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EFFECT OF HCV INFECTION ON CAUSE-SPECIFIC MORTALITY FOLLOWING HIV SEROCONVERSION BEFORE AND AFTER 1997

Short title: HIV/HCV coinfection and mortality

Jannie van der Helm¹, Ronald Geskus^{1,2}, Caroline Sabin³, Laurence Meyer⁴, Julia del Amo⁵, Geneviève Chêne⁶, Maria Dorrucchi⁷, Roberto Muga⁸, Kholoud Porter⁹, Maria Prins^{1,10} on behalf of CASCADE collaboration in EuroCoord

From the ¹Public Health Service Amsterdam, Amsterdam, the Netherlands; ²Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; ³Research Department of Infection and Population Health, UCL, London, United Kingdom; ⁴Service d'Epidémiologie et de Santé Publique, Hôpital de Bicêtre, AP-HP; INSERM U1018; Univ Paris Sud, France; ⁵Instituto de Salud Carlos III, Madrid, Spain; ⁶Univ. Bordeaux Ségalen; INSERM U897 & CIC-EC7; CHU de Bordeaux, Bordeaux, France; ⁷Istituto Superiore di Sanità, Rome, Italy; ⁸Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; ⁹MRC Clinical Trials Unit, London, UK; ¹⁰Academic Medical Center, University of Amsterdam, CINIMA, Amsterdam, the Netherlands.

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Abbreviations: aHR, adjusted hazard rate; cART, combination antiretroviral therapy; COD, causes of death; HCV, hepatitis C virus; IDU, injecting drug user; MSM, men who have sex with men; MSW, sex between men and women.

Correspondence to Jannie J. van der Helm, Public Health Service, Cluster Infectious Diseases, Nieuwe Achtergracht 100, 1018 WT Amsterdam, the Netherlands

Phone: +31(20)5555061, Fax: +31(20)5555533, E-mail: jvdhelm@ggd.amsterdam.nl

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Jannie van der Helm; acquisition of data, drafting of the manuscript, statistical analysis, analysis and interpretation of data.

Ronald Geskus; acquisition of data, study concept and design, statistical analysis, analysis and interpretation of data and critical revision of the manuscript for important intellectual content, analysis supervision.

Caroline Sabin, Laurence Meyer, Julia del Amo, Geneviève Chêne, Maria Dorrucci, Roberto Muga: acquisition of data, analysis and interpretation of data and critical revision of the manuscript for important intellectual content.

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Abstract

Background and Aims: Individuals with HIV infection are frequently also infected with hepatitis C virus (HCV) (co-infection), but little is known about its effects on progression of HIV-associated disease. We aimed to determine the effects of co-infection on mortality from HIV and/or AIDS, and hepatitis or liver disease, adjusting for duration of HIV infection.

Methods: We analyzed data from the 16 cohorts of the Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) Collaboration that included information on HCV infection and cause of death. A competing risks proportional sub-distribution hazards model was used to evaluate the effect of HCV infection on the following causes of death: HIV- and/or AIDS-related, hepatitis- or liver-related, natural, and non-natural.

Results: Of 9164 individuals with HIV infection and a known date of seroconversion, 2015 (22.0%) were also infected with HCV. Of 718 deaths, 395 (55.0%) were due to HIV infection and/or AIDS, and 39 (5.4%) to hepatitis or liver-related disease. Among individuals infected with only HIV or with co-infection, the mortality from HIV infection and/or AIDS-related causes and hepatitis or liver disease decreased significantly after 1997, when combination antiretroviral therapy (cART) became widely available. However, after 1997, HIV and/or AIDS-related mortality was higher among co-infected individuals than those with only HIV infection in each risk group: injection-drug use (adjusted hazard ratio [aHR], 2.43; 95% confidence interval [CI], 1.14-5.20), sex between men and women or hemophilia (aHR, 3.43; 95% CI, 1.70-6.93) and sex between men (aHR, 3.11; 95% CI, 1.49-6.48). Compared to individuals infected with only HIV, co-infected individuals had higher risk of death from hepatitis or liver disease.

Conclusions: Based on analysis of data from the CASCADE Collaboration, since 1997, when cART became widely available, individuals co-infected with HIV and HCV have had a higher risk of death from HIV and/or AIDS, and from hepatitis or liver disease, than patients infected with only HIV. It is necessary to evaluate the effects of HCV therapy on HIV progression.

Keywords: Epidemiology; cART; disease progression; immune deficiency

Introduction

Due to shared transmission routes, HIV-infected persons are at risk of other blood-borne and sexually-transmitted infections. Hepatitis C virus (HCV) infection, which is predominantly transmitted parenterally, is common in this group. As HIV-infected persons live longer in the era of combination antiretroviral therapy (cART), they are increasingly more likely to die from non-HIV related causes¹, with the sequelae of hepatitis infections being a leading cause of non-HIV deaths². HIV infection adversely affects both the natural history and therapy outcome of HCV³ and even in the cART era HIV continues to accelerate HCV disease progression⁴. However, there is conflicting evidence as to whether HCV co-infection accelerates HIV disease progression. A recent meta-analysis including 10 studies from the pre-cART era and 27 studies from the cART era⁵, reported that HIV-HCV co-infected individuals were not at higher risk of all-cause mortality compared to those with HIV mono-infection in the pre-cART era, but were at a higher risk of all-cause mortality in the cART-era. However, no effect of co-infection on the risk of AIDS-defining events in the cART era was observed. Liver-related mortality was not studied in the meta-analysis but another study reported an increased risk of liver-related mortality in HIV-HCV co-infected individuals compared to HIV-mono-infected individuals in the cART era⁶. The effect of HCV on specific causes of mortality, other than HIV and/or AIDS and liver-related causes, in HIV co-infected individuals is very limited⁷.

