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Impact of Hepatitis C cure on risk of mortality and morbidity in people with HIV after ART initiation

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Key points

Compared to people with HIV (PWH), PWH and Hepatitis C who reached sustained virological response (SVR):

- Were not at higher risk of mortality.
- Were at higher risk of non-AIDS non-liver cancer when SVR was reached after a direct acting antiviral treatment.

ABSTRACT

Objective: Hepatitis C Virus (HCV) co-infection is associated with increased morbidity and mortality in people with HIV (PWH). Sustained virological response (SVR) decreases the risk of HCV-associated morbidity. We compared mortality, risk of AIDS-defining events, and non-AIDS non-liver (NANL) cancers between HCV co-infected PWH who reached SVR and mono-infected PWH.

Design: Adult PWH from 21 cohorts in Europe and North America that collected HCV treatment data were eligible if they were HCV-free at time of ART initiation.

Methods: Up to 10 mono-infected PWH were matched (on age, sex, date of ART start, HIV acquisition route, and being followed at the time of SVR) to each HCV co-infected PWH who

reached SVR. Cox models were used to estimate relative hazards (HR) of all-cause mortality, AIDS-defining events, and NANL cancers after adjustment.

Results: Among 62,495 PWH, 2,756 acquired HCV, of whom 649 reached SVR. For 582 of these, ≥1 mono-infected PWH could be matched, producing a total of 5,062 mono-infected PWH. The estimated HRs comparing HCV co-infected PWH who reached SVR with mono-infected PWH were 0.29 [95%CI 0.12-0.73] for mortality, 0.85 [0.42-1.74] for AIDS-defining events, and 1.21 [0.86-1.72] for NANL cancer.

Conclusion: PWH who reached SVR a short time after HCV acquisition were not at higher risk of overall mortality compared to mono-infected PWH. However, the apparent higher risk of NANL cancers in HCV co-infected PWH who reached SVR after a DAA-based treatment compared to mono-infected PWH, though compatible with a null association, suggests a need for monitoring of those events following SVR.

Keywords: HIV infection – Sustained virological response – Mortality – AIDS defining events – Non-AIDS non-liver cancer

STATEMENTS AND DECLARATIONS

Competing interests: The authors have declared no competing interests relevant to this article.

INTRODUCTION

Hepatitis C virus (HCV) co-infection is frequent in people with HIV (PWH) (1,2) and affects 2.3 million PWH worldwide (3). The natural course of HCV-infection is affected by HIV co-infection, with a faster progression of fibrosis (4,5), poorer response to anti-HCV treatment (1), and higher risk of morbidity and mortality (6,7). HCV co-infection in PWH leads to increased risk of hospitalizations (8), non-liver-related complications such as non-AIDS defining cancers (9,10), and mortality (11,12). Early administration of combination antiretroviral therapy (ART) and durable suppression of HIV replication have improved overall survival and delayed disease progression related to HIV and HCV (13). Nevertheless, liver-related mortality was an important cause of death in HIV patients in several studies (14,15), in particular because of hepatitis co-infection even after ART initiation (16,17).

Direct acting antiviral (DAA) treatment for HCV infection became increasingly available from 2014. DAAs are highly effective, with sustained virological response (SVR) in more than 95% of those treated irrespective of HIV (18,19). Several studies showed reductions in liver-related events (20,21), non-liver-related events (20), and overall mortality (22,23) after SVR induced by DAA or other types of HCV treatment.

Therefore, SVR has the potential to reduce or remove the excess risk of death in HCV co-infected PWH. However, some studies including only people living with HCV have reported that, despite achieving SVR, an elevated risk of HCV-related events and mortality (21,24) remains. This is associated with cumulative deleterious effects of pre-existing liver fibrosis and long-lived inflammation, long-term untreated HCV viremia, as well as behavioral exposures tied to HCV acquisition, especially seen during the INF-era. We compared the risks of overall mortality, AIDS defining events, and non-AIDS defining non-liver-related (NANL) cancers between HCV co-infected PWH who reached SVR and matched mono-infected PWH with similar time since first starting ART.

METHODS

Population

The Antiretroviral Therapy Cohort Collaboration (ART-CC) combines data from 21 HIV cohorts in Europe and North America. Eligible PWH were aged at least 16 years and started ART on at least three drugs without having previously taken antiretroviral therapy. All contributing cohorts have been approved to use their data for research by institutional review boards or ethics committees. Data are collected during the regular clinical follow-up scheduled for the participants using standardized methods (25). For this study we included PWH from cohorts providing measures of HCV co-infection, data on HCV treatment and HCV-RNA testing for participants who received HCV treatment regardless of the HCV treatment type (all-oral DAA/INF-based). In order to be able to determine when PWH acquired HCV, PWH were excluded from the analysis if they had HCV or were missing data on HCV co-infection at the time of starting ART, or if they were from a cohort without data on HCV treatment or HIV acquisition route.

Sustained virological response

PWH who had started ART were defined to be HCV co-infected at the time of their first detectable HCV-RNA. SVR was defined as an undetectable HCV viral load 24 weeks after the end of an interferon-based treatment and 12 weeks after receiving a DAA-based treatment. The date of SVR was defined as 12 or 24 weeks after the end of the treatment for participants receiving DAA- or interferon-based treatment.

Matching

A maximum of 10 mono-infected PWH were matched to each HCV co-infected PWH who reached SVR. Mono-infected PWH from the same cohort were matched to HCV co-infected PWH on the basis of age (±2 years) and birth sex, date of ART initiation (±1 year), route of HIV acquisition, and being in follow-up at the time of SVR.

Outcomes

The main outcome was all-cause mortality. Data on deaths were obtained through either linkage with vital statistics agencies and hospitals or through active follow-up and physician reports, depending on the cohort. Secondary outcomes were i) the occurrence of an AIDS defining event, defined according to Center for Disease Control and prevention criteria; ii) the occurrence of a NANL cancer, defined as the occurrence of any cancer which was not a Kaposi sarcoma, cervical cancer, Hodgkin lymphoma, or hepatocellular carcinoma (HCC). For each analysis of a specific event, people with prevalent events of interest were excluded.

