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Lack of decline in Hepatitis C Virus incidence among HIV-positive men who have sex with men during 1990-2014

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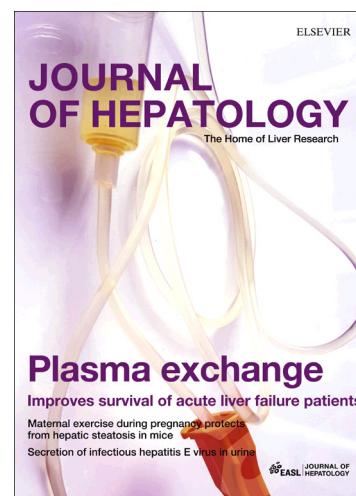
1 **Title page**

2

3 **Lack of decline in Hepatitis C Virus incidence among HIV-positive men who**

4 **have sex with men during 1990-2014**

5

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1 **Abbreviations**

2 HCV   Hepatitis C Virus

3 HIV   Human immunodeficiency virus

4 MSM   Men who have sex with men

5 CASCADE   Concerted Action on SeroConversion to AIDS and Death in Europe

6 STIs   Sexually transmitted infections

7 AIC   Akaike Information Criterion

8 cART   Combination antiretroviral therapy

9

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13

14 **Conflicts of Interest and Source of Funding:**

18 **Conflict of interest:**

19 Kholoud Porter has served on the Dolutegravir Advisory Board.

20 **Author's contribution:**

21 DvS performed the statistical analyses together with RG, also interpreted the data,

22 and wrote the manuscript. JvdH provided substantial contributions to the analyses

23 and interpretation of the data as well as the manuscript. MP and RG designed and

24 supervised the overall study, and substantially contributed to the analyses,

1   interpretation of the data and manuscript. <u>KP obtained funding for the study</u>. All

2   authors contributed to the design, additional HCV testing, interpretation of the data,

3   subsequent drafts and approved the final version of the manuscript.

1 Abstract

2 **Background and aims:** Hepatitis C virus (HCV) incidence among HIV-positive men

3 who have sex with men (MSM) has increased since 2000, though regional

4 differences have been documented in recent years. We aimed to 1) estimate trends

5 in HCV incidence among HIV-positive MSM, 2) assess the association between

6 incidence and geographical region, age and HIV-related measurements and, 3)

7 assess temporal changes in time from HIV seroconversion to HCV infection.

8

9 **Methods:** We used data from MSM with well-estimated dates of HIV seroconversion

10 from the CASCADE Collaboration (1990-2014). We allowed for smoothly varying

11 trends in HCV incidence over calendar time using restricted cubic splines. We

12 assessed the association of calendar year, age, CD4 count (lagged), HIV RNA

13 (lagged), geographical region and HIV infection stage (recent vs. chronic) with HCV

14 incidence using Poisson regression.

15

16 **Results:** Of 5,941 MSM, 337 acquired HCV during follow-up. HCV incidence

17 significantly increased from 0.7/1000 person-years (py) in 1990 to 18/1000 py in

18 2014. Recent calendar years, younger age, recent HIV infection and higher HIV RNA

19 levels were significantly associated with HCV incidence, while CD4 count was not.

20 Trends differed by geographical region; while incidence appears to have stabilized in

21 Western Europe and remained stable in Southern Europe, it continued to increase in

22 Northern Europe in recent years. Time from HIV to HCV infection significantly

23 decreased over calendar time (p<0.001).

24

1 **Conclusions:** HCV has continued to spread among HIV-positive MSM in recent

2 years, but trends differ by geographical region. Interventions to decrease the risk of

3 HCV acquisition and increase early diagnosis are warranted.

4

5 **Lay summary:** Hepatitis C virus infection continues to spread among HIV-positive

6 men who have sex with men, especially among younger individuals. However, trends

7 seem to differ by European region in recent years. Furthermore, men who have sex

8 with men with a higher HIV RNA load were more likely to get infected with the

9 hepatitis C virus. During recent HIV infection, MSM appear to be at higher risk of

10 acquiring hepatitis C.

