



## **Mortality in hepatitis C virus-cured vs. hepatitis C virus-uninfected people with HIV: a matched analysis in the ANRS CO4 FHDH cohort**

Maria-Bernarda Requena, Sophie Grabar, Emilie Lanoy, Gilles Pialoux, Eric Billaud, Claudine Duvivier, Philippe Merle, Lionel Piroth, Pierre Tattevin, Dominique Salmon, et al.

### **► To cite this version:**

Maria-Bernarda Requena, Sophie Grabar, Emilie Lanoy, Gilles Pialoux, Eric Billaud, et al.. Mortality in hepatitis C virus-cured vs. hepatitis C virus-uninfected people with HIV: a matched analysis in the ANRS CO4 FHDH cohort. *AIDS. Official journal of the international AIDS Society*, 2023, 37 (8), pp.1297-1306. <10.1097/QAD.0000000000003569>. <hal-04074291>

**HAL Id: hal-04074291**

**<https://hal.science/hal-04074291v1>**

Submitted on 19 Apr 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC 4.0 - Attribution - Non-commercial use - International License

**Mortality in HCV-cured versus HCV-uninfected people with HIV: a matched analysis in the ANRS CO4 FHDH cohort.**

**Running head:** “Mortality of PWH/HCV-cured compared to PWH only”

Maria-Bernarda REQUENA,<sup>1</sup> Sophie GRABAR,<sup>1,2</sup> Emilie LANOY,<sup>1</sup> Gilles PIALOUX<sup>3</sup> Eric BILLAUD,<sup>4</sup> Claudine DUVIVIER,<sup>5</sup> Philippe MERLE,<sup>6</sup> Lionel PIROTH,<sup>7</sup> Pierre TATTEVIN,<sup>8</sup> Dominique SALMON,<sup>9</sup> Laurence WEISS,<sup>9</sup> Dominique COSTAGLIOLA,<sup>1</sup> Karine LACOMBE.<sup>1,10</sup>

<sup>1</sup> Sorbonne Université, INSERM, Pierre Louis Institute of Epidemiology and Public Health, IPLESP, Paris, France.

<sup>2</sup> AP-HP, Public Health Unit, Saint-Antoine Hospital, Paris, France.

<sup>3</sup> Sorbonne Université, AP-HP, Department of Infectious Diseases, Tenon Hospital, Paris, France.

<sup>4</sup> Université de Nantes, INSERM UIC 1413, Department of Infectious Diseases, CHU Hôtel Dieu, Nantes, France.

<sup>5</sup> Université de Paris Cité, AP-HP, Necker Hospital, Department of Infectious Diseases, INSERM, U1016, Institut Cochin, CNRS, UMR8104, Necker-Pasteur Infectiology Center, IHU Imagine, Institut Pasteur, Necker-Pasteur Infectiology Center, Paris, France.

<sup>6</sup> Université Lyon 1, Department of Hepatology, de la Croix-Rousse Hospital, Hospices Civils de Lyon, Lyon, France.

<sup>7</sup> University of Bourgogne-Franche-Comté, INSERM, Clinical Epidemiology unit CIC1432, Department of Infectious Diseases, Dijon University Hospital, Dijon, France.

<sup>8</sup> Department of Infectious Diseases and Intensive Care Medicine, CHU de Rennes, Rennes, France.

<sup>9</sup> Université Paris Cité, Department of Immunology and Infectious Diseases, AP-HP Hôtel-Dieu, Paris, France.

<sup>10</sup> AP-HP, Department of Infectious Diseases, Saint-Antoine Hospital, Paris, France.

## Corresponding author:

Dr. Maria-Bernarda Requena

Inserm UMR-S1136. 27 rue Chaligny, 75012, Paris, France.

Email: maria.requena@iplesp.upmc.fr

## Alternate corresponding author:

Pr. Karine Lacombe

Services de Maladies Infectieuses et Tropicales, Hôpital Saint-Antoine

184 Rue du Faubourg St. Antoine, 75571 Paris Cedex 12, France

Tel: +33 1 49 28 24 38 / Fax: +33 1 49 28 21 49

Email: karine.lacombe2@aphp.fr

**Funding source:** Sidaction, ANRS/MIE, INSERM, and the French Ministry of Health.

**Posted history:** This manuscript was previously posted to SSRN:

doi: <https://dx.doi.org/10.2139/ssrn.4196958>

## Abstract

**Objective:** It is unknown whether HCV-cured people with HIV (PWH) without cirrhosis reached the same mortality risk as HCV-uninfected PWH. We aimed to compare mortality in PWH cured of HCV by direct-acting antivirals (DAAs) to mortality in individuals with HIV monoinfection.

**Design:** Nationwide hospital cohort.

**Methods:** HIV-controlled participants without cirrhosis and HCV-cured by DAAs started between 09/2013 and 09/2020, were matched on age ( $\pm 5$  years), sex, HIV transmission group, AIDS status, and BMI ( $\pm 1$  kg/m<sup>2</sup>) to up to ten participants with a virally suppressed HIV monoinfection followed at the time of HCV cure  $\pm 6$  months. Poisson regression models with robust variance estimates were used to compare mortality in both groups after adjusting for confounders.

**Results:** The analysis included 3961 HCV-cured PWH (G1) and 33 872 HCV-uninfected PWH (G2). Median follow-up was 3.7 years in G1 (interquartile range (IQR): 2.0–4.6), and 3.3 years

(IQR: 1.7–4.4) in G2. Median age was 52.0 years (IQR: 47.0–56.0), and 29 116 (77.0%) were men. There were 150 deaths in G1 (adjusted incidence rate (aIR): 12.2/1000 person-years) and 509 (aIR: 6.3/1000 person-years) in G2, with an incidence rate ratio (IRR): 1.9 [95%CI, 1.4–2.7]. The risk remained elevated 12 months post HCV cure (IRR: 2.4 [95%CI, 1.6–3.5]). Non-AIDS/non-liver-related malignancy was the most common cause of death in G1 (28 deaths).

**Conclusions:** Despite HCV cure and HIV viral suppression, after controlling on factors related to mortality, DAA-cured PWH without cirrhosis remain at higher risk of all-cause mortality than people with HIV monoinfection. A better understanding of the determinants of mortality is needed in this population.

