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Is Response to Anti-HCV Treatment Predictive of Mortality in HCV/HIV Positive Patients?

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**RUNNING TITLE:** MORTALITY IN HCV TREATED HIV PATIENTS

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## ABSTRACT

**Background:** Long-term clinical outcomes after HCV treatment of HIV/HCV patients are not well described. We aimed to compare the risk of all-cause and liver-related death according to HCV treatment response in HIV/HCV patients in the multi-cohort study COHERE.

**Methods:** All patients who had started PEG-interferon + ribavirin (baseline) and followed for  $\geq 72$  weeks after baseline were included. Patients were categorized into three response groups depending on treatment duration and HCV-RNA measured in the window 24-72 weeks after baseline. Patients who received  $\geq 24$  weeks of therapy were defined as responders if their last HCV-RNA measured between 24-72 weeks after baseline was negative, and having "unknown response" if HCV-RNA was unknown. Non-responders were treated for less than 24 weeks or were HCV-RNA+ between 24-72 weeks after baseline.

Mortality rates were compared using survival analysis, and Cox regression used to compare hazard ratios of death between response groups.

**Results:** 3,755 patients were included: 1031 (27.5%) responders, 1,639 (43.6%) non-responders and 1085 (28.9%) with unknown response. Rates (per 1,000 PYFU, 95% CI) of all-cause death were 17.59 (14.88-20.78), 10.43 (7.62-14.28) and 11.00 (8.54-14.23) for non-responders, responders and unknown responders, respectively. After adjustment, the relative hazard (non-responders vs. responders) for all-cause death, liver-related death and non-liver-related death was 1.53 (95% CI 1.06-2.22), 3.39 (95% CI 1.32-8.75) and 1.22 (95% CI 0.80-1.84), respectively.

**Conclusion:** HIV/HCV patients with a favourable virological response to PEG-interferon + ribavirin had reduced risk of all-cause and liver-related death, while there was no difference in risk of non-liver-related death when comparing responders and non-responders.

**Keywords:** HIV; HEPATITIS C; HCV; MORTALITY; INTERFERON; RIBAVIRIN

## Introduction

Treatment with pegylated interferon (PEG-IFN) and ribavirin (RBV) has until recently been the standard of care for treatment of HCV infection. Patients who achieve a sustained virologic response (SVR) i.e. they remain HCV-RNA negative 6 months after end of HCV treatment, are considered virologically cured. An SVR has been shown to halt or reverse progression of liver fibrosis [1, 2], but due to the slow evolution of liver disease in most patients, the clinical benefit of an SVR in terms of lower risk of liver-related complications and death, may take several years to manifest. During that period competing risk of death and risk of HCV re-infection could offset some of the benefit of HCV therapy [3]. Furthermore, due to the numerous adverse effects and contraindications to IFN-based therapy, particularly in HIV positive persons, HCV treatment was often not offered to those most in need of treatment [4]. Hence an evaluation of the clinical benefit of HCV treatment requires a large study population and long term follow up.

In studies of HCV mono-infected patients, it has been shown that achieving an SVR is associated with a lower risk of liver-related [5-8] and all-cause mortality [6, 7]. The benefit is most pronounced for hepatic failure, and less so for risk of hepatocellular carcinoma (HCC).

In HIV/HCV co-infected people the long-term clinical outcome of HCV treatment has not been evaluated in prospective studies of unselected patients. In a mixed retrospective-prospective study from Spain, Berenguer et al found that non-responders to HCV treatment had an almost nine-fold increased risk of liver-related clinical events compared with patients who achieved an SVR [9]. Two subsequent studies from the same group found that co-infected patients who achieved an SVR also had a reduced risk of HIV progression and non-liver-related death [10] and risk of all-cause mortality and liver-related events among patients with METAVIR  $\leq$ F2 fibrosis at the time of treatment initiation [11].

Compared with HCV mono-infected patients, the benefit of HCV treatment could theoretically be either greater due to accelerated fibrosis progression in co-infected patients, or lower due to differences in the prevalence of competing risk factors (both HIV-related and lifestyle factors) for mortality.

The objectives of our study were to compare the long-term risk of all-cause mortality and liver-related death according to response to PEG-IFN/RBV in HIV/HCV co-infected people enrolled in the large prospective multi-cohort study COHERE.