Statistical methods

For HCV co-infected PWH who reached SVR, baseline was defined as their SVR date. For mono-infected PWH, baseline was defined as the date of SVR of the HCV co-infected PWH to whom they were matched. Follow-up continued until occurrence of the outcome, death, or last follow-up visit. Incidence rates of each event (with 95% confidence intervals (CI)) in mono-infected PWH and HCV co-infected PWH who reached SVR were estimated using Poisson models. Hazard ratios comparing HCV co-infected PWH who achieved SVR with mono-infected PWH were estimated using Cox models adjusted for age (in years) using restricted cubic splines with three knots located at the terciles of the values of age, calendar year of ART initiation, ART initiation types (2 nucleoside reverse transcriptase inhibitors (NRTI) + 1 non-nucleoside reverse transcriptase inhibitor (NNRTI), 2NRTI + 1 protease inhibitor (PI), 2NRTI + 1 integrase inhibitor (INI), and others), and CD4 count, birth sex, HIV acquisition route (men who have sex with men (MSM), person who injects drugs, heterosexual sex, other, or unknown) and detectable HIV-RNA viral load. Variables were measured in a three-month window before baseline. Baseline hazards were stratified by cohort. As SVR could be associated with different outcome risks depending on treatment type, in subgroup analyses we estimated mortality hazard ratios separately for HCV co-infected PWH who reached SVR after an interferon-based treatment and after a DAA treatment. To take into account the progressive impact of HCV on the risk of severe clinical outcome, a sensitivity analysis was implemented by stratifying for the time between the first HCV-seropositivity and the occurrence of SVR; HCV co-infected PWH with a time between first HCV seropositivity and SVR inferior or equal to 3 years (median value observed in the population), and those with a time superior to 3 years, along with their matched mono-infected PWH, were analyzed separately using the same methods as for the main analysis.

RESULTS

Study population

Of 122,636 PWH included in the full ART-CC dataset, 13,825 were living with HCV at the time of ART initiation, 18,971 did not have data on HCV co-infection before ART initiation, 14,243 were participants in a cohort without information on HCV treatment, and 13,102 did not have data on HIV acquisition routes. Among the 62,495 eligible PWH from 11 cohorts (AHIVCOS, Alberta, AMACS, Aquitaine, ATHENA, CoRIS, PISCIS, SHCS, UW, VACH

Vanderbilt), 2,756 became HCV co-infected after ART initiation, 984 received at least one HCV treatment and 649 (305 after interferon, 51 protease inhibitor, and 293 DAA) achieved SVR. Of these, 582 could be matched with at least one mono-infected PWH: a total of 5,062 mono-infected PWH were included after matching (Figure 1).

At baseline, the median ages in HCV co-infected PWH who achieved SVR and mono-infected PWH were 45.5 years [Interquartile range (IQR): 37.9; 51.3] and 45.2 years [IQR: 37.9; 50.8], respectively. Among both HCV co-infected and mono-infected PWH, most PWH were men: 94.7% and 96.8%, respectively. In HCV co-infected PWH who achieved SVR, HIV acquisition route was more frequently through injecting drug use (11.0% vs 3.0%) and less frequently in MSM (79.0% vs 89.4%) compared to mono-infected PWH, despite matching. The median baseline CD4 count was lower in HCV co-infected PWH who achieved SVR (580 cells/mm^3 [399; 761]) than mono-infected PWH (640 cells/mm^3 [480; 840]). ART were initiated between 1999 and 2019, and most frequently between 2004 and 2007 (20.4% and 20.3%, respectively for HCV co-infected and mono-infected PWH) and between 2008 and 2011 (27.5% and 29.2%, respectively). The most frequent ART regimens were combinations of 2NRTIs + 1NNRTI (46.2% and 49.9%, respectively), 2 NRTIs + 1PI (39.0% and 34.7%, respectively) and 2 NRTIs and 1 integrase inhibitor (5.8% and 6.9%, respectively) (Table 1).

Among HCV co-infected PWH who achieved SVR, the median time between ART initiation and first HCV seropositivity was 3.4 years [1.4; 6.7], and between HCV seropositivity and SVR 2.0 years [1.3; 3.7]. Among those who reached SVR, 227 (39.0%) were treated by interferon, 56 (9.6%) by protease inhibitors and 299 (51.4%) by DAA. Most SVR occurred from 2015 onwards (49.0%).

Among HCV co-infected PWH who achieved SVR, median follow-up between baseline and death or last follow-up was 3.1 years [2.0; 6.6] corresponding to 2,637.0 person-years. In matched mono-infected PWH, median follow-up was 3.0 years [2.0; 6.1], between baseline and death, HCV co-infection, or last follow-up, corresponding to 21,684.3 person-years of follow-up.

Mortality

Overall, there were 7 deaths from any cause in HCV co-infected PWH who achieved SVR and 113 deaths in mono-infected PWH. The incidence of all-cause mortality was lower in HCV co-infected PWH who reached SVR (2.7 per 1000 person-years [95% CI 1.1; 5.5] than in mono-infected PWH (5.2 per 1000 person-years [4.3; 6.3]) (Table 2, Figure 2). After adjustment, the estimated hazard ratio (HR) for overall mortality was 0.29 [0.11; 0.74] (Table 3) comparing HCV co-infected PWH who achieved SVR to mono-infected PWH. The estimated mortality HR in HCV co-infected PWH who achieved SVR after interferon-based treatment, compared to mono-infected PWH, was 0.26 [0.09; 0.73]. The corresponding HR after DAA treatment was 0.44 [0.06; 3.39]. In participants who reached SVR less than 3 years after the first HCV-seropositivity, the estimated mortality HR was similar to the one of the main analysis. In participants who reached SVR more than 3 years after the first HCV-seropositivity the

association between SVR and mortality could not be estimated due to the low number of events. (Table 3).