**Keywords:** HIV/Hepatitis C coinfection, Direct-acting antiviral agents, Sustained Virologic Response, Mortality.

## Introduction

Over the past 20 years, all-cause mortality in people living with HIV (PWH) has declined thanks to combination antiretroviral therapy (cART) [1,2]. However, mortality remains higher than in the general population [1,3]. Among causes of death, AIDS-defining events were predominant before 2012 and were often associated to late HIV diagnosis [4]. Yet, deaths related to AIDS-defining events tended to be replaced by non-AIDS defining causes : non-AIDS infections, cancers, cardiovascular disease, liver disease, and substance use-related deaths [1,5]. Coinfections with chronic hepatitis viruses, including hepatitis C virus (HCV), were particularly associated with a higher mortality [6–8]. Predictors for death in this population were poor HIV control with lower CD4 cell counts and a higher HIV viral load [9]. The introduction of interferon-free therapies with direct-acting antivirals (DAAs) in 2014 resulted in the cure of more than 90% of persons living with HCV with and without HIV infection [10], and positively impacted overall mortality in the following years [11,12]. Still, despite recovery from HCV, people with HIV coinfection have a higher residual risk of death than people with an HCV monoinfection, and this risk persists long after HCV cure [13]. This is mainly due to the presence of non-hepatic factors often existing in individuals living with HIV/HCV, such as cardiovascular disease, diabetes, alcohol consumption, drug use, and smoking [14]. Few studies have compared the mortality in people with HIV monoinfection to the mortality in PWH cured of HCV by DAAs in the absence of cirrhosis and studied potential predictors of mortality risk in HCV-cured PWH. To better explore mortality in HCV-cured PWH without severe hepatic disease and with HIV control this study estimated the incidence of death and compared all-cause mortality in PWH achieving HIV viral suppression ( $< 200$  copies/mL) and cured of HCV by DAAs without cirrhosis, to all-cause mortality in individuals with a virally suppressed HIV monoinfection.

## Methods and participants

### *ANRS CO4 FHDH cohort*

For this analysis, participants were selected from the ANRS CO4 FHDH Cohort Study, a nationwide hospital-based multicenter, open cohort with ongoing inclusions since 1989. By December 2020, 217 257 participants with HIV infection had been included from 186 hospital centers located throughout France. Individuals are included in FHDH if they have documented HIV-1 or HIV-2 infection and have given their written informed consent for their data to be used for research purposes. Participants are followed at each outpatient visit or hospital admission, and standardized variables are collected if a new clinical manifestation, a new treatment, or a change in biological markers is noted in a six-month interval[15].

The cohort was initially approved by the French data protection agency (Commission Nationale de l'Informatique et des Libertés; CNIL) on 27 November 1991 (Journal Officiel, 17 January 1992). The research authorization was updated to comply with the new regulations, including the General Data Protection Regulation. The ANRS CO4 FHDH cohort was approved by the CEREES (Comité d'Expertise pour les Recherches, les Études et les Évaluations dans le domaine de la Santé) on 20 July 2018 and as a hospital data warehouse by the CNIL on 19 February 2021. The CNIL authorized the cohort to conduct research projects on the data warehouse on 30 March 2021.

### *Data collection*

Demographic characteristics are collected at study inclusion. HIV-related biomarkers, AIDS and non-AIDS clinical events, and antiretroviral treatment are collected prospectively at study entry and at each follow-up visit. Since 2005, information on coinfection with hepatitis B and C has been added to the database. Data on hepatitis C includes HCV-related biomarkers and information on HCV treatments at study entry and each follow-up visit. Deaths are also recorded prospectively with their date and cause, using the Cause of Death (CoDe) in HIV protocol[3], which is specifically designed for classifying causes of death in HIV-infected persons.

### *Eligibility criteria*

#### *Participants with HIV/HCV coinfection and HCV cured with DAAs*

For this analysis, participants with HIV/HCV coinfection cured by DAAs (Group 1 [G1]) were eligible if they were over 18 years old, if they had at least one cohort visit after baseline, at least one HIV viral load <200 copies/mL within 6 months before the index date (date of HCV cure), and if they started DAAs between September 2013 and September 2020. The <200 copies/mL threshold was used for HIV suppression to account for changes in lower detection limits of viral load assays. We included participants that were enrolled in clinical trials in 2013-2014 and received DAAs before marketing authorization, as well as non-responders to interferon therapy. Participants treated with boceprevir or telaprevir (first generation DAAs)

and those who did not have at least one cohort visit after baseline were excluded from the analysis, as well as participants with reinfection, defined as the first positive HCV RNA test after the index date. Participants with cirrhosis, as determined by the algorithm provided in Figure S1, <http://links.lww.com/QAD/C862>, were also excluded. This was done to avoid selection bias, as cirrhosis prevalence was higher in G1, probably due to a better screening in this group, and is related to liver mortality. These participants were included in a sensitivity analysis. Follow-up began at the index date, i.e., the date of HCV cure in participants living with HIV/HCV.

HCV cure was determined by the presence of a sustained virological response (SVR12), defined as an undetectable HCV RNA in serum or plasma ( $\leq 15$  IU/mL) 12 weeks after DAA completion, as defined by the European Association for the Study of the Liver (EASL) [16]. Since some participants did not have an SVR strictly evaluated at 12 weeks after the end of treatment, and since median treatment duration was 12 weeks [12;13] for 3898/3961 participants with available DAA treatment dates on medical records, a negative HCV PCR > 24 weeks after treatment initiation or an SVR12 date registered in the database before the end date for this analysis (31/12/2020) were used as a surrogate definition for SVR12.

#### *Participants with HIV monoinfection*

Up to ten participants with HIV monoinfection followed at the index date were matched to PWH cured of HCV by DAAs. In participants with HIV monoinfection, the index date corresponded to the HCV cure date of the matched participant living with HIV/HCV  $\pm 6$  months. Participants with HIV monoinfection were selected if they were over 18 years old, had at least one follow-up visit after the index date, had at least one HIV plasma viral load <200 copies/mL within 6 months before the index date, did not have cirrhosis, and if they never had a positive HCV-RNA or anti-HCV antibody test. Matching was performed on age ( $\pm 5$  years), HIV transmission group (men who have sex with men (MSM), injecting drug users (IDUs), or other), AIDS status, and body mass index (BMI) ( $\pm 1$  kg/m<sup>2</sup>). Multiple selections of a given participant with HIV-monoinfection, possibly at different index dates, were allowed. When BMI values were missing, participants living with HIV cured of HCV by DAAs were matched only on the other matching factors.

#### *Statistical analysis*

Continuous baseline characteristics were described by their median (interquartile range), and categorical baseline characteristics by their absolute and relative frequencies. The Pearson  $\chi^2$  test was used to compare categorical variables, and the Wilcoxon test for continuous variables.