## **Methods**

### ***Patients***

The Collaboration of Observational HIV Epidemiological Research in Europe (COHERE, <http://www.cohere.org>) COHERE is a collaboration of 33 cohorts from across Europe and is part of the EuroCoord network ([www.EuroCoord.net](http://www.EuroCoord.net)). COHERE was established in 2005 with the aim of conducting epidemiological research on the prognosis and outcome of HIV positive persons, which the individual contributing cohorts cannot address themselves because of sample size or heterogeneity of specific subgroups of HIV-positive persons. Each cohort submits data using the standardized HIV Collaboration Data Exchange Protocol (HICDEP) including information on patient demographics, HBV and HCV status and treatment, CD4 counts, use of cART, AIDS, and deaths. Eighteen European cohorts provided data for the present analysis. Our analyses were based on data merged in July 2013.

All HCV infected patients in COHERE who had ever started PEG-IFN/RBV and who were followed-up for at least 72 weeks after treatment initiation were included. Baseline is defined as

the date of HCV treatment initiation, while time T0 is the date 72 weeks after treatment initiation. During most of the study period, 48 weeks of HCV treatment was standard of care for co-infected patients. The earliest time point at which SVR24 can be assessed would be 72 weeks after treatment initiation for most patients.

### ***Definitions of HCV treatment response***

Follow up HCV-RNA values were not reported for all patients after end of therapy. We therefore categorized patients into three different HCV treatment response groups depending on HCV treatment duration and HCV-RNA results measured in the window 24-72 weeks after baseline. Patients who received at least 24 weeks of IFN/RBV were defined as “responders” if their latest HCV-RNA measured in the window 24-72 weeks after baseline was negative, and having “unknown response” if they had no HCV-RNA measured in the week 24-72 window. Patients were defined as “non-responders” if they had received less than 24 weeks of HCV therapy or if their latest HCV-RNA measured the week 24-72 window after baseline was positive. To define positive HCV-RNA values both qualitative (+/-) and quantitative measures ( $>615$  IU/mL) were used.

### ***Biomarkers of fibrosis***

Levels of fibrosis were determined in the time window [-6;0] months prior to initiation of HCV treatment by measurement of the aspartate aminotransferase-to-platelet ratio index (APRI) [ $100 \times (\text{aspartate aminotransferase} / \text{upper limit of normal}) / \text{platelet count} (10^9/l)$ ]. Significant fibrosis ( $\geq$ F2 on the METAVIR scale) and cirrhosis were defined as APRI  $>1.5$  and APRI  $>2.0$ , respectively [12].

### *Statistical methods*

Main characteristics of the patients are described and compared according to whether a person was classified as responder, non-responder or unknown response using Chi-square or non-parametric Kruskal-Wallis tests as appropriate.

Three different endpoints were analysed: all-cause mortality, liver-related death (LRD) and non-liver related death. Causes of death were adjudicated individually by the participating cohorts in COHERE. Incidence rates were calculated as number of deaths divided by person-years of follow-up (PYFU) at risk. Confidence intervals around these estimates were calculated assuming a Poisson distribution. Mortality rates in the three groups were compared using standard survival analysis. Survival times accrued from the time T0 up to the date of death or last available follow-up. In the analysis of time to cause-specific death people who died for other reasons were censored administratively at the date of last follow-up according to a competing-risk approach to analysis. People who died between baseline and T0 were excluded. Kaplan-Meier plots have been used to compare the cumulative risk of survival in the three exposure groups (responders, non-responders and unknown response to IFN/RBV). Univariable and multivariable Cox regression models were used to compare hazard ratios of death between these groups after controlling for a number of pre-specified confounders. We used a manual build-up of the multivariable models adjusting sequentially for subset of time-fixed confounders measured at the time of IFN/RBV initiation and grouped according to common features (e.g. demographics, HIV-related factors and HCV-related factors). We only included in these sets of potential confounders factors that have been previously described to be a common cause of treatment

initiation and risk of death, i.e. age, gender, origin, year of baseline, mode of HIV transmission, prior AIDS, current CD4 count, CD4 nadir, HIV RNA, HIV treatment at T0, HBsAg and APRI.

