

AIDS

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

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Corresponding Author:	Daniela K van Santen, MSc Public Health Service of Amsterdam Amsterdam, NETHERLANDS
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Public Health Service of Amsterdam
Corresponding Author's Secondary Institution:	
First Author:	Daniela K van Santen, MSc
First Author Secondary Information:	
Order of Authors:	Daniela K van Santen, MSc
	Jannie J van der Helm
	Giota Touloumi
	Nikos Pantazis
	Roberto Muga
	Barbara Gunsenheimer-Bartmeyer
	M John Gill
	Eduard Sanders
	Anthony Kelleher
	Robert Zangerle
	Kholoud Porter
	Maria Prins
	Ronald B Gekus
Order of Authors Secondary Information:	
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Suggested Reviewers:	<p>Marina Klein marina.klein@mcgill.ca</p>
	<p>Andrew Phillips andrew.phillips@ucl.ac.uk</p>
	<p>Patrick Ingiliz ingiliz@zibp.de</p>
Opposed Reviewers:	

Abstract

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

Authors:

Daniela K. van Santen, MSc¹, Jannie J. van der Helm, PhD^{1,2}, Giota Touloumi, Prof.³, Nikos Pantazis, PhD³, Roberto Muga, MD⁴, Barbara Günsenheimer-Bartmeyer, PhD⁵, M. John Gill, Prof.⁶, Eduard Sanders, Prof.^{7,8}, Anthony Kelleher, Prof.⁹, Robert Zangerle, Prof.¹⁰, Kholoud Porter, Prof.¹¹, Maria Prins, Prof.^{1,12*} and Ronald B. Geskus, PhD^{1,8,13,14*}, on behalf of the CASCADE Collaboration within EuroCoord

* Maria Prins and Ronald Geskus contributed equally as senior co-authors.

Affiliations:

1. Department of Infectious Disease Research and Prevention, Public Health Service of Amsterdam, Amsterdam, the Netherlands

2. Centre for Environmental Safety and Security, National Institute of Public Health and the Environment, Bilthoven, The Netherlands.

3. Department of Hygiene, Epidemiology and Medical Statistics, Faculty of Medicine, National and Kapodistrian University of Athens, Athens, Greece

4. Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain

5. Robert Koch Institute, Berlin, Germany

6. Department of Medicine University of Calgary, Alberta, Canada

7. KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya

8. Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

9. Kirby Institute, UNSW Sydney, NSW, Australia

10. Medical University of Innsbruck, Innsbruck, Austria

11. Institute for Global Health, University College London, London, United Kingdom

12. Department of Infectious Diseases, Amsterdam Infection and Immunity Institute (AI&II), Academic Medical Center (AMC), Amsterdam, the Netherlands

13. Department of clinical epidemiology, biostatistics and bioinformatics, Academic Medical Center (AMC), Amsterdam, the Netherlands

1 14. Oxford University Clinical Research Unit, Wellcome Trust Major Overseas
2 Programme, Ho Chi Minh City, Vietnam

3

4 **Declaration of interests:**

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Abstract

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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.

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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.

1 **Methods**

2 **Study population**

3 We used data from the CASCADE Collaboration within EuroCoord that includes
4 cohorts across Europe, Australia, Canada and Sub-Saharan Africa. Details of
5 CASCADE have been previously described[9]. All cohorts include data from HIV-
6 positive individuals with dates of HIVsc that could be reliably estimated based on the
7 midpoint between the last HIV-negative and first HIV-positive test dates (at most 36
8 months apart) or, with evidence of acute HIV infection. We included 17 of the 28
9 participating cohorts. Eleven cohorts were excluded because they had no MSM or
10 <50% of the MSM had an HCV test result (Figure 1). We included only men who
11 were self-reported as having acquired HIV through sex between men and whose
12 potential HIV transmission route excluded injection drug use.

