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Effect of incident hepatitis C infection on CD4 count and HIV RNA trajectories based on a multinational HIV seroconversion cohort

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Abstract

Background: Most studies on hepatitis C virus (HCV)/HIV co-infection do not account for the order and duration of these two infections. We aimed to assess the effect of incident HCV infection, and its timing relative to HIV seroconversion (HIVsc) in HIV-positive men who have sex with men (MSM) on their subsequent CD4 T-cell count (CD4) and HIV-RNA viral load (VL) trajectories.

Methods: We included MSM with well-estimated dates of HIVsc from 17 cohorts within the CASCADE Collaboration. HCV co-infected MSM were matched to as many HIV mono-infected MSM as possible by HIV-infection duration and cART use. We used multilevel random-effects models stratified by cART use to assess differences in CD4 and VL trajectories by HCV co-infection status.

Findings: We matched 214 (ART-naïve) and 147 (on cART) HCV co-infected MSM to 5,384 and 3,954 respectively matched controls. The timing of HCVsc relative to HIVsc had no demonstrable effect on VL or CD4 trajectories. In the first 2-3 years following HCVsc CD4 counts were lower among HCV co-infected MSM, but became comparable to HIV mono-infected MSM thereafter. In ART-naïve MSM, during the first two years after HCVsc, VL levels were lower or comparable to HIV mono-infected, tending to be higher thereafter. In MSM on cART, HCV had no significant effect on having a detectable VL.

Interpretation: Irrespective of the duration of HIV infection when HCV is acquired, CD4 counts were temporarily lower following HCVsc, even when on cART. The clinical implications of our findings remain to be further elucidated.

Keywords: HIV, Hepatitis C virus (HCV), HIV RNA, CD4, men who have sex with men (MSM)

Introduction

At the beginning of the millennium, a hepatitis C virus (HCV) epidemic emerged in HIV-positive men who have sex with men (MSM)[1]. In recent years, HCV has continued to spread in this group[2,3]. HIV infection often precedes HCV infection in MSM. This differs from the main risk groups in early studies of HIV/HCV co-infection, people who inject drugs (PWID) and haemophiliacs, in whom HCV was generally acquired before HIV infection[4,5]. It has been suggested that the order of HIV and HCV acquisition may influence the effect of HCV co-infection on disease progression [6]. Moreover, given that the extent of excessive alcohol use and other factors associated with HCV and HIV disease progression differ between groups at risk of HCV infection, HIV/HCV co-infected individuals are not a homogeneous population.

One recent meta-analysis concluded that among ART-naïve HIV-positive individuals, those co-infected with HCV had similar HIV RNA viral loads (VL) to HIV mono-infected individuals[5], while other studies have reported that they do have faster CD4 T-cell count (CD4) decline[7,8]. Among individuals on cART, another meta-analysis reported that HCV co-infection leads to significantly lower CD4 counts shortly after initiating cART, but that HCV co-infection has no effect on achieving viral suppression[4]. Most studies in both of these meta-analyses included a heterogeneous risk group population (e.g. PWID and haemophiliacs), assessed the difference in VL using a single measurement in ART-naïve individuals, and included individuals with a prevalent HIV and/or HCV infection[4,5]. They were therefore unable to distinguish the sequence or duration of the two viral infections. Consequently, little is known about the effect of incident HCV infection and its timing relative to duration of HIV infection on subsequent HIV disease progression among MSM. Using data from the CASCADE Collaboration with a large number of MSM with well-estimated dates of HIV seroconversion (HIVsc), we are uniquely positioned to study HIV/HCV co-infection in this group. In this study, we aimed to assess the effect of HCV seroconversion (HCVsc) and its timing, relative to HIVsc, on the VL and CD4 trajectories following HCVsc among MSM with newly-acquired HCV while ART-naïve and while on cART.

Methods

Study population

We used data from the CASCADE Collaboration within EuroCoord that includes cohorts across Europe, Australia, Canada and Sub-Saharan Africa. Details of CASCADE have been previously described[9]. All cohorts include data from HIV-positive individuals with dates of HIVsc that could be reliably estimated based on the midpoint between the last HIV-negative and first HIV-positive test dates (at most 36 months apart) or, with evidence of acute HIV infection. We included 17 of the 28 participating cohorts. Eleven cohorts were excluded because they had no MSM or <50% of the MSM had an HCV test result (Figure 1). We included only men who were self-reported as having acquired HIV through sex between men and whose potential HIV transmission route excluded injection drug use.

Definitions and exclusion criteria

HCV negative status throughout follow-up was based on having at least one HCV-negative test result and never being tested HCV positive. To optimize testing frequency, we performed additional HCV testing in nine cohorts that had stored specimens, as previously described[3]. HCV-positive status was based on any positive HCV test (RNA, antibodies and/or antigen). For MSM who acquired HCV during follow-up, we assumed that HCV seroconversion (HCVsc) occurred at the midpoint date between the last HCV-negative and first HCV-positive test. The date of HCVsc was based on a negative- and a positive-antibody test results in 77.8% of cases. The remained was based on RNA tests or a combination of antibody and RNA test results. Individuals who were HCV-positive before cART initiation were excluded from the cART analyses (n=207), and thus our analyses do not consider the effect of incident HCV while ART-naïve on CD4 and VL trajectories after cART initiation (Figure 1). To determine the timing of HCVsc as precisely as possible, we excluded MSM with an HCVsc interval of more than two years (n=69). Men with only HCV-positive test results throughout follow-up were excluded if the first HCV-positive test result was more than one year after HIVsc (n=119). For MSM with a positive HCV test within one year of HIVsc but without a recorded HCV-negative one (n=127), the date of HCVsc was estimated as the midpoint date between HIVsc and first HCV-positive test date, as HCV infection is not common among HIV-negative MSM[10,11]. MSM with an HCV-positive test before HIVsc (n=28) were excluded.