AIDS defining events

After excluding people with an AIDS-defining event at or before baseline, 582 HCV co-infected PWH who achieved SVR and 4,695 mono-infected PWH were included. There were 9 AIDS-defining events (incidence per 1000 person-years 9 [95% CI 1.8; 7.4] in HCV co-infected PWH who achieved SVR) and 101 AIDS-defining events (incidence per 1000 person-years 5.1 [4.2; 6.3] in mono-infected PWH) (Table 2, Figure 2). The HR for AIDS-defining events was 0.85 [0.42; 1.74] comparing HCV co-infected PWH who achieved SVR to mono-infected PWH (Table 3). The corresponding HRs for AIDS-defining events after interferon-based and DAA treatment were 0.85 [0.37; 1.92] and 0.59 [0.10; 3.48] respectively. The AIDS-defining HRs of SVR were 1.12 [0.40; 3.15] and 0.65 [0.23; 1.87] in participants who reached SVR less than 3 years, and more than 3 years, after the first HCV-seropositivity, respectively (Table 3).

Non-AIDS defining non-liver-related cancers

After excluding people with a NANL cancer history, 579 HCV co-infected PWH who achieved SVR and 4,748 mono-infected PWH were included. There were 38 NANL cancers among HCV co-infected PWH who achieved SVR and 295 among mono-infected PWH. In both populations, anal cancers were the main observed NANL cancers, with 33 (86.8%) and 217 (73.6%) cancers observed, respectively. In PWH and HCV, colon-rectal cancers were the second most observed cancers (5.3%). For other types of cancers, a maximum of one cancer was reported. In mono-infected PWH, the other most observed cancers were prostate cancers (3.7%), Hodgkin's lymphoma (3.4%), and lung cancers (3.1%). NANL cancer incidence was similar in PWH post-SVR (15.4 per 1000 person-years [10.9; 21.2]) and mono-infected PWH (14.9 per 1000 person-years [13.2; 16.7]) (Table 2, Figure 2). After adjustment, the HR of NANL cancers was 1.21 [0.86; 1.72] comparing HCV co-infected PWH who achieved SVR to mono-infected PWH (Table 3). The corresponding HRs of NANL cancers by treatment type were 1.05 [0.67; 1.63] and 1.62 [0.91; 2.89] for interferon-based and DAA treatment, respectively. The NANL cancers HRs of SVR were 1.14 [0.67; 1.94] and 1.28 [0.81; 2.03] in participants who reached SVR less than 3 years, and more than 3 years, after the first HCV-seropositivity, respectively (Table 3).

DISCUSSION

Among PWH on ART, compared to PWH mono-infected, HCV co-infected PWH who reached SVR had lower incidences of overall mortality and similar incidence of AIDS-defining events and NANL cancer, when matched on age, birth sex, and time since ART initiation. After adjustment, lower risk of overall mortality was observed in HCV co-infected PWH who reached SVR compared to mono-infected PWH. This lower risk was mainly observed in HCV co-infected PWH who reached SVR after an interferon-based treatment. HCV co-infected PWH who reached SVR after a DAA treatment seemed to be at higher risk of NANL cancer than mono-infected PWH. When stratifying on the time between first HCV-serology and SVR, to

take into account the progressive impact of HCV-infection on the risk of outcomes, the results were similar.

To our knowledge no other studies have compared the risk of overall mortality, AIDS defining events, and NANL cancers, between HCV co-infected PWH, who reached SVR, and mono-infected PWH never infected by HCV who had the same time of ART exposure. We observed a lower risk of overall mortality in HCV co-infected PWH who reached SVR compared to mono-infected PWH. This result is contrary to previous literature, which found that, despite SVR decreasing the risk of mortality in people with HCV, they still had a non-negligible risk of mortality compare to the general population, especially among people with cirrhosis (21,24). However, in this study we included only PWH without HCV at baseline, who got infected during clinical follow-up. Therefore, time between HCV acquisition and SVR is short (median 2.0 years [1.3; 3.7]). In the previous studies, PWH were with HCV for much longer times and therefore had higher liver damage at anti-HCV treatment than in our study. This could explain the discordant results. However, when stratifying the analysis on the time between the first HCV-serology and SVR (+/- 3 years), associations were similar to those of the main analysis. In addition, the selection of PWH who reached SVR and who were probably in better health than the overall population of PWH living with HCV could have led to these results, particularly for SVR before the DAA era. Indeed, DAAs are now recommended for all people without contraindication and are associated with high SVR rates in all subpopulations, but this was not the case for interferon-based treatment. In particular, these treatments were not recommended and induced low SVR rates in people with advanced fibrosis stage (26,27). Fibrosis stage and cirrhosis are the main factors reflecting HCV disease evolution and are important risk factors of mortality in this population (1). As many of those who reached SVR received interferon-based treatment, and they had longer follow-up than those who reached SVR after a DAA treatment, that could have induced selection of an SVR population in better health and thus at lower risk of mortality.

The risk of AIDS-defining events was similar in HCV co-infected PWH who reached SVR compared to PWH who never had HCV. In the literature, some studies found HCV to be associated with a lower immunological and virological restoration after ART (28,29) whereas others did not estimate any association (30,31). However, even in those concluding a harmful effect of HCV co-infection on the course of HIV infection, it seems to disappear over time (32,33). In addition, in HIV elite controllers, HCV co-infection was associated with the risk of non-HIV related complications but not with the progression of HIV disease (34). SVR did not seem to impact the progression of HIV disease either (35).

Finally, when restricting the population to PWH with HCV co-infection who received a DAA treatment and their matched mono-infected PWH we observed a higher risk of NANL cancer in HCV co-infected PWH compared to mono-infected PWH, despite a large confidence interval. Due to chronic inflammation and other mechanisms, HCV co-infection is associated with an increased risk of several non-liver-related cancers (36). It is possible that, for people that had HCV for a long time, SVR did not reduce the risk induced by previous long duration of HCV, as the development of cancer is a long-term mechanism. In people with HCV, some

studies identified that SVR was associated with a decreased risk of non-liver-related cancers (37,38). However, in a study of HCV co-infected PWH, Mocroft et al. did not observe differences in the risk of NANL cancers between people with and cured-of HCV (39).