Only a few studies, all from individual countries, have explored changes in the impact of HCV co-infection on HIV disease progression in the cART era compared to the pre-cART era⁸⁻¹³, and reported conflicting results. These studies are, however, limited by their design as they did not consider competing causes of death and accurate estimates of the duration of HCV and HIV infection were not available, except for one study which estimated HIV infection duration⁸. Moreover, individuals with missing HCV status were often excluded from analysis, which can introduce serious bias¹⁴. Better estimates of the effect of HCV co-infection on cause-specific mortality, including HIV and/or AIDS-related mortality, are needed to improve our understanding of prognosis and to guide the care of co-infected patients. The CASCADE collaboration, which includes a large group of HIV seroconverters, provides a unique opportunity to study the impact of HCV co-infection on both HIV and/or AIDS and hepatitis or liver-related mortality, adjusting for duration of HIV infection. We studied the impact of

HCV co-infection in HIV-infected persons on deaths from different causes and evaluated whether any effect changed after the introduction of cART.

Materials and Methods

Study population

CASCADE (Concerted Action on SeroConversion to AIDS and Death in Europe), a collaboration within EuroCoord (www.EuroCoord.net) currently of 28 HIV seroconverter cohort studies in Europe, Australia, Canada, and sub-Saharan Africa. Details of CASCADE is described elsewhere¹⁵. In brief, all cohorts included HIV-1 infected individuals for whom a date of HIV seroconversion could be estimated reliably. The end date used for this analysis was June 2007, when 21 seroconverter cohorts were included in the collaboration: one Canadian, two Australian, and 19 European.

Analyses were restricted to 16 cohorts from Europe and Canada for which the cause of death was available for at least 50% of reported deaths, and HCV status was known for at least 50% of study participants. Survival of individuals from the included and excluded cohorts was compared and did not differ significantly. Individuals younger than 15 years of age at HIV seroconversion and those with a time period of more than three years between the last HIV seronegative and first HIV seropositive test were excluded. For each cohort we collected information on the start date of routine HCV data collection/testing. HCV positivity was defined as any positive HCV test (anti-HCV antibody, HCV-RNA or test for HCV infection not recorded) during follow-up. HCV positive individuals were assumed to be HCV positive from HIV seroconversion onwards. Classification of cause of death (COD) was based on the 1993 clinical definition of AIDS from the Centers for Disease Control and the International Classification of Diseases 10th revision. Furthermore, the 'Coding of Death in HIV' (CoDe) classification system was used to standardize causes of death reported by cohorts¹⁶. COD were grouped into four categories: HIV and/or AIDS-related, hepatitis- or liver-related, other natural causes, and non-natural death. When more than one cause of death was given, the most likely underlying cause of death was scored independently by members of the CASCADE Clinical Advisory Board.

Statistical analysis

As effective cART became widely available in 1997, we split follow-up into two periods: pre-1997 and 1997 onwards, reflecting the pre-cART and cART eras, respectively. Follow-up was calculated from the estimated date of seroconversion until the earliest of: death, loss to follow-up or the cohort censor date, being latest June 2007. Individuals who contributed to both calendar periods were left-truncated for the cART era at 31 December 1996. Those who were enrolled retrospectively after seroconversion into the cohort were included in the risk set from their time of cohort enrolment (i.e. left truncation was applied to control for survivorship bias). Moreover, we applied additional left truncation at the first date of routine data collection on HCV for the cohorts that started collecting this information later than the date of their cohort start because information on HCV status before routine data collection might be biased (e.g. retrospective testing may be more likely for individuals suspected of having HCV infection)¹⁷. As a substantial number of individuals remained with missing HCV status after the start of routine HCV data collection, we used multivariate imputation of HCV status by chained equations (MICE) and created five imputed datasets^{18,19}. We assumed that after the start of routine data collection the decision to test for HCV was not related to HCV status. Missing COD was also imputed. The same variables used in the survival analysis were used in the imputation models, i.e. risk group, sex, age at HIV seroconversion, co-infection status, cause of death, calendar period, left truncation time and follow-up time. For all analyses, the results from the five imputed datasets were combined using Rubin's method²⁰. We validated the imputation procedure and checked whether the imputed values were reasonable under the assumptions that values were missing at random²¹. Furthermore, the imputation model was checked by including country of the cohort site.

To describe whether differences in outcomes were related to use of cART, we compared uptake of antiretroviral therapy, achieving an HIV RNA response ≤ 500 copies/mL following therapy initiation and virological failure (defined as the first of two consecutive viral loads > 500 copies/mL) following initial suppression between monoinfected and co-infected individuals using a Cox proportional hazards model, adjusting for sex, risk group, age at HIV seroconversion. Also, an

interaction between age at HIV seroconversion and co-infection status was included. Adjusted hazard ratio [aHR] and 95% confidence interval are presented in brackets.

We estimated all-cause mortality, stratified by cART period and co-infection status through Kaplan-Meier survival estimates. In a Cox proportional hazards model, the effects of co-infection and calendar period, and their interaction, were adjusted for sex, risk group and age at HIV seroconversion. Furthermore we included an interaction between risk group and calendar period and an interaction between age at HIV seroconversion and co-infection status. This latter interaction was included to correct for time since HCV infection. We assume mortality to be increasingly different between monoinfected and co-infected individuals with increasing HCV infection duration. So, age at HIV seroconversion was used as proxy for duration of HCV infection. We did not include an interaction between risk group and co-infection status due to collinearity (e.g. all haemophilic men were co-infected).