Timing of HCVsc relative to HIVsc (hereafter referred to as "timing") was calculated as the interval between the estimated dates of HIVsc and HCVsc. In those who acquired HCV while on cART, we calculated the cumulative time on cART, excluding time off cART due to a treatment interruption (hereafter referred to as "cumulative cART exposure"). We defined cART as a 3 drug ART regimen containing 2 different classes, or 3 nucleoside reverse transcriptase inhibitors (NRTIs), provided tenofovir or abacavir were included in the regimen.

Statistical analyses

Follow-up data

Individuals could contribute data from the first clinic/cohort visit after the estimated date of HIVsc from 1983 until 2014. For all cohorts, we used all available follow-up data, except for MSM from the French PRIMO cohort who were censored at the 31st December 2005 as routine HCV test results were only recorded until that year. ART-naïve MSM were censored at start of (c)ART, or last study visit if they remained (c)ART naïve. MSM on cART were censored at the moment of a treatment interruption (if off cART for more than a week) or last study visit.

Matching

We performed separate analyses for ART-naïve MSM and MSM on cART. To assess the effect of incident HCV infection and its timing, each HCV-infected individual (the "case") was matched to all eligible HCV-negative MSM (the 'controls') by HIV infection duration (For details on matching criteria see supplementary text 1, http://links.lww.com/QAD/B375). Hence, we could compare CD4 and VL trajectories following the estimated date of HCVsc of an HCV co-infected MSM to that of an HIV mono-infected MSM with a similar duration of HIV infection. Hereafter we refer to 'matched time' of the control as the matched duration since HIVsc. The duration since HIVsc used to matched cases and controls was determined by the moment of HCVsc relative to HIVsc of the case.

Statistical models

The time origin is the estimated date of HCVsc of each case, and their control's matched time. From this time origin onwards, we modelled trends in CD4 and VL over time using multilevel random-effects models including a random intercept and slope. Based on the scatterplot, we decided to use the 8th root transformation of VL, which gave a more symmetric distribution

than the $\log_{10}$ transformation. For CD4 we used the cube root transformation. Given the small numbers of records with a detectable VL among MSM on cART (8.9% of all VL measurements), we assessed the effect of HCV on having a detectable VL (defined as: VL >400 copies/mL) using a multilevel random-effects logistic regression model. In the multilevel model structure, measurements were nested within individuals (second level) and individuals were nested within case-control groups (first level).

The multivariable models included duration from HIVsc to HCVsc (i.e. 'timing') and the following co-variables as potential confounders and/or effect modifiers: age and calendar year at matched time. For the ART-naïve model we also included method of HIVsc determination (i.e. midpoint or (laboratory) evidence of acute infection). For those on cART, we also included cumulative cART exposure. We used restricted cubic splines to model the effect of continuous variables, with four knots based on 5th, 33rd, 66th, 95th percentiles. We included interaction terms between time since HCVsc/matched time, HCV co-infection status and timing to assess whether HCV co-infection or its timing influenced CD4 and VL trajectories. Furthermore, we included interaction terms to assess whether the effect of HCV co-infection and its timing on the CD4 and VL trajectory differed by age or calendar year, and for those on cART, cumulative cART exposure (model details in supplementary text 2, http://links.lww.com/QAD/B375).

Sensitivity analyses

First, for ART-naïve MSM with an HCV-positive test result but without a recorded HCV-negative test result, we applied two alternative strategies to estimate the moment of HCVsc. In the first strategy, we assumed that risk behaviour led to simultaneous infection with both HCV and HIV. In the second strategy, we assumed they became HCV infected at the time of their first HCV-positive test result. Second, we repeated the analyses restricting our population to ART-naïve cases with both an HCV-negative and an HCV-positive test during follow-up and their matched controls.

Third, we examined the effect of HCV co-infection on CD4 and VL trajectories using joint models[12] (except for the analysis with detectable VL as outcome) in order to correct for informative censoring (due to cART initiation among ART-naïve, and cART interruption among MSM on cART).

Results

Of 17,429 MSM included in CASCADE, 8,604 MSM from 17 cohorts were eligible after applying the exclusion criteria (Figure 1). Of these individuals, 7,692 (89.4%) were ART-naïve during the first visit after HIVsc and 5,224 (60.7%) had available data while on cART. A total of 214 HCV co-infected ART-naïve MSM and 147 HCV co-infected MSM on cART were included in the study, of whom 95 and 139 had well-estimated dates of HCVsc, respectively. HCV co-infected MSM were successfully matched at random to 5,384 and 3,954 HIV mono-infected ART-naïve MSM and MSM on cART, respectively (Table 1). Median time from HIVsc to HCVsc was 0.4 years [IQR=0.1-1.0] among ART-naïve and 6.2 years [IQR=3.3-10.7] among MSM on cART. Among HCV co-infected MSM on cART, median cumulative cART exposure at HCVsc was 3.2 years [IQR=1.0-6.1] and 75.5% of these MSM were on their first cART regimen when they acquired HCV.