This study has several limitations. First, due to the adverse effects of earlier HCV treatments, i.e., interferon-based treatments and the different rates of HCV-cure according to the characteristics of patients, HCV co-infected PWH reaching SVR might represent a select population among HCV co-infected PWH. Indeed, interferon-based treatment were contraindicated and less effective in participants with cirrhosis (26,27), and were not recommended in person with injecting drug use in a first time (40). Advanced fibrosis and cirrhosis are the main factors related to liver-related events and to overall mortality in people living with HCV with or without SVR (1). Thus, our results may need to be confirmed in a population exclusively cured by DAA-based treatments. Second, data on liver disease were frequently missing, especially in mono-infected PWH. Consequently, it was not possible to quantify and take into account these differences in the models. Finally, due to their co-infection with HCV, this group could have a closer follow-up than mono-infected PWH. The closer follow-up could have led not only to a better management of their HIV infection and thus to a decreased risk of complications, but also to an earlier diagnosis of AIDS defining events and of NANL cancers and artificially increased the difference between mono-infected PWH and HCV co-infected PWH who reached SVR.

This study has also several strengths. As the ART-CC collaboration collected data from PWH who initiated ART treatment from 1996, there was substantial follow-up time, which allowed us to observe a large number of events. The matching on age, sex, and time since ART initiation made the two considered populations more comparable. HCV co-infected PWH who reached SVR and mono-infected PWH are difficult to compare due to the differences between them, especially concerning the route of acquisition, and missing date of HCV infection. This is why we chose to include people without HCV at time of ART initiation. The first positive HCV serology was thus observed during follow-up and should be close to the date of HCV co-infection as the HIV population is frequently followed up whilst on ART.

To conclude, when compared to mono-infected PWH, PWH with HCV co-infection for a short time and who reached SVR, whatever the treatment generation, were at lower risk of overall mortality. Nevertheless, participants who reached SVR after a DAA-based treatment still exhibited a higher risk of NANL cancer after SVR despite an important incertitude in the estimate with a large confidence interval. Treatment guidelines and the limited efficacy of pre-DAA HCV treatments could have resulted in a selection of the SVR population and therefore artificially decreased the risk of events in the SVR population. A study comparing HIV mono-infected participants and HCV-cured participants following highly effective DAA treatment could overcome this issue.

REFERENCES

1. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol. 2014 Nov;61(1 Suppl):S58-68.

2. Platt L, Easterbrook P, Gower E, McDonald B, Sabin K, McGowan C, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lancet Infect Dis. 2016 Jul;16(7):797–808.

3. World Health Organization. Global hepatitis report 2017 [Internet]. Geneva: World Health Organization; 2017. Available from: https://apps.who.int/iris/handle/10665/255016

4. Pol S, Lamorthe B, Thi NT, Thiers V, Carnot F, Zylberberg H, et al. Retrospective analysis of the impact of HIV infection and alcohol use on chronic hepatitis C in a large cohort of drug users. J Hepatol. 1998 Jun 1;28(6):945–50.

5. Soto B, Sánchez-Quijano A, Rodrigo L, del Olmo JA, García-Bengoechea M, Hernández-Quero J, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol. 1997 Jan;26(1):1–5.

6. Ingiliz P, Rockstroh JK. Natural history of liver disease and effect of hepatitis C virus on HIV disease progression. Curr Opin HIV AIDS. 2015 Sep;10(5):303–8.

7. Rockstroh JK, Mohr R, Behrens G, Spengler U. Liver fibrosis in HIV: which role does HIV itself, long-term drug toxicities and metabolic changes play? Curr Opin HIV AIDS. 2014 Jul;9(4):365–70.

8. Crowell TA, Gebo KA, Balagopal A, Fleishman JA, Agwu AL, Berry SA. Impact of Hepatitis Co-Infection on Hospitalization Rates and Causes in a Multi-Center Cohort of Persons Living with HIV. J Acquir Immune Defic Syndr 1999. 2014 Apr 1;65(4):429–37.

9. Meijide H, Pértega S, Rodríguez-Osorio I, Castro-Iglesias Á, Baliñas J, Rodríguez-Martínez G, et al. Increased incidence of cancer observed in HIV/hepatitis C virus-coinfected patients versus HIV-monoinfected. AIDS Lond Engl. 2017 15;31(8):1099–107.

10. Wang Q, De Luca A, Smith C, Zangerle R, Sambatakou H, Bonnet F, et al. Chronic Hepatitis B and C Virus Infection and Risk for Non-Hodgkin Lymphoma in HIV-Infected Patients: A Cohort Study. Ann Intern Med. 2017 Jan 3;166(1):9–17.

11. Kovari H, Ledergerber B, Cavassini M, Ambrosioni J, Bregenzer A, Stöckle M, et al. High hepatic and extrahepatic mortality and low treatment uptake in HCV-coinfected

persons in the Swiss HIV cohort study between 2001 and 2013. J Hepatol. 2015 Sep;63(3):573–80.

12. May MT, Justice AC, Birnie K, Ingle SM, Smit C, Smith C, et al. Injection Drug Use and Hepatitis C as Risk Factors for Mortality in HIV-Infected Individuals: The Antiretroviral Therapy Cohort Collaboration. J Acquir Immune Defic Syndr 1999. 2015 Jul 1;69(3):348–54.

13. 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 May 10;

14. Klein MB, Rollet-Kurhajec KC, Moodie EEM, Yaphe S, Tyndall M, Walmsley S, et al. Mortality in HIV-hepatitis C co-infected patients in Canada compared to the general Canadian population (2003-2013). AIDS Lond Engl. 2014 Aug 24;28(13):1957–65.

