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Increased mortality in HIV/HCV-coinfected compared to HCV-monoinfected patients in the DAA era due to non-liver-related death

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18 Dominique Salmon, Fabrice Carrat, Linda Wittkop
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27 **Clinical trial number:**

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30 ANRS CO13 HEPAVIH: NCT03324633
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34 ANRS CO22 HEPATHER: ClinicalTrials.gov Identifier: NCT01953458
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37 **Data availability statement:**
38

39
40 The ANRS CO13 HEPAVIH cohort is a French nationwide cohort sponsored by the
41 ANRS (France REcherche Nord&sud Sida-hiv Hepatites). Data is owned by ANRS and
42 there are also legal restrictions to share data publicly. Nonetheless, data can be
43 accessed upon demand to the scientific committee and the ANRS which can allow a
44 contractual access for collaboration purposes (laure.esterle@u-
45 bordeaux.fr/secretariat-clinique @anrs.fr). Applicants will be asked to complete a
46 Research Application Form specifying details for their planned study which will then be
47 reviewed by the ANRS CO13 Hepavih Scientific committee. The ANRS CO13 Hepavih
48 cohort is keen to promote collaboration among researchers and to see our unique co-
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infected HIV-HCV patients database and biobank used in studies which meet our ethics and consenting process.

ABSTRACT

Background & Aims: Direct acting antivirals (DAA) lead to high sustained virological response (SVR) rates and decreased the risk of disease progression. We compared SVR rates and all-cause, liver- and non-liver-related deaths, liver-related events and non-liver-related cancers in HIV/HCV co-infected and HCV mono-infected participants from two French cohort studies after initiation of DAA treatment.

Methods: Up to 4 HCV mono-infected participants from the ANRS CO22 HEPATHER cohort were matched on age and sex to each HIV/HCV co-infected from the ANRS CO13 HEPAVIH cohort; both are nationwide, prospective, multicentre and observational. Participants initiated DAA between March 2014 and December 2017. Cox proportional Hazards models adjusted on age, sex, duration since HCV diagnosis, HCV transmission routes, HCV genotypes, cirrhosis, tobacco, alcohol consumption, and SVR (time dependent) were used.

Results: 592 HIV/HCV co-infected and 2049 HCV mono-infected participants were included. Median age was 53.3 years (interquartile range: 49.6-56.9) and 52.9 years (49.6 ; 56.7), and 1498 (73.1%) and 436 (73.6%) were men, and 159 (28.8%) and 793 (41.2%) were cirrhotic, respectively. SVR was observed in 92.9% and 94.6%, respectively. HIV co-infection was associated with higher risk of all-cause death (hazard ratio [HR] 1.93; 95% confidence interval [CI] 1.01-3.69), non-liver-related death (HR 2.84; 95%CI 1.27-6.36) and non-liver-related cancer (HR 3.26; 95%CI 1.50-7.08), but not with liver-related-death (HR 1.04; 95%CI 0.34-3.15) or liver-related events (HR 0.66; 95% CI 0.31-1.44).

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Conclusion: After DAA treatment, HIV co-infected had similar SVR rates and risk of liver-related deaths and events compared to HCV mono-infected but higher risk of all-cause and non-liver-related deaths and non-liver-related cancers.

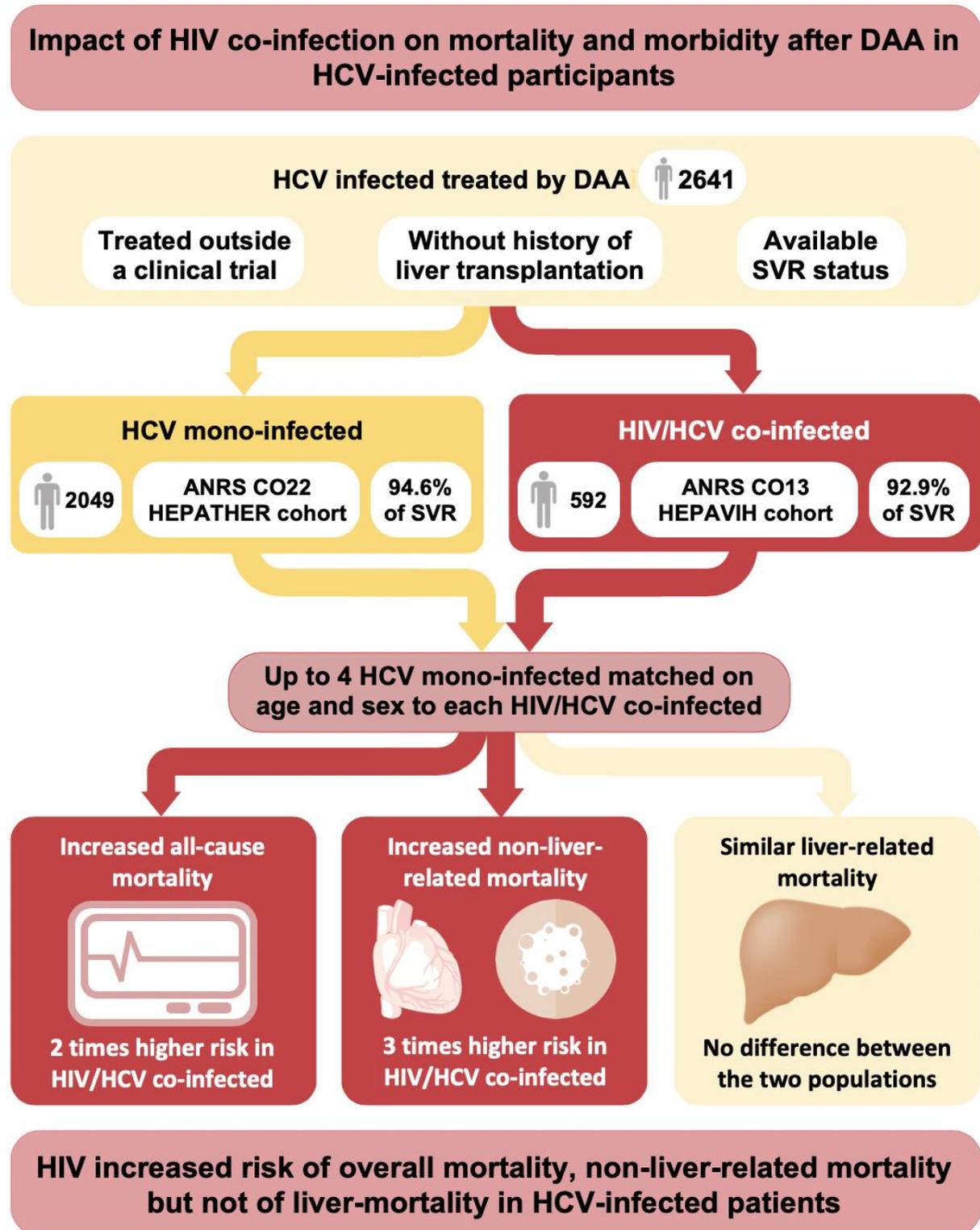
Abstract (259 words/275 words allowed)

Lay summary: We compared the risk of several clinical events in participants infected by human immunodeficiency virus and hepatitis C virus with those infected with hepatitis C virus alone, matched on age and sex, after treatment with contemporary direct acting antivirals. We found a higher risk of all-cause deaths, non-liver-related deaths and non-liver-related cancers in participants co-infected with the human immunodeficiency virus and hepatitis C virus, and no differences for the risk of liver-related deaths or events.