11

12 **Word count abstract:** 252

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16

17

1 **Introduction**

2

3 Since 2000, hepatitis C virus (HCV) incidence has increased among HIV-positive

4 men who have sex with men (MSM) [1,2]. Using data from the CASCADE

5 Collaboration (Concerted Action on SeroConversion to AIDS and Death in Europe) in

6 EuroCoord, we previously showed that HCV incidence increased in MSM with well-

7 estimated HIV seroconversion dates after 1990, but the main expansion of the HCV

8 epidemic was observed from 2002 until 2007, the censoring date of the analysis [1].

9 A recent meta-analysis showed that HCV incidence has continued to increase, with

10 an estimated pooled incidence of 13/1000 person-years (py) in 2010 to an

11 extrapolated incidence estimate of 19/1000 py in 2015 [2]. However, other studies

12 have shown varying trends in HCV incidence among MSM over the past years [3,4].

13 In Amsterdam, the Netherlands, HCV incidence seems to be stabilizing [3], whereas

14 in Switzerland an increasing incidence among MSM has been observed [4].

15

16 A number of factors such as fisting, the presence of sexually-transmitted infections

17 (STIs), use of recreational drugs, and condomless anal intercourse have been

18 shown to be significantly associated with acute HCV infection [4-10]. In addition, one

19 study from the US reported that older age was independently associated with an

20 acquired HCV infection [10], whereas another study from the Netherlands reported

21 that younger MSM had a higher risk [3]. As acute HCV infections are predominantly

22 found among HIV-positive MSM, it has been suggested that HIV facilitates sexual

23 transmission of HCV [11]. However, contrasting results on the association between

24 CD4$^+$ T-cell count (CD4 count) and HCV incidence have been reported [4,9,10,12].

25 Additionally, few studies have investigated the association with HIV RNA and, those

1 that have, either dichotomized HIV RNA and/or could only assess the association in

2 univariable analyses [4,9,12]. The role that HIV-related factors play in the spread of

3 HCV among HIV-positive MSM is currently still being debated.

4

5 Using data among MSM with well-estimated dates of HIV seroconversion from the

6 CASCADE Collaboration we aimed to 1) update trends in HCV incidence; overall

7 and by geographical region, 2) assess the associations between HCV incidence and

8 <u>HIV-related measurements</u>, geographical region, age and calendar year, and 3)

9 assess whether the time interval between HIV seroconversion and HCV infection has

10 changed over calendar time.

11

1 **Methods**

2 We used data from 16 out of 28 cohorts from the CASCADE Collaboration across

3 Europe, Australia and Canada. Of the excluded cohorts, 5 were non-MSM cohorts

4 and 6 cohorts had tested less than 50% of MSM for HCV and could not provide

5 stored samples for HCV testing (missing HCV status data from 57.2% to 96.2%)

6 (Fig. 1). The <u>Kenyan</u> cohort (IAVI; n=92) was also excluded as we believe that the

7 HCV epidemic among MSM in Kenya differs from that in high-income countries (no

8 incident HCV infections were observed). All cohorts include data from HIV-positive

9 individuals with dates of HIV seroconversion that could be reliably estimated based

10 on the midpoint between the last HIV-negative and first HIV-positive test (at most 36

11 months apart) or, evidence of acute HIV infection. Details of CASCADE have been

12 previously described [13]. <u>We included only men from the 16 cohorts who were</u>

13 <u>recorded as having acquired HIV through sex between men and whose potential HIV</u>

14 <u>transmission route excluded injecting drug use</u>. For all cohorts, we used all available

15 data, except for MSM from the French PRIMO cohort who were censored at the 31st

16 of December 2005 as routine HCV testing was only recorded until that year. <u>All</u>

17 <u>collaborating cohorts received approval from their regulatory or national ethic boards</u>

18 <u>(see Appendix) and informed consent was obtained for all participants.</u>

19

20 HCV negative status <u>throughout follow-up</u> was based on at least one HCV-negative

21 test result <u>and never testing HCV positive</u>. HCV infection was based on any positive

22 HCV test (RNA, antibodies and/or antigen). Among MSM who acquired HCV during

23 follow-up, the date of HCV infection was estimated as the midpoint between the last

24 HCV-negative and first HCV-positive test. To optimize testing frequency, we

25 performed additional HCV testing in cohorts that had stored specimens (8 cohorts).