14 **Definitions and exclusion criteria**

15 HCV negative status throughout follow-up was based on having at least one HCV-
16 negative test result and never being tested HCV positive. To optimize testing
17 frequency, we performed additional HCV testing in nine cohorts that had stored
18 specimens, as previously described[3]. HCV-positive status was based on any
19 positive HCV test (RNA, antibodies and/or antigen). For MSM who acquired HCV
20 during follow-up, we assumed that HCV seroconversion (HCVsc) occurred at the
21 midpoint date between the last HCV-negative and first HCV-positive test. The date of
22 HCVsc was based on a negative- and a positive-antibody test results in 77.8% of
23 cases. The remained was based on RNA tests or a combination of antibody and RNA
24 test results. Individuals who were HCV-positive before cART initiation were excluded
25 from the cART analyses (n=207), and thus our analyses do not consider the effect of
26 incident HCV while ART-naïve on CD4 and VL trajectories after cART initiation
27 (Figure 1). To determine the timing of HCVsc as precisely as possible, we excluded
28 MSM with an HCVsc interval of more than two years (n=69). Men with only HCV-
29 positive test results throughout follow-up were excluded if the first HCV-positive test
30 result was more than one year after HIVsc (n=119). For MSM with a positive HCV
31 test within one year of HIVsc but without a recorded HCV-negative one (n=127), the
32 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). 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 log₁₀ 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).

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,

1 we repeated the analyses restricting our population to ART-naïve cases with both an
2 HCV-negative and an HCV-positive test during follow-up and their matched controls.

3

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

8

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

1 was highly significant ($p<0.001$), but this difference did not depend on HCVsc to
2 HIVsc timing ($p=0.78$). CD4 decreased more rapidly during the first years following
3 HCVsc in HCV co-infected MSM, but after three years following HCVsc values
4 became comparable to those of HIV mono-infected MSM. For example, when
5 comparing MSM who seroconverted for HIV and HCV simultaneously and their
6 controls, the difference in CD4 at one year following HCVsc/matched time was 43
7 CD4 cells/ μ l (figure 2B, first panel). The effect of HCV co-infection on CD4 trajectory
8 did not significantly differ by age ($p=0.50$).

10 **MSM on cART**

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

19 At the time origin, CD4 did not significantly differ between cases and controls
20 ($p=0.33$) (Figure 3B). Similar to ART-naïve MSM, CD4 trajectories were significantly
21 different between cases and controls ($p<0.001$), and did not depend on the timing of
22 HCVsc ($p=0.69$). During the first two to three years after HCVsc, CD4 were
23 significantly lower among HCV co-infected MSM, but became comparable to HIV
24 mono-infected MSM thereafter. For example, when comparing MSM who
25 seroconverted for HCV three years after HIVsc (Figure 3B, first panel) to their
26 controls, the difference in CD4 count at one year following HCVsc/matched time was
27 83 CD4 cells/ μ l. The effect of HCV co-infection on CD4 trajectory did not significantly
28 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). 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 spontaneously 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

1 HCV and convergence of CD4 trajectories between cases and controls occurred
2 irrespective of cART use. Hence, the attenuation of the effect of HCV co-infection is
3 probably not affected by cART use only.

4
5 The clinical short- and long-term implications of the temporary CD4 decline warrant
6 further research. It is unknown whether the observed temporary CD4 decline
7 attributes to the faster liver fibrosis progression observed in HIV/HCV co-infected
8 individuals when compared to HCV mono-infected individuals[17] and the classical
9 HCV co-infected risk groups[18-20], and whether it could potentially affect HCV
10 treatment effectiveness. However, cure rates with direct-acting antivirals among HIV
11 co-infected patients are similar to those in HCV mono-infected patients[21,22].
12 Additionally, whether the temporary CD4 decline contributes to a faster HIV disease
13 progression still needs to be elucidated. A previous study using data from the
14 CASCADE Collaboration showed that in the cART era (>1996), HCV co-infected
15 MSM have a higher HIV/AIDS mortality than HIV mono-infected MSM[23].
16 Furthermore, ART response may be affected by HCV infection if ART initiation takes
17 place during the temporary CD4 decline[24]. One could argue that HCV treatment
18 shortly after an HCV infection is justifiable to prevent accelerated liver disease
19 progression and a CD4 decline. Notwithstanding, continued follow-up after HCV
20 infection is warranted to assess the long-term effects of HCV on liver fibrosis and HIV
21 disease progression.