## **Results**

### ***Baseline characteristics***

We included a total of 3,755 patients, who had started HCV treatment and had at least 72 weeks of follow up after treatment was started (figure 1). Fifty-two patients had died between the date of HCV treatment start and week 72 (T0) of follow up. Median (IQR) duration PEG-IFN/RBV treatment was 9 (5 – 12) months. Among included patients, 1031 (27.5%) were responders, 1639 (43.6%) non-responders and 1085 (28.9%) had unknown HCV treatment response. Compared with non-responders, responders started HCV treatment later (2007 vs. 2005), were more likely to be MSM (31% vs. 12%) and HBsAg positive (4.5% vs. 2.6%), had higher CD4 cell count (455 vs. 405 cells/mm<sup>3</sup>), lower HCV-RNA levels (5.85 vs. 6.03 log<sub>10</sub> IU/mL) and less likely to be female (20% vs. 25%) and have a prior AIDS diagnosis (22% vs. 27%). The median APRI score was slightly higher among responders (0.9 vs. 0.8 (table 1). Among patients with available data, the prevalence of cirrhosis, defined as APRI>2.0, was 16.0% in those with unknown response (104/650), 20.0% in non-responders (200/999) and 26.7% in responders (182/681). There were no differences between the response groups in time from baseline to assessment of APRI.

### ***All-cause mortality according to HCV treatment response***

After a median of 4.0 (IQR 2.0-6.5) years of follow up from T0, a total of 236 deaths had occurred. One hundred and thirty-eight (8.4%) of HCV treatment non-responders had died vs. 39 (3.8%) deaths among responders and 59 (5.4%) with unknown HCV treatment response. The

rates (per 1,000 PYFU, 95% CI) of all cause death were 17.59 (14.88 – 20.78), 10.43 (7.62 – 14.28) and 11.0 (8.54 – 14.23) for non-responders, responders and unknown responders, respectively.

Figure 2 shows a Kaplan-Meier plot of the cumulative risk of all-cause mortality. For non-responders the 7-year risk (95% CI) of all-cause death was 11.6% (9.5 - 13.7), while the 7-year risk was significantly lower for responders 8.0% (5.1 - 10.8) and for patients with unknown treatment response 7.8% (5.6 – 10.1).

In the unadjusted Cox regression analysis, non-responders had a relative hazard of 1.64 (95% CI 1.15 - 2.34) for all-cause death compared with responders. Results were similar after adjusting for demographics, HIV related (prior AIDS, on cART at T0 and current HIV-RNA and CD4+ cell count) and hepatitis related factors (HBsAg and APRI) in separate models (Figure 3). In the fully adjusted analysis, the relative hazard (non-responders vs. responders) for all cause death was 1.53 (95% CI 1.06 - 2.22). In all analyses, the relative hazard for all-cause death was not significant when comparing responders with unknown responders.

### ***Liver-related mortality according to HCV treatment response***

Liver-related death accounted for a third of all deaths among non-responders 48/138 (34.8%), but only 12.8% (5/39) among responders and 22.0% (13/59) among patients with unknown response. The rates (per 1000 PYFU, 95% CI) of liver-related death were 6.12 (4.61 – 8.12), 1.34 (0.56 – 3.21) and 2.40 (1.41 – 4.18) for non-responders, responders and unknown responders, respectively.

Among the five responders who died from LRD, two had a baseline APRI score indicating cirrhosis, one had significant fibrosis, and two had no information about fibrosis level. One

patient had evidence of HCV re-infection, while the four other remained HCV-RNA negative during follow up. None were diagnosed with hepatocellular carcinoma.

The differences in risk of liver-related death between responders and non-responders were more pronounced than for all-cause death, but the confidence intervals were quite wide reflecting the relative low number of liver-related deaths in each group. The 7-year cumulative risk of liver-related death was significantly higher for non-responders (4.2%, 95% CI 2.9 - 5.5) compared with the risk for responders (1.6%, 95% CI 0.0 – 3.3) and for patients with unknown treatment response (1.4%, 95% CI 0.4 - 2.4) (Figure 4).