1   Stored samples from HCV-negative MSM were tested using a sample closest to the

2   date of their last clinic visit if more than 2 years had elapsed since their last HCV-

3   negative test date. For HCV-positive MSM without a previous HCV-negative test

4   date, the sample closest to HIV seroconversion but up to one year of it was tested to

5   assess whether they had become HCV infected during follow-up; if HCV negative,

6   midpoint samples were tested until the HCV seroconversion interval was a maximum

7   of 2 years. For MSM with a recorded HCV infection during follow-up but with an HCV

8   test interval >2 years, samples with dates which fell in the interval between their last

9   HCV-negative and first HCV-positive test date were tested. All cohorts provided a

10   date of start of routine HCV testing (defined by testing of all MSM for HCV according

11   to prevailing guidelines or practices) and details on HCV testing strategies (e.g.,

12   retrospective testing).

13

14   **HCV incidence**

15   We estimated overall HCV incidence trends between 1990 and 2014 and stratified

16   by European geographical region between 1997 until 2013 as not all regions have

17   available data for the total study period. Geographical region was defined based on

18   the United Nations classification criteria [14], namely Western (the Netherlands,

19   Switzerland, France, Austria and Germany), Northern (United Kingdom and Norway),

20   and Southern Europe (Italy, Spain and Greece), North America (Canada) and

21   Australia and New Zealand (Australia) (Table 1). We only illustrate HCV incidence by

22   geographic region for the three European regions as Canada and Australia had

23   relatively small numbers of MSM and few HCV infections were observed. MSM were

24   considered at risk from the latest of: HIV seroconversion, routine HCV testing date

25   per cohort or enrolment in the cohort (Table 1). We used two methods to calculate

follow-up time as previously described [1]. In both methods, MSM with one or more

HCV-positive tests but without a previous HCV-negative test were excluded (Fig. 1).

In method 1, follow-up time began from the moment MSM were considered at risk

and will likely underestimate HCV incidence as some of the excluded MSM, who only

had HCV-positive tests under active follow-up, could have become infected between

the moment they were considered at risk and their first HCV test. Appreciating this

possible underestimation, we applied another method (method 2) where follow-up

began from the first HCV-negative test after becoming at risk (i.e., left truncation).

This approach, however, leads to a shorter follow-up time for MSM who remained

HCV-negative throughout follow-up as they are less likely to have been tested

retrospectively compared to MSM who became HCV-positive. Consequently, this

method is likely to overestimate HCV incidence. In both methods follow-up was

calculated until the last HCV-negative date or, in case of HCV infection, the midpoint

date. Only the first observed HCV infection during follow-up within an individual was

included in the analyses. We used Poisson regression models where HCV incidence

was allowed to vary smoothly over calendar time using restricted cubic splines for

the overall and the stratified analyses (i.e., by geographical region). We performed a

sensitivity analysis using an interval-censored approach as previously described [2]

(Supplementary text 1).

HCV risk factor analyses

We used three Poisson regression models that included calendar year using the

method 1 approach to calculate follow-up. We assessed variation of HCV incidence

by geographical region (model 1) and the associations with age (model 2), and HIV-

related measurements: CD4 count, HIV RNA and HIV infection stage (model 3). All

1   continuous variables were included as restricted cubic splines (calendar year,

2   current age, $\log_{10}$ HIV RNA and cube root CD4 count). The knots were chosen based

3   on the 2.5, 25, 50, 75 and 97.5 percentiles.

4   **Model 1**

5   We compared the fit of three submodels by means of the Akaike information criterion

6   (AIC) - model 1.1=calendar year only, model 1.2=calendar year and region as main

7   effects, model 1.3=calendar year, region, and their interaction.