15. 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 May 15;28(8):1181–91.

16. Sanmartín R, Tor J, Sanvisens A, López JJ, Jou A, Muga R, et al. Progression of liver fibrosis in HIV/hepatitis C virus-coinfected individuals on antiretroviral therapy with early stages of liver fibrosis at baseline. HIV Med. 2014 Apr;15(4):203–12.

17. Gjærde LI, Shepherd L, Jablonowska E, Lazzarin A, Rougemont M, Darling K, et al. Trends in Incidences and Risk Factors for Hepatocellular Carcinoma and Other Liver Events in HIV and Hepatitis C Virus-coinfected Individuals From 2001 to 2014: A Multicohort Study. Clin Infect Dis Off Publ Infect Dis Soc Am. 2016 Sep 15;63(6):821–9.

18. Rockstroh JK, Nelson M, Katlama C, Lalezari J, Mallolas J, Bloch M, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. Lancet HIV. 2015 Aug;2(8):e319-327.

19. Chalouni M, Pol S, Sogni P, Fontaine H, Lacombe K, Jean-Marc-Lacombe null, 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. 2020 Aug 13;

20. Nahon P, Bourcier V, Layese R, Audureau E, Cagnot C, Marcellin P, et al. Eradication of Hepatitis C Virus Infection in Patients With Cirrhosis Reduces Risk of Liver and Non-Liver Complications. Gastroenterology. 2017 Jan;152(1):142-156.e2.

21. El-Serag HB, Kanwal F, Richardson P, Kramer J. Risk of hepatocellular carcinoma after sustained virological response in Veterans with hepatitis C virus infection. Hepatol

Baltim Md. 2016 Jul;64(1):130–7.

22. Butt AA, Yan P, Simon TG, Abou-Samra AB. Effect of Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir and Ledipasvir/Sofosbuvir Regimens on Survival Compared With Untreated Hepatitis C Virus-Infected Persons: Results From ERCHIVES. Clin Infect Dis Off Publ Infect Dis Soc Am. 2017 Sep 15;65(6):1006–11.

23. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012 Dec 26;308(24):2584–93.

24. van der Meer AJ, Berenguer M. Reversion of disease manifestations after HCV eradication. J Hepatol. 2016 Oct;65(1 Suppl):S95–108.

25. May MT, Ingle SM, Costagliola D, Justice AC, de Wolf F, Cavassini M, et al. Cohort profile: Antiretroviral Therapy Cohort Collaboration (ART-CC). Int J Epidemiol. 2014 Jun;43(3):691–702.

26. Heathcote EJ. Treatment considerations in patients with hepatitis C and cirrhosis. J Clin Gastroenterol. 2003 Dec;37(5):395–8.

27. Fried MW. Side effects of therapy of hepatitis C and their management. Hepatol Baltim Md. 2002 Nov;36(5 Suppl 1):S237-244.

28. Portocarrero Nuñez JA, Gonzalez-Garcia J, Berenguer J, Gallego MJV, Loyarte JAI, Metola L, et al. Impact of co-infection by hepatitis C virus on immunological and virological response to antiretroviral therapy in HIV-positive patients. Medicine (Baltimore). 2018 Sep;97(38):e12238.

29. Taye S, Lakew M. Impact of hepatitis C virus co-infection on HIV patients before and after highly active antiretroviral therapy: an immunological and clinical chemistry observation, Addis Ababa, Ethiopia. BMC Immunol. 2013 May 17;14:23.

30. Weis N, Lindhardt BO, Kronborg G, Hansen ABE, Laursen AL, Christensen PB, et al. Impact of hepatitis C virus coinfection on response to highly active antiretroviral therapy and outcome in HIV-infected individuals: a nationwide cohort study. Clin Infect Dis Off Publ Infect Dis Soc Am. 2006 May 15;42(10):1481–7.

31. Sullivan PS, Hanson DL, Teshale EH, Wotring LL, Brooks JT. Effect of hepatitis C infection on progression of HIV disease and early response to initial antiretroviral therapy. AIDS Lond Engl. 2006 May 12;20(8):1171–9.

32. Law WP, Duncombe CJ, Mahanontharit A, Boyd MA, Ruxrungtham K, Lange JMA, et al. Impact of viral hepatitis co-infection on response to antiretroviral therapy and HIV

disease progression in the HIV-NAT cohort. AIDS Lond Engl. 2004 May 21;18(8):1169–77.

33. Santin M, Mestre M, Shaw E, Barbera MJ, Casanova A, Niubo J, et al. Impact of hepatitis C virus coinfection on immune restoration during successful antiretroviral therapy in chronic human immunodeficiency virus type 1 disease. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol. 2008 Jan;27(1):65–73.

34. Stafford KA, Rikhtegaran Tehrani Z, Saadat S, Ebadi M, Redfield RR, Sajadi MM. Long-term follow-up of elite controllers. Medicine (Baltimore) [Internet]. 2017 Jun 30 [cited 2021 May 28];96(26). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5500077/

35. Saracino A, Bruno G, Scudeller L, Ladisa N, de Gennaro N, Allegrini M, et al. CD4 and CD4/CD8 ratio progression in HIV-HCV infected patients after achievement of SVR. J Clin Virol Off Publ Pan Am Soc Clin Virol. 2016 Aug;81:94–9.

36. Cacoub P, Saadoun D. Extrahepatic Manifestations of Chronic HCV Infection. N Engl J Med. 2021 Mar 18;384(11):1038–52.