We estimated cause-specific cumulative incidence curves stratified by co-infection status for the pre-cART and cART eras separately. In a multivariable model, the impact of co-infection on each cause of death was analysed using a proportional sub-distribution hazards model. In contrast to a proportional cause-specific hazards model, a proportional sub-distribution hazards model quantifies the effect of each covariable on the cumulative scale, taking into account the effects of other competing causes. Since some COD were rare, some effects of covariables were assumed to be equal for different COD as described in detail in the supplement²². The effect of HCV status was allowed to depend on age, i.e. we included an interaction between age and HCV status. We present the results for those aged 30 years as this was the median age in the population. In a sensitivity analysis individuals who seroconverted for HIV in the pre-cART era and contributed to the cART era were excluded as there may have been differences in the proportions surviving into the cART era between mono- and co-infected individuals. For the competing risks analyses, we used the approach described by Geskus²³, in which individuals who experienced a competing event remained in the risk set with a weight that was determined by the censoring pattern. Analyses were performed using R version 2.10.1²⁴. The package `mstate`²⁵ was used to calculate the weights.

Results

Description of the study population

Of the 9164 HIV seroconverters included in the analyses 1279 contributed to both calendar periods. HCV status was available for 7892 (86.1%) and imputed for 1272 (13.9%). After imputation, 2015 (22%) were HCV co-infected. Total person-years (PY) of follow-up was 7158 in the pre-cART era and 22230 in the cART era (Table 1). Men having sex with men (MSM) was the main risk for HIV transmission (57%) followed by sex between men and women (MSW) (25%), injection drug use (IDU) (16%) and hemophilia (2%). Compared to the pre-cART era, the proportion of IDU and haemophilic patients under follow-up was lower whereas that of MSW and MSM was higher in the cART era. HCV infection was much more frequent among those infected through IDU (90%) and hemophilia (99%) compared with MSM (7%) and MSW (9%). Consequently, 936 (53%) were HCV co-infected in the pre-cART era and 1767 (20%) in the cART era. In both periods, co-infected individuals were younger at HIV seroconversion than monoinfected individuals. In the cART era, co-infected individuals were infected with HIV in an earlier calendar year than monoinfected individuals. After adjustment for sex, risk group, age at HIV seroconversion, and the interaction between age at HIV seroconversion and HCV status, neither uptake of therapy (adjusted hazard ratio [aHR], 1.10; 95% confidence interval, 0.93-1.31 for those aged 25-29 years) nor achieving an HIV RNA response ≤ 500 copies/mL following therapy initiation differed significantly between monoinfected and co-infected individuals from all age groups in the cART era (aHR, 0.97; 0.82-1.15 for those <25 years, 0.92; 0.80-1.06 for those aged 25-29 years, 0.97; 0.80-1.17 for those aged 30-34 and 1.00; 0.82-1.21 for those aged ≥ 35 years). Virological failure following initial suppression was comparable for monoinfected and co-infected individuals in all age groups ≥ 25 years (aHR, 1.05; 0.85-1.30 for those aged 25-29 years, 1.02; 0.80-1.31 for those aged 30-34 years and 0.98; 0.75-1.26 for those aged ≥ 35 years). However, coinfecting individuals aged <25 years had a slightly higher risk of virological failure (aHR, 1.23; 1.02-1.48). In total 718 individuals died. A specific cause of death was available for 576 (80%) individuals and 142 (20%) causes of death were imputed. After imputation 395 deaths were due to HIV and/or AIDS and 39 due to hepatitis or liver-related causes.

All-cause mortality

All-cause mortality, unadjusted for possible confounders is shown in Figure 1. In the pre-cART era all-cause mortality was higher, although not significant, among monoinfected than co-infected individuals, with 78% (59%-88%) of the monoinfected group estimated to die within 15 years following HIV seroconversion compared to 58% (50%-64%) of the co-infected group. In contrast, in the cART era, co-infected individuals had significantly higher mortality than monoinfected individuals, 35% (31%-39%) vs. 11% (9%-14%), respectively, by 15 years following HIV seroconversion. After adjustment for sex, risk group and age, all-cause mortality did not significantly differ between co-infected and monoinfected individuals in the pre-cART era (aHR, 0.75; 0.41-1.37), but remained higher in co-infected individuals in the cART era (aHR, 1.84; 1.16-2.93). In each calendar period there was a significant difference in all-cause mortality by risk group ($p < 0.001$). Compared to MSM, all-cause mortality in the pre-cART era was 62% higher for IDU (aHR, 1.62; 0.97-2.71), almost equal in those with hemophilia (aHR, 0.98; 95% CI, 0.55-1.74) and 54% lower (aHR, 0.46; 0.24-1.88) for MSW. In the cART era, all-cause mortality was higher among all risk groups compared to MSM (aHR, 3.52; 2.35-5.26 for IDU, 4.77; 2.65-8.58 for those with hemophilia, and 1.51; 1.03-2.20 for MSW). Overall, there was a significant age effect, but the interaction between age and HCV status was not significant ($p = 0.55$).

Cause-specific cumulative incidences

Cumulative incidences for each specific COD in the pre-cART era are shown in Figure 2 (upper panel). In this era, deaths from HIV and/or AIDS had the highest cumulative incidence in both co-infected and monoinfected individuals. The cumulative probability of dying from HIV and/or AIDS within 15 years from HIV seroconversion was lower in co-infected individuals than in monoinfected individuals. In contrast, the probability of dying of hepatitis or liver-related causes within 15 years from HIV seroconversion was 4.1% (1.7-6.6) in co-infected individuals but only 0.4% (0-1.2) in monoinfected individuals.