In the unadjusted Cox regression analysis, non-responders had a 4.43 (95% CI 1.76 – 11.14) increased risk of liver-related death compared with responders. Again, when adjusting for demographic, HIV related and hepatitis related factors there was little change in the incidence rate ratios (Figure 5). In the fully adjusted analysis, the relative hazard (non-responders vs. responders) of liver-related death was 3.39 (95% CI 1.32 – 8.75).

#### ***Non-liver-related mortality according to HCV treatment response***

A total of 34 and 90 non-liver-related deaths occurred among responders and non-responders, respectively. In both groups non-HCC malignancy was the predominant cause of death (5/34 and 16/90, respectively) followed by “unknown cause” (5/34 and 16/90, respectively). Four non-responders died from AIDS, while there were no AIDS-related deaths in the responder group. To investigate whether a positive HCV treatment outcome also results in a lower risk of non-hepatic mortality, we repeated the analyses excluding all liver-related deaths. In the unadjusted analysis there was no difference (non-responders vs. responders) in incidence of non-liver-related death (hazard ratio 1.23, 95% CI 0.83 – 1.83). Results were similar after adjustment for demographic

factors (1.19, 95% CI 0.79 – 1.78), HIV related factors (1.22, 95% CI 0.81 -1.82) and APRI and HBsAg status (1.35, 95% CI 0.91 -2.01). In the fully adjusted model the relative hazard was (1.22, 95% CI 0.80 – 1.84). Similarly, there was no difference when comparing responders with patients with unknown response (results not shown).

## **Discussion**

In this large prospective study we included 3,755 HIV/HCV co-infected patients, who had received PEG-IFN/RBV. After a median of 4.0 years follow up from week 72 after treatment initiation, we found that patients who had a favorable treatment response had a significantly improved all-cause and liver-related mortality compared with patients who were non-responders. Our findings confirm the survival benefit of an SVR, shown in previous studies of HCV mono-infected [6, 7] and HIV/HCV co-infected patients [9, 13]. However, compared with these studies the improved survival in our study was relatively modest (hazard ratio 1.53 for comparing responders with non-responders). In the Spanish study by Berenguer et al [9], which is the only other large observational study to include HIV/HCV co-infected patients from routine clinical practice, the incidence of all-cause mortality among patients with SVR was lower compared with the incidence among responders in our study (0.46 vs. 1.04 per 100 PYFU), whereas the all-cause mortality was higher among non-responders in their study (3.12 vs. 1.76 per 100 PYFU). The excess all-cause mortality among non-responders in the Spanish study, seems to be mainly explained by a high prevalence (39%) of patients with advanced fibrosis or cirrhosis, resulting in a high incidence of liver-related death among non-responders compared to the incidence among non-responders observed in our study (1.65 vs. 0.61 per 100 PYFU).

In our study, only five out of 37 deaths in the treatment response group were from liver-related causes, and none of them due to HCC. Two of the five patients had evidence of cirrhosis at the time of treatment initiation, while one had evidence of HCV re-infection. Other studies have documented, that although an SVR reduces the risk, liver-related complications can occur several years after SVR. This is particularly the case with HCC in patients with cirrhosis at the time of treatment [14, 15]. Longer follow-up of our cohort is warranted to determine whether the incidence of HCC and other liver-related clinical events remains low for patients with treatment response.

Since interferon is contra-indicated in patients with advanced cirrhosis due to the risk of liver decompensation, it is likely that patients with more advanced liver disease, who would have gained more clinical benefits from HCV eradication, were excluded. It is therefore conceivable that with the new tolerable and effective interferon-free direct-acting antivirals we will be able to prevent more liver- and, possibly, non-liver related complications, and this should be addressed in further observations. Although IFN-based therapy is no longer standard of care, the data presented in this paper are still of relevance to inform the prognosis for the many patients who were treated and cured with IFN before the arrival of DAA. Furthermore, IFN-based therapy is still commonly used in some countries that cannot afford the market price of DAA. In addition, consequences of cure are likely to be similar regardless of which treatment was used to achieve success.