CD4 and VL trajectories

ART-naïve MSM

At the time origin (i.e. HCVsc or matched time), VL was not significantly different between cases (i.e. HCV co-infected) and controls (i.e. HIV mono-infected) (p=0.32). The difference in VL trajectory between cases and control was statistically significant (p=0.03). VL trajectories by HCV co-infection status, although not statically significant (p=0.24), differed by the timing of HCVsc. If HCV and HIV seroconversion occurred around the same time, both cases and controls showed a strong downward trend in VL during the first year following HIV and HCV seroconversion (Figure 2A, first panel). In MSM who seroconverted for HCV at one year after HIVsc or later, we observed a downward trend in VL for about one year following HCVsc, which was not observed in the controls. After two years from HCVsc, HCV co-infected MSM appeared to have a faster increase in VL, and some suggestion of a higher VL later on compared to HIV mono-infected MSM (Figure 2A, second and third panel). However differences in actual VL values at any time point were small. The effect of HCV co-infection on VL trajectory did not significantly differ by age (p=0.21).

At the time origin, CD4 did not significantly differ between cases and controls (p=0.90) (Figure 2B). The difference in CD4 trajectory between cases and controls was highly significant (p<0.001), but this difference did not depend on HCVsc to HIVsc timing (p=0.78). CD4 decreased more rapidly during the first years following HCVsc in HCV co-infected MSM, but after three years following HCVsc values became comparable to those of HIV

mono-infected MSM. For example, when comparing MSM who seroconverted for HIV and HCV simultaneously and their controls, the difference in CD4 at one year following HCVsc/matched time was 43 CD4 cells/µl (figure 2B, first panel). The effect of HCV co-infection on CD4 trajectory did not significantly differ by age (p=0.50).

MSM on cART

For an "average" individual, the probability of having a detectable VL was below 2% for both cases and controls, and did not significantly differ by HCV co-infection status over time following HCVsc/matched time (p=0.17) (Figure 3A). However, controls had a borderline higher probability of having a VL at the time origin (p=0.05). The timing of HCVsc had no effect on VL (p=0.35). The effect of HCV co-infection on VL trajectory did not significantly differ by age (p=0.76) nor by cumulative cART exposure (p=0.60).

At the time origin, CD4 did not significantly differ between cases and controls (p=0.33) (Figure 3B). Similar to ART-naïve MSM, CD4 trajectories were significantly different between cases and controls (p=<0.001), and did not depend on the timing of HCVsc (p=0.69). During the first two to three years after HCVsc, CD4 were significantly lower among HCV co-infected MSM, but became comparable to HIV mono-infected MSM thereafter. For example, when comparing MSM who seroconverted for HCV three years after HIVsc (Figure 3B, first panel) to their controls, the difference in CD4 count at one year following HCVsc/matched time was 83 CD4 cells/µl. The effect of HCV co-infection on CD4 trajectory did not significantly differ by age (p=0.38) nor by cumulative cART exposure (p=0.99).

Sensitivity analyses

When we assumed that HCVsc took place simultaneously with HIV or at the time of the first HCV-positive test among HCV co-infected ART-naïve MSM without HCV-negative results, comparable results to the main analyses were obtained. When analyses were restricted to ART-naïve MSM with a documented HCVsc during follow-up, the difference in CD4 and VL trajectory was still statistically significant (p_{CD4}<0.001; p_{VL}=0.04) (Supplementary Figure 2, http://links.lww.com/QAD/B375). However, a lower VL in cases than controls was no longer observable, while differences in VL trajectory were more pronounced after two years from HCVsc, especially when HCVsc was closer to HIVsc (p_{timing}=0.09). The effect of timing was not significant for the CD4 model. Furthermore, joint models yielded similar results to the main analysis, although the effect of HCV co-infection on VL trajectory became borderline non-significant (p=0.05).

Discussion

We investigated in MSM with pre-existing HIV infection the effect of newly-acquired HCV infection, and its timing relative to HIVsc, on subsequent VL and CD4 count trajectories. First, in HCV co-infected MSM, CD4 counts were temporarily lower during the first two to three years following HCVsc compared to HIV mono-infected MSM, in both ART-naïve MSM and MSM on cART. Second, we found that HCV co-infection had an effect on the VL trajectories in ART-naïve MSM, but we did not find a change in the probability of having a detectable VL following HCVsc in MSM on cART. Third, timing of HCV acquisition relative to HIVsc was not found to affect VL and CD4 trajectories, suggesting that the observed changes in these trajectories can occur at any moment after HIV seroconversion.

Few studies have been able to assess the effect of HCV co-infection on CD4 trajectories among ART-naïve HIV-positive individuals. Two studies, with relatively small sample sizes and with an unknown sequence of HIV and HCV acquisition[7,8], also reported a steeper CD4 decline in HCV co-infected individuals when compared to HIV mono-infected individuals [8] or individuals who spontaneous cleared HCV as the control group[7]. However, the effect of HCV co-infection was not found to be statistically significant in the latter study[7]. To the best of our knowledge, only one study from the UK among ART-naïve patients (i.e. PWID, MSM and heterosexuals), with known HIV seroconversion dates, measured the effect of HCV co-infection on CD4 trajectories and also found that CD4 counts were temporary lower[13].

Similar to our findings among MSM on cART, a meta-analysis and an original study among HIV-positive MSM with acute HCV also found an initial decline in CD4 among HCV co-infected individuals[4,14]. The primary outcome in the meta-analysis however was difference in CD4 increase 3 to 12 months after cART initiation whereas our study examined CD4 trajectories after HCV seroconversion. In addition, they did not account for the sequence and duration of both infections. These factors might explain why some of the individual studies in this meta-analysis did not find an effect of HCV on CD4 trajectories[4]. The temporary effect of HCV co-infection on CD4 might be mediated through a heightened state of chronic inflammation, leading to enhanced CD4 apoptosis[15,16]. Interestingly, in our study the negative effect of HCV and convergence of CD4 trajectories between cases and controls occurred irrespective of cART use. Hence, the attenuation of the effect of HCV co-infection is probably not affected by cART use only.