The primary outcome was death. Follow-up began at the index date and continued until the date of death, last visit, 31 December 2020, or 60 months, whichever occurred first. Loss to follow-up was defined as not having a visit for 18 months or more. The maximum follow-up (60 months) was selected based on the DAA availability for PWH (2015). Follow-up of participants with HIV-monoinfection was right-censored to the follow-up duration of the

participant with DAA-cured HIV/HCV-coinfection to which they were matched, as the main interest was to measure the effect of past coinfection in participants with HIV/HCV coinfection and HCV cured with DAAs.

Kaplan-Meier 5-year survival rates were estimated in participants with DAA-cured HIV/HCV-coinfection and in those with HIV-monoinfection. All-cause death rates per 1000 person-years (PY) and 95% confidence intervals (CI) were estimated using Poisson regression with robust sandwich variance estimators calculated using a GEE model with an independent correlation structure; to account for clustering and multiple selection of a given participant with HIV-monoinfection [17]. Poisson regression models with robust sandwich variance estimators were used to compare mortality between participants with DAA-cured HIV/HCV-coinfection and those with HIV-monoinfection adjusting for age, sex, HIV transmission group, AIDS status, year of HIV diagnosis, CD4 T-cell nadir, and BMI. Primary analyses were done to evaluate the risk of death from 0 to 60 months, and separate models evaluated the risk between 0–12 and 12–60 months. The 12-month cutoff was selected according to the incidences per 6-month period of follow-up as shown in Table S1, <http://links.lww.com/QAD/C856>. Four sensitivity analyses were performed, adding time with ART exposure in the model, including participants with cirrhosis, restricting analyses to participants with HIV viral load <200 copies, and modelling with Cox Proportional Hazards. Statistical significance was defined as a p-value <0.05. All statistical analyses were completed using SAS software, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

### ***Role of the funding source***

The funding sources did not have any role in study design, collection of data, analysis, manuscript writing or the decision to submit for publication.

## **Results**

### ***Population characteristics***

G1 participant selection is described in Figure 1. In the ANRS-CO4 FHDH cohort, there were 3970 participants living with HIV cured of HCV by DAAs (G1) who had at least one HIV-1 viral load <200 copies/mL in the 6-month period before HCV cure, and no HCV reinfection nor cirrhosis. Of these, 3961 were matched to 33 872 participants with HIV monoinfection (G2) who had at least one HIV-1 viral load <200 copies/mL in the 6-month period preceding the index date. Matching on the five criteria was possible for 3690 (93%) G1 participants, and there were 30 835 participants in G2 that were matched more than once. Participants in G1 who inject drugs had a smaller number of matched participants with HIV monoinfection than the other HIV transmission groups, resulting in some imbalance of the baseline characteristics of the two groups despite matching.

Participants' characteristics are described in Table 1. Median age was 52.0 years (interquartile range IQR, 47.0–56.0). Male participants were predominant (n=29 116, 77.0%). Median BMI

was 22.9 (IQR 20.8–25.2). The HIV transmission group was IDUs for 12 326 participants (32.6%) and MSM for 12 480 (33.0%). Also, 7892 participants (20.9%) had an AIDS status before the index date.

Compared to those in G2, participants in G1 were diagnosed with HIV infection at an earlier period (median: 1993 vs. 2000) and had a lower median CD4 T-cell nadir before HCV cure (183 [81–304] vs. 214 [88–341] cells/mm<sup>3</sup>). Median time between first positive anti-HCV antibody test and DAA treatment was 14.0 years (IQR 3.2–22.5) in G1. The proportion of HBV coinfection was low in both groups. The median testing frequency for HCV antibodies during the study period was every 343 days (IQR: 167–552).

Median follow-up time was 3.7 years in G1 (IQR = 2.0–4.6), and 3.3 years (IQR = 1.7–4.4) in G2, corresponding to 12 915 PY and 103 778 PY, respectively. Overall, 307 (7.8%) individuals in G1 and 2368 (7.0%) in G2 were lost to follow-up, respectively.

### ***Incidence of all-cause mortality***

During the first 5 years of follow-up, 150 participants died in G1 and 509 in G2, yielding respective 5-year death probability estimates of 6% (95% CI 5–7%) and 2% (95% CI 2–3%) respectively (Figure 2). The adjusted incidence rate (aIR) was 12.2/1000 PY (95% CI 8.7–17.1) in G1 and 6.3/1000 PY (95% CI 4.9–8.0) in G2 (Table 2). The absolute risk of death in G1 was not significantly different in the 0–12 and 12–60 months periods (aIR/1000 PY 9.8 [5.9; 16.4] vs. 12.1 [7.9; 18.7] respectively,  $p = 0.06$ ), while the risk of death in G2 was lower in the 12–60 months period compared to the 0–12-month period (aIR/1000 PY 0–12 months: 8.1 [5.8; 11.3] vs. 12–60 months: 5.1 [3.8; 7.0],  $p < 0.0001$ ) (Table 2).

### ***Causes of death***

During the 0–60 month- period of follow-up, cause of death was reported for 118 of the 150 deaths in G1 and 400 of the 509 deaths in G2. The most common causes of death in G1 were non-AIDS/non-liver related malignancies ( $n=28$  [17.3%]), liver-related disease ( $n=26$  [17.3%]), cardiovascular disease ( $n=12$  [8.0%]), and AIDS-defining disease ( $n=11$  [7.3%]). G2 had a higher proportion of non-AIDS/non-liver related malignancies ( $n=134$  [26.3%]) and cardiovascular disease ( $n=59$  [11.6%]) but a lower proportion of AIDS-defining disease ( $n=23$  [4.5%]) and liver-related disease ( $n=20$  [3.9%]). There were 5 deaths (2.5%) attributed to overdose in G1 and 0 in G2. Liver-related deaths were deaths related to HCC: 8 in G1 and 10 in G2; hepatic failure: 1 in G1 and 1 in G2; and progression of viral hepatitis disease: 17 in G1 and 9 in G2 (Table S2, <http://links.lww.com/QAD/C857>).

### ***Risk factors of death after HCV cure***

Results from model evaluating the risk of death from 0 to 60 months are presented in Table 3. HCV past coinfection was associated with a higher risk of all-cause death despite cure (Incidence rate ratio IRR = 1.9, 95% CI 1.4–2.7), as first HIV diagnosis before 2000 (IRR = 2.7, 95% CI 1.7–4.3), and BMI <18.5 (IRR = 2.1, 95% CI 1.5–3.1).