The link between chronic HCV infection and different autoimmune and lymphoproliferative conditions, e.g. mixed cryoglobulinaemia and some types of lymphoma, is well established [16]. There is also emerging evidence of an association between HCV infection and risk of

cardiovascular disease and other extra-hepatic diseases [16-18]. If the association is causal, one would expect a decrease in risk of non-liver-related death after SVR. In our study, we did not find a lower risk of non-liver-related death among those with a favorable HCV treatment response. This is in contrast to a national Spanish study that found a three-fold lower risk of non-liver-related death in HIV/HCV co-infected patients with SVR compared with patients who did not achieve an SVR [10]. The reason for this difference is not clear, but with only five and 32 non-liver-related deaths among patients with and without SVR, respectively, that study had limited power to investigate the question. It is possible that some of the apparent extra-hepatic health benefit of an SVR is related to behavioural differences after treatment and not the treatment outcome per se, as demonstrated by a Scottish observational study of HCV mono-infected patients where patients who achieved SVR after IFN-based therapy had lower risk of hospitalization for alcohol intoxication and violence-related injury after treatment compared with non-responders to HCV treatment [19]. These findings should be explored in other cohorts and in patients undergoing DAA therapy.

The major strengths of this analysis are the large number of co-infected patients recruited from a diverse geographical area throughout Europe, the long prospective follow up after HCV treatment and our ability to adjust for relevant risk factors for all-cause and LRD. However, like in all observational studies, there remains the possibility of unmeasured confounding. Another limitation is the lack of follow-up HCV-RNA measurements on all patients at least six months after end of therapy. In addition, some of the patients categorized as responders could have had HCV-RNA relapse, and some patients categorized as non-responders could have achieved an SVR. However, this limitation would only tend to underestimate the survival benefit of HCV

therapy. Unexpectedly, the prevalence of cirrhosis, as determined by the APRI score, was higher among responders than among non-responders. Data to calculate the APRI score were only available for 66% and 61% of responders and non-responders, respectively. If the reason for not having an APRI score is associated to disease status selection bias could have been introduced.

In conclusion, we have shown that among HIV/HCV co-infected patients, a favourable virological response to HCV treatment is associated with reduced risk of both liver-related death and improved overall survival in the IFN era. Whether this holds true with the new direct-acting antivirals remains to be investigated.

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**Figure legends:**

**Figure 1:** Selection of patients

**Figure 2:** Cumulative risk of all-cause mortality in the three HCV treatment response groups

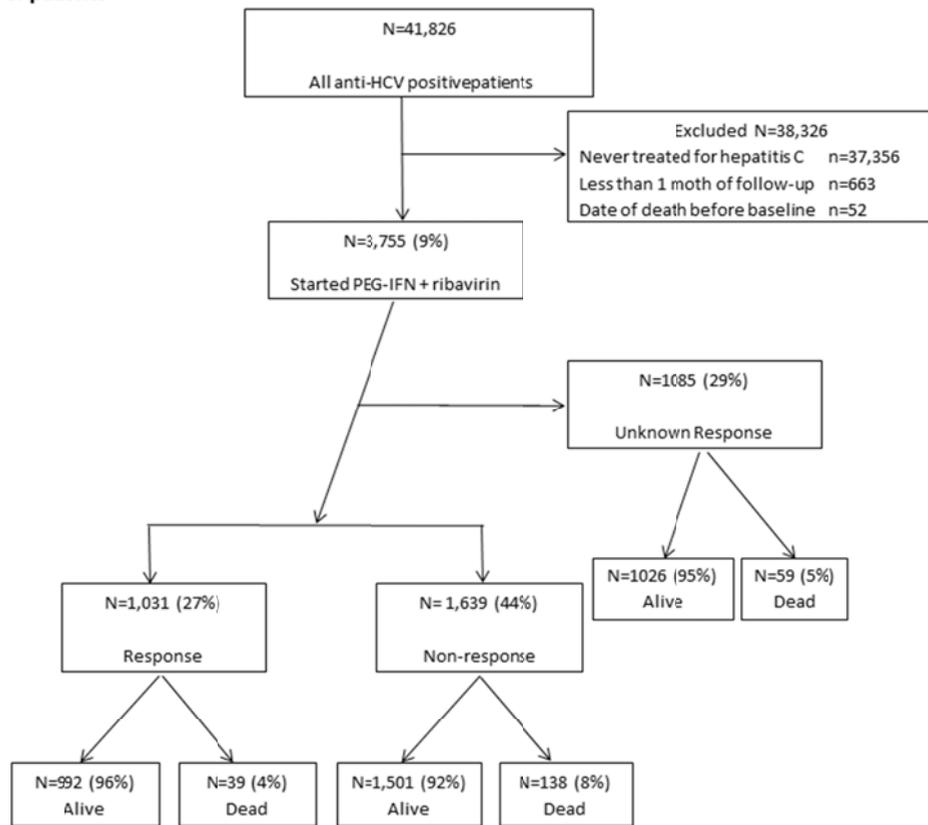
**Figure 3:** Adjusted hazard ratio for all-cause mortality according to HCV treatment response.