8   **Model 2**

9   We then added age to the best fitting model 1. In this model, we tested the

10   interaction between age and both region and calendar year. Significant interactions

11   were included in this model.

12   **Model 3**

13   This multivariable model included: age, calendar year, region, HIV RNA and CD4

14   count. The CD4 count and HIV RNA value from the previous visit were used, but had

15   to be no more than one year before. Missing HIV RNA and CD4 count data were

16   imputed based on individual predicted values from random-effects models adjusted

17   for age and stratified by combination antiretroviral therapy (cART) use: treatment

18   naïve, on cART, and during cART interruption among cART-experienced

19   (Supplementary text 2). <u>For this model we defined a</u> treatment interruption as a stop

20   of cART for >1 week. When a person had no CD4/HIV RNA values throughout

21   follow-up, we used the predicted values based on the fixed effects. We defined cART

22   as a 3 drug ART regimen containing 2 different classes, or 3 nucleoside reverse

23   transcriptase inhibitors (NRTIs), provided Tenofovir or Abacavir were included in the

24   regimen. <u>In additional analyses we assessed whether a recent HIV infection (defined</u>

25   <u>as the period from estimated HIV seroconversion to less than 0.7 years hereafter)</u>

was associated with HCV incidence using model 3. We also tested the interaction between HIV RNA and HIV infection stage (recent vs. chronic). We used the likelihood ratio test to test significance in model 2 and 3. Instead of reporting incidence ratios, we illustrate the association between age, CD4 count and HIV RNA and incidence by plotting the absolute incidence with 95% confidence intervals, choosing representative values (e.g., median values) for the other covariates.

Sensitivity analyses

We performed four sensitivity analyses. As we imputed missing CD4 and HIV RNA values, first, we performed the analyses using predicted values instead of using a combination of predicted and observed values. Second, we performed a complete case analyses in which only observed values were included. Third, an analysis was performed where the antepenultimate CD4 count and HIV RNA value were used. The reason for the third analysis is that antibody development might be delayed in HIV-positive individuals [15,16] and in our study 83.4% (n=281) of HCV infections were based on HCV antibody seroconversion and 15.7% (n=53) were based on a positive HCV RNA test and an HCV-antibody negative test result. Lastly, although additional HCV testing was performed in the Italian cohort (ICoNA), we performed the overall HCV incidence analyses without this cohort as currently there is no routine HCV testing in place.

1 **Time from HIV to HCV**

2 Kaplan-Meier curves were constructed applying the method 1 follow-up calculation to

3 compare cumulative HCV incidences by calendar period of HIV seroconversion. We

4 modelled whether HCV incidence depended on calendar year using a Cox

5 proportional hazards model, including calendar year of HIV seroconversion as a

6 continuous variable using restricted cubic splines.

7

8 Statistical analyses were performed using R [17] and Stata [18] software.

9

10

1   **Results**

2   Of 17,429 HIV-positive MSM, 7,368 MSM were excluded from 6 cohorts with more

3   than 50% missing HCV status data and that could not provide stored samples for

4   HCV testing (Fig. 1). Of the remaining 10,061 MSM, 9,014 had at least one HCV test

5   result of whom 8,311 tested only HCV negative and 703 had at least one HCV-

6   positive test result. MSM with HCV test results did not differ by age or ethnicity from

7   MSM without test results, but were more likely to have a post-secondary education

8   (37% vs. 32%). The median and mean number of HCV tests during follow-up among

9   cohorts that routinely and prospectively collected HCV data (n=13) was 3.0

10   (Interquartile range (IQR)=2-6) and 4.1 (Standard deviation=3.6), respectively. A

11   total of 7,864 MSM had follow-up and at least one HCV test result (Table 1). Among

12   these MSM, 57.0% were white and median age was 34 years (IQR=28-41) at

13   inclusion. The median year of HIV seroconversion was 2004 (IQR=1999-2008). Over

14   the total study period, the median observed CD4 count was 509 cells/µl (IQR=367-

15   684), median observed HIV RNA was 70 copies/mL (IQR=50-15522) and 70.3%

16   started or were on cART.