In the cART era (Figure 2 lower panel), HIV and/or AIDS-related mortality decreased drastically, compared to the pre-cART era for both monoinfected and co-infected individuals, although less

pronounced for the latter with cumulative incidence at 15 years of 3.7% (2.2-5.1) and 14.5% (11.1-17.7) for monoinfected and co-infected, respectively. HIV and/or AIDS and non-natural causes were the most likely COD in co-infected individuals whereas HIV and/or AIDS and natural causes were the most likely COD in monoinfected individuals. The probability of dying from hepatitis or liver-related causes in monoinfected individuals in the cART era remained extremely low and was comparable to that in the pre-cART era (0.4% within 15 years; 0-0.9). Deaths from hepatitis or liver-related causes among co-infected individuals remained more frequent in the cART era (2.4% within 15 years; 0.8-4.0) but still decreased and had a somewhat later onset after HIV seroconversion.

Comparison of the risk of cause-specific mortality by HCV status

Sub-distribution hazards ratios for the relationship between death from each specific cause and HCV status are shown in Table 2. In the pre-cART era progression to HIV and/or AIDS-related death was comparable for co-infected and monoinfected individuals from the same risk group, except for IDU, whose risk was reduced if they were co-infected (aHR, 0.55; 0.33-0.90). In the cART era this association was reversed, with co-infected individuals from all four risk groups having a higher risk of progression to HIV and/or AIDS-related death than monoinfected individuals: IDU (aHR, 2.43; 1.14-5.20), MSW or those with hemophilia (aHR, 3.43; 1.70-6.93) and MSM (aHR, 3.11; 1.49-6.48), compared to monoinfected individuals of the same risk group. In the pre-cART era, co-infected individuals had a much higher risk of hepatitis or liver-related mortality than monoinfected individuals (aHR, 21.8; 6.26-75.9 for IDU and aHR, 27.9; 8.39-92.6 for all other risk groups combined). The same association was seen in the cART era, although hazard ratios were slightly less elevated (aHR, 7.86; 2.56-24.1 for IDU and aHR, 10.0; 3.14-32.2 for all other groups). In the pre-cART era the risk of dying from natural causes was lower for co-infected individuals from all risk groups (aHR, 0.36; 0.16-0.82 for MSW or those with hemophilia, aHR, 0.33; 0.13-0.84 for MSM and aHR, 0.26; 0.10-0.63 for IDU), while in the cART era hazard rates for this COD were comparable for co-infected and monoinfected individuals from the same risk group. The risk of dying from non-natural causes did not differ significantly for co-infected and monoinfected individuals from all risk groups in both the pre-

and post-cART eras, with the exception of a higher risk of mortality in the cART era among co-infected MSW or those with hemophilia (aHR, 2.91; 1.02-8.29).

Changes in the risk of cause-specific death in the cART era within groups with the same HCV status

Sub-distribution hazards for the relationship between death from each specific cause and calendar period are shown in Table 3. Among co-infected MSM or MSW or men with hemophilia, the risk of death from both HIV and/or AIDS (aHR, 0.19; 0.10-0.35) and hepatitis or liver-related causes (aHR, 0.36; 0.16-0.81) was significantly lower in the cART compared to the pre-cART era within the same risk group. A similar pattern was seen for co-infected IDUs (aHR, 0.34; 0.22-0.52 and aHR, 0.36; 0.16-0.81 respectively). For the co-infected groups, the risk of natural and non-natural causes of death did not significantly differ between the pre-cART and cART eras. Among monoinfected MSM or MSW or men with hemophilia the risk of death from both HIV- and/or AIDS-related (aHR, 0.043; 0.03-0.07) and natural causes (aHR, 0.34; 0.20-0.58) was lower in the cART era compared to the pre-cART era, with similar patterns among the monoinfected IDUs (aHR, 0.077; 0.031-0.19 and aHR, 0.20; 0.07-0.57, respectively). Due to the small numbers of hepatitis or liver-related deaths among monoinfected individuals the effect of risk group could not be estimated.

In a sensitivity analysis where country of cohort site was included in the imputation model, results did not change. Additionally, in a sensitivity analysis that excluded individuals from the cART era who seroconverted in the pre-cART era (n=4414), the direction of the aHR for HIV- and/or AIDS-related causes remained unchanged, although the reduced size of the sample meant that these sensitivity analyses were no longer sufficiently powered to detect significant effects (data not shown).

Discussion

Our study has a number of clinically-relevant findings. Firstly we found that, although all-cause mortality did not differ significantly between co-infected and monoinfected individuals in the pre-cART era, it became significantly higher for co-infected individuals in the cART era. This is in concordance with a recent meta-analysis which reported an increased risk of all-cause mortality for co-infected compared to monoinfected individuals in the cART era⁵. Secondly, among co-infected individuals, we found that their risk of hepatitis or liver-related mortality decreased in the cART era compared to the pre-cART era. In addition, despite the reduction in hepatitis or liver-related mortality in the cART era, co-infected individuals still experienced a higher rate of death from these causes compared to monoinfected individuals. Thirdly, and importantly, we found that, in the cART era, HCV co-infection increased the risk of HIV- and/or AIDS-related mortality. In fact, we found that co-infected individuals from all risk groups were at increased risk of HIV- and/or AIDS-related mortality, compared to monoinfected individuals from the same risk group. This is in contrast to the meta-analysis whose authors concluded that increased overall mortality was unrelated to HIV disease progression in the cART era because the risk of AIDS-defining events was not increased⁵. Interestingly, although HIV- and/or AIDS-related mortality was not assessed in that review, the pooled risk ratio of 1.49 reported for a combination of AIDS and death as outcome was statistically significant and in line with our finding. Conflicting results might be due to differences in follow-up duration, inability to correct for duration of HIV infection, different statistical methods and differences in patient population (e.g. ethnic background)^{26,27}.