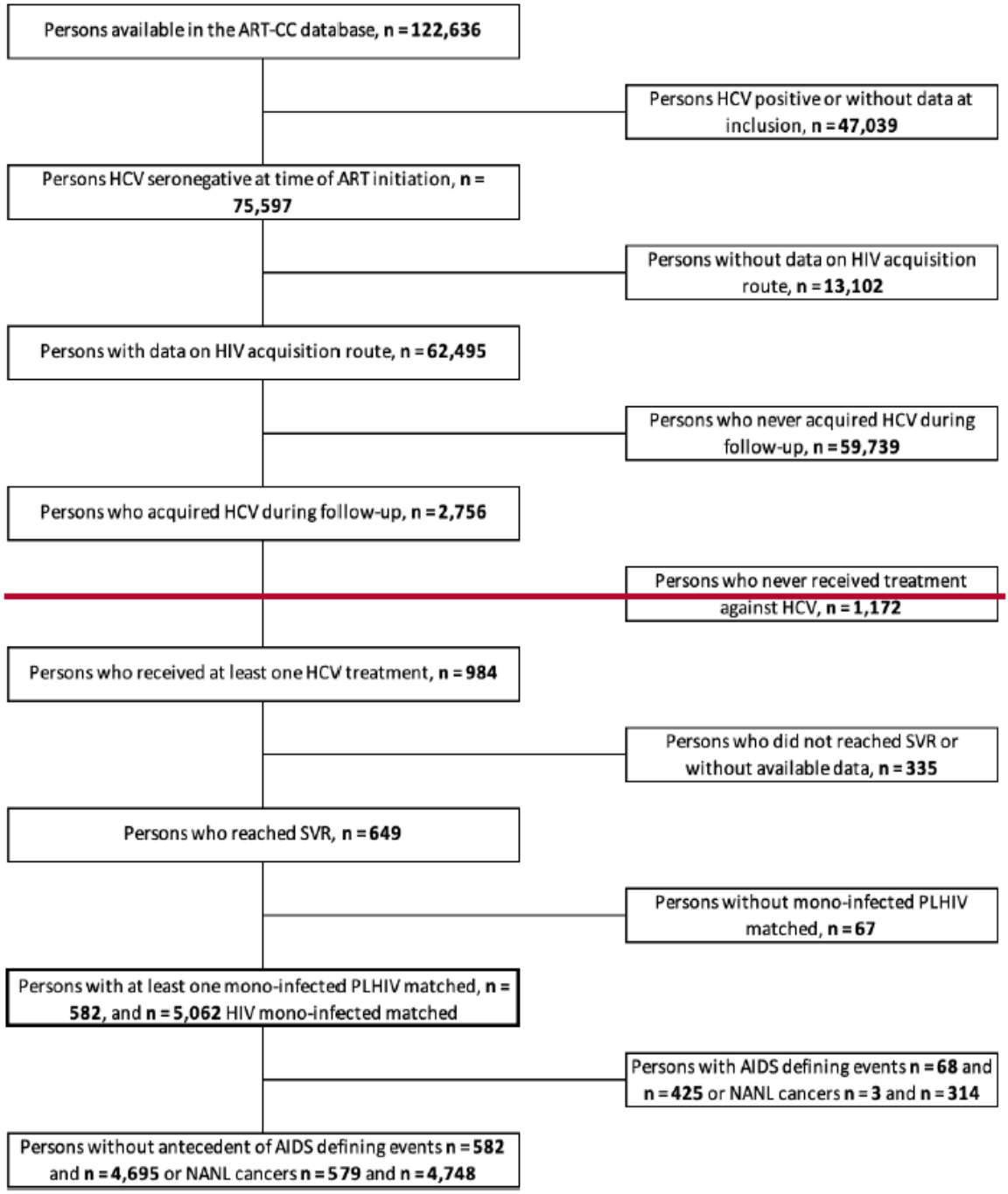
37. Mahale P, Engels EA, Li R, Torres HA, Hwang LY, Brown EL, et al. The effect of sustained virological response on the risk of extrahepatic manifestations of hepatitis C virus infection. Gut. 2018 Mar;67(3):553–61.

38. Wang W, Lo Re V, Guo Y, Xiao H, Brown J, Park H. Impact of hepatitis C virus treatment on the risk of non-hepatic cancers among hepatitis C virus-infected patients in the US. Aliment Pharmacol Ther. 2020 Nov;52(10):1592–602.

39. Mocroft A, Lundgren J, Gerstoft J, Rasmussen LD, Bhagani S, Aho I, et al. Clinical Outcomes in Persons Coinfected With Human Immunodeficiency Virus and Hepatitis C Virus: Impact of Hepatitis C Virus Treatment. Clin Infect Dis Off Publ Infect Dis Soc Am. 2020 May 6;70(10):2131–40.

40. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: An update. Hepatol Baltim Md. 2009 Apr;49(4):1335–74.