22
23 Our results on the effect of HCV on VL in ART-naïve individuals are not in agreement
24 with a meta-analysis reporting no difference in VL by HCV co-infection status[5].
25 However, the primary outcome in this meta-analysis was based on the mean VL
26 difference from a single VL measurement and most of the included studies did not
27 account for HIV and HCV infection duration[5]. Interestingly, 4 of the 15 individual
28 studies in the meta-analysis reported a significantly higher VL among HIV mono-
29 infected individuals, which was also observed in our main analysis during the first
30 year following HCVsc. However, when our analyses were restricted to those with a
31 documented HCVsc during follow-up, we did not observe a lower VL in HCV co-
32 infected MSM. Importantly, although VL differences by HCV co-infection status in our
33 study were small, it has been demonstrated that even small increments in VL among
34 ART-naïve individuals are associated with a higher risk of heterosexual transmission

1 and AIDS-defining event or death[25]. The bystander effect of HCV on VL replication
2 stresses the need for early HCV infection detection and could support the role of
3 these individuals as a source of HIV transmission when left untreated for HCV. Our
4 results of VL among MSM on cART are in line with the previously described meta-
5 analysis where authors also reported that virological control of HIV infection after
6 cART initiation remains unaffected by the presence of HCV[4].

7
8 There are some limitations in our study. Due to a lack of systematic data on HCV
9 treatment, we could not account for it. A study among HIV/HCV co-infected patients
10 comparing CD4 changes before and after pegylated-interferon/ribavirin treatment
11 reported that CD4 decreased during the first 12 weeks of treatment, increasing
12 thereafter and stabilizing from week 24 onwards[26]. However, HCV treatment alone
13 could not explain the temporarily lower CD4 among HCV co-infected MSM as we
14 observed an effect of HCV on CD4 trajectories for at least two to three years
15 following HCVsc. We also did not account for spontaneous HCV clearance. This may
16 have led to an underestimation of the effect of chronic HCV co-infection on CD4 and
17 VL trajectories. However, around 15% of HIV-positive individuals clear HCV
18 spontaneously[27]. Also, we did not account for other factors that could influence
19 CD4 and VL trajectories such as ART adherence, HIV super-infection and other
20 sexually-transmitted infections[28,29]. However, if these factors play an important
21 role in the observed differences, we cannot explain why CD4 converged three years
22 after HCVsc.

23
24 One of the major strengths in our study is our relatively large group of MSM with well-
25 estimated dates of HIV and HCV seroconversion, hence, we could account for
26 infection duration, and study the effect of the timing of HCVsc relative to HIVsc.
27 Additionally, unlike most studies, we used all available CD4 and VL measurement to
28 assess differences in trajectories by HCV co-infection status. Given the temporary
29 effect of HCV co-infection on CD4 and VL trajectory by HCV co-infection, our findings
30 emphasize the need to account infection duration.

31
32 In conclusion, we found no difference in CD4 and VL trajectories following HCVsc by
33 its timing relative to HIVsc. Importantly, CD4 counts are temporarily lower during the
34 first two to three years following HCVsc among HIV-positive MSM. Even though it is

1 expected that more MSM will start cART earlier in the coming years, reflecting
2 changing guidelines[30], CD4 counts are temporarily negatively affected following
3 HCVsc despite cART use. Our findings would point to a consideration by clinicians to
4 test for HCV if their HIV-positive patient's CD4 count drops while on cART. HCV co-
5 infected ART-naïve MSM appear to have a higher VL trajectory two years after
6 HCVsc than HIV mono-infected MSM, whereas we did not observe an effect of HCV
7 on the probability of having a detectable VL among MSM on cART. Continued HCV
8 prevention, testing and treatment are warranted in this group. The short- and long-
9 term clinical implications of our findings still need to be further elucidated.

10

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.

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Appendix

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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

CASCADE Collaborators: 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); Austria Austrian HIV Cohort Study (Robert Zangerle); Canada South Alberta clinic (John Gill); Estonia Tartu Ülikool (Irja Lutsar); France ANRS CO3 Aquitaine cohort (Geneviève Chêne, Francois Dabis, Rodolphe Thiebaut), 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 HIV-1 seroconverter cohort (Osamah Hamouda, Karolin Meixenberger, Norbert Bannert, Barbara Bartmeyer); Greece AMACS (Anastasia Antoniadou, Georgios Chrysos, Georgios L. Daikos); Greek Haemophilia cohort (Giota Touloumi, Nikos Pantazis, Olga Katsarou); Italy Italian Seroconversion Study (Giovanni Rezza, Maria Dorrucci), 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 University Hospital cohorts (Mette Sannes, 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); Sweden Swedish InfCare HIV Cohort, Sweden (Anders Sönnernborg); Switzerland Swiss HIV Cohort Study (Heiner C. Bucher, Huldrych Günthard, Alexandra Scherrer); Ukraine Perinatal