Highlights:

- Similar rates of SVR between HIV/HCV co-infected and HCV mono-infected participants
- Higher risk of all-cause deaths, non-liver-related deaths and cancers in HIV/HCV co-infected
- Similar risk of liver-related deaths and liver-related events in both populations

Graphical abstract:



INTRODUCTION

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2
3 Hepatitis C virus (HCV) infection can lead to several liver-related (e.g liver
4 decompensation, hepatocellular carcinoma [HCC], liver-related deaths)¹ and non-liver-
5 related (e.g cardiovascular², non-liver cancer³, non-liver-related deaths⁴) events.
6
7 Owing to similar transmission routes, HCV co-infection is common in patients infected
8 with human immunodeficiency virus (HIV)⁵. Among HIV/HCV co-infected patients, risk
9 factors for HCV-related events included detectable HIV viral load and low levels of CD4
10 counts^{1,6}. However, in the era of combination antiretroviral therapy risk, HIV- and HCV-
11 related complications have decreased substantially^{7,8}. Direct-acting antivirals (DAA)
12 lead to a sustained virological response (SVR; corresponding to HCV cure) in more
13 than 90% of treated patients, both in HCV mono-infected patients and in HIV/HCV co-
14 infected patients^{9,10}. HCV cure positively affects the course of HCV infection, both in
15 HCV mono-infected and in HIV/HCV co-infected patients¹¹⁻¹⁷. Nevertheless, disease
16 evolution after DAA treatment in HIV/HCV co-infected compared with HCV mono-
17 infected patients has rarely been studied. Our main objectives were to compare SVR
18 rates as well as risk of all-cause death, liver-related and non-liver-related deaths, liver-
19 related events, and non-liver-related cancers, between HIV/HCV co-infected and HCV
20 mono-infected after DAA initiation using data from two large, prospective, nationwide
21 French cohort studies.
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POPULATION AND METHODS

Patients

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54 HIV/HCV co-infected participants from the ANRS CO13 HEPAVIH cohort
55 (ClinicalTrials.gov Identifier: NCT03324633) and HCV mono-infected participants from
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1 the ANRS CO22 HEPATHER cohort (ClinicalTrials.gov Identifier: NCT01953458) were
2 included. Both are multicentre, prospective, nationwide French cohort studies.
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4 The ANRS CO13 HEPAVIH cohort started in 2005 and included HIV infected adults
5 with past or present HCV infection (2005-2010). From 2011, patients treated with first-
6 generation protease inhibitor HCV treatments, and from 2014 onwards patients treated
7 by any anti-HCV treatment, were eligible for enrolment. The main objectives of the
8 study are to characterize the natural history of HCV infection, to identify factors
9 associated with the development of liver complications, and to study the interactions
10 between HIV and HCV. From 2011 onwards, one of the main objectives was to study
11 the efficacy and safety of anti-HCV treatments in everyday clinical practice.
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14 The ANRS CO22 HEPATHER cohort started in 2012 and included participants with
15 active or inactive hepatitis B virus or past or present HCV infection. The main objectives
16 of the study are to quantify the clinical efficacy and safety of new hepatitis treatments
17 in everyday clinical practice. The main exclusion criteria are HIV co-infection and
18 ongoing treatment for HCV at inclusion. We included only participants with chronic
19 HCV infection in the current analysis.
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22 Follow-up visits are scheduled annually in both studies with supplementary visits
23 during anti-HCV treatment. Participants with cirrhosis in the ANRS CO13 HEPAVIH
24 cohort attend a supplementary visit every 6 months.
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27 Written informed consent was obtained from all participants. Both studies followed the
28 ethical principles laid out by the World Medical Association (Declaration of Helsinki)
29 and were approved by an Institutional Review board (Comité de Protection des
30 Personnes (CPP) Ile de France III, Paris, France – ANRS CO13 HEPAVIH and ANRS
31 CO22 HEPATHER).
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Participants treated with DAA (with or without ribavirin and/or peg-interferon) between 1st March 2014 and 31st December 2017, who were not enrolled in a clinical trial, with no history of liver transplantation and with an available SVR status were included in the present analysis. Participants with previous liver-related events or non-liver-related cancers were excluded from the analyses that assessed the risk of these events. Baseline was defined as the date of DAA initiation.

For each co-infected participant, up to 4 HCV mono-infected participants were matched on age (± 3 years) at treatment initiation and sex.

Outcomes

The primary study outcomes were SVR rates and the time between baseline and the occurrence of a death from any cause, liver-related death, non-liver-related death, liver-related events, and non-liver-related cancers. Participants were classified as having reached SVR if they had undetectable HCV RNA at least 12 weeks after the end of DAA treatment. Participants with detectable HCV RNA at any time after the end of DAA treatment were classified as not having reached SVR. Cause of death was validated by an adjudication committee. Liver-related death was defined as that due to a liver-decompensation (liver encephalopathy, hepatorenal syndrome, oesophageal varices bleeding, oedemato-ascites decompensation, icterus), HCC or liver transplantation. Non-liver-related death was defined as death from any other cause. Liver-related events were defined as the occurrence of a liver decompensation, liver cancer (HCC or cholangiocarcinoma), liver transplantation or liver-related death. Non-liver-related cancer was defined as the occurrence of any non-liver-related cancer. Participants were followed until death (or a non-liver-related cancer or a liver-related event) or last follow-up visit, whichever came first.

Statistical analysis

1 SVR rates were compared between HIV/HCV co-infected and HCV mono-infected
2 patients according to DAA treatment (with/without ribavirin) overall, and stratified by
3
4 sex, cirrhosis, HCV genotype and prescribed HCV treatment duration (12 or 24 weeks).
5
6 Risk of all-cause death, liver-related death, non-liver-related death, liver-related events
7 and non-liver-related cancers between HIV/HCV co-infected and HCV mono-infected
8 patients was compared using cause-specific Cox proportional hazard models adjusted
9
10 on age at treatment initiation, sex, alcohol and tobacco consumption (both defined as
11
12 never, past or current), time since first HCV seropositivity, HCV transmission route
13
14 (drug use, sexual, transfusion, unknown, other), HCV genotype, SVR (as a time-
15
16 dependent variable) and cirrhosis. Cirrhosis was defined by cohort-specific algorithms.
17
18 For HIV/HCV co-infected participants, cirrhosis was defined as: an F4 classification on
19
20 the Metavir Score by liver biopsy at any time before DAA treatment; or liver-stiffness \geq
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22 12.5 kPa (assessed by FibroScan) in a 3-month window before the initiation of DAA;
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24 or a fibrosis-4 index value \geq 3.25 in a 3-month window before DAA initiation for
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26 participants without an available liver-stiffness value. For HCV mono-infected
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28 participants, cirrhosis was defined as a platelet count \leq 150,000/ml or a prothrombin
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30 time \leq 70%. These criteria were validated in patients who had been classified as having
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32 cirrhosis using other techniques \leq 1 year before, and up to 3 months after, the time of
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34 evaluation¹⁵. Participants who died from a cause other than that studied were censured
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36 at time of death.
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49 Confounding factors were identified using directed acyclic graph (DAG) methodology.
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51 We estimated predicted event probabilities over time for each event according to
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53 parameters estimated by the Cox models described above for HIV/HCV co-infected
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55 and HCV mono-infected participants. Therefore, we set all co-variables used in the
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57 model as follows: mean observed age and time since first seropositivity, male sex,
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1 infected by HCV genotype 1 due to drug use, non-consumers of alcohol and tobacco
2 and without cirrhosis. We compared participants with at least 1 missing datum for
3 variables included in the analysis to participants without missing data. Assuming data
4 were missing at random, missing data for explanatory variables included in the models
5 were imputed by multiple imputation methods using chained equations in R 3.6.2
6 software using mice package ¹⁸. Ten tables were generated by 10 iterations.
7 Quantitative variables were imputed using linear models and qualitative variables by
8 logistic regression or multinomial regression, as appropriate. Imputation models
9 included history of each event and of anti-HCV treatment, class and duration of DAA
10 treatment, platelets and albumin values, body mass index (BMI), and diabetes, in
11 addition to variables listed above and included in the multivariable models for the main
12 analyses. Normality of quantitative variables included in the imputation model was
13 checked graphically. As a sensitivity analysis, we studied the effect of HIV co-infection
14 on the risk of all-cause, liver-related and non-liver-related death, liver-related events
15 and non-liver-related cancer in complete case analysis. Cumulative incidences of each
16 event were estimated using the Fine and Gray methodology ¹⁹ in a sensitivity analysis.