The clinical short- and long-term implications of the temporary CD4 decline warrant further research. It is unknown whether the observed temporary CD4 decline attributes to the faster liver fibrosis progression observed in HIV/HCV co-infected individuals when compared to HCV mono-infected individuals[17] and the classical HCV co-infected risk groups[18-20], and whether it could potentially affect HCV treatment effectiveness. However, cure rates with direct-acting antivirals among HIV co-infected patients are similar to those in HCV mono-infected patients[21,22]. Additionally, whether the temporary CD4 decline contributes to a faster HIV disease progression still needs to be elucidated. A previous study using data from the CASCADE Collaboration showed that in the cART era (>1996), HCV co-infected MSM have a higher HIV/AIDS mortality than HIV mono-infected MSM[23]. Furthermore, ART response may be affected by HCV infection if ART initiation takes place during the temporary CD4 decline[24]. One could argue that HCV treatment shortly after an HCV infection is justifiable to prevent accelerated liver disease progression and a CD4 decline. Notwithstanding, continued follow-up after HCV infection is warranted to assess the long-term effects of HCV on liver fibrosis and HIV disease progression.

Our results on the effect of HCV on VL in ART-naïve individuals are not in agreement with a meta-analysis reporting no difference in VL by HCV co-infection status[5]. However, the primary outcome in this meta-analysis was based on the mean VL difference from a single VL measurement and most of the included studies did not account for HIV and HCV infection duration[5]. Interestingly, 4 of the 15 individual studies in the meta-analysis reported a significantly higher VL among HIV mono-infected individuals, which was also observed in our main analysis during the first year following HCVsc. However, when our analyses were restricted to those with a documented HCVsc during follow-up, we did not observe a lower VL in HCV co-infected MSM. Importantly, although VL differences by HCV co-infection status in our study were small, it has been demonstrated that even small increments in VL among ART-naïve individuals are associated with a higher risk of heterosexual transmission and AIDS-defining event or death[25]. The bystander effect of HCV on VL replication stresses the need for early HCV infection detection and could support the role of these individuals as a source of HIV transmission when left untreated for HCV. Our results of VL among MSM on cART are in line with the previously described meta-analysis where authors also reported that virological control of HIV infection after cART initiation remains unaffected by the presence of HCV[4].

There are some limitations in our study. Due to a lack of systematic data on HCV treatment, we could not account for it. A study among HIV/HCV co-infected patients comparing CD4 changes before and after pegylated-interferon/ribavirin treatment reported that CD4 decreased during the first 12 weeks of treatment, increasing thereafter and stabilizing from week 24 onwards[26]. However, HCV treatment alone could not explain the temporarily lower CD4 among HCV co-infected MSM as we observed an effect of HCV on CD4 trajectories for at least two to three years following HCVsc. We also did not account for spontaneous HCV clearance. This may have led to an underestimation of the effect of chronic HCV co-infection on CD4 and VL trajectories. However, around 15% of HIV-positive individuals clear HCV spontaneously[27]. Also, we did not account for other factors that could influence CD4 and VL trajectories such as ART adherence, HIV super-infection and other sexually-transmitted infections[28,29]. However, if these factors play an important role in the observed differences, we cannot explain why CD4 converged three years after HCVsc.

One of the major strengths in our study is our relatively large group of MSM with well-estimated dates of HIV and HCV seroconversion, hence, we could account for infection duration, and study the effect of the timing of HCVsc relative to HIVsc. Additionally, unlike most studies, we used all available CD4 and VL measurement to assess differences in trajectories by HCV co-infection status. Given the temporary effect of HCV co-infection on CD4 and VL trajectory by HCV co-infection, our findings emphasize the need to account infection duration.

In conclusion, we found no difference in CD4 and VL trajectories following HCVsc by its timing relative to HIVsc. Importantly, CD4 counts are temporarily lower during the first two to three years following HCVsc among HIV-positive MSM. Even though it is expected that more MSM will start cART earlier in the coming years, reflecting changing guidelines[30], CD4 counts are temporarily negatively affected following HCVsc despite cART use. Our findings would point to a consideration by clinicians to test for HCV if their HIV-positive patient's CD4 count drops while on cART. HCV co-infected ART-naïve MSM appear to have a higher VL trajectory two years after HCVsc than HIV mono-infected MSM, whereas we did not observe an effect of HCV on the probability of having a detectable VL among MSM on cART. Continued HCV prevention, testing and treatment are warranted in this group. The short- and long-term clinical implications of our findings still need to be further elucidated.

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Appendix

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, Andrea Cartier, Lorraine Fradette, Sarah Walker, Abdel Babiker.

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

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Genital Shedding Study (US: Charles Morrison; Family Health International, Robert Salata, Case Western Reserve University, Uganda: Roy Mugerwa, Makerere University, Zimbabwe: Tsungai Chipato, University of Zimbabwe); International AIDS Vaccine Initiative (IAVI) Early Infections Cohort (Kenya, Rwanda, South Africa, Uganda, Zambia: Matt A. Price, IAVI, USA; Jill Gilmour, IAVI, UK; Anatoli Kamali, IAVI, Kenya; Etienne Karita, Projet San Francisco, Rwanda).