In the first 12 months of follow-up, HCV past coinfection was not associated with mortality (IRR = 1.2, 95% CI 0.78–1.9) (Table S3, <http://links.lww.com/QAD/C858>). After 12 months of follow-up, the risk of death was higher in G1 compared to G2 (IRR = 2.4, 95% CI 1.6–3.5). The same factors identified in the model with 0–60 months of follow-up were associated with the risk of death after 12 months of follow-up (Table S4, <http://links.lww.com/QAD/C859>). Sensitivity analyses adding time with ART to the model with 0–60 months of follow-up, resampling the dataset to include 362 (in G1) and 118 (in G2) patients with cirrhosis, and restricting analyses to participants with HIV viral load <200 copies during follow-up retrieved similar results (Table S5, <http://links.lww.com/QAD/C860>). A time-to-event analysis using a Cox proportional hazards model with robust sandwich variance estimators for paired data that excluded participants with HIV VL <200 copies during follow-up and adjusted for matching variables, year of HIV diagnosis, time-varying CD4 T-cell values, and BMI also retrieved similar results (Table S6, <http://links.lww.com/QAD/C861>).

## Discussion

In the ANRS-CO4-FHDH cohort [15] the overall mortality in participants with HIV and a DAA-virologically cured HCV infection without cirrhosis was found to be higher compared to participants with HIV monoinfection, all with cART-mediated HIV suppression (12.2/1000 PY vs. 6.3/1000 PY, adjusted IRR = 1.9 95% CI 1.4–2.7). The risk of death was significantly higher after 12 months following HCV cure while there was no difference in the first 12 months of follow-up.

One of our major results is that, despite being HCV cured and after adjusting for potential confounding factors such as CD4 cell counts and group of transmission described in previous studies, participants with HIV/HCV cured with DAAs were more likely to die than participants with HIV monoinfection in the first 5 years following cure [6]. In a study of HIV/HCV coinfecting and HCV-monoinfected participants by Chalouni *et al.*, individuals with HIV/HCV were found to remain at a higher risk of all-cause mortality than participants with an HCV monoinfection, despite HCV cure with DAAs [18]. In conjunction with our results, this suggests that HIV/HCV coinfection leads to worse survival outcomes than either HIV or HCV monoinfection, even after HCV cure, at least in the first 5 years following cure. Chalouni *et al.* also found that the higher risk of all-cause death in participants with HIV/HCV compared to those with HCV monoinfection was related to an elevated risk of non-liver-related death, in a population of tobacco and alcohol users [18]. This concurs with our findings, where non-liver non-AIDS related malignancies account for a high proportion of deaths in participants with a previous coinfection, whatever the period of follow-up considered.

Contrary to Chalouni *et al.* [18], we found that liver-related deaths are still a common cause of death in this population despite HCV cure even in the absence of cirrhosis at time of DAA treatment. We also found that all-cause mortality was associated with male sex, HIV diagnosis before 2000, AIDS status, and low BMI—risk factors that have also been described elsewhere [19,20]. In vitro studies have shown a persistent T-cell exhaustion after HCV-RNA cure in HCV infection that depends on time with the infection. In addition, persistence of low levels

of chronic immune activation as well as an immune suppressive environment may contribute in some cases to an increased risk of cardiovascular diseases and to decreased immune control against cancer and viral reactivation, especially in people with an HIV/HCV coinfection [21,22]. Participants in the HIV/HCV coinfection group in our study had a median time between first positive anti-HCV antibody and DAA treatment of 14.9 years [3.7; 22.8]. This could support the hypothesis of a longstanding HCV infection that could lead to worse outcomes in the group of people with HIV/HCV coinfection compared with people with HIV monoinfection. A longer follow-up may show whether this will disappear overtime.

Another finding in our analysis was that participants with HIV monoinfection had a lower risk of death after the first 12 months from baseline compared to the first 12 months, while the absolute risk of death was consistent at 0-12 months and at 12-60 months in participants living with HIV/HCV cured of HCV with DAAs.

A higher risk of all-cause mortality compared to the general population has been described to persist in HCV monoinfected patients in the years following HCV cure [23,24]. It has been hypothesized that late presentation and frequent lost-to-follow-up periods in people living with HCV, due to the silent progression of the disease and experience with previous ineffective HCV treatments, hinders the care cascade and results in poorer outcomes [25,26]. To our knowledge, the difference in mortality between periods in participants with HIV/HCV cured by DAAs and in those with HIV-monoinfection has not been described elsewhere, due to the relatively recent arrival of DAA treatments and thus short follow-up periods after DAA cure.

### ***Strengths and limitations***

A major strength in our study is the large number of participants. As a result, the comparison between the mortality of participants living with HIV/HCV to participants with HIV monoinfection can yield estimates that are more precise. This, combined with a median follow-up of 3.7 and 3.3 years for G1 and G2, respectively, permitted the observation of a sufficient number of events in both groups. Moreover, our population is comparable to other major European and American cohorts and population-based studies: [27,28] The EUROSIDA study reported 74% of males, a median age of 56 years, 27.8% of prior AIDS diagnosis, and 8% of cirrhosis in 1178 participants with HIV/HCV from Western European countries.[27] Similarly, a U.S. based study including 1346 Medicare beneficiaries with HIV/HCV and who were DAA treated had 87.5% men, a median age of 56 years, and 7.3% participants with cirrhosis [28]. These findings give us greater confidence in the generalization of results for the HIV/HCV and DAA-cured population globally.

This study has several limitations. First, behavioral data were often missing (alcohol and tobacco) or not collected (active IDU). These factors have been independently associated with mortality in previous studies [29,30]. Secondly, there may be an underreporting of deaths in the ANRS CO4 FHDH cohort but, if so, the proportion of underreported deaths should be the same in G1 and G2, as illustrated by the similar percentage of lost-to-follow-up participants in the two groups. In addition, not all causes of death were available, but most were well

characterized. Thirdly, as we considered only treatments that are currently the standard of care, PWH cured for HCV with interferon were excluded from our study. This is a potentially different HCV-cured population, which used to be carefully selected for treatment, without decompensated liver disease or other comorbidities. Lastly, we observed an absolute risk of death that remains high in HIV/HCV participants cured of HCV after 12 months while it decreases in HIV monoinfected patients. A longer period of follow-up may change this estimation and be necessary to eventually witness a decrease in mortality.

## **Conclusions**

PWH enrolled in the ANRS-CO4 cohort with HCV infection, without cirrhosis, and cured with oral DAAs have worse survival outcomes than participants with HIV monoinfection, despite HIV viral suppression, after adjusting for confounding factors, with no significant difference in the first 12 months, and a significant difference from 12 to 60 months. Tailoring health services to reach WHO targets for HCV micro-elimination in the HIV population is one component of the strategy to defeat HCV as a public health threat [31]. In addition, it is paramount to address the issue of mortality in PWH with cured HCV, even in those who do not have cirrhosis. A closer and longer follow-up and further research on the determinants, including the social and behavioral ones, of liver and non-liver-related causes of death are needed to elucidate the reasons for the persistence of a higher relative risk of death over the first 5 years in people with HIV who are cured of HCV compared to people with HIV monoinfection.

