**Supplementary text**

**1. Matching criteria**

The following criteria were applied to match cases and controls: 1) during the first year following HIV seroconversion (HIVsc), the matched follow-up visit of the control had to be at most 36 days apart (i.e., 0.1 years) from the first visit of the case at or following the estimated date of HCV seroconversion (HCVsc) – as acute HIV infection is a phase characterized by fluctuating and dynamic CD4 T-cell counts (CD4) and HIV RNA viral load (VL) values [1] – and 2) after one year following HIVsc, the matched visits had to be ≤0.5 years apart – as changes in CD4 and VL are more gradual during the chronic HIV infection phase [1]. Additionally, for ART-naïve MSM, we matched by country of the cohort, to adjust for unmeasured differences (e.g., HIV-related care guidelines) that may influence CD4 and VL trajectories. MSM on cART were matched additionally for cumulative cART exposure. Although we intended to also match MSM on cART by country of cohort, due to difficulties in finding matches for some MSM, we omitted this matching criterion. Each case was matched to as many HIV mono-infected MSM as possible who fulfilled all matching criteria. Every control could only be matched once to an HCV co-infected MSM when ART-naïve or when on cART, but an individual (i.e., controls or cases who acquired HCV while on cART) could contribute data to both the ART-naïve and on cART analyses. Furthermore, as illustrated in supplementary figure 1, follow-up time following the matched time and the reason for censoring could differ between cases and controls.

**2. Multivariable models**

**2.1 Covariates and interaction terms**

In the multivariable models, calendar year at matched time was included as a proxy for unmeasured HCV treatment, as this increased over time among men who have sex with men (MSM) [2, 3]. Also, better cART regimes over time may have influenced CD4 and VL trajectories. The method of HIVsc determination was included because those MSM whose HIVsc was determined through evidence of acute (symptomatic) HIV infection might have a more accurate estimate of the date of HIV seroconversion. In addition, CD4 and VL trajectories might differ between MSM with and without symptomatic acute HIV infection [4]. In the interaction terms, all continuous variables were modelled linearly, except for the interaction between time since HCVsc or matched time (i.e., time origin) and timing of HCVsc relative to HIVsc, which was modelled using restricted cubic splines. For MSM on cART, the interaction term between time since HCVsc or matched time and cumulative cART exposure was also modelled via splines. We graphically illustrate the VL and CD4 trajectories (back-transformed to 10-log VL copies/ml and CD4 cells/µl) by HCV-infection status at the median value for the other continuous co-variables (e.g., age) and the most frequent category for the dichotomous variables (i.e., method of HIVsc determination). Similarly, we illustrate the effect of HCV co-infection on having a detectable VL while on cART by translating the results from the random-effects logistic regression models into predicted probabilities for an average individual, i.e., an individual with values zero for the random effect terms.

**2.2 Code used in R**

Example of the model used to model VL trajectories among ART-naïve MSM.

|  |  |
| --- | --- |
| **Variable** | **Description:** |
| VL | HIV RNA viral load |
| Case 1 | HIV/HCV (co)-infection status (case/control) |
| Time (in years) | Time from HCV seroconversion or matched time onwards (i.e., time origin) |
| Age (in years) | Age at matched time |
| Calendaryr | Calendar year at matched time |
| Timing (in years) | Timing of HCV seroconversion relative to HIV seroconversion |
| Serohow 1 | HIV seroconversion determination method |
| Groupmatch | Case and controls matched group |

*1 Dichotomous variables. The remainder are continuous variables.*

**Code:**

lme((HIV RNA)^(1/8)

~ns(time,kn=c(0.5,2),

Bo=c(0,7))\*case

**Explanation:**

*VL at the time origina (baseline) and VL trajectory (over follow-up time) can differ by HCV co-infection status*

+ns(age,kn=c(32,40),Bo=c(24,52)) *VL at the time origin can depend on age in a non-linear way*

+time:age *VL trajectory can depend on age*

+time:case:age *Effect of age on VL trajectory can differ by HCV co-infection status*

**Effect of the timing:**

+ns(timing,kn=c(0.3,1.1),Bo=c(0,4)) *VL at the time origin can depend on timing in a non-linear way*

+ns(time,kn=c(0.5,2),Bo=c(0,7)): *VL trajectory can depend on timing in* ns(timing,kn= c(0.3,1.1),Bo=c(0,4)) a *non-linear way*

+timing:age *Effect of timing on VL at time origin can differ by age*

+time:case:timing *Effect of timing on VL trajectory can differ by HCV co-infection status*

+time:timing:age *Effect of the timing on VL trajectory can depend on age*

+time:case:timing:age *Effect of the timing on VL trajectory can depend on age, and this effect can differ by HIV/HCV co-infection status*

**Effect of calendar year:**

+ns(calendaryr,kn=c(2002,2007), *VL at the time origin can depend on* Bo=c(1991,2011)) *calendar year*

+calendaryr:time *VL trajectory can depend on calendar year*

+calendaryr:time:case *Effect of calendar year on VL trajectory can differ by HIV/HCV co- infection status.*

**Effect of HIV seroconversion method of estimation:**

+serohow *VL at the time origin can depend on method of HIVsc determination*

+serohow:case *Effect of the method of HIVsc determination on the overall VL can depend on HIV/HCV co-infection status*

+serohow:time *VL trajectory can depend on method of HIVsc determination*

random=list(groupmatch=~1,patient=~time)) *Multilevel model with random intercept & slope per individual, nested within matched groups*

Abbreviations: ns,natural spline function; kn, Knots; Bo, Boundary.Knots; HIVsc, HIV seroconversion

*aTime origin:* The time origin of our analyses is the estimated date of HCV seroconversion of each case, and their control’s matched time.

In the cART model we added “*cumulative time on cART*” in the same way as the variable “timing”. Also, a 4-way interaction including cumulative time on cART “timing:timingcART:case:time” was included.

**Supplementary figures**



**Supplementary Figure 1. Graphical illustration of the matching process and follow-up among ART-naïve MSM (1A & 1B) and MSM on cART (1C & 1D) using four examples.**

Red arrows represent the timing of HCV seroconversion relative to HIV seroconversion and the red horizontal brackets represent the included follow-up in our study. Green arrows represent the first visit after HCVsc in cases and the matched visit of the controls. Blue dotted lines among MSM on cART represent follow-up while ART-naïve. Example 1A and 1C, represent matched cases and controls with the same follow-up period following HCV seroconversion, whereas in example 1B and 1D, follow-up after HIV seroconversion is shorter among controls. However, in other case-control groups follow-up may be longer in controls. Among HCV co-infected MSM, the median time from HCVsc to the first matched visit was 0.1 years for both ART-naïve MSM and for MSM on cART.

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**Supplementary Figure 2: CD4 counts and HIV viral load trajectories from HCV seroconversion or matched time onwards per timing of HCV seroconversion relative to HIV seroconversion, among ART-naive MSM with a recorded HCV-negative and a HCV-positive test date 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).

Reference list

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[4] Lodi S, Phillips A, Touloumi G, Pantazis N, Bucher HC, Babiker A, et al. CD4 decline in seroconverter and seroprevalent individuals in the precombination of antiretroviral therapy era. AIDS 2010;24:2697-2704.