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EuroCoord Council of Partners: Jean-Pierre Aboulker, Institut National de la Santé et de la Recherche Médicale, France; Jan Albert, Karolinska Institute, Sweden; Silvia Asandi, Romanian Angel Appeal Foundation, Romania; Geneviève Chêne, University of Bordeaux, France; Dominique Costagliola (chair), INSERM, France; Antonella d'Arminio Monforte, ICoNA Foundation, Italy; Stéphane De Wit, St. Pierre University Hospital, Belgium; Peter Reiss, Stichting HIV Monitoring, Netherlands; Julia Del Amo, Instituto de Salud Carlos III, Spain; José Gatell, Fundació Privada Clínic per a la Recerca Bíomèdica, Spain; Carlo Giaquinto, Fondazione PENTA, Italy; Osamah Hamouda, Robert Koch Institut, Germany; Igor Karpov, University of Minsk, Belarus; Bruno Ledergerber, University of Zurich, Switzerland; Jens Lundgren, Region Hovedstaden, Denmark; Ruslan Malyuta, Perinatal Prevention of AIDS Initiative, Ukraine; Claus Møller, Cadpeople A/S, Denmark; Kholoud Porter, University College London, United Kingdom; Maria Prins, Academic Medical Centre, Netherlands; Aza Rakhmanova, St. Petersburg City AIDS Centre, Russian Federation; Jürgen Rockstroh, University of Bonn, Germany; Magda Rosinska, National Institute of Public Health, National Institute of Hygiene, Poland; Manjinder Sandhu, Genome Research Limited; Claire Thorne, University College London, UK; Giota Touloumi, National and Kapodistrian University of Athens, Greece; Alain Volny Anne, European AIDS Treatment Group, France.

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

EuroCoord Secretariat: Silvia Faggion, Fondazione PENTA, Italy; Lorraine Fradette, University College London, UK; Richard Frost, University College London, UK; Andrea Cartier, University College London, UK; Dorthe Raben, Region Hovedstaden, Denmark; Christine Schwimmer, University of Bordeaux, France; Martin Scott, UCL European Research & Innovation Office, UK.

Ethics committees:

Ethics approval has been granted by the following committees: Austrian HIV Cohort Study: Ethik-Kommission der Medizinischen Universität Wien, Medizinische Universität Graz – Ethikkommission, Ethikkommission der Medizinischen Universität Innsbruck, Ethikkommission des Landes Oberösterreich, Ethikkommission für das Bundesland Salzburg; PHAEDRA cohort: St Vincent's Hospital, Human Research Ethics Committee; Southern Alberta Clinic Cohort: Conjoint Health Research Ethics Board of the Faculties of Medicine, Nursing and Kinesiology, University of Calgary; Aquitaine Cohort: Commission Nationale de l'Informatique et des Libertés; French PRIMO Cohort: Comite Consultatif de Protection des Personnes dans la Recherché Biomedicale; German HIV-1 Seroconverter Study: Charité, University Medicine Berlin; AMACS: Bioethics & Deontology Committee of Athens University Medical School and the National Organization of Medicines; Greek Haemophilia Cohort: Bioethics & Deontology Committee of Athens University Medical School and the National Organization of Medicines; ICoNA cohort: San Paolo Hospital Ethic Committee; Amsterdam Cohort Studies in Homosexual Men: Academic Medical Centre, University of Amsterdam; Oslo University Hospital Cohorts: Regional komite for medisinsk forskningsetikk - Øst- Norge (REK 1); CoRIS-scv: Comité Ético de Investigación Clínica de La Rioja; Madrid Cohort: Ethics Committee of Universidad Miguel Hernandez de Elche; Swiss HIV Cohort Study: Kantonale Ethikkommission, spezialisierte Unterkommission Innere Medizin, Ethikkommission beider Basel, Kantonale Ethikkommission Bern, Comité départemental d'éthique de médecine et médecine communautaire, Commission d'éthique de la recherche clinique, Université de Lausanne, Comitato etico cantonale, Ethikkommission des Kantons St.Gallen; UK Register of HIV Seroconverters: South Birmigham REC; Early Infection Cohorts: Kenya Medical Research Institute, Kenyatta National Hospital.

Table 1: General and clinical characteristics of HIV-positive MSM with and without HCV infection from the CASCADE Collaboration by cART use

	ART-naïve MSM		MSM on cART	
	HIV/HCV co-infected	**HIV mono-infected**	**HIV/HCV co-infected**	**HIV mono-infected**
N	214	5,384	147	3,954
Age, m (IQR)[a,b]	35 (29-41)	34 (28-40)	40 (35-47)	38 (32-45)
HIVsc estimation method				
Midpoint, n (%)	154 (72.3%)	3,998 (75.2%)	121 (82.3%)	2,752 (69.6%)
Acute HIV, n (%)	59 (27.7%)	1,321 (24.8%)	26 (17.7%)	1,202 (30.4%)
HCV+ and HCV- test result[c]	95	*NA*	139	*NA*
Width HCV infection interval, m (IQR)[b,c]	0.7 (0.4-1.2)	*NA*	0.8 (0.5-1.1)	*NA*
Matches per case, m (IQR)	21 (15-30)	*NA*	19 (10-38)	*NA*
Time from HIVsc to matched time[b,d]	0.4 (0.1-1.0)	0.5 (0.1-1.4)	6.2 (3.3-10.7)	3.7 (1.9-6.3)
Follow-up, m (IQR)[b,e]	1.1 (0.3-2.6)	0.7 (0.04-2.2)	2.1 (0.9-3.9)	1.5 (0.5-3.6)
Calendar year of HIVsc, m (IQR)	2005 (2002-2008)	2006 (2002-2009)	2001 (1996-2004)	2003 (1998-2007)
Calendar year, m (IQR)[a]	2007 (2004-2009)	2007 (2003-2010)	2008 (2005-2011)	2008 (2004-2011)
CD4 cell count (cells/µl), m (IQR)[a]	483 (358-660)	494 (363-663)	508 (367-710)	535 (398-700)
VL (copies/ml), m (IQR)[a]	46,175 (15,950-150,037)	40,900 (10,455-130,612)	50 (40-50)	50 (40-104)
Detectable VL, %[f]	93.7%	95.3%	3.6%	9.2%
Cumulative cART exposure, m (IQR)[a,b]	*NA*	*NA*	3.2 (1.0-6.1)	1.0 (0.3-2.7)