38 **RESULTS**

39 **Baseline characteristics**

40 We included 592 HIV/HCV co-infected and 2049 HCV mono-infected participants.
41 Median age at treatment initiation was 52.9 (interquartile range [IQR]: 49.6-56.7) and
42 53.3 [IQR 49.6-56.9] years; and 73.6% and 73.1% were men (Table 1). Compared with
43 HCV mono-infected participants, HIV/HCV co-infected less frequently had cirrhosis
44 (28.8% vs 41.2%), had lower BMI (22.7 [IQR 20.2-25.3] vs 24.7 [IQR 22.3-27.5] kg/m²),
45 a higher proportion of current alcohol (53.4% vs 2.1%) and tobacco (60.6% vs 48.5%)
46 use, had HCV seropositivity for a longer time (18.0 [IQR 12.4-22.2] vs 14.5 [IQR 6.4-

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20.8] years), were less frequently infected by HCV genotype 1 (53.7% vs 63.6%) and more frequently infected by HCV genotype 4 (27.4% vs 15.0%).

Overall, 914 participants had at least one missing datum for variables included in the analysis models (145 in HIV/HCV co-infected and 769 in HCV mono-infected participants; Supplementary Table 1). Participants with missing data appeared to differ from participants without missing data for some characteristics in both populations (Supplementary Table 2).

SVR rates

Overall, 550 (92.9%) HIV/HCV co-infected and 1939 (94.6%) of HCV mono-infected reached SVR. In participants treated without ribavirin, SVR rates were 93.5% in HIV/HCV co-infected and 95.8% in HCV mono-infected participants whereas in participants treated with DAA and ribavirin, SVR rates were 91.0% in HIV/HCV co-infected and of 92.0% in HCV mono-infected participants (Table 2). HCV mono-infected cirrhotic participants appeared to have lower SVR rates than non-cirrhotic participants (respectively, 91.5% vs 97.7% in participants treated without ribavirin and 89.4% vs 95.8% in participants treated with DAA and ribavirin). Cirrhotic status did not seem to affect SVR rates in HIV/HCV co-infected participants (respectively, 93.0% vs 93.5% in participants treated without ribavirin and 91.1% and 92.0% in participants treated with DAA and ribavirin). SVR rates were inferior to 90% only in participants infected by HCV genotype 2 treated with DAA and ribavirin (83.3% in HIV/HCV co-infected and 80.0% in HCV mono-infected respectively).

Risk of death

All-cause death

1 After a median follow-up of 1.8 years [1.1 ; 2.5] in HIV/HCV co-infected and 2.3 years
2 [1.6 ; 3.1] in HCV mono-infected participants, 82 participants died. Cumulative
3
4 incidence of death is shown in Supplementary Fig. 1A. Twenty-six deaths were
5
6 observed in HIV/HCV co-infected participants (8 liver-related, 6 non-liver-related
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8 cancer, 3 cardiovascular, 1 HIV and 8 other) and 56 in HCV mono-infected participants
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10 (28 liver-related, 3 non-liver-related cancer, 4 cardiovascular and 21 other)
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12 (Supplementary Table 3). Among the 26 HIV/HCV co-infected participants who died,
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14 23 (88.5%) had reached SVR. Of the 56 HCV mono-infected participants who died, 46
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16 (82.1%) had reached SVR.
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21 After adjusting on confounding factors, HIV co-infection was associated with a higher
22
23 risk of all-cause death (HR 1.93, confidence interval at 95% (CI) 1.01-3.69) in HCV
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25 infected participants after DAA treatment was observed (Table 3 and Fig. 1A). The
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27 association between HIV co-infection and risk of all-cause death was similar in
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29 complete case analysis (HR 1.99, 95% CI 1.04-3.83) (Supplementary Table 4).
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34 ***Liver-related death***

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36 In HIV/HCV co-infected participants, 8 liver-related-deaths (5 due to an HCC, 2 liver
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38 decompensation, 1 liver transplantation) occurred after initiation of DAA therapy, of
39
40 which 6 were observed in cirrhotic participants, one in a non-cirrhotic participant and
41
42 one in a participant without available data on cirrhosis at initiation of DAA treatment.
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44 Among HCV mono-infected participants, 28 liver-related deaths were observed (15
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46 due to an HCC, 9 liver decompensation, 2 liver transplantation, 2 cholangiocarcinoma),
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48 of which 26 were observed in cirrhotic participants (Supplementary Table 3 and
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50 Supplementary Fig. 1B). Among the 8 liver-related deaths observed in HIV/HCV co-
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52 infected, 6 occurred in those who reached SVR; 21 HCV mono-infected participants
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54 died after reaching SVR.
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1 After adjusting on confounding factors, no association between HIV co-infection and
2 the risk of liver-related death was found (HR 1.04; 95% CI 0.34-3.15) in HCV infected
3 participants treated with DAA (Table 3 and Fig. 1B). In complete case analysis, there
4 was also no effect of HIV co-infection on the risk of liver-related death after DAA
5 treatment (HR 1.09; 95% CI 0.35-3.35) (Supplementary Table 4).
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11 ***Non-liver-related death***

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13 Forty-six participants died from non-liver-related causes. In HIV/HCV co-infected
14 participants, 18 died from a non-liver-related cause (6 non-liver-related cancer, 3
15 cardiovascular, 1 HIV, 8 other) and 28 in HCV mono-infected participants (3 non-liver-
16 related cancer, 4 cardiovascular, 21 other) (Supplementary Table 3 and
17 Supplementary Fig. 1C). Seventeen HIV/HCV co-infected participants and 25 HCV
18 mono-infected participants died after reaching SVR.
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31 After adjustment, HIV co-infection was associated with a higher risk of non-liver-related
32 death (HR 2.84 95% CI 1.27-6.36) compared with HCV infected participants treated
33 with DAA (Table 5 and Fig. 1C). In complete case analysis HIV co-infection was also
34 associated with an higher risk of non-liver-related death (HR: 2.92 [1.29 ; 6.60])
35 (Supplementary Table 4).
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45 **Risk of liver-related events and non-liver-related cancers**

46 ***Liver-related events***

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48 Eighty-three participants developed at least one liver-related event after the initiation
49 of DAA therapy: 17 HIV/HCV co-infected participants (8 liver-decompensation, 5 HCC,
50 4 liver-related deaths) and 66 HCV mono-infected (55 HCC, 10 liver decompensation,
51 1 liver-related death) (Supplementary Table 3 and Supplementary Fig. 2A). In
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1 HIV/HCV co-infected participants, 11 participants developed a first liver-related event
2 after reaching SVR, 4 developed a liver-related event then reached SVR, and 2 liver-
3 related events occurred in participants who did not reach SVR. In HCV mono-infected
4 participants, 41 participants developed a liver-related event after reaching SVR, 11
5 before reaching SVR, and 14 participants developed a liver-related event and did not
6 reach SVR.
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13 In adjusted analysis, HIV infection was not associated with risk of liver-related events
14 (HR 0.66; 95% CI 0.31-1.44) in HCV infected participants treated with DAA (Table 4
15 and Fig. 2A). Similar results were found in complete case analysis (HR = 0.40 [0.20 ;
16 0.81]).
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25 **Non-liver-related cancers**