**Acknowledgments:** We thank the ANRS CO4 FHDH (French Hospital Database on HIV) team for providing the data and Jonathan Bellet for providing useful computer algorithms.

**Funding:** This work was funded by Sidaction, grant n°12275. The French Hospital Database on HIV is funded by ANRS | Maladies infectieuses émergentes, Institut National de la Santé et de la Recherche Médicale (INSERM), and the French Ministry of Health.

**Author contributions:** KL and MBR conceptualized the study and obtained funding. MBR, EL, SG, and DC had full access to the data. DC and SG coordinated data analysis and data collection. MBR and EL were responsible for data management. MBR did the statistical analysis. This manuscript was drafted by MBR, SG, DC, and KL. MBR, SG, CD, DS, GP, EB, LP, LW, PM, PT, DC, and KL edited the manuscript for important intellectual content. All authors approved the final version for publication and had ultimate responsibility for the decision to submit for publication.

**Declaration of interests:** DC reports an HIV grant from Janssen (2019-2020), personal fees from Gilead (2020) and Pfizer (2022) for lectures outside the submitted work. KL reports support for boards, educational activities, and travel grants from Gilead, MSD, Janssen, Abbvie, and ViiV Healthcare outside the submitted work. EB reports support for attending meetings from Gilead and MSD outside the submitted work. All other authors declare no competing interests.

**Data sharing:** The data that support the findings of this study are available upon reasonable request and will be subject to approval by the scientific committee. The data are not publicly available due to privacy or ethical restrictions.

**Disclosure of results before publication:** Part of this work was presented at the International Liver Congress 2021 under poster number PO-2836.

**Open access:** For the purpose of Open Access, a CC-BY public copyright license has been applied by the authors to the present document and will be applied to all subsequent versions up to the Author Accepted Manuscript arising from this submission. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

## References

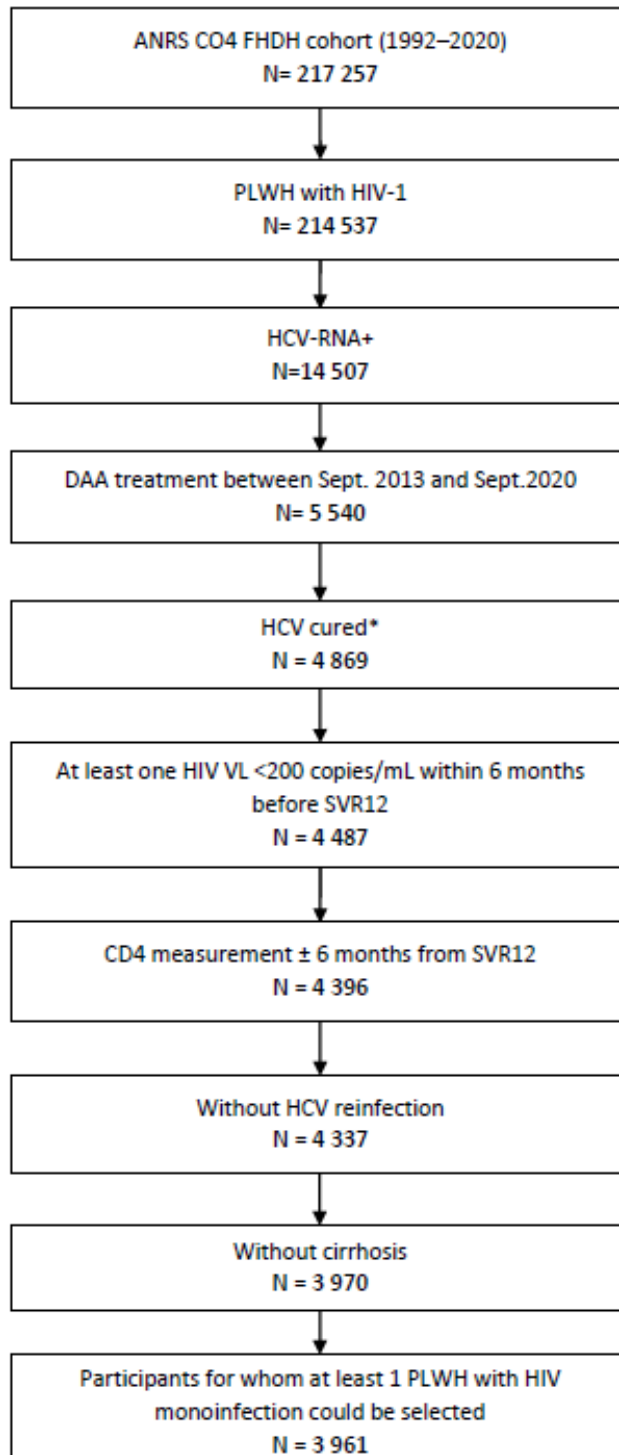
- 1 Croxford S, Kitching A, Desai S, Kall M, Edelstein M, Skingsley A, *et al.* **Mortality and causes of death in people diagnosed with HIV in the era of highly active antiretroviral therapy compared with the general population: an analysis of a national observational cohort.** *Lancet Public Health* 2017; **2**:e35–e46.
- 2 Antiretroviral Therapy Cohort Collaboration. **Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies.** *Lancet HIV* 2017; **4**:e349–e356.
- 3 Edwards JK, Cole SR, Breger TL, Rudolph JE, Filiatreau LM, Buchacz K, *et al.* **Mortality Among Persons Entering HIV Care Compared With the General U.S. Population : An Observational Study.** *Ann Intern Med* Published Online First: 6 July 2021. doi:10.7326/M21-0065
- 4 Revised Surveillance Case Definitions for HIV Infection Among Adults, Adolescents, and Children Aged <18 Months and for HIV Infection and AIDS Among Children Aged 18 Months to <13 Years --- United States, 2008</FONT>. <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a1.htm> (accessed 25 Aug2021).
- 5 Morlat P, Roussillon C, Henard S, Salmon D, Bonnet F, Cacoub P, *et al.* **Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000.** *AIDS Lond Engl* 2014; **28**:1181–1191.
- 6 Butt ZA, Wong S, Rossi C, Binka M, Wong J, Yu A, *et al.* **Concurrent Hepatitis C and B Virus and Human Immunodeficiency Virus Infections Are Associated With Higher Mortality Risk Illustrating the Impact of Syndemics on Health Outcomes.** *Open Forum Infect Dis* 2020; **7**:ofaa347.