Thus, although the effect of HCV on HIV disease progression is still under debate, our large study provides strong evidence of an increased risk of HIV- and/or AIDS-related mortality among co-infected individuals in the cART era. The underlying mechanisms by which HCV affects HIV disease progression are not known, however, although, it has been suggested that high levels of T-cell activation in co-infected individuals may lead to immune dysfunction²⁸. Cirrhosis and advanced liver disease might act as possible intermediate variables. These conditions affect immune function, thereby promoting AIDS-defining conditions, which might result in classification as an AIDS-related death. In addition, although therapy uptake in the cART era is similar for co-infected and monoinfected

individuals, it might be that cART effectiveness was less in co-infected individuals by increasing the risk of drug-related hepatotoxicity which might explain the poorer outcome²⁹. Another explanation might be lower adherence. In line with previous studies, we found no significant difference in the probability of experiencing an initial viral load response after starting therapy between co-infected and monoinfected individuals^{26,30}. Moreover, virological failure did not differ between co-infected and monoinfected individuals aged ≥ 25 years and differed only slightly among the youngest age group. We cannot unravel whether this is due to toxicity or adherence. The difference in virological failure is unlikely to be due to progressive liver disease as in general duration of HCV infection is longer in older individuals. More research on the effect of HCV coinfection on virologic failure is necessary³¹.

Co-infected individuals had a much higher risk of hepatitis or liver-related mortality compared to monoinfected individuals in the pre-cART as well as the cART eras. This has previously been reported⁶, although a substantial proportion ($>40\%$) of the study population in that seroprevalent cohort with missing HCV status were excluded. Individuals with missing HCV status are often excluded from studies^{6,8,11} and can bias the results¹⁴. To overcome this, we imputed missing HCV status and applied additional left truncation from the start of routine HCV data collection in each cohort.

Among co-infected individuals in our study, mortality from hepatitis or liver-related causes was lower in the cART era compared to the pre-cART era. This decrease might be explained by the use of cART, and by the wide availability of HCV therapy since 2001. We were not able to estimate at a population level the effect of cART before HCV therapy became available due to the small number of hepatitis or liver-related deaths observed between 1997 and 2000. Furthermore, no data on HCV treatment were available in the current CASCADE dataset. However, coverage and effectiveness of HCV treatment is low in co-infected individuals³² especially in co-infected drug users who account for the majority of HCV infections in this population³³. Several studies have shown that use of cART is associated with a lower rate of liver fibrosis and cirrhosis^{34,35} and that these benefits outweigh the risks of hepatotoxicity due to cART³⁶, but these studies are limited as they did not take time since HIV infection into account.

In monoinfected patients, guidelines recommend that the decision to start treatment for HCV infection is based on the degree of liver fibrosis and HCV genotype³⁷. An increased risk of both HIV and/or AIDS and hepatitis or liver-related mortality among co-infected individuals in the cART era might suggest that co-infected patients should start HIV and HCV treatment sooner after diagnosis to reduce the likelihood of disease progression, even in the absence of liver fibrosis^{28,38}. Direct acting antivirals (DAA) against HCV are likely to be available in the near future; these may provide a cure to a large number of HIV/HCV co-infected patients³⁹. Although results with the HCV protease inhibitors telaprevir and boceprevir are highly encouraging, their effects in co-infected patients are still in trial phase. This emphasises the need for careful evaluation of uptake and effectiveness of the DAA in co-infected individuals. Extended follow-up in the cART era will also provide insight into the effect of current and future HCV therapy regimens on mortality.

CD4 cell count and HIV RNA were not taken into account in our analysis as they might be intermediate variables in the causal pathway of the effect of HCV on mortality. Then the residual effect of HCV on mortality, over-and-above that driven through immunological or virological progression, would be reflected instead of the effect of HCV on mortality in the population. This would be of interest for future research. Since HCV status is measured frequently in only a small group of individuals, HCV status could not be included as a time-dependent covariable in our analyses. In addition, a substantial proportion of individuals were not tested for HCV RNA, but it is most likely that they are chronically-infected as spontaneous clearance of HCV in HIV-infected individuals is rare⁴⁰.

Although information on duration of HIV infection is known for all patients, information on duration of HCV infection for all is lacking. Thus co-infected individuals were assumed to be HCV positive from the time of HIV seroconversion onwards. This is likely to be true for IDUs and those with hemophilia but MSM are more likely to be infected with HIV before HCV infection as HIV is spread more efficiently sexually than HCV. As the main expansion of the HCV epidemic started after 2002¹⁷, most of the MSM in our study will have been infected with HCV for a relatively short time and this may be too short a time for us to witness the sequelae of HCV infection⁴. The increase in the

proportion of recently HCV-infected MSM in the cART era might, in addition to cART use, explain a later onset of death following HIV seroconversion from hepatitis or liver-related causes among co-infected individuals in the cART, compared to pre-cART, era. We included an interaction between age at HIV seroconversion and co-infection status in the analysis as proxy for duration of HCV infection. Although the lack of direct information on duration of HCV infection is a potential limitation of our study, studies with information on the timing of both infections and sufficient follow-up to permit analyses of mortality are non-existent.

Several potential limitations of our study should be mentioned. As classification of COD might not have been uniform within cohorts, we cannot exclude the possibility of misclassification in COD. Furthermore, as all cohorts were initiated to evaluate the consequences of HIV infection, COD might have been more likely to be classified as HIV and/or AIDS when individuals had a low CD4 cell count. On the other hand, we did not have sufficient information on hepatitis B status and alcohol use, which might have resulted in hepatitis or liver-related death⁴¹.