1 Prevention of AIDS Initiative (Ruslan Malyuta); United Kingdom Public Health
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3 Johnson, Andrew Phillips, Abdel Babiker), University College London (Deenan
4 Pillay); African cohorts: Genital Shedding Study (US: Charles Morrison; Family
5 Health International, Robert Salata, Case Western Reserve University, Uganda: Roy
6 Mugerwa, Makerere University, Zimbabwe: Tsungai Chipato, University of
7 Zimbabwe); International AIDS Vaccine Initiative (IAVI) Early Infections Cohort
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18 **Ethics committees:**

19 Ethics approval has been granted by the following committees: Austrian HIV Cohort
20 Study: Ethik-Kommission der Medizinischen Universität Wien, Medizinische
21 Universität Graz – Ethikkommission, Ethikkommission der Medizinischen Universität
22 Innsbruck, Ethikkommission des Landes Oberösterreich, Ethikkommission für das
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2 Investigación Clínica de La Rioja; Madrid Cohort: Ethics Committee of Universidad
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4 spezialisierte Unterkommission Innere Medizin, Ethikkommission beider Basel,
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8 Register of HIV Seroconverters: South Birmingham REC; Early Infection Cohorts:
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Effect of HCV and its timing on CD4 and VL in MSM

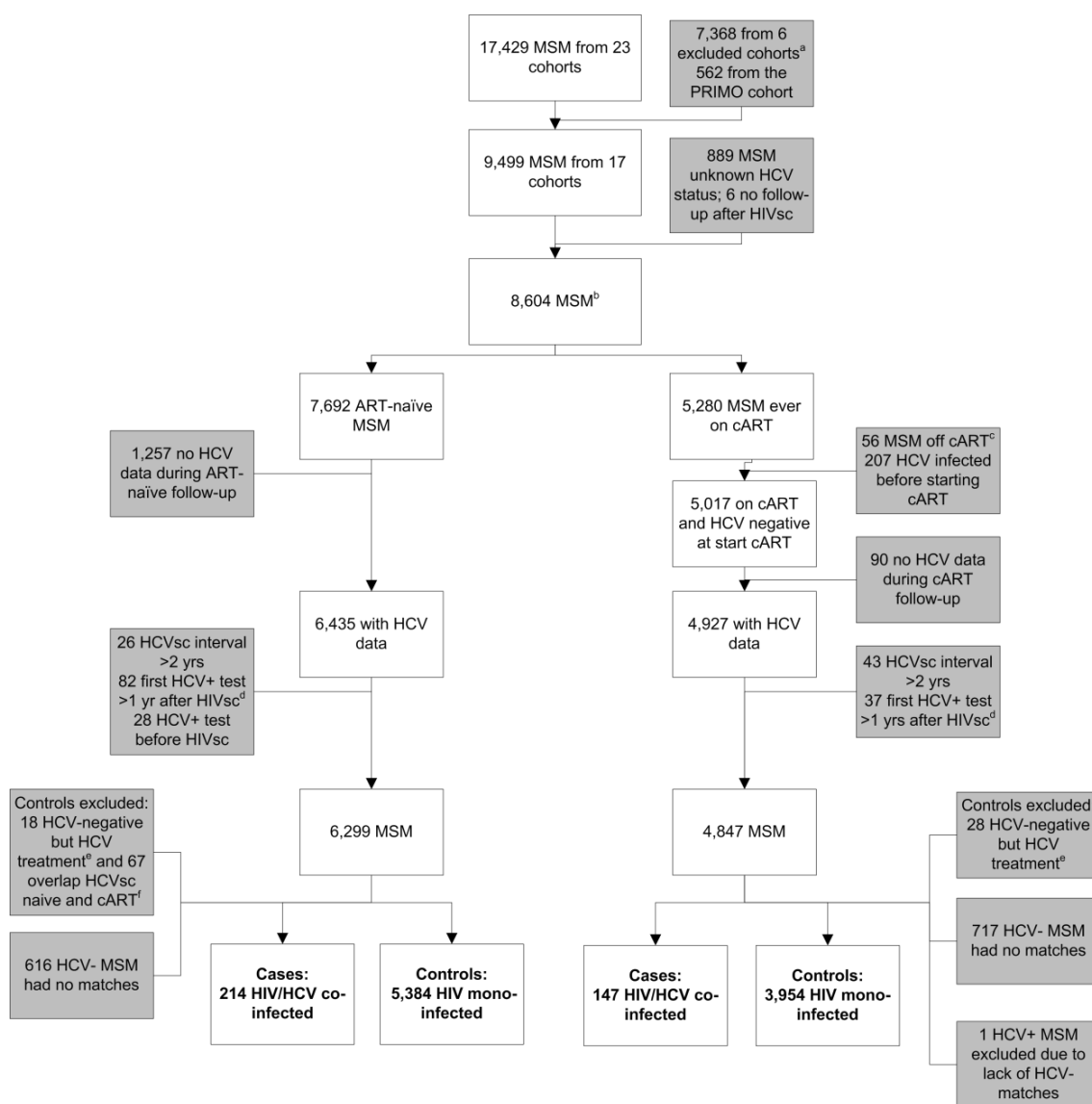


Figure 1: Flow diagram of the study population selection for ART-naïve MSM and MSM on cART from the CASCADE Collaboration

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.

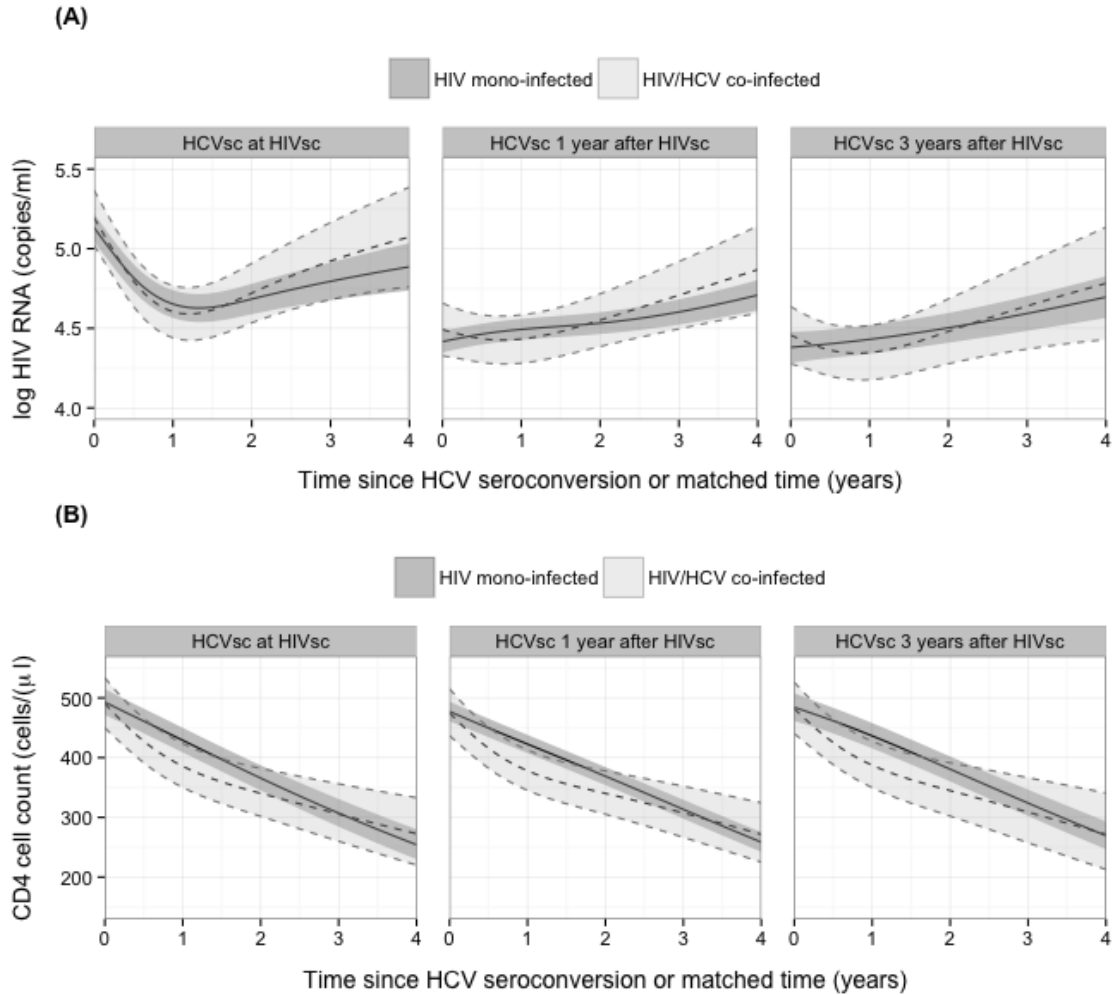


Figure 2: CD4 counts and HIV RNA viral load trajectories from HCV seroconversion or matched time onwards per timing of HCV seroconversion relative to HIV seroconversion, among ART-naïve MSM from the CASCADE Collaboration.