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27 Non-liver-related cancers occurred in 50 participants; 22 in HIV/HCV co-infected
28 participants and 28 in HCV mono-infected participants. Among the non-liver-related
29 cancers observed in HIV/HCV co-infected participants, 2 were acquired immune
30 deficiency syndrome (AIDS) defining events (1 cervical cancer, 1 non-Hodgkin's
31 lymphoma) (Supplementary Table 3 and Supplementary Fig. 2B). Among HIV/HCV co-
32 infected participants, 15 developed a non-liver-related cancer after reaching SVR, 6
33 developed a non-liver-related cancer and then reached SVR, and 1 who did not reach
34 SVR developed a non-liver-related cancer. In HCV mono-infected participants, 26
35 developed a non-liver-related cancer after reaching SVR, 1 reached SVR after
36 developing a non-liver-related cancer, and 1 did not reach SVR and developed a non-
37 liver-related cancer.
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54 After adjustment, HIV co-infection was significantly associated with a higher risk of
55 non-liver-related cancer (HR 3.26; 95% CI 1.50-7.08) compared with HCV infected
56 participants treated by DAA (Table 5 and Fig. 2B). In complete case analysis, HIV co-
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1 infection was also associated with an higher risk of non-liver-related cancer (HR 3.26
2 [1.49 ; 7.10]) (Supplementary Table 5).
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5 **DISCUSSION**

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9 In a population of HCV infected participants treated with DAA, we observed similar
10 SVR rates between HIV/HCV co-infected and HCV mono-infected participants. After
11 adjustment on confounding factors, HIV co-infection was associated with an increased
12 risk of all-cause death after DAA initiation compared with HCV mono-infected
13 participants. This increased risk of all-cause death appears due to a higher risk of non-
14 liver-related death. Indeed, after adjustment on confounding factors, HIV co-infection
15 was strongly associated with the risk of non-liver-related death and was not associated
16 with the risk of liver-related death in participants infected by HCV. HIV/HCV co-infected
17 also had a higher risk than HCV mono-infected participants of developing non-liver-
18 related cancers after DAA initiation. Finally, we did not observe an association between
19 HIV co-infection and the risk of liver-related events, after DAA initiation in HCV infected
20 participants.
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39 In this study, the SVR rates were high and were similar between HIV/HCV co-infected
40 and HCV mono-infected participants, overall and by subgroup. These results are in
41 agreement with previous report ²⁰⁻²². Neukam et al. reported a lower rate of SVR in an
42 HIV/HCV co-infected cohort compared to an HCV mono-infected cohort ²³.
43 Nevertheless, in their study, HIV co-infected were more frequently cirrhotic, infected
44 by HCV genotype 4 and had been exposed to anti-HCV therapy, which may explain
45 the difference in SVR rates observed between the two populations.
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56 We compared the risk of all-cause death between HIV/HCV co-infected and HCV
57 mono-infected participants treated by DAA. Similar to the study by Salmon et al. ²⁴,
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1 which included cirrhotic participants from the ANRS CO13 HEPAVIH cohort (the same
2 cohort as in the present study) and the ANRS CO12 CirVir cohort (a cohort including
3 Child A biopsy-proven cirrhosis), we observed a higher risk of all-cause death, linked
4 to a higher risk of non-liver-related death, in HIV co-infected compared to HCV mono-
5 infected participants.
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12 In our study, the higher risk of all-cause death in HIV/HCV co-infected was essentially
13 due to a higher risk of non-liver-related death, whereas the risk of liver-related death
14 was similar between the two populations. To our knowledge, no other study has
15 compared the risk of non-liver-related death between HIV/HCV co-infected and HCV
16 mono-infected participants after DAA therapy. Salmon et al. also identified an higher
17 risk of non-liver-related death in HIV co-infected participants compared to HCV mono-
18 infected participants in a cirrhotic population that included both DAA-treated and
19 untreated participants ²⁴. From the 18 non-liver-related deaths observed in HIV/HCV
20 co-infected participants, only 1 was related to HIV. Several studies in HIV populations
21 highlight a high risk of non-AIDS defining cancers ^{25,26}. The higher risk of non-AIDS
22 death in HIV infected patients can be explained by chronic inflammation and immune
23 system dysregulation due to the HIV infection ^{25,27-29}, but also to high-risk behaviours
24 such as tobacco smoking and alcohol consumption ^{30,31}. High-risk behaviours were
25 observed in our study in HIV/HCV co-infected participants, with high rates of tobacco
26 (60.6%) and alcohol (53.4%) consumption. The higher risk of non-liver-related cancers
27 observed in HIV/HCV co-infected participants treated with DAA compared to HCV
28 mono-infected participants could not be explained by a higher incidence of AIDS
29 defining malignancies. Indeed, among the 22 non-liver-related cancers observed in
30 HIV/HCV co-infected participants, only 2 (non-Hodgkin's lymphoma and cervical
31 cancer) were AIDS-defining. As for non-liver-related death, the higher risk of non-liver-
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1 related cancers in HIV/HCV co-infected participants could be partly explained by the
2 immunodepression induced by HIV. HIV induced immunodeficiency appears to
3
4 increase the risk of non-AIDS-defining cancers through the reduced control of
5
6 oncogenic virus infection and the reduced surveillance of malignant cells ³². The
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8 chronic inflammation and coagulation defects induced by HIV could also explained the
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10 higher risk of non-AIDS-defining cancers ³³. Finally, the higher risk of non-liver-related
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12 cancers in HIV co-infected participants may also be explained by the higher
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14 consumption of alcohol and tobacco in this population ^{30,31}.
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20 Finally, we observed similar risks of liver-related death and liver-related events
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22 between HIV/HCV co-infected and HCV mono-infected participants after DAA
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24 treatment. In two previous studies, no differences were found between these
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26 populations. Salmon et al. did not observe any difference in risk of liver
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28 decompensation and HCC between HIV/HCV co-infected and HCV mono-infected
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30 cirrhotic participants ²⁴. In another study comparing participants with advanced fibrosis,
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32 co-infection by HIV was not associated with the risk of liver complications in HCV
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34 participants who achieved SVR with DAA therapy ³⁴. Several reasons may explain
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36 these results. First, owing to French recommendations, HCV mono-infected appeared
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38 to be more frequently cirrhotic (41.2%) than HIV/HCV co-infected (28.8%). Second, in
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40 this study, co-infected patients had an optimal immune virological status, demonstrated
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42 by the median CD4 value was of 614.0 cells/mm³, 97.5% were treated by antiretroviral
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44 therapy and 86.8% had an undetectable HIV viral load at DAA therapy initiation. These
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46 factors are protective factors against the development of a liver-related event ^{1,6}. Third,
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48 potentially better follow-up of HIV co-infected participants before the emergence of
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50 DAA therapies, due to their HIV infection could have led to better control of HCV
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52 infection and a decreased risk of liver-related events.
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1 This study has several limitations. First, owing to recommendations for initiation of DAA
2 treatment, HCV mono-infected were more frequently cirrhotic than HIV/HCV co-
3 infected at treatment start-up. This may explain why we did not observe differences
4 between HIV/HCV co-infected and HCV mono-infected participants in the risk of liver-
5 related events and liver-related death. Even if all analysis were adjusted for cirrhosis,
6 residual confounding could persist. Second, as we included participants from two
7 different cohorts, data on events, specifically non-liver-related events, were not
8 necessarily collected in the same way, which may have led to misclassification. In
9 addition, a supplementary semiannual visit was scheduled for cirrhotic HIV/HCV co-
10 infected participants but not for cirrhotic HCV mono-infected participants. This
11 difference in follow-up could have led to earlier diagnosis of liver-related events and
12 non-liver-related cancers in cirrhotic HIV/HCV co-infected participants, and thus to an
13 overestimation of the effect of HIV co-infection on the risk of these events.
14 Nevertheless, the recommendation of semiannual hepatic ultrasonography in cirrhotic
15 HCV mono-infected participants was highly respected. In addition, event collection was
16 independent of follow-up. Thus, it seems unlikely that this supplementary semiannual
17 follow-up in HIV/HCV co-infected affected the estimated association between HIV co-
18 infection and the risk of events in HCV infected participants. Furthermore, we cannot
19 exclude closer follow-up of events in HIV/HCV co-infected compared to HCV mono-
20 infected participants due to their HIV infection, leading to overestimation of the risk of
21 non-liver-related cancers induced by HIV infection. However, both cohorts used similar
22 procedures to report all serious adverse events that occurred during the follow-up, with
23 extensive data-quality controls and monitoring. Third, participants with missing data for
24 SVR were excluded from the analysis. It can be expected that missing data for SVR
25 was related to higher risks of liver-related and non-liver-related events, potentially