17

18   A total of 5,941 and 4,326 MSM were eligible according to method 1 and 2,

19   respectively (Fig. 1;Table 1). These MSM accounted for a total of 28,600 and 19,480

20   person-years and 337 and 279 HCV infections in method 1 and 2, respectively. The

21   median follow-up time was 4.0 (IQR=1.7-7.2) and 3.9 (IQR=2.0-6.3) years in method

22   1 and 2, respectively. Of the 337 incident HCV infection observed during follow-up,

23   25 (7.4%) occurred during recent HIV infection.

24

HCV incidence

HCV incidence significantly increased from 1990 onwards ($p_{method1}$<0.001;$p_{method2}$=0.04); with an estimated incidence ranging from: 0.7/1000 py (95% confidence interval (CI)=0.1-5) in 1990 to 18/1000 py (95%CI=9-37) in 2014 in method 1 and from 3/1000 py (95%CI=0.4-18) in 1990 to 21/1000 py (95%CI=10-42) in 2014 in method 2 (Fig. 2). The interval-censored method showed a similar increasing trend (Supplementary Fig. 1). Excluding one cohort (ICoNA) from the overall analyses, led to similar statistically significant increasing trends by both methods, although the estimations were slightly lower (Supplementary Fig. 2). The stratified analyses by geographical region showed that in recent years HCV incidence seems to have increased in Northern Europe, but calendar year was only statistically significant in method 2 (p=0.02) (Fig. 3). In Southern Europe, a stable trend was observed and calendar year was not significant. In Western Europe the trend was significant in both methods ($p_{method1}$=0.001;$p_{method2}$=0.005); based on method 1, HCV incidence increased sharply from 14/1000 py (95%CI=10-20) in 2006 to 23/1000 py (95%CI=17-31) in 2009, but declined thereafter to 9/1000 py (95%CI=3-27) in 2013 (Fig. 3).

HCV risk factor analyses

The first analysis showed that the model with region and calendar year as main effects only (model 1.2) had the lowest AIC of the three submodels, thus the best fit. The second model showed that younger HIV-positive MSM had a higher risk of HCV infection (p=0.005) (Fig. 4A). The interaction term between age and region was

1 borderline significant (p=0.05). Based on the model with the interaction term, in

2 Western Europe, HCV incidence remained highest and stable until around age 35

3 and declined thereafter (Supplementary Fig. 3). In Northern and Southern Europe,

4 HCV incidence increased until age 35, and declined thereafter.

5 In the third model, a higher HIV RNA was associated with higher HCV incidence

6 (p=0.001) (Fig. 4C), especially when $\log_{10}$ HIV RNA was ≥5 copies/mL, whereas

7 CD4 count (Fig. 4B) was not (p=0.53). When we added "HIV infection stage" to the

8 model, the association between HIV RNA and HCV incidence was attenuated

9 (p=0.01) (Fig. 4D). HCV incidence was higher during recent HIV infection than during

10 chronic HIV infection (Incidence Rate Ratio$_{recent\ vs.\ chronic}$=1.8, 95%CI=1.1-2.7,

11 p=0.02). The interaction term between HIV infection stage and HIV RNA was not

12 significant (p=0.60), and was left out of the model. The association with CD4 count

13 remained non-significant (p=0.53).

14

Sensitivity analyses

16 All sensitivity analyses showed comparable associations of HIV RNA, CD4 count

17 and calendar year with HCV incidence and the conclusions were not altered.

18 However, in the complete case analyses, HIV RNA was non-significant (p=0.25)

19 (Supplementary Fig. 4).

20 In the model that included HIV infection stage, two sensitivity analyses (i.e.,

21 antepenultimate and predicted values) showed comparable associations between

22 HIV RNA and HCV incidence, but when antepenultimate HIV RNA values were used,

1   the association was no longer statistically significant (p=0.09). In the complete case

2   analyses, there was no association (p=0.40).