- 7 Thornton AC, Jose S, Bhagani S, Chadwick D, Dunn D, Gilson R, *et al.* **Hepatitis B, hepatitis C, and mortality among HIV-positive individuals.** *AIDS Lond Engl* 2017; **31**:2525–2532.
- 8 Alejos B, Hernando V, Iribarren J, Gonzalez-García J, Hernando A, Santos J, *et al.* **Overall and cause-specific excess mortality in HIV-positive persons compared with the general population: Role of HCV coinfection.** *Medicine (Baltimore)* 2016; **95**:e4727.
- 9 Kronfli N, Bhatnagar SR, Hull MW, Moodie EEM, Cox J, Walmsley S, *et al.* **Trends in cause-specific mortality in HIV-Hepatitis C co-infection following hepatitis C treatment scale-up.** *AIDS Lond Engl* Published Online First: 12 January 2019. doi:10.1097/QAD.0000000000002156
- 10 Schlabe S, Rockstroh JK. **Advances in the treatment of HIV/HCV coinfection in adults.** *Expert Opin Pharmacother* 2018; **19**:49–64.
- 11 Carrat F, Fontaine H, Dorival C, Simony M, Diallo A, Hezode C, *et al.* **Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study.** *The Lancet* 2019; **0**. doi:10.1016/S0140-6736(18)32111-1
- 12 Berenguer J, Rodríguez-Castellano E, Carrero A, Von Wichmann MA, Montero M, Galindo MJ, *et al.* **Eradication of hepatitis C virus and non-liver-related non-acquired immune deficiency syndrome-related events in human immunodeficiency virus/hepatitis C virus coinfection.** *Hepatology* 2017; **66**:344–356.
- 13 Chalouni M, Pol S, Sogni P, Fontaine H, Lacombe K, Jean-Marc-Lacombe, *et al.* **Increased mortality in HIV/HCV-coinfected compared to HCV-monoinfected patients in the DAA era due to non-liver-related death.** *J Hepatology* 2020; **0**. doi:10.1016/j.jhep.2020.08.008
- 14 Tacke F, Boeker KHW, Klinker H, Heyne R, Buggisch P, Pathil A, *et al.* **Baseline risk factors determine lack of biochemical response after SVR in chronic hepatitis C patients treated with DAAs.** *Liver Int Off J Int Assoc Study Liver* Published Online First: 26 June 2019. doi:10.1111/liv.14186
- 15 Mary-Krause M, Grabar S, Lievre L, Abgrall S, Billaud E, Boue F, *et al.* **Cohort Profile: French hospital database on HIV (FHDH-ANRS CO4).** *Int J Epidemiol* 2014; **43**:1425–1436.
- 16 Pawlotsky J-M, Negro F, Aghemo A, Berenguer M, Dalgard O, Dusheiko G, *et al.* **EASL recommendations on treatment of hepatitis C: Final update of the series.** *J Hepatology* 2020; **73**:1170–1218.

- 17 Royall RM. **Model Robust Confidence Intervals Using Maximum Likelihood Estimators.** *Int Stat Rev Rev Int Stat* 1986; **54**:221–226.
- 18 Chalouni M, Pol S, Sogni P, Fontaine H, Lacombe K, Marc-Lacombe J, *et al.* **Increased mortality in HIV/HCV-coinfected compared to HCV-monoinfected patients in the DAA era due to non-liver-related death.** *J Hepatol* 2021; **74**:37–47.
- 19 Shili-Masmoudi S, Sogni P, de Ledinghen V, Esterle L, Valantin M-A, Poizot-Martin I, *et al.* **Increased liver stiffness is associated with mortality in HIV/HCV coinfectd subjects: The French nationwide ANRS CO13 HEPAVIH cohort study.** *PLOS ONE* 2019; **14**:e0211286.
- 20 Janjua NZ, Wong S, Abdia Y, Jeong D, Buller-Taylor T, Adu PA, *et al.* **Impact of direct-acting antivirals for HCV on mortality in a large population-based cohort study.** *J Hepatol* 2021; :S0168827821004013.
- 21 Tonnerre P, Wolski D, Subudhi S, Aljabban J, Hoogeveen RC, Damasio M, *et al.* **Differentiation of exhausted CD8+ T cells after termination of chronic antigen stimulation stops short of achieving functional T cell memory.** *Nat Immunol* 2021; **22**:1030–1041.
- 22 Gobran ST, Ancuta P, Shoukry NH. **A Tale of Two Viruses: Immunological Insights Into HCV/HIV Coinfection.** *Front Immunol* 2021; **12**:3192.
- 23 D'Ambrosio R, Degasperis E, Anolli MP, Fanetti I, Borghi M, Soffredini R, *et al.* **Incidence of liver- and non-liver-related outcomes in patients with HCV-cirrhosis after SVR.** *J Hepatol* 2022; **76**:302–310.
- 24 Innes H, McDonald S, Hayes P, Dillon JF, Allen S, Goldberg D, *et al.* **Mortality in hepatitis C patients who achieve a sustained viral response compared to the general population.** *J Hepatol* 2017; **66**:19–27.
- 25 Santos M, Protopopescu C, Delarocque-Astagneau E, Bourlière M, Petrov-Sanchez V, Di Beo V, *et al.* **Late presentation for HCV care: Time to target people with diabetes and/or hazardous alcohol use (ANRS CO22 HEPATHER cohort).** *Liver Int Off J Int Assoc Study Liver* 2022; **42**:38–49.
- 26 Aleman S, Söderholm J, Büsch K, Kövamees J, Duberg A-S. **Frequent loss to follow-up after diagnosis of hepatitis C virus infection: A barrier towards the elimination of hepatitis C virus.** *Liver Int* 2020; **40**:1832–1840.
- 27 Fursa O, Mocroft A, Lazarus JV, Amele S, Lundgren J, Matulionyte R, *et al.* **The hepatitis C cascade of care in HIV/HCV-coinfected individuals in Europe– regional and intra-regional differences.** *AIDS* Published Online First: 24 November 2021. doi:10.1097/QAD.0000000000003112

- 28 Yin X, Kong L, Du P, Jung J. **Effects of direct-acting antiviral treatment on reducing mortality among Medicare beneficiaries with HIV and HCV coinfection.** *AIDS Care* 2021; **0**:1–8.
- 29 Santos ME, Protopopescu C, Sogni P, Yaya I, Piroth L, Bailly F, *et al.* **HCV-Related Mortality Among HIV/HCV Co-infected Patients: The Importance of Behaviors in the HCV Cure Era (ANRS CO13 HEPAVIH Cohort).** *AIDS Behav* Published Online First: 8 July 2019. doi:10.1007/s10461-019-02585-7
- 30 Cotte L, Hocqueloux L, Lefebvre M, Pradat P, Bani-Sadr F, Huleux T, *et al.* **Microelimination or Not? The Changing Epidemiology of Human Immunodeficiency Virus-Hepatitis C Virus Coinfection in France 2012–2018.** *Clin Infect Dis* 2021; **73**:e3266–e3274.
- 31 Mangia A, Cotugno R, Cocomazzi G, Squillante MM, Piazzolla V. **Hepatitis C virus micro-elimination: Where do we stand?** *World J Gastroenterol* 2021; **27**:1728–1737.
- 32 Loko M-A, Salmon D, Carrieri P, Winnock M, Mora M, Merchadou L, *et al.* **The French national prospective cohort of patients co-infected with HIV and HCV (ANRS CO13 HEPAVIH): early findings, 2006-2010.** *BMC Infect Dis* 2010; **10**:303.