Adjustments were made for pre-specified demographic-, HIV- and hepatitis-related factors in three separate Cox regression models as well as for all factors combined.

**Figure 4:** The figure shows the cumulative risk of liver-related death in the three HCV treatment response groups

**Figure 5:** The figure shows the adjusted hazard ratio for liver-related death according to HCV treatment response. Adjustments were made for pre-specified demographic-, HIV- and hepatitis-related factors in three separate Cox regression models as well as for all factors combined.

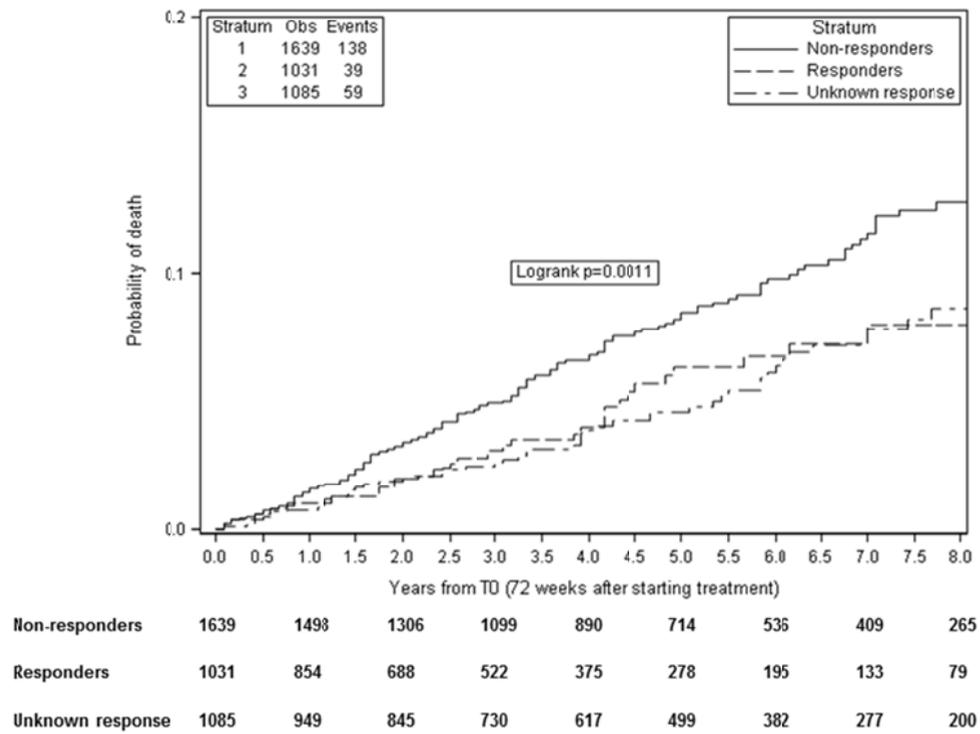