3

4   **Time from HIV to HCV**

5   Among 5,680 MSM who seroconverted for HIV at or after 1990, median time from

6   HIV seroconversion to HCV infection was 5.2 years. The time from HIV

7   seroconversion until HCV infection significantly decreased over calendar periods

8   ($p_{log-rank}$<0.001). At 3 years after HIV seroconversion, the cumulative HCV incidence

9   was 5.9% (95%CI=3.8-9.2%) in 2010-2014 compared to 2.0% (95%CI=0.5-7.8%) in

10   1990-1994 (Fig. 5). The Cox model showed that MSM who seroconverted for HIV in

11   2010, had a 6.1 (95%CI=2.8-13.3) times higher hazard of acquiring HCV than MSM

12   who seroconverted in 1990 (p<0.001) (Supplementary Fig. 5).

13

1 **Discussion**

2 Using data from the CASCADE Collaboration among HIV-positive MSM with well-

3 estimated dates of HIV seroconversion, we showed that HCV incidence significantly

4 increased from 1990 onwards and no decline was observed in recent years. This

5 suggests on-going transmission of HCV among HIV-positive MSM. However, trends

6 seem to differ by geographical region. While HCV incidence appears to have

7 stabilized in Western Europe and remained stable in Southern Europe, a recent

8 increase in HCV incidence was observed in Northern Europe. Interestingly, higher

9 HIV RNA levels, recent HIV infection and younger age were associated with higher

10 HCV incidence. The time from HIV seroconversion to HCV infection has significantly

11 shortened in recent years. Hence, routine and continued surveillance following HIV

12 diagnosis is needed.

13

14 The increasing trend in HCV incidence over time is comparable with the trend

15 observed in a recent meta-analysis [2]. We estimated that in 2014 HCV incidence

16 was between 18 and 21/1000 py and in the meta-analysis the extrapolated estimate

17 was 19/1000 py in 2015 [2]. A recent study from EuroSida, not restricted to HIV

18 seroconverters, also reported that HCV incidence differed by European geographical

19 region; Eastern, Northern and Southern Europe had higher odds for HCV

20 seroconversion than Western Europe [19]. Interestingly, no HCV infections were

21 observed among MSM from the Kenyan cohort, while another Kenyan study reported

22 that 10% (30/300) of HIV-positive male and female patients were HCV-coinfected

23 [20]. This might suggest that HCV has not yet been introduced in the Kenyan MSM

24 population. The decline in HCV incidence that we observed after 2009 in Western

1 Europe might be ascribed to earlier introduction or recognition of HCV.

2 Consequently, as previously suggested [3], this might have led to a saturation effect

3 among MSM at higher risk for HCV infection and/or increased HCV awareness,

4 leading to more HCV testing and treatment, as well as safer-sex practices.

5 Conversely, since the introduction of cART, condom use has decreased over time

6 among MSM [21,22], which probably led to the increase in syphilis incidence across

7 European countries in recent years, especially among HIV-positive MSM [23]. In

8 Northern Europe (UK and Norway) HCV incidence seems to have increased in

9 recent years, although the overall effect of calendar year was only significant when

10 method 2 was used. An European survey in 2010 among MSM showed that the

11 prevalence of drug use associated with 'chemsex' – i.e., drug use to enhance sexual

12 arousal [24] – was highest in three UK cities [25]; as injecting and non-injecting drug

13 use have been associated with acute HCV among HIV-positive MSM [6,8-10],

14 differences in HCV trends might be partly explained by differences in drug use

15 across European countries. However, we cannot discern whether that study is

16 representative for MSM across Europe. Given the overall continued rise of HCV

17 incidence, HCV-treatment guidelines should consider recommending direct-acting

18 antivirals during acute HCV infection - when registered [26] - to prevent on-going

19 transmission. As suggested by modelling studies, the greatest population benefit

20 among HIV-positive MSM can be achieved when HCV treatment is provided within 1

21 year of HCV diagnosis, together with behavioural interventions [27, 28].