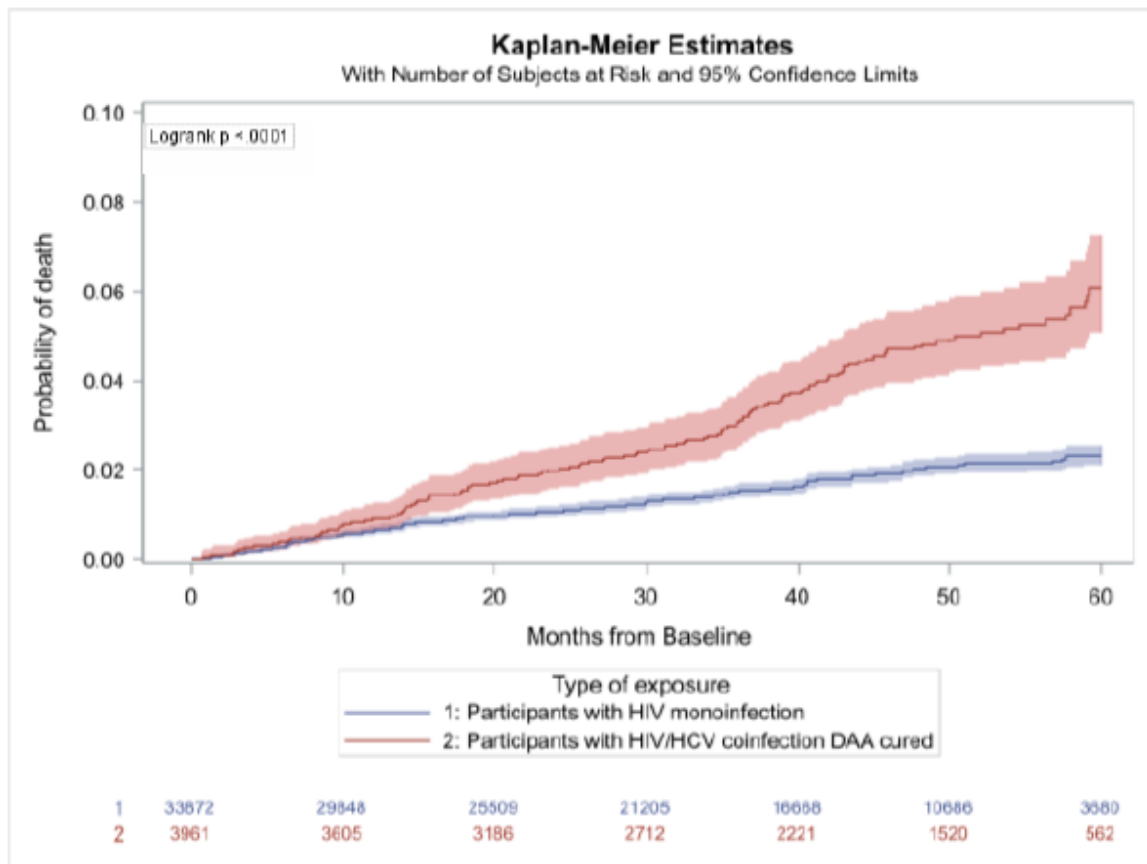
**Figure 1. Participant Selection – Group 1: Participants with DAA-Cured HIV/HCV Coinfection.** Abbreviations: HCV: hepatitis C virus; HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome; DAA: direct-acting antiviral; SVR12: sustained virologic response 12 weeks after the end of treatment



\*HCV cure: evidence of negative HCV PCR >24 weeks after treatment initiation or HCV cure date registered before December 2020.



**Figure 2. Predicted probability of death over time according to HCV coinfection.**



Log-log transformation was used to compute confidence intervals.

**Table 1. Participants' Baseline Characteristics.**

	<b>Participants with HIV/HCV coinfection cured by DAAs - Group 1* (n = 3961)</b>		<b>Participants with HIV monoinfection - Group 2* (n = 33 872)†</b>	
<b>Characteristics at index date (date of HCV cure from matched participant with HIV/HCV coinfection ±6 months)</b>	<b>N</b>	<b>Median [IQR] or n (%)</b>	<b>N</b>	<b>Median [IQR] or n (%)</b>
Age (years)‡	3961	52.4 [47.5; 56.4]	33 872	51.9 [46.9; 56.0]
Men‡	3961	2963 (74.8%)	33 872	26 153 (77.2%)
Origin	3961		33 872	
<i>Metropolitan France</i>		2915 (73.6%)		24 231 (71.5%)
<i>Sub-Saharan Africa</i>		289 (7.3%)		4465 (13.2%)
<i>Other §</i>		757 (19.1%)		5176 (15.3%)
HIV acquisition group‡	3961		33 872	
<i>IDU</i>		1625 (41.0%)		10 701 (31.6%)
<i>MSM</i>		1140 (28.8%)		11 340 (33.5%)
<i>Other</i>		1196 (30.2%)		11 831 (34.9%)
Year of HIV+ diagnosis	3952	1993 [1987; 2004]	33 828	2000 [1992; 2008]
Time with HIV VL <200 copies/mL (years)	3961	9.0 [5.0; 13.5]	33 872	8.0 [4.0; 12.5]
Time with ART (years)	3948	17.2 [8.2; 21.1]	33 813	13.9 [6.1; 19.8]
AIDS before index date‡	3961	948 (23.9%)	33 872	6944 (20.5%)
BMI (kg/m <sup>2</sup> ) ‡	3804	22.8 [20.4; 25.2]	33 611	22.9 [20.8; 25.2]
CD4 count ± 6 months (cells/mm <sup>3</sup> )	3961	665 [470; 896]	33 872	660 [464; 878]
CD4 T-cell nadir (cells/mm <sup>3</sup> )	3961	183 [81; 304]	33 872	214 [88; 341]
Alcohol consumption (daily)	2185		4505	