In order to reliably impute missing HCV status and COD, the analyses were restricted to cohorts for whom information on COD was available for at least 50% of reported deaths and HCV status was known for at least 50% of individuals. There is no reason to expect the effect of HCV on HIV disease progression to differ between cohorts that collect data on COD and/or co-infection status, and those that do not. Furthermore, the relative hazard of dying did not differ significantly between the 16 included and the five excluded cohorts (data not shown) and, given that our dataset is international, we believe that results are generalizable to high-income countries⁴².

In conclusion, HCV co-infected individuals appear to be at increased risk of HIV- and/or AIDS-related mortality in the cART era. Although the risk of hepatitis or liver-related mortality has decreased since cART became available, it is higher among co-infected individuals compared to those with only HIV. This underscores the importance of early diagnosis of HCV infection in HIV-infected individuals and the need for routine screening of HCV among high risk groups, including those not (yet) infected with

HIV. Our findings highlight the importance of interventions to increase the uptake of HCV treatment in co-infected individuals.

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CASCADE Steering Committee: Julia Del Amo (Chair), Laurence Meyer (Vice Chair), Heiner C. Bucher, Geneviève Chêne, Osamah Hamouda, Deenan Pillay, Maria Prins, Magda Rosinska, Caroline Sabin, Giota Touloumi.

CASCADE Co-ordinating Centre: Kholoud Porter (Project Leader), Ashley Olson, Kate Coughlin, Sarah Walker, Abdel Babiker.

CASCADE Clinical Advisory Board: Heiner C. Bucher, Andrea De Luca, Martin Fisher, Roberto Muga

CASCADE Collaborators: **Austria:** Austrian HIV Cohort Study (Robert Zangerle); **Australia** PHAEDRA cohort (Tony Kelleher, David Cooper, Pat Grey, Robert Finlayson, Mark Bloch) Sydney AIDS Prospective Study and Sydney Primary HIV Infection cohort (Tony Kelleher, Tim Ramacciotti, Linda Gelgor, David Cooper, Don Smith); **Canada** South Alberta clinic (John Gill); **Estonia** Tartu Ülikool (Irja Lutsar); **France** ANRS CO3 Aquitaine cohort (Geneviève Chêne, Francois Dabis, Rodolphe Thiebaut, Bernard Masquelier), ANRS CO4 French Hospital Database (Dominique Costagliola, Marguerite Guiguet), Lyon Primary Infection cohort (Philippe Vanhems), French ANRS CO6 PRIMO cohort (Marie-Laure Chaix, Jade Ghosn), ANRS CO2 SEROCO cohort (Laurence Meyer, Faroudy Boufassa); **Germany** German cohort (Osamah Hamouda, Claudia Kücherer, Barbara Bartmeyer); **Greece** AMACS (Paparizos V, Gargalianos-Kakolyris P, Lazanas M); Greek Hemophilia cohort (Giota Touloumi, Nikos Pantazis, Olga Katsarou); **Italy** Italian Seroconversion Study (Giovanni Rezza, Maria Dorrucchi), ICONA cohort (Antonella d'Arminio Monforte, Andrea De Luca.) **Netherlands** Amsterdam Cohort Studies among homosexual men and drug users (Maria Prins, Ronald Geskus, Jannie van der Helm, Hanneke Schuitemaker); **Norway** Oslo and Ullevål Hospital cohorts (Mette Sannes, Oddbjorn Brubakk, Anne-Marte Bakken Kran); **Poland** National Institute of Hygiene (Magdalena Rosinska); **Spain** Badalona IDU hospital cohort (Roberto Muga, Jordi Tor), Barcelona IDU Cohort (Patricia Garcia de Olalla, Joan Cayla), CoRIS-scV (Julia del Amo, Santiago Moreno, Susana Monge; Madrid cohort (Julia Del Amo, Jorge del Romero), Valencia IDU cohort (Santiago Pérez-Hoyos); **Switzerland** Swiss HIV Cohort Study (Heiner C. Bucher, Martin Rickenbach, Patrick Francioli); **Ukraine** Perinatal Prevention of AIDS Initiative (Ruslan Malyuta); **United Kingdom**

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EuroCoord Executive Board: Geneviève Chêne, University Bordeaux Segalen, France; Dominique Costagliola, Institut National de la Santé et de la Recherche Médicale, France Julia Del Amo, Instituto de Salud Carlos III, Spain; Carlo Giaquinto, Fondazione PENTA, Italy; Di Gibb, Medical Research Council, UK; Jesper Grarup, Københavns Universitet, Denmark; Ole Kirk, Københavns Universitet, Denmark; Bruno Ledergerber, University of Zurich, Switzerland; Laurence Meyer, Institut National de la Santé et de la Recherche Médicale, France; Alex Panteleev, St. Petersburg City AIDS Centre, Russian Federation; Andrew Phillips, University College London, UK, Kholoud Porter (Chair), Medical Research Council, UK; Caroline Sabin (Scientific Coordinator), University College London, UK, Claire Thorne, University College London, UK; Stephen Welch, Fondazione PENTA, UK.

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EuroCoord External Advisory Board: David Cooper, University of New South Wales, Australia; Nikos Dedes, Positive Voice, Greece; Kevin Fenton, Centers for Disease Control and Prevention, USA; David Pizzuti, Gilead Sciences, USA; Marco Vitoria, World Health Organisation, Switzerland.

EuroCoord Secretariat: Kate Coughlin, MRC Clinical Trials Unit, UK; Michelle Ellefson, Københavns Universitet, Denmark; Silvia Faggion, Fondazione PENTA, Italy; Richard Frost, MRC Regional Centre London, UK; Christine Schwimmer, University Bordeaux Segalen, France; Martin Scott, UCL European Research & Development Office, UK.