Figure 1. Flow-chart of the participants from the ART-CC collaboration



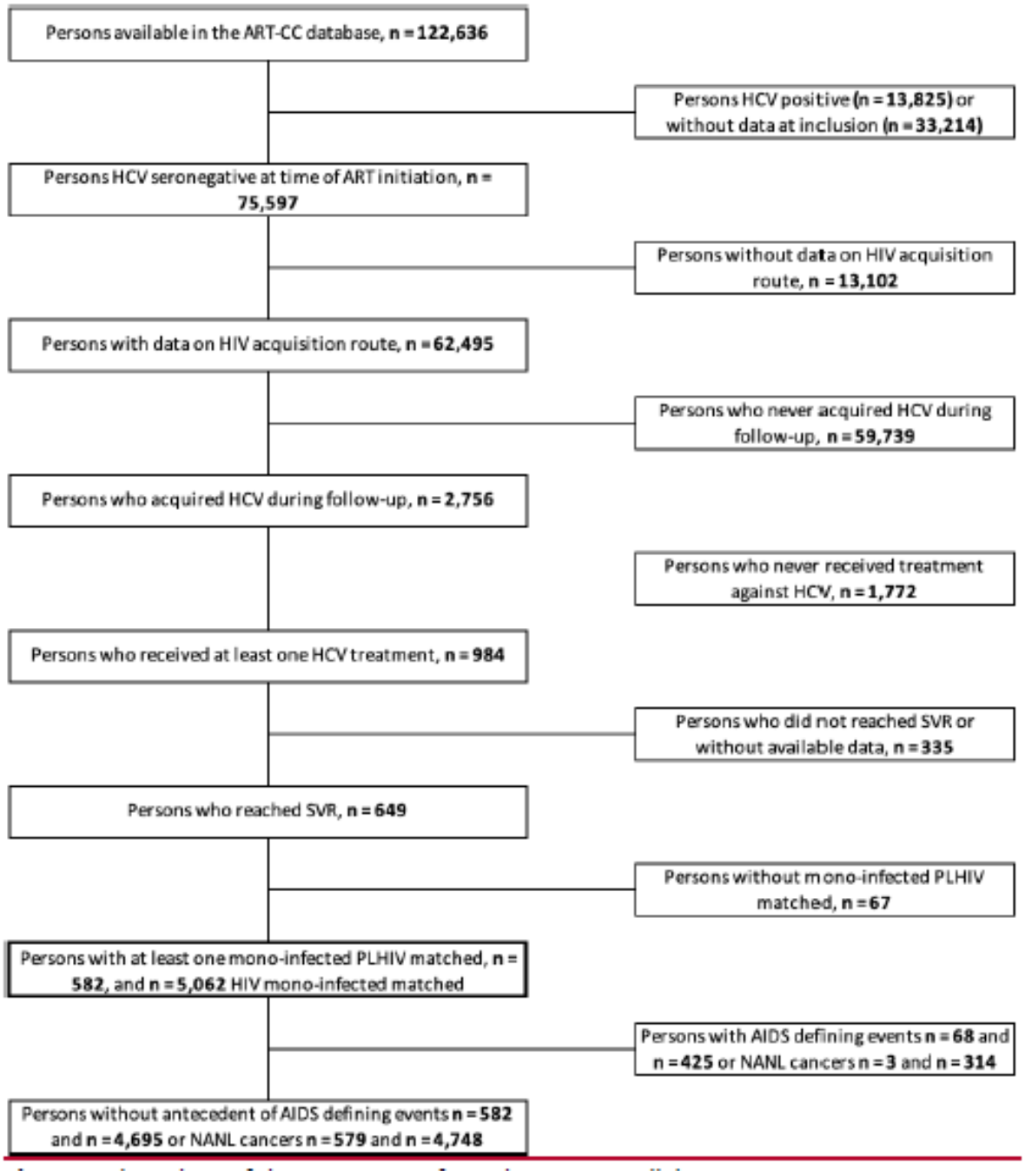


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Figure 2. Cumulative probabilities of overall mortality, AIDS defining events and non-AIDS non-liver-related cancers according to the SVR status in participants from the ART-CC collaboration

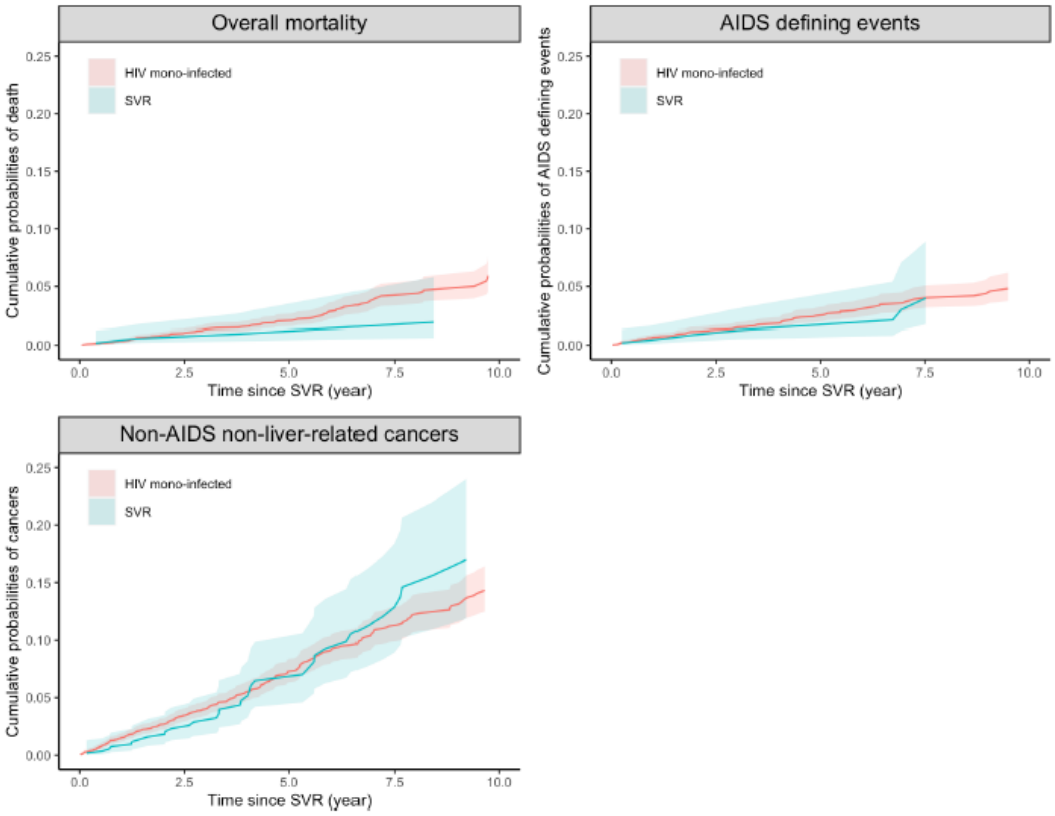

Table 1. Characteristics at baseline in participants from the ART-CC collaboration according to the sustained virological response status