<i>None</i>		1281 (58.6%)		2811 (62.4%)
<i>&lt;40 g</i>		732 (33.5%)		1513 (33.6%)
<i>&gt;40 g</i>		172 (7.9%)		181 (4.0%)
Positive HBsAg $\pm$ 6 months	1131	48 (4.2%)	10 741	529 (4.9%)
Year of HCV cure	3958	2017 [2016; 2018]	-	-
Time between first positive anti-HCV antibody and DAA treatment (years)	3961	14.0 [3.2; 22.5]	-	-
HCV genotype	3593		-	
<i>1</i>		1881 (52.3%)		-
<i>2</i>		121 (3.4%)		-
<i>3</i>		565 (15.7%)		-
<i>4</i>		1012 (28.2%)		-
<i>Other</i>		14 (0.4%)		-
	Participants with HIV/HCV coinfection cured by DAAs – Group 1* (n = 3961)		Participants with HIV mono-infection - Group 2* (n = 33 872)	
	N	n (%)	N	n (%)
HIV treatment	3898		33 365	
<i>2 NRTI + 1 INSTI</i>		1649 (42.3%)		10 983 (32.9%)
<i>2 NRTI + 1 NNRTI</i>		955 (24.5%)		10 212 (30.6%)
<i>2 NRTI + 1 boosted PI</i>		438 (11.2%)		4497 (13.5%)
<i>Other triple therapy or &gt; 3 ARV</i>		401 (10.3%)		3515 (10.5%)
<i>Dual therapy</i>		385 (9.9%)		3513 (10.5%)
<i>PI boosted monotherapy</i>		70 (1.8%)		645 (2.0%)
HCV treatment	3961		-	
<i>Sofosbuvir/Ledipasvir</i>		2011 (50.8%)		-
<i>Sofosbuvir/Velpatasvir</i>		590 (14.9%)		-

<i>Daclatasvir/Sofosbuvir</i>		535 (13.5%)		-
<i>Sofosbuvir/Ribavirin</i>		393 (9.9%)		-
<i>Other</i>		432 (10.9%)		-

\*Note: Having at least one HIV VL < 200 copies/mL 6 months before the index date was required for baseline.

† The dataset of participants with HIV monoinfection (Group 2) includes participants that were matched to more than one participant in Group 1 and that were therefore repeated.

‡ Matching criteria- No t-test performed

§ Other origins were: Western Europe, northern Africa, Eastern Europe, Asia, Central & South America, Middle East, French Antilles, other French West Indies countries, North America, non-French West Indies, and French Guyana

Abbreviations: HCV: hepatitis C virus; HIV: human immunodeficiency virus; MSM: men who have sex with men; IDU: injecting drug user; VL: viral load; AIDS: acquired immunodeficiency syndrome; BMI: body mass index; DAAs: direct-acting antivirals; INSTI: integrase strand transfer inhibitor; NRTI: nucleos(t)ide reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor.

**Table 2. Adjusted Analysis for the Association of HIV/HCV Coinfection Group and Mortality – Comparison between Overall, 0–12 Months, 12–60 Months Analysis**

Analysis	Overall censored at 60 months		0–12 months		12–60 months	
Exposure	<i>N</i>	<i>deaths</i>	<i>N</i>	<i>deaths</i>	<i>N</i>	<i>deaths</i>
<i>HIV/HCV Coinfection DAA cured – Group 1</i>	3961	150	3961	33	3531	117
<i>HIV Monoinfection – Group 2*</i>	33 872	509	33 872	197	28 996	312
<b>Adjusted incidence rate/1000 PY [95% CI]</b>						
in Group 1	12.2	[8.7; 17.1]	9.8	[5.9; 6.4]	12.1	[7.9; 18.7]
in Group 2*	6.3	[4.9; 8.0]	8.1	[5.8; 1.3]	5.1	[3.8; 7.0]
<b>Incidence Rate Ratio Group 1/Group 2†</b>	1.9	[1.4; 2.7]	1.2	[0.78; .9]	2.4	[1.6; 3.5]

\*The dataset of participants with HIV monoinfection (Group 2)- includes participants that were matched to more than one participant in Group 1 and that therefore were repeated.

†Adjusted for age, sex, HIV transmission route, AIDS status, year of HIV diagnosis, CD4 T-cell nadir, and BMI

Abbreviations: PY: person years; CI: confidence interval; IR: incidence rate; IRR: incidence rate ratio; HCV: hepatitis C virus; HIV: human immunodeficiency virus; DAAs: direct-acting antivirals

**Table 3. Factors Associated with Death. Data Censored at 60 Months of Follow-Up**

	N	deaths	Unadjusted IR/ 1000 PY [95% CI]	Adjusted IR*/ 1000 PY [95% CI]	Unadjusted IRR [95% CI]	Adjusted IRR* [95% CI]	p-value
Exposure							<.0001
<i>HIV/HCV Coinfection DAA cured</i>	3961	150	11.6 [9.9;13.6]	12.2 [8.7;17.1]	2.3 [1.7;3.1]	1.9 [1.4;2.7]	
<i>HIV Monoinfection</i>	33 872	509	5.0 [3.9;6.4]	6.3 [4.9;8.0]	1.00	1.00	
Year of the HIV diagnosis							0.0002
<2000	19 460	500	7.9 [6.3;10.0]	13.3 [10.5;16.2]	1.00	1.00	
≥ 2000	18 320	158	3.1 [2.2;4.3]	5.9 [3.9;8.8]	0.4 [0.3;0.6]	0.5 [0.3;0.7]	
BMI (kg/m <sup>2</sup> )							<.0001
<18.5	2435	87	11.8 [8.6;16.2]	12.7 [8.7;18.6]	2.2 [1.5;3.3]	2.1 [1.5;3.1]	
≥ 18.5	34 980	564	5.3 [4.2;6.6]	6.0 [4.8;7.5]	1.00	1.00	

\*Adjusted for age, sex, HIV transmission route, AIDS status, year of HIV diagnosis, CD4<sup>+</sup> nadir, and BMI Abbreviations: HCV: hepatitis C virus; HIV: human immunodeficiency virus; MSM: men who have sex with men; IDU: injecting drug user; DAAs: direct-acting antivirals; SVR12: sustained virologic response 12 weeks after the end of treatment; AIDS: acquired immunodeficiency syndrome; BMI: body mass index; IR: incidence rate; IRR: incidence rate ratio; PY: person years; CI: confidence interval.