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Table 1

General characteristics of 9164 HIV-infected individuals with a known interval of HIV-seroconversion, stratified by HCV infection status and period of follow-up (pre-cART [<1997] and cART [≥ 1997]) in CASCADE Collaboration.

Note that 1279 individuals contributed to both periods.

Characteristic	Pre-cART (n=1769)		cART (n=8674)	
	HCV+ N=936	HCV- N=833	HCV+ n=1767	HCV- n=6907
Person years (PY) of follow-up	4211	2947	6923	15307
Age at HIV seroconversion, median (IQR)	25.9 (22.6-30.3)	30.4 (25.5-37.7)	27.4 (23.6-32.9)	30.9 (25.9-37.8)
Mode of HIV infection (%)				
Sex between men	51 (5)	605 (73)	329 (19)	4,727 (68)
Injection-drug use	726 (78)	70 (8)	1,164 (66)	132 (2)
Hemophilia	141 (15)	0 (0)	68 (4)	2 (0.03)
Sex between men and women	19 (2)	157 (19)	206 (12)	2,046 (30)
Sex (%)				
Men	696 (74)	719 (86)	1,254 (71)	5,574 (81)
Calendar year of HIV seroconversion, median (IQR)	1991 (1987-1993)	1991 (1987-1993)	1993 (1990-1997)	1997 (1993-2002)
Total deaths	191	176	223	128
Causes of death (%)				
HIV and/or AIDS related	123 (64)	140 (80)	91 (41)	41 (32)
Hepatitis or liver related	15 (8)	1 (1)	20 (9)	3 (2)
Non-natural	40 (21)	6 (3)	63 (28)	21 (16)
Natural	13 (7)	29 (16)	49 (22)	63 (49)

As results in this table are based on rounded mean values of the five imputed datasets, results may not always count up exactly to the total value.

Table 2

Sub-distribution hazards and 95% confidence intervals (CI) for the relationship between death from each specific cause and HCV status in the pre-cART and cART era, CASCADE Collaboration.

	Pre-cART aHR (95% CI)	Pre-cART IDU aHR (95% CI)	cART aHR (95% CI)	cART IDU aHR (95% CI)
HIV and/or AIDS				
HCV- MSM or MSW or those with hemophilia	1 (ref)		1 (ref)	
HCV+ MSM	0.70 (0.42-1.17)		3.11 (1.49-6.48)	
HCV+ MSW or those with hemophilia	0.78 (0.56-1.07)		3.43 (1.70-6.93)	
HCV+ IDU	0.74 (0.53-1.05)	0.55 (0.33-0.90)	5.90 (3.66-9.51)	2.43 (1.14-5.20)
HCV- IDU	1.35 (0.82-2.23)	1 (ref)	2.43 (1.17-5.04)	1 (ref)
Hepatitis or liver*				
HCV- MSM or MSW or those with hemophilia or IDU	1 (ref)		1 (ref)	
HCV+ IDU	21.8 (6.26-75.9)		7.86 (2.56-24.1)	
HCV+ MSM or MSW or those with hemophilia	27.9 (8.39-92.6)		10.0 (3.14-32.2)	
Natural				
HCV- MSM or MSW or those with hemophilia	1 (ref)		1 (ref)	
HCV+ MSM	0.33 (0.13-0.84)		1.49 (0.79-2.79)	
HCV+ MSW or those with hemophilia	0.36 (0.16-0.82)		1.64 (0.87-3.08)	
HCV+ IDU	0.52 (0.23-1.15)	0.26 (0.10-0.63)	1.38 (0.84-2.27)	1.16 (0.57-2.36)
HCV- IDU	2.02 (0.87-4.70)	1 (ref)	1.19 (0.58-2.46)	1 (ref)
Non-natural				
HCV- MSM or MSW or those with hemophilia	1 (ref)		1 (ref)	
HCV+ MSM	1.78 (0.50-6.35)		2.64 (0.95-7.34)	
HCV+ MSW or those with hemophilia	1.96 (0.58-6.66)		2.91 (1.02-8.29)	
HCV+ IDU	12.5 (4.45-35.4)	1.43 (0.44-4.70)	10.9 (5.81-20.5)	2.12 (0.59-7.64)
HCV- IDU	8.77 (2.69-28.6)	1 (ref)	5.15 (1.60-16.6)	1 (ref)

aHR, adjusted hazard rate (adjusted by sex and age); 95% CI, 95% confidence interval; HCV, hepatitis C virus; MSM, men who have sex with men; MSW, sex between men and women; IDU, injection-drug users

*Due to low number of events no further distinction between risk groups could be made.

Table 3

Sub-distribution hazards and 95% confidence intervals (CI) for the relationship between death from each specific cause and calendar period for HCV positive and HCV negative HIV-infected individuals, CASCADE Collaboration.