Figure 1: Selection of patients



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Figure 2

### Cumulative risk of all-cause mortality

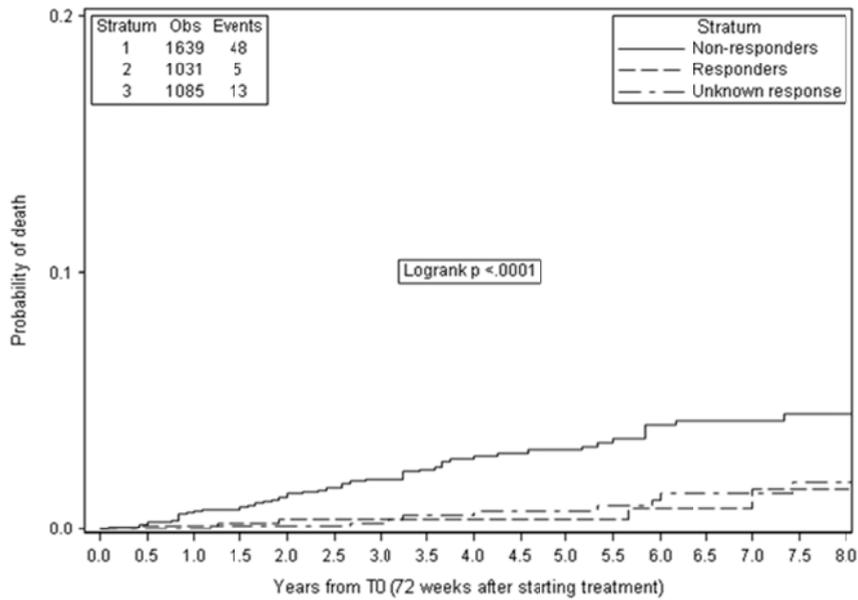


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Figure 4

### Cumulative risk of liver-related death

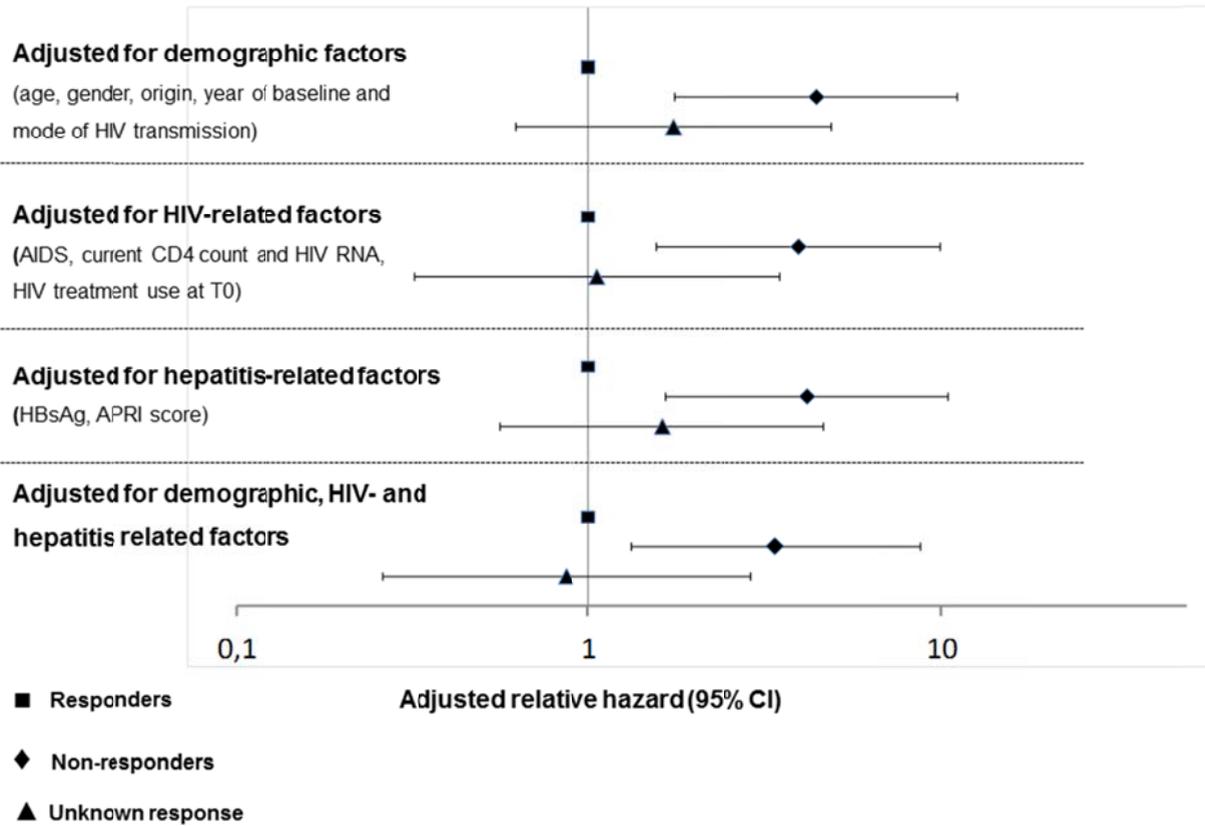


Non-responders	1639	1498	1306	1099	890	714	536	409	265
Responders	1031	854	688	522	375	278	195	133	79
Unknown response	1085	949	845	730	617	499	382	277	200