1 leading to an underestimation of events in both cohorts. Fourth, to study the risk of
2 non-liver-related events in HIV/HCV co-infected participants treated with DAA a
3 comparison with HIV infected participants who were never infected by HCV, or with the
4 general population, may be more suitable. Finally, we matched on age and sex, which
5 led to the exclusion of 76 HIV/HCV co-infected participants (12.8% of the total
6 population). The reduced sample size could have led to a loss of statistical power.
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10 This study also had several strengths. First, this study included more participants than
11 similar previous studies ^{24,34}. Second, the main confounding factors identified using
12 DAG methodology were included in our models, limiting the risk of confusion bias.
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14 Third, both cohorts are prospective, nationwide French cohorts, underlying strict data
15 quality and monitoring rules, allowing for high-quality data. Finally, to our knowledge,
16 this is the first study comparing the risk of non-liver-related cancers between HIV/HCV
17 co-infected and HCV mono-infected participants after DAA therapy.
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32 In conclusion, in a population of HIV/HCV co-infected participants with a controlled HIV
33 infection, no difference of SVR rates after DAA therapy was observed compared with
34 HCV mono-infected participants. After DAA therapy, we observed an almost twofold
35 higher risk of all-cause death, due to a higher risk of non-liver-related deaths in
36 HIV/HCV co-infected compared to HCV mono-infected participants. We also observed
37 a threefold higher risk of non-liver-related cancer in HIV/HCV co-infected compared to
38 HCV mono-infected participants, whereas no differences were observed in risk of liver-
39 related death or events after DAA therapy.
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Table 1. Characteristics at time of DAA initiation according to HIV co-infection in HCV infected participants from the ANRS CO13 HEPAVIH and ANRS CO22 HEPATHER cohorts.

| Characteristics | HIV ⁺ /HCV* co-infected (<i>n</i> = 592) | | HCV* mono-infected (<i>n</i> = 2049) | |
|---|--|------------------------|---------------------------------------|------------------------|
| | N | Median [IQR*] or n (%) | N | Median [IQR*] or n (%) |
| Age (years) | 592 | 52.9 [49.6 ; 56.7] | 2049 | 53.3 [49.6 ; 56.9] |
| Men | 592 | 436 (73.6%) | 2049 | 1498 (73.1%) |
| BMI^A (kg/m²) | 586 | 22.7 [20.2 ; 25.3] | 2042 | 24.7 [22.3 ; 27.5] |
| < 18.5 | | 61 (10.4%) | | 53 (2.6%) |
| 18.5 ; 25.0[| | 370 (63.1%) | | 1043 (51.1%) |
| 25.0 ; 30.0[| | 122 (20.8%) | | 693 (33.9%) |
| ≥ 30 | | 33 (5.6%) | | 253 (12.4%) |
| Alcohol consumption | 581 | | 1375 | |
| Never | | 134 (23.1%) | | 832 (60.5%) |
| Past | | 137 (23.6%) | | 514 (37.4%) |
| Current | | 310 (53.4%) | | 29 (2.1%) |
| Tobacco consumption | 578 | | 2045 | |
| Never | | 98 (17.0%) | | 504 (24.6%) |
| Past | | 130 (22.5%) | | 550 (26.9%) |
| Current | | 350 (60.6%) | | 991 (48.5%) |
| Diabetes | 592 | 56 (9.5%) | 2049 | 228 (11.1%) |
| Time since first HCV* seropositivity (years) | 566 | 18.0 [12.4. ; 22.2] | 2049 | 14.5 [6.4 ; 20.8] |
| HCV* contamination routes | 520 | | 2037 | |
| Drug use | | 325 (62.5%) | | 765 (37.6%) |
| Sexual | | 92 (17.7%) | | 21 (1.0%) |
| Transfusion | | 40 (7.7%) | | 476 (23.4%) |
| Unknown | | 57 (11.0%) | | 465 (22.8%) |

| | | | | |
|--|-----|-----------------------|------|-----------------------|
| Other | | 6 (1.2%) | | 310 (15.2%) |
| HCV* genotype | 583 | | 2034 | |
| 1 | | | | |
| 2 | | 313 (53.7%) | | 1293 (63.6%) |
| 3 | | 22 (3.8%) | | 80 (3.9%) |
| 4 | | 85 (14.6%) | | 334 (16.4%) |
| 5 | | 160 (27.4%) | | 306 (15.0%) |
| 6 | | 3 (0.5%) | | 21 (1.0%) |
| 7 | | | | |
| 8 | | | | |
| 9 | | | | |
| 10 | | | | |
| 11 | | | | |
| 12 | | | | |
| 13 | | | | |
| 14 | | | | |
| History of anti-HCV* treatment | 592 | 343 (57.9%) | 1927 | 1072 (55.7%) |
| Cirrhosis | 553 | 159 (28.8%) | 1927 | 793 (41.2%) |
| Platelets (10^3 cells/mm³) | 574 | 179.0 [138.0 ; 222.0] | 2029 | 185.0 [138.0 ; 233.0] |
| Albumin (g/L) | 469 | 42.0 [39.0 ; 44.2] | 1905 | 42.0 [38.8 ; 44.7] |
| Time since first HIV[‡] seropositivity (years) | 590 | 24.7 [18.8 ; 28.2] | - | - |
| CD4 count (cells/mm³) | 587 | 614.0 [411.0 ; 861.0] | - | - |
| ≥ 500 | | 375 (63.9%) | | - |
| 200 ; 500] | | 175 (29.8%) | | - |
| ≤ 200 | | 37 (6.3%) | | - |
| Undetectable HIV[‡] viral load | 562 | 488 (86.8%) | - | - |
| ARV^ψ intake | 592 | 577 (97.5%) | - | - |
| Time since ARV^ψ initiation (years) | 577 | 17.6 [10.9 ; 20.3] | - | - |

* Hepatitis C virus, ‡ Human Immunodeficiency virus, ¥ Interquartile range, Δ Body mass index, ψ Antiretroviral