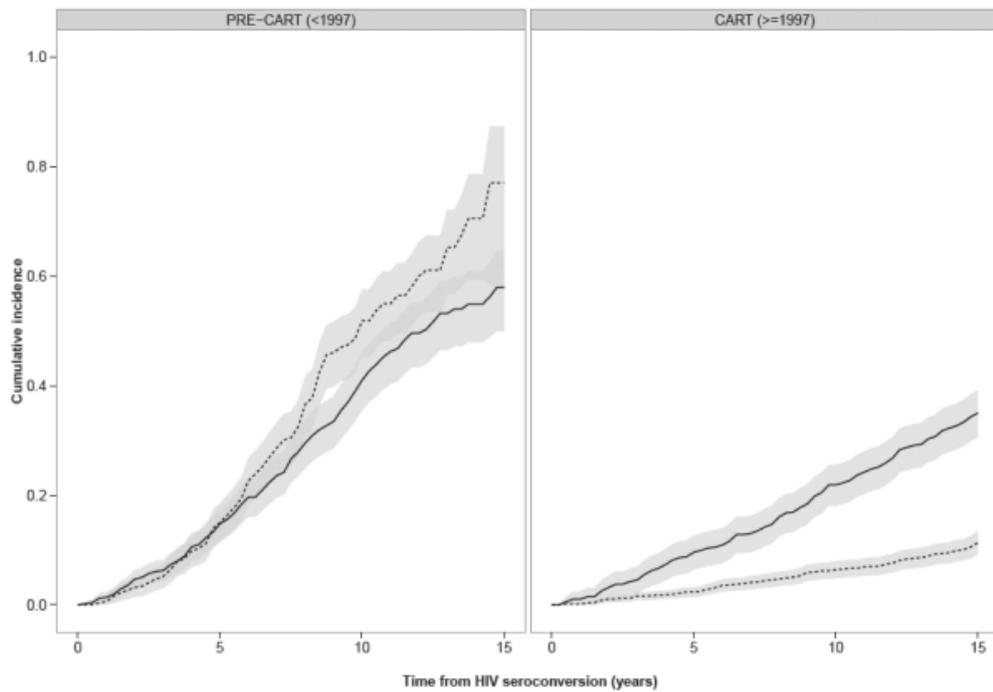
	HCV+ aHR (95% CI)	HCV- aHR (95% CI)
HIV and/or AIDS		
Pre-cART (within risk group)	1 (ref)	1 (ref)
cART MSM or MSW or those with hemophilia	0.19 (0.10-0.35)	0.04 (0.03-0.07)
cART IDU	0.34 (0.22-0.52)	0.07 (0.03-0.19)
Hepatitis or liver*		
Pre-cART (within risk group)	1	NA
cART MSM or MSW or those with hemophilia or IDU	0.36 (0.16-0.81)	NA
Natural		
Pre-cART (within risk group)	1 (ref)	1 (ref)
cART MSM or MSW or those with hemophilia	1.53 (0.62-3.74)	0.34 (0.20-0.58)
cART IDU	0.90 (0.41-1.94)	0.20 (0.07-0.57)
Non-natural		
Pre-cART MSM (within risk group)	1 (ref)	1 (ref)
cART MSM or MSW or those with hemophilia	1.76 (0.72-4.30)	1.18 (0.39-3.58)
cART IDU	1.03 (0.64-1.66)	0.70 (0.17-2.84)

aHR, adjusted hazard rate (adjusted by sex and age); 95% CI, 95% confidence interval; HCV, hepatitis C virus; MSM, men who have sex with men; MSW, sex between men and women; IDU, injection-drug users; NA, not applicable

*Due to low number of events no further distinction between risk groups could be made.

Figure 1

Cumulative incidence of all-cause mortality for monoinfected and co-infected individuals in the pre-cART and cART eras in the CASCADE Collaboration.

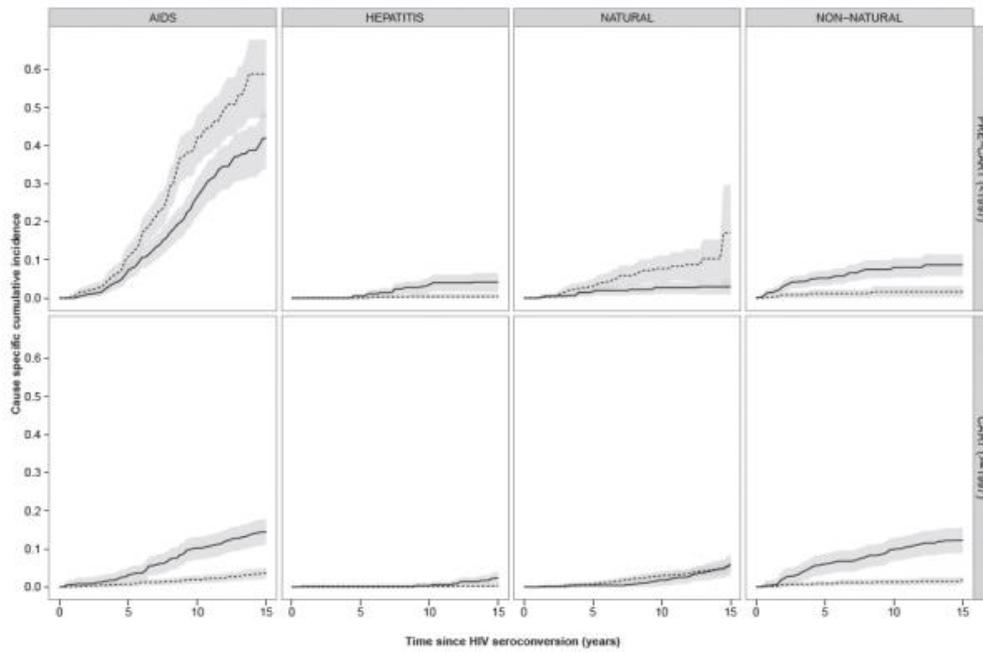


Dashed line, HIV monoinfected individuals; solid line, HIV/HCV co-infected individuals. Gray area around line, 95% confidence interval.

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Figure 2

Cause-specific cumulative incidence of death from a) HIV and/or AIDS, b) hepatitis or liver-related causes, c) natural causes and d) non-natural causes for monoinfected and co-infected individuals in the pre-cART and cART eras in the CASCADE Collaboration.



Dashed line, HIV monoinfected individuals; solid line, HIV/HCV co-infected individuals. Gray area around line, 95% confidence interval.