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/ μ l. 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).

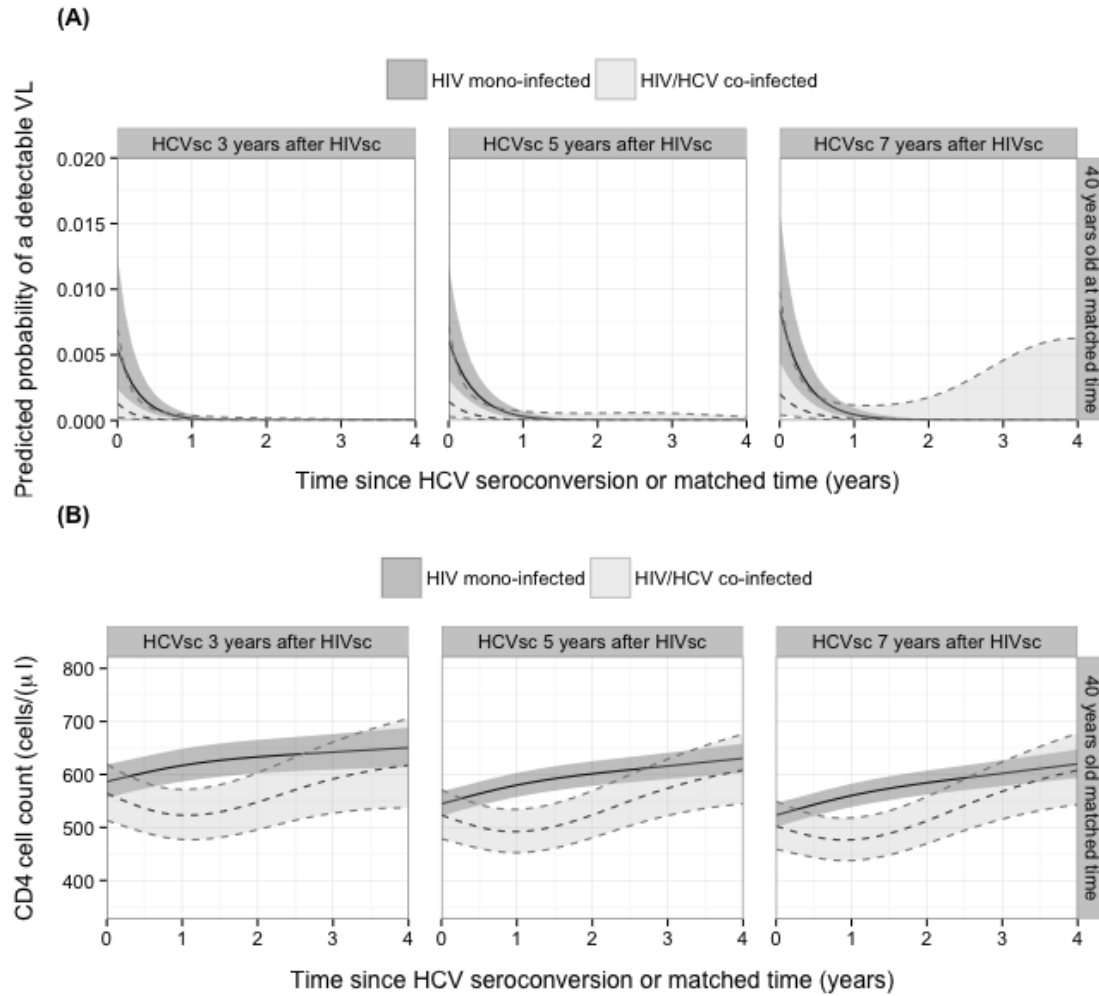
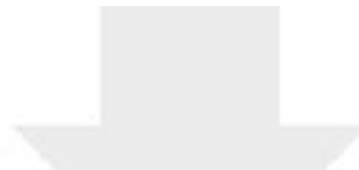


Figure 3: CD4 counts trajectories and predicted probabilities of having a detectable HIV RNA viral load from HCV seroconversion or matched time onwards per timing of HCV seroconversion relative to HIV seroconversion, among MSM on cART from the CASCADE Collaboration

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/ μ l. 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).



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