Table 2. Sustained virological response according to HIV co-infection and use of ribavirin in HCV infected participants from the ANRS CO13 HEPAVIH and ANRS CO22 HEPATHER cohorts

| Characteristics | HIV [‡] /HCV* co-infected (<i>n</i> = 482) | | | | HCV* mono-infected (<i>n</i> = 1736) | | | |
|--|--|-------------|--------------------------|-------------------------|---------------------------------------|--------------|--------------------------|-------------------------|
| | DAA** | | DAA** + RBV ^ψ | | DAA** | | DAA** + RBV ^ψ | |
| | N | n (%) | N | n (%) | N | n (%) | N | n (%) |
| Overall | 447 | 418 (93.5%) | 145 | 132 (91.0%) | 1411 | 1352 (95.8%) | 638 | 587 (92.0%) |
| Men | 324 | 314 (93.8%) | 112 | 102 (91.1%) | 988 | 945 (95.6%) | 510 | 468 (91.8%) |
| Women | 123 | 114 (92.7%) | 33 | 30 (90.9%) | 423 | 407 (96.2%) | 128 | 119 (93.0%) |
| Cirrhotic | 114 | 106 (93.0%) | 45 | 41 (91.1%) | 434 | 397 (91.5%) | 359 | 321 (89.4%) |
| Non-cirrhotic | 306 | 286 (93.5%) | 88 | 81 (92.0%) | 897 | 876 (97.7%) | 237 | 227 (95.8%) |
| Treatment naïve | 213 | 198 (93.0%) | 36 | 32 (88.9%) | 645 | 630 (97.7%) | 209 | 196 (93.8%) |
| Treatment experienced | 234 | 220 (94.0%) | 109 | 100 (91.7%) | 691 | 650 (94.1%) | 381 | 348 (91.3%) |
| Genotype 1 | 258 | 243 (94.2%) | 55 | 51 (92.7%) | 1001 | 971 (97.0%) | 292 | 274 (93.8%) |
| Genotype 2 | 10 | 10 (100.0%) | 12 | 10 (83.3%) [§] | 25 | 25 (100.0%) | 55 | 44 (80.0%) ^Δ |
| Genotype 3 | 43 | 41 (95.3%) | 42 | 39 (92.9%) | 168 | 150 (89.3%) | 166 | 152 (91.6%) |
| Genotype 4 | 126 | 115 (91.3%) | 34 | 30 (88.1%) | 186 | 176 (94.6%) | 120 | 112 (93.3%) |
| Genotype 5/6/7 | 3 | 3 (100.0%) | 0 | - | 17 | 17 (100.0%) | 4 | 4 (100.0%) |
| Treated for 12 weeks | 338 | 312 (92.3%) | 82 | 74 (90.2%) | 1181 | 1138 (96.4%) | 437 | 401 (91.8%) |
| Treated for 24 weeks | 109 | 106 (97.2%) | 63 | 58 (92.1%) | 230 | 214 (93.0%) | 201 | 186 (92.5%) |
| Undetectable HIV[‡] viral load | 362 | 342 (94.5%) | 126 | 115 (91.3%) | - | - | - | - |
| Detectable HIV[‡] viral load | 62 | 55 (88.7%) | 12 | 11 (91.7%) | - | - | - | - |

* Hepatitis C virus, [‡]Human immunodeficiency virus, ** Direct acting antiviral, ^ψ Ribavirin, [§] Participants treated by Sofosbuvir + interferon (1), or Sofosbuvir (53) or Sofosbuvir + Simeprevir (1), ^Δ Participants treated by Sofosbuvir (11) or Sofosbuvir + Daclatasvir (1)

Table 3. Association between HIV co-infection and risk of all-cause, liver-related and non-liver-related death in HCV infected participants from the ANRS CO13 HEPAVIH and ANRS CO22 HEPATHER cohorts.

| | All-cause death | | Liver-related death | | Non-liver-related death | |
|--|--------------------|---------|---------------------|---------|-------------------------|---------|
| | HR* [CI95%**] | p-value | HR* [CI95%**] | p-value | HR* [CI95%**] | p-value |
| HCV[‡] mono-infected | Ref | 0.05 | ref | 0.95 | ref | 0.01 |
| HIV^Ψ/HCV[‡] co-infected | 1.93 [1.01 ; 3.69] | | 1.04 [0.34 ; 3.15] | | 2.84 [1.27 ; 6.36] | |

* Hazard ratio, ** Confidence interval at 95%, [‡]Hepatitis C virus, ^Ψ Human immunodeficiency virus

Adjusted on age, sex, time since first HCV seropositivity, HCV transmission routes, HCV genotype, cirrhosis, time dependent SVR, alcohol consumption and tobacco consumption

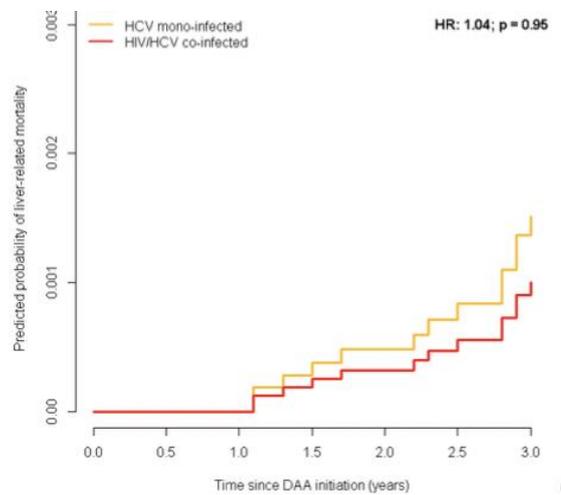
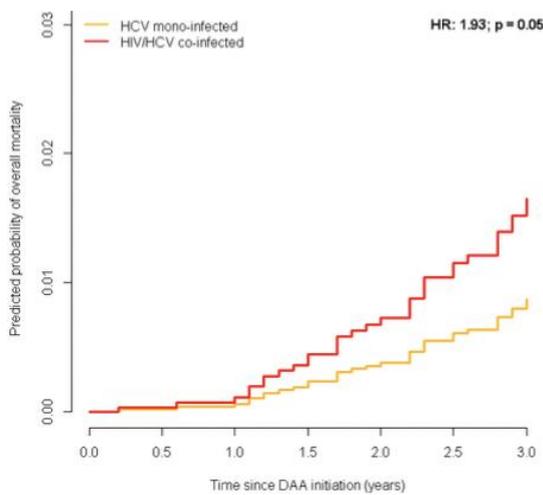
Table 4. Association between HIV co-infection and risk of liver-related events and non-liver-related cancers in HCV infected participants from the ANRS CO13 HEPAVIH and ANRS CO22 HEPATHER cohorts.

| | Liver-related events | | | Non-liver-related cancer | | |
|--|----------------------|---------------|---------|--------------------------|---------------|---------|
| | HR* | CI95%** | p-value | HR* | CI95%** | p-value |
| HCV[‡] mono-infected | ref | - | 0.30 | ref | - | < 0.01 |
| HIV^Ψ/HCV[‡] co-infected | 0.66 | [0.31 ; 1.44] | | 3.26 | [1.50 ; 7.08] | |

* Hazard ratio, confidence interval at 95%, [‡]Hepatitis C virus, ^ΨHuman Immunodeficiency virus

Adjusted on age, sex, time since first HCV seropositivity, HCV transmission routes, HCV genotype, cirrhosis, time dependent SVR, alcohol consumption and tobacco consumption