Abbreviations: N, number; n, median; IQR, interquartile range; VL, HIV RNA viral load; HIVsc, HIV seroconversion; NA, not applicable; HCV+, HCV positive; HCV-, HCV negative.

[a] At matched time[d]
[b] Represented in years.
[c] MSM with an HCV-negative and HCV-positive test result during follow-up.
[d] Matched time: HCV seroconversion among HCV co-infected MSM and matched time among HIV mono-infected.
[e] From matched time onwards; i.e. time origin.
[f] Percentage of detectable VL records during follow-up since matched time onwards.

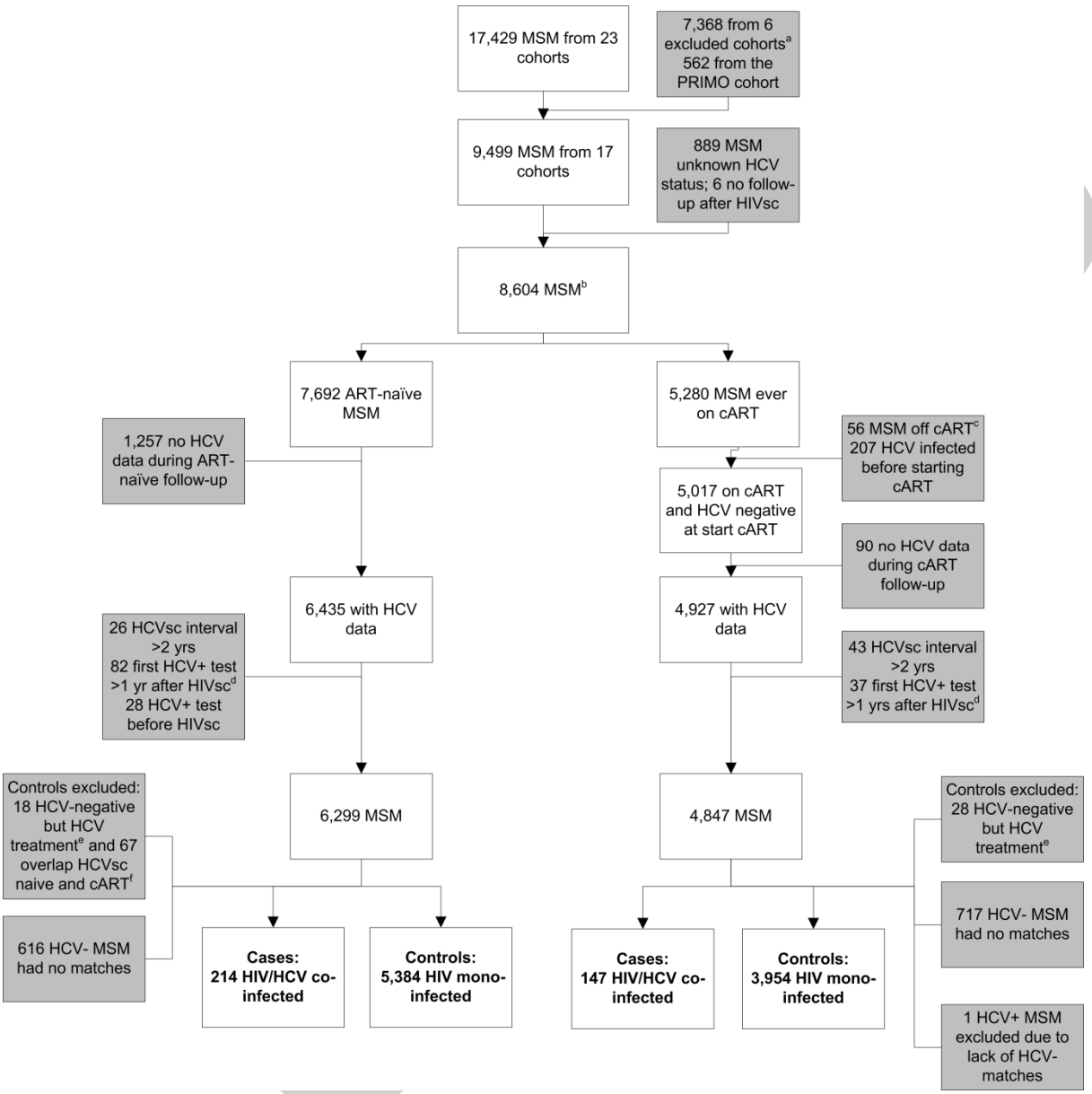

Figure 1: Flow diagram of the study population selection for ART-naïve MSM and MSM on cART from the CASCADE Collaboration

Abbreviations: yr(s), year(s), HIVsc, HIV seroconversion; HCV, Hepatitis C virus; HCVsc, HCV seroconversion; cART, combination antiretroviral therapy; HCV+, HCV-positive MSM; HCV-, HCV-negative MSM

The grey boxes depict MSM who were excluded from the analyses.
[a] Excluded cohorts: cohorts of which > 50% of MSM had a missing HCV status.
[b] Of 8,604 MSM, 4,502 (53.2%) MSM contributed data as ART-naïve as well as when on cART.
[c] 56 MSM had ever been on cART, but were off cART during follow-up.
[d] MSM without a recorded HCV-negative test results.