ACCV

Figure 5

### Hazard ratio for liver-related death



ACCCV

Table 1. Patient characteristics at the date of HCV treatment initiation

Characteristics	Responders N= 1031	Non-responders N= 1639	Unknown response N= 1085	p-value*	Total N= 3755
Age, median years (IQR)	42 (37, 46)	42 (37, 46)	41 (37, 46)	0.672	42 (37, 46)
Female, n (%)	210 (20.4%)	401 (24.5%)	245 (22.6%)	0.048	856 (22.8%)
Year of treatment initiation, median (IQR)	2007 (2005, 2009)	2005 (2003, 2008)	2005 (2003, 2008)	<.001	2006 (2003, 2008)
Region of birth, n (%)				0.002	
Europe	789 (83.2%)	1328 (87.8%)	820 (82.6%)		2937 (85.1%)
Other	83 (8.1%)	127 (7.7%)	92 (16.1%)		302 (8.0%)
Unknown	159 (16.8%)	184 (12.2%)	173 (17.4%)		516 (14.9%)
Mode of HIV transmission, n (%)				<.001	
MSM	322 (31.2%)	211 (12.9%)	130 (12.0%)		663 (17.7%)
Heterosexual contact	133 (12.9%)	216 (13.2%)	169 (15.6%)		518 (13.8%)
Injecting drug use	467 (45.3%)	1049 (64.0%)	693 (63.9%)		2209 (58.8%)
Other/unknown	109 (10.6%)	163 (9.9%)	93 (8.6%)		365 (9.7%)
Prior AIDS diagnosis, n (%)	226 (21.9%)	443 (27.0%)	254 (23.4%)	<.001	923 (24.6%)
On ART, n (%)	864 (83.8%)	1429 (87.2%)	927 (85.4%)	0.048	3220 (85.8%)
CD4 count, median (IQR) cells/mm <sup>3</sup>	455 (180, 656)	405 (170, 582)	447 (248, 627)	<.001	423 (200, 619)
HIV-RNA, median (IQR) log <sub>10</sub> cp/mL	3.01 (1.96, 4.34)	3.04 (1.72, 4.14)	2.97 (1.90, 4.13)	0.383	3.01 (1.84, 4.17)
HCV RNA, median (IQR) log <sub>10</sub> IU/mL	5.85 (5.11, 6.34)	6.03 (5.51, 6.60)	5.98 (5.53, 6.51)	<.001	5.95 (5.35, 6.51)
HCV genotype 1, n (%)*	274 (26.6%)	371 (22.6%)	158 (14.6%)	<.001	803 (21.4%)
HBsAg-positive, n (%) <sup>#</sup>	46 (3.8%)	42 (5.4%)	29 (4.2%)	<.001	117 (4.4%)
Haemoglobin, median (IQR) g/dL	15 (12, 16)	15 (13, 16)	15 (14, 16)	0.046	15 (13, 16)
Platelet count, median (IQR) 10 <sup>9</sup> /L	168 (123, 216)	171 (124, 221)	178 (131, 229)	0.006	173 (126, 222)
ALT, median (IQR) IU/L	95 (51, 164)	71 (44, 121)	71 (44, 112)	<.001	71 (44, 112)
AST, median (IQR) IU/L	65 (41, 122)	59 (39, 95)	55 (37, 85)	<.001	60 (39, 100)
APRI score, median (IQR)**	0.9 (0.5, 2.2)	0.8 (0.5, 1.7)	0.8 (0.5, 1.4)	<.001	0.8 (0.5, 1.7)

MSM: men who have sex with men; ART: antiretroviral therapy; HBsAg: hepatitis B surface antigen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; APRI: AST to platelet ratio index

\*N with data: 1437

<sup>#</sup>N with data= 2653

\*\* N with data=2330