January 2001 were included and were divided into five groups based on time-updated HCV-RNA and HCV treatment status:

Group	Anti-HCV	HCV RNA	HCV treatment	HCV Group
1	Negative	Negative	N/A	Anti-HCV negative
2	Positive	Negative	Untreated	Spontaneous HCV-RNA clearers
3	Positive	Positive	Untreated	Chronic HCV infection
4	Positive	Negative	Treated	Successfully treated
5	Positive	Positive	Treated	Treatment failure

- Separate analyses were performed for three clinical events; ESLD (including hepatocellular carcinoma [HCC]), NADM (excluding HCC) and CVD (myocardial infarction, stroke, angioplasty, coronary bypass, carotid endarterectomy). Poisson regression was used to compare incidence rates between HCV groups.

RESULTS

- Of 22,826 persons enrolled in EuroSIDA, 18,736 persons had known anti-HCV and HCV-RNA status, and were eligible for inclusion into this analysis. The largest group was those anti-HCV negative (n=10433, 62.0%).
- Overall, most were male (74%), of white ethnic origin (85.2%), ever exposed to 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) but as expected, there was considerable heterogeneity between the 5 groups at baseline (**Table**).

Characteristics at Baseline

		Group 1 Anti-HCV negative		Group 2 Spontaneous clearers		Group 3 Chronic infection		Group 4 Successfully treated		Group 5 Treatment failure	
		N	%	N	%	N	%	N	%	N	%
All		10433	62.0	919	5.5	3756	22.3	828	4.9	892	5.3
Gender	Male	7945	76.2	604	65.9	2641	70.3	613	74.0	646	72.4
MSM risk	MSM	5485	52.7	118	12.9	415	11.0	211	25.5	176	20.0
	IDU	287	2.8	549	59.8	2528	66.8	454	54.8	523	58.3
Ethnicity	White	8785	84.0	760	82.7	3367	89.6	665	79.7	775	87.8
HBsAg	Positive	738	7.1	133	14.6	262	7.0	54	6.5	54	6.3
HIV-RNA	<500	6714	64.4	658	71.6	2549	67.8	748	90.3	739	83.8
Comorbidities	AIDS	2823	27.1	245	26.7	889	23.9	151	18.2	178	20.2
	CVD	226	2.2	13	1.4	55	1.5	24	2.9	17	1.9
	NADM	184	1.8	21	2.3	71	1.9	19	2.3	23	2.6
	ESLD	41	0.4	14	1.5	67	1.8	35	3.8	27	4.0
	Hypertension	2358	22.6	194	21.1	713	19.0	210	25.4	201	22.8
	Diabetes	423	4.1	29	3.2	109	2.9	57	6.9	53	6.0
	CKD*	55	0.3	4	0.5	26	0.7	22	2.7	12	1.4
Smoking	Current	4923	47.3	633	68.9	2644	70.4	441	53.3	482	54.0
Fibrosis	Cirrhosis	33	0.3	35	3.8	203	5.4	87	10.5	110	12.5
	Unknown	6976	66.8	354	38.5	1450	38.7	84	10.1	143	16.2
		Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age	years	41	34-49	41	35-49	40	34-46	48	43-54	48	39-52
CD4	cells/µl	438	280-613	442	277-642	420	265-620	525	347-742	521	360-748
Baseline	MHorg	12/03	01/01-07/08	5/09	02/02-12/14	1/2006	11/01-10/14	03/15	09/14-10/15	10/14	4/10-4/15

Figure 1

Type of Clinical Events by Hepatitis C Strata

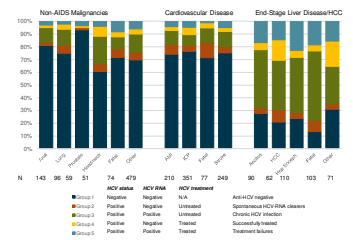
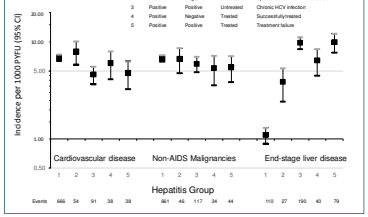


Figure 2

Crude Incidence Rates of Clinical Events



RESULTS (CONTINUED)

- During a median follow-up of 8.3 (IQR 3.1 – 13.7) years, there was a total of 887 CVD, 902 NADM and 436 ESLD events. **Figure 1** shows a breakdown of the clinical events within each of these event categories. The crude incidence of NADM, ESLD and CVD are shown in **Figure 2**.
- **Figure 3** shows the univariate and adjusted rate ratios of CVD, NADM and ESLD, using those who were successfully treated for HCV (group 4) as the reference group. Persons with chronic infection (group 3; adjusted incidence rate ratio [aIRR] 1.47; 95% CI 1.02 – 2.13; p=0.041) or treatment failure (group 5; aIRR 1.80; 95% CI 1.22 – 2.66; p=0.0033) had significantly increased incidence rates of ESLD compared to those successfully treated (group 4). Spontaneous clearers also had marginally significantly lower incidence rates of ESLD compared to those successfully treated (group 3; aIRR 0.61; 95% CI 0.36 – 1.02; p=0.058).
- There were no statistically significant differences in incidence of CVD or NADM across the five groups. There was also no evidence that the association between HCV strata and each of the clinical events differed according to age (above or below 50, all p-interaction >0.15).
- In sensitivity analyses there were no differences between the 5 groups and CVD and NADM when excluding persons from Central East and Eastern Europe who tend to be younger and therefore have been infected with HCV for a shorter period of time.
- Analysing myocardial infarctions and strokes separately also showed no differences between the HCV groups.

LIMITATIONS

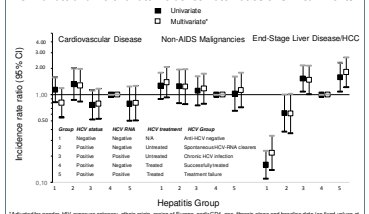
- Measurement of HCV-RNA varies considerably across EuroSIDA countries, which means we had to define HCV treatment outcome on HCV-RNA measurements regardless of when they were measured after treatment.
- Grouping different types of NADM and CVD events together resulted in increased power, and while results were similar for AMI and stroke separately, the study was not sufficiently powered to investigate different types of malignancies.

CONCLUSIONS

- We found no evidence of any impact of HCV infection status or HCV treatment on incidence of both non-AIDS defining malignancies and cardiovascular disease in HIV coinfected persons while successful HCV treatment lowered the incidence of end-stage liver disease and hepatocellular carcinoma compared to those chronically infected or those failing HCV treatment.
- Our results underline the importance of early and effective HCV treatment for reducing liver-related complications in HIV/HCV infected persons.

Figure 3

Univariate and Multivariate Incidence Rate Ratios of Clinical Events



*Adjusted for gender, HIV exposure category, ethnic origin, region of Europe, radic CDK, age, fibrosis stage and baseline date (as fixed values at baseline), and 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.

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