[e] Excluded due to possible HCV treatment, defined as having ever received pegylated-interferon and/or ribavirin, and never having an HCV-positive test result.
[f] Excluded as the interval between HCVsc while on cART and last visit while ART-naïve was less than two years.

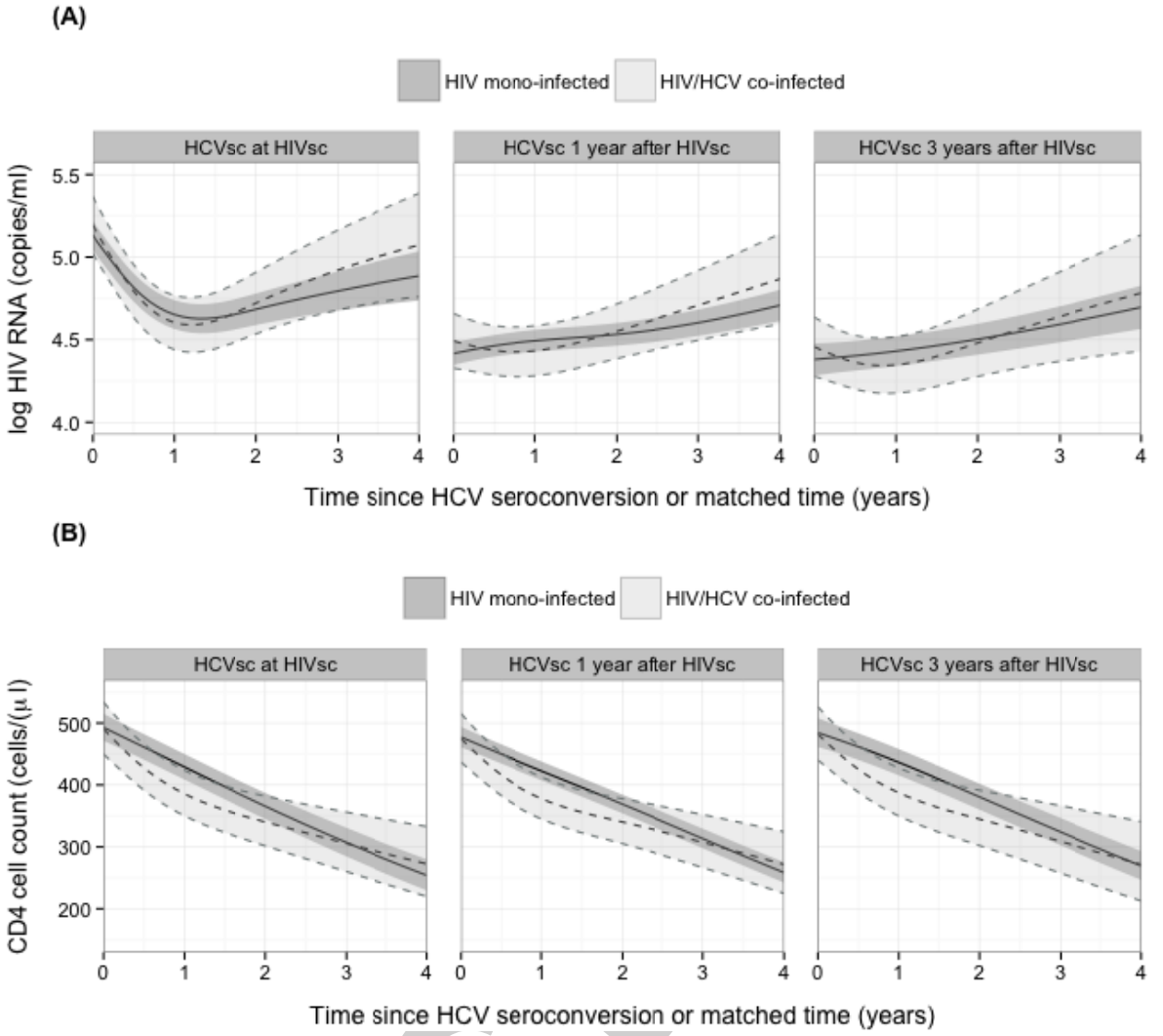

Figure 2: CD4 counts and HIV RNA viral load trajectories from HCV seroconversion or matched time onwards per timing of HCV seroconversion relative to HIV seroconversion, among ART-naive MSM from the CASCADE Collaboration.

Figure 2A: HIV RNA viral load trajectories; Figure 2B: CD4 cell count trajectories

Abbreviations: HCVsc, HCV seroconversion; HIVsc, HIV seroconversion

The solid lines represent median HIV RNA viral load (VL) and CD4 counts trajectories for HIV mono-infected MSM, with 95%CI illustrated in gray. Dashed lines represent median VL and CD4 counts trajectories for HIV/HCV co-infected MSM, with 95%CI illustrated with light gray dashed lines. VL and CD4 counts were back-transformed from 8th root of VL to 10-log VL copies/ml and cube root CD4 counts to CD4 counts cells/µl. The first (left) panel (i.e. "HCVsc at HIVsc", timing=0) represents VL or CD4 counts trajectory for those individuals who acquired HCV concurrently with HIV. The second (middle) panel represents MSM who seroconverted for HCV 1 year following HIVsc, and the third (last) panel represents MSM whose HCV seroconversion took place 3 years after HIVsc. All graphs are illustrated for an individual aged 35 years whose HIV seroconversion was estimated based on the midpoint date of a negative and a positive antibody test date, and seroconverted for HCV in 2005 (or matched calendar year for HIV mono-infected).