Fig. 1. Predicted probability over time of death according to HIV co-infection. (A) Predicted probability of all-cause death. **(B)** Predicted probability of liver-related death. **(C)** Predicted probability of non-liver-related death. Estimates reflect the probability of an event for 53-year-old, male participants infected by HCV genotype 1 due to drug use, seropositive for HCV for 15 years, non-alcohol, non tobacco consumer, without cirrhosis at time of DAA initiation. Estimated in participants from the ANRS CO13 HEPAVIH and ANRS CO22 HEPATHER cohorts, treated by DAA between March 2014 and December 2017

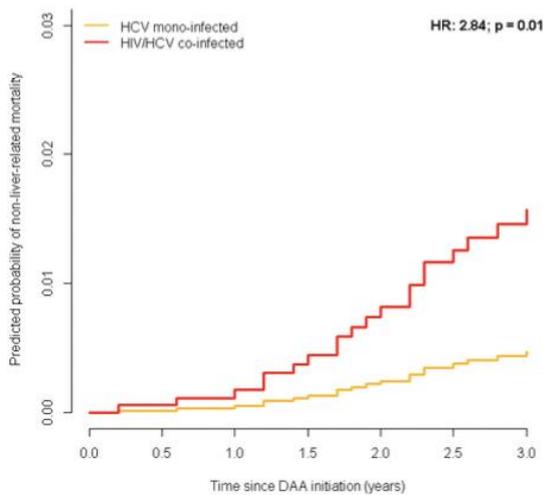


Patients at risk:

| | | | | |
|----------------|------|------|------|-----|
| HIV/HCV | 592 | 514 | 363 | 214 |
| HCV | 2047 | 1827 | 1419 | 967 |

Patients at risk:

| | | | | |
|----------------|------|------|------|-----|
| HIV/HCV | 592 | 514 | 363 | 214 |
| HCV | 2047 | 1827 | 1419 | 967 |

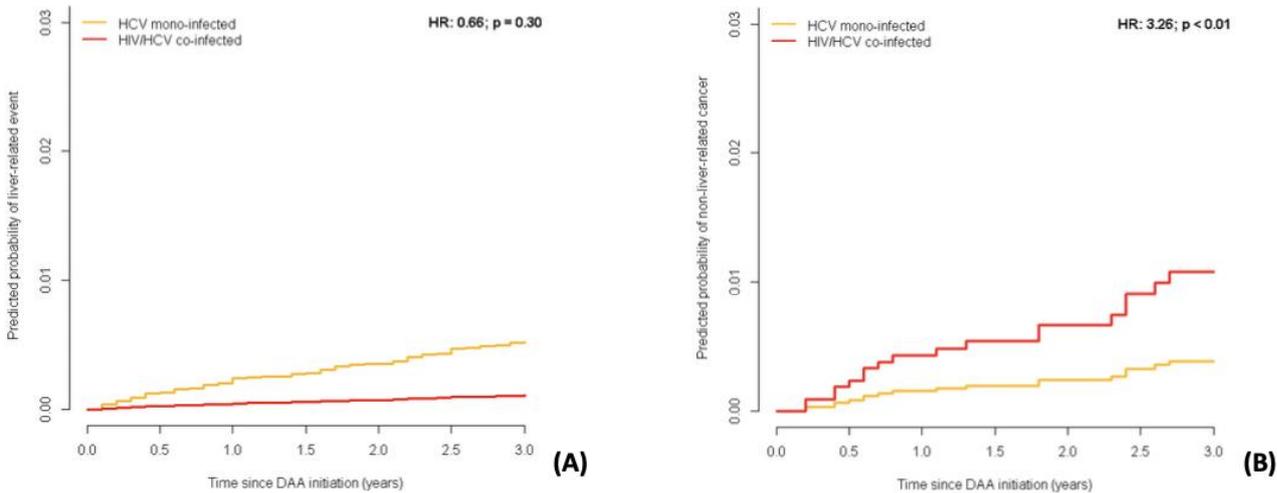


Patients at risk:

| | | | | |
|----------------|------|------|------|-----|
| HIV/HCV | 592 | 514 | 363 | 214 |
| HCV | 2047 | 1827 | 1419 | 967 |

Fig. 2. Predicted probability over time of events according to HIV co-infection.

(A) Predicted probability over-time of liver-related-events. (B) Predicted probability over-time of non-liver-related cancers. Estimates reflect the probability of an event for 53-year-old, male participants infected by HCV genotype 1 due to drug use, seropositive for HCV for 15 years, non-alcohol, non tobacco consumer, without cirrhosis at time of DAA initiation. Estimated in participants from the ANRS CO13 HEPAVIH and ANRS CO22 HEPATHER cohorts treated by DAA between March 2014 and December 2017.



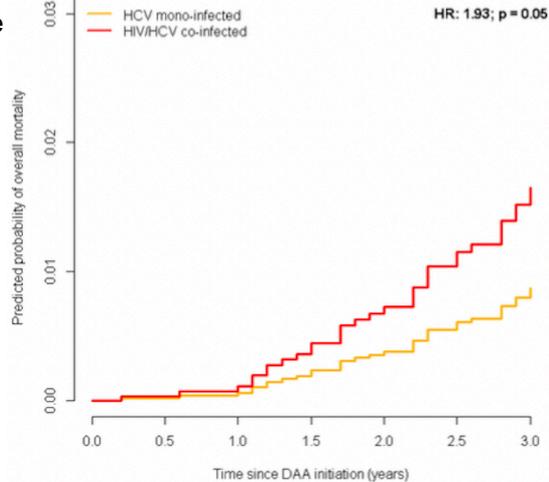
Patients at risk:

| | | | | |
|----------------|------|------|------|-----|
| HIV/HCV | 575 | 493 | 344 | 199 |
| HCV | 1848 | 1611 | 1236 | 807 |

Patients at risk:

| | | | | |
|----------------|------|------|------|-----|
| HIV/HCV | 548 | 459 | 335 | 189 |
| HCV | 2016 | 1787 | 1377 | 934 |

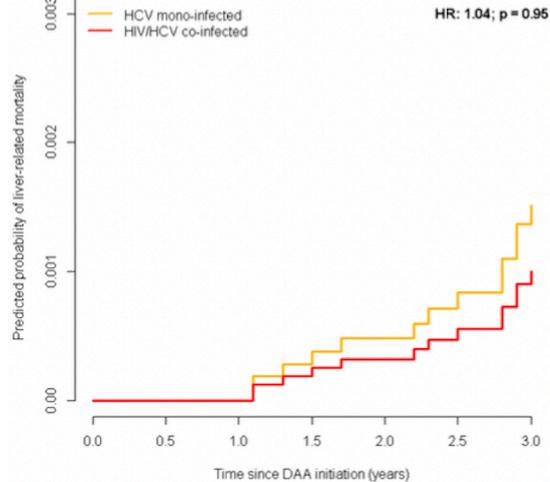
Figure



Patients at risk:

| | | | | |
|---------|------|------|------|-----|
| HIV/HCV | 592 | 514 | 363 | 214 |
| HCV | 2047 | 1827 | 1419 | 967 |

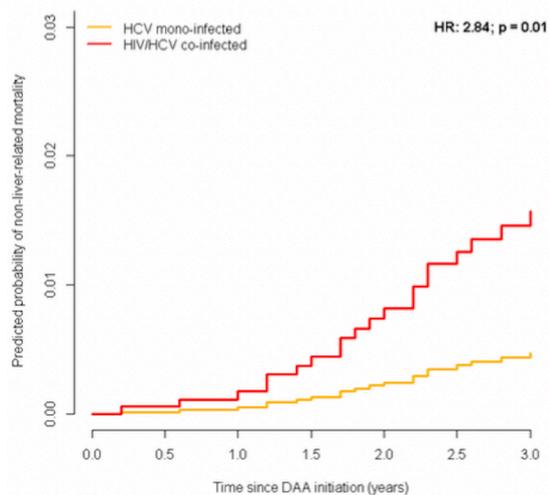
(A)