	HCV co-infected PWH who achieved SVR (n = 582)		Mono-infected PWH (n = 5,062)	
Characteristics	**N**	**Median [IQR] or n (%)**	**N**	**Median [IQR] or n (%)**
Age (years)	582	45.5 [37.9; 51.3]	5,062	45.2 [37.9; 50.8]
Women	582	31 (5.3%)	5,062	162 (3.2%)
Alcohol consumption	147	112 (76.2%)	1,476	1,140 (76.2%)
Tobacco consumption	474	232 (48.9%)	3,979	1,992 (50.1%)
HIV acquisition routes	582		5,062	
Homo/bisexual sex		460 (79.0%)		4,524 (89.4%)
Injecting drug use		64 (11.0%)		152 (3.0%)
Heterosexual sex		47 (8.1%)		364 (7.2%)
Other		2 (0.3%)		2 (0.0%)
Unknown		9 (1.5%)		20 (0.4%)
ART initiation year	582		5,062	
1996-1999		88 (15.1%)		666 (13.2%)
2000-2003		95 (16.3%)		722 (14.3%)
2004-2007		119 (20.4%)		1,028 (20.3%)
2008-2011		160 (27.5%)		1,479 (29.2%)
2012-2015		109 (18.7%)		1,060 (20.9%)
2016-2019		11 (1.9%)		107 (2.1%)
ART regimens	582		5,062	
2NRTI + 1NNRTI		269 (46.2%)		2,528 (49.9%)
2NRTI + 1PI		227 (39.0%)		1,755 (34.7%)
2NRTI + 1INI		34 (5.8%)		350 (6.9%)
Others		52 (8.9%)		429 (8.5%)
CD4 (cells/mm^3)	582	580 [399; 840]	5,062	640 [480; 840]
< 50		0 (0.0%)		12 (0.2%)
50-99		2 (0.3%)		24 (0.5%)
100-199		19 (3.3%)		91 (1.8%)
200-349		71 (12.2%)		355 (7.0%)
350-499		122 (21.0%)		749 (14.8%)
≥ 500		330 (58.1%)		3,318 (65.5%)
AIDS[£] stage	582	0 (0.0%)	5,062	367 (7.3%)

	HCV co-infected PWH who achieved SVR (n = 582)		Mono-infected PWH (n = 5,062)	
Characteristics	**N**	**Median [IQR] or n (%)**	**N**	**Median [IQR] or n (%)**
FIB-4	426	1.1 [0.8; 1.6]	2,6852	0.9 [0.7; 1.2]
< 1.45		305 (71.6%)		2,281 (84.9%)
1.45; 3.25		112 (26.3%)		379 (14.1%)
≥ 3.25		29 (6.8%)		25 (0.9%)
AST (IU/L)	464	27.0 [22.0; 33.0]	2,833	26.0 [21.0; 32.0]
ALT (IU/L)	485	23.7 [18.0; 32.0]	3,977	28.0 [21.0; 38.0]
Platelets (10^9/L)	471	214 [177; 259]	3,654	230 [198; 267]
HCV treatment	582		-	
Interferon		227 (39.0%)		-
PI		56 (9.6%)		-
DAA		299 (51.4%)		-
SVR year	582		-	
2000-2003		7 (1.2%)		-
2004-2007		27 (4.6%)		-
2008-2011		104 (17.9%)		-
2012-2015		159 (27.3%)		-
2016-2019		285 (49.0%)		-

HCV: Hepatitis C virus, PWH: People with HIV, ART: Antiretroviral therapy, IQR: Interquartile range, NRTI: Nucleotide reverse transcriptase inhibitor, NNRTI: Non nucleotide transcriptase inhibitor, PI: Protease inhibitor, INI: Integrase inhibitor, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, DAA: Direct acting antiviral

Table 2. Incidence of overall mortality, AIDS defining events and non-liver-related non-AIDS defining cancers according to SVR status in participants from the ART-CC collaboration

	Overall mortality		AIDS events		NANL cancers	
Population	**Inc**	**95% CI**	**Inc**	**95% CI**	**Inc**	**95% CI**
HIV mono-infected	5.2	[4.3; 6.3]	5.1	[4.2; 6.3]	14.9	[13.2; 16.7]
SVR participants	2.7	[1.1; 5.5]	3.9	[1.8; 7.4]	15.4	[10.9; 21.2]

HCV: Hepatitis C virus, SVR: Sustained virological response, Inc: Incidence for 1000 Persons-Years, 95% CI: Confidence interval at 95%, NANL: Non-acquired immunodeficiency virus syndrome defining non-liver-related cancers

Table 3. Comparison of HIV/HCV co-infected with HIV mono-infected participants after SVR for the risk of overall mortality, AIDS defining events and non-AIDS non-liver-related cancers in participants from the ART-CC collaboration

	Overall mortality	**AIDS defining events**	**NANL cancers**
Population	**HR [95% CI]***	**HR [95% CI]***	**HR [95% CI]***
Overall			
HIV mono-infected	ref	ref	ref
SVR	0.29 [0.11; 0.74]	0.85 [0.42; 1.74]	1.22 [0.86; 1.72]
SVR after an INF-based treatment			
HIV mono-infected	ref	ref	ref
SVR	0.26 [0.09; 0.73]	0.85 [0.37; 1.92]	1.05 [0.67; 1.63]
SVR after a DAA based treatment			
HIV mono-infected	ref	ref	ref
SVR	0.44 [0.06; 3.39]	0.59 [0.10; 3.48]	1.62 [0.91; 2.89]
SVR ≤ 3 years after first HCV-seropositivity			
HIV mono-infected	ref	ref	ref
SVR	0.29 [0.09; 0.99]	1.12 [0.40; 3.15]	1.14 [0.67; 1.94]
SVR > 3 years after first HCV-seropositivity			
HIV mono-infected	ref	ref	ref
SVR	-	0.65 [0.23; 1.87]	1.28 [0.81; 2.03]

SVR: Sustained virological response, HR: Hazards ratio, 95% CI: Confidence interval at 95%, NANL: Non-acquired immunodeficiency virus syndrome defining non-liver-related cancers

* Adjusted for age (in years) using restricted cubic splines with three knots located at the terciles of the values of age, calendar year of ART initiation, ART type, and CD4 count, birth sex, HIV acquisition route (men who have sex with men (MSM), person who injects drugs, heterosexual sex, other, or unknown) and detectable HIV-RNA viral load