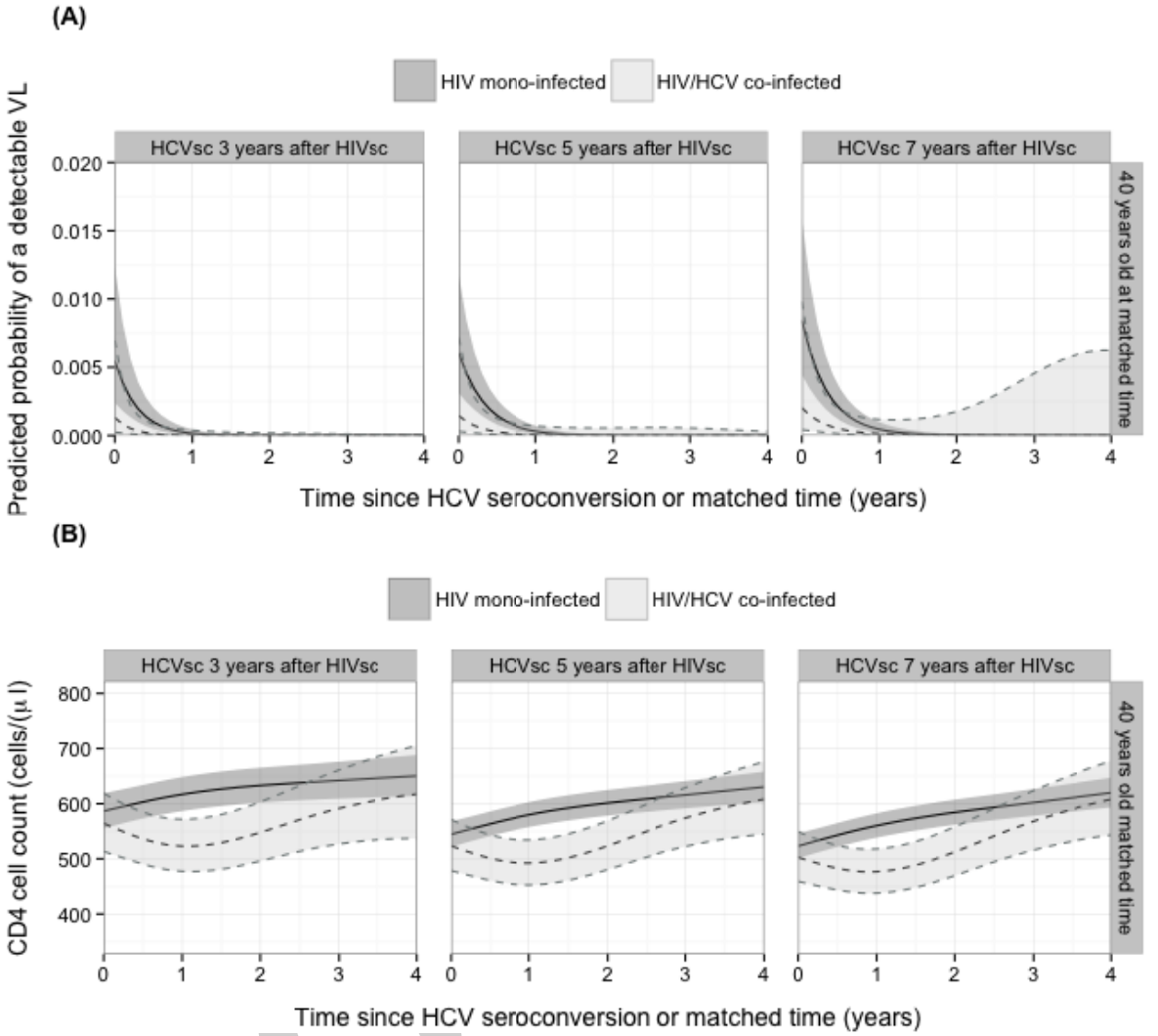

Figure 3: CD4 counts trajectories and predicted probabilities of having a detectable HIV RNA viral load from HCV seroconversion or matched time onwards per timing of HCV seroconversion relative to HIV seroconversion, among MSM on cART from the CASCADE Collaboration

Figure 3A: Predicted probabilities of having detectable HIV RNA viral load; Figure 3B: CD4 cell count trajectories

Abbreviations: HCVsc, HCV seroconversion; VL,HIV RNA viral load; HIVsc, HIV seroconversion

The solid lines represent predicted probabilities of having a detectable HIV RNA viral load (VL) and median CD4 counts trajectories estimate for HIV mono-infected MSM, with 95%CI illustrated in gray. Dashed lines represent the predicted probabilities and median CD4 counts

trajectories estimate for HIV/HCV co-infected MSM, with 95%CI illustrated with light gray dashed lines. Cube root CD4 counts were back-transformed to CD4 counts cells/μl. First (left), second (middle) and third (right) panel represent MSM who seroconverted for HCV 3, 5 and 7 years after HIVsc, respectively. All graphs are illustrated for an individual aged 40 years who had been on cART for 3 years at the matched visit and seroconverted for HCV in 2008 (or matched calendar year for HIV-monoinfected).