Patients at risk:

| | | | | |
|---------|------|------|------|-----|
| HIV/HCV | 592 | 514 | 363 | 214 |
| HCV | 2047 | 1827 | 1419 | 967 |

(B)

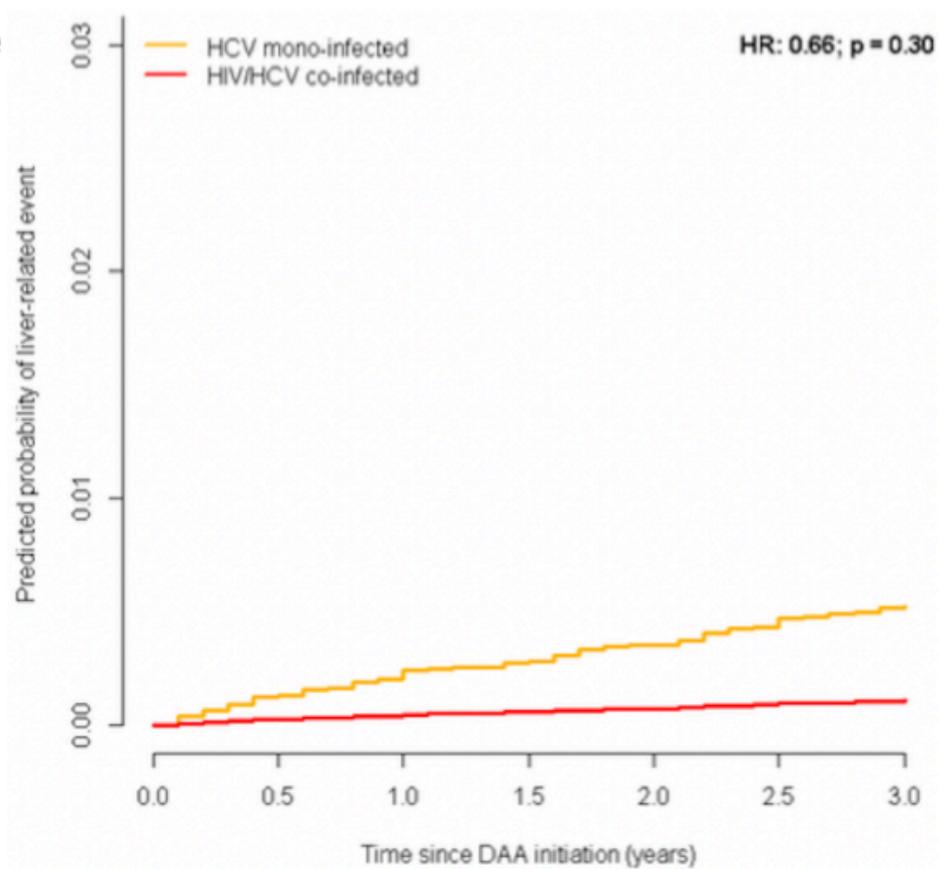


Patients at risk:

| | | | | |
|---------|------|------|------|-----|
| HIV/HCV | 592 | 514 | 363 | 214 |
| HCV | 2047 | 1827 | 1419 | 967 |

(C)

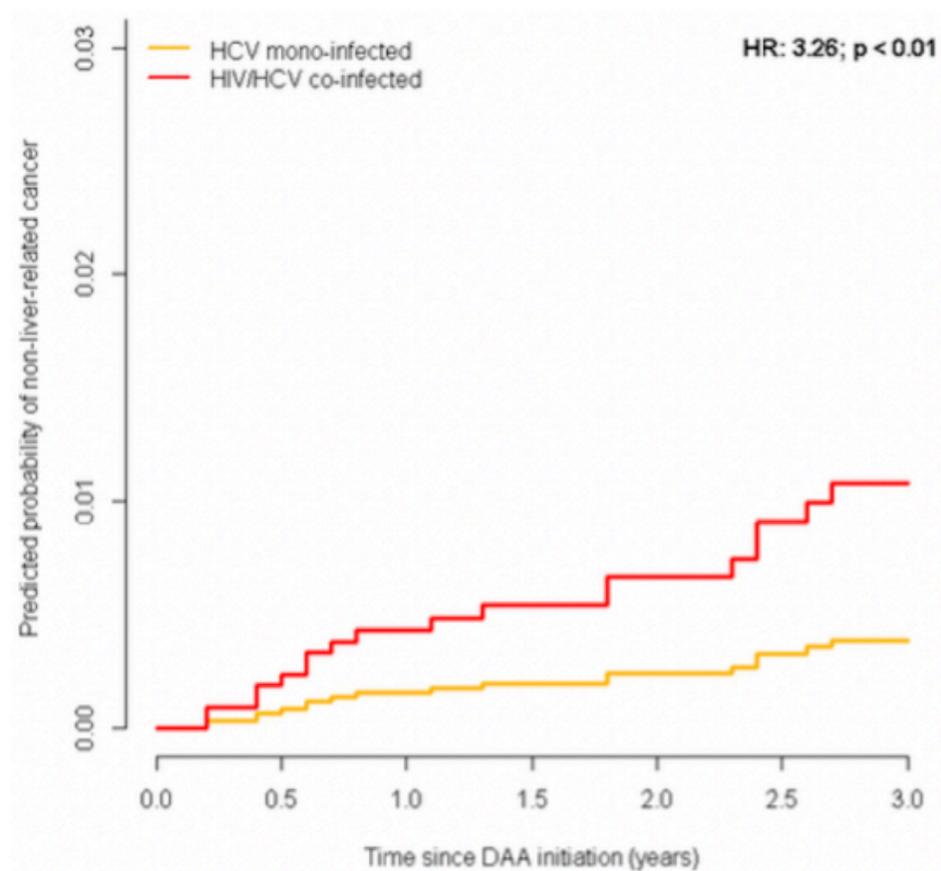
Figure



(A)

Patients at risk:

| | | | | |
|---------|------|------|------|-----|
| HIV/HCV | 575 | 493 | 344 | 199 |
| HCV | 1848 | 1611 | 1236 | 807 |



(B)

Patients at risk:

| | | | | |
|---------|------|------|------|-----|
| HIV/HCV | 548 | 459 | 335 | 189 |
| HCV | 2016 | 1787 | 1377 | 934 |

Impact of HIV co-infection on mortality and morbidity after DAA in HCV-infected participants

HCV infected treated by DAA  2641

Treated outside a clinical trial

Without history of liver transplantation

Available SVR status

HCV mono-infected

 2049

ANRS CO22
HEPATHER cohort

94.6%
of SVR

HIV/HCV co-infected

 592

ANRS CO13
HEPAVIH cohort

92.9%
of SVR

Up to 4 HCV mono-infected matched on age and sex to each HIV/HCV co-infected

Increased all-cause mortality



2 times higher risk in HIV/HCV co-infected

Increased non-liver-related mortality



3 times higher risk in HIV/HCV co-infected

Similar liver-related mortality



No difference between the two populations

HIV increased risk of overall mortality, non-liver-related mortality but not of liver-mortality in HCV-infected patients

Highlights:

- Similar rates of SVR between HIV/HCV co-infected and HCV mono-infected participants
- Higher risk of all-cause deaths, non-liver-related deaths and cancers in HIV/HCV co-infected
- Similar risk of liver-related deaths and liver-related events in both populations



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Supplementary material

SUPPLEMENTARY MATERIALS_2.0.docx