22

23 Furthermore, we found that younger MSM, peaking at around age 35, are at higher

24 risk for HCV infection, in line with findings from the Netherlands [3] but in contrast to

25 a study in the USA, where older MSM had a higher risk of HCV infection [10].

Regional differences in the HCV epidemic among HIV-positive MSM could explain this discrepancy, in line with our finding of a borderline significant interaction between age and region.

HIV RNA was significantly associated with HCV incidence, especially when $\log_{10}$ HIV RNA was ≥5 copies/mL. Few studies have assessed the association between HIV RNA and HCV incidence [4,9,12] and, to the best of our knowledge, this is the only study to have modelled HIV RNA as a continuous variable in multivariable analysis. In univariable analyses, two observational cohort studies [4,9] found a significant association between HIV RNA with HCV incidence, whereas a clinical HIV cohort did not [1]. Although, in the Swiss Cohort study, this association was no longer significant in multivariable analysis [4]; but ART use was included in that multivariable model which may mask the effect of HIV RNA as it may lie on the causal pathway. However, in our study, the association between HIV RNA and HCV incidence was attenuated when HIV infection stage was included in the model. The overlap in risk behaviour between HIV and HCV might result in the acquisition of both viruses simultaneously. We found that HCV infection is more likely during recent HIV infection and this is a period characterized by high HIV RNA levels, which might explain the stronger association between HCV incidence and HIV RNA when HIV infection stage is not included in the model. Additionally, until recently, these individuals might not be on cART. Our finding underscores the importance of monitoring HCV incidence and risk factors among HIV seroconverters.

Yet HIV RNA remained statistically significant. HIV RNA might partly explain why HIV-positive MSM have a higher risk of HCV infection than HIV-negative MSM [11].

1   The biological mechanism behind the association with HIV RNA may be through the

2   activation of Langerhans cells (LCs) that results in the facilitation of HCV

3   transmission, as immature LCs capture but do not transmit HCV, while activated LCs

4   (due to HIV replication) are able to transmit the virus [29]. Alternatively, having an

5   STI, a risk factor for HCV infection [4,6,9,10,12] leads to an increase in HIV RNA

6   levels [30]. In that case, HIV RNA would be merely a proxy for having an STI. Also,

7   higher HIV RNA levels might be surrogate for poor adherence to cART.

8   Unfortunately, we could not assess the effect of STIs and cART adherence on HCV

9   incidence, as most cohorts do not collect these data.

10

11 We found no association between HCV incidence and CD4 count, which is in line

12 with most studies [3,4,6,12]. However, one showed that HIV-positive MSM with lower

13 CD4 counts had a higher risk of acquiring HCV [9] while another study only found an

14 association with CD4 count below 500 cell/µl [10]. However, both studies did not

15 exclusively include HIV seroconverters and did not account for time since HIV

16 infection.

17

18 A previous study using data from the CASCADE Collaboration and the same

19 estimating procedures, reported a similar increasing trend in HCV incidence until

20 2007 [1]. However, HCV incidence in 2007 using method 2 was considerably higher

21 than our estimation (51/1000 vs. 21/1000 py); although confidence intervals were

22 wide after 2005 and our estimates fall within this confidence intervals previously

23 estimated [1]. The present study provides a more accurate estimate of HCV

1 incidence after 2000 as additional HCV testing was performed to minimize bias

2 related to selective testing and more MSM were included.

3

4 Our study has some limitations. First, as HCV infection was based on any kind of

5 HCV test, an observed HCV infection might be a re-infection; although 99.1%

6 (334/337) of HCV infections in our study were based on HCV-antibody

7 seroconversion or evidence of acute/recent primary HCV infection. Also, since we

8 lacked data on the mode of HCV transmission, we could not assess whether all HCV

9 infections were sexually transmitted and whether changes in risk behaviour over time

10 (e.g., increase in injecting drug use (IDU)) are driving the HCV epidemic. However,

11 studies have reported HCV acquisition in the absence of traditional HCV risk factors,

12 such as IDU, in the majority of MSM [4,5,7-10,12]. Hence, the increase in sexual risk

13 behaviour among MSM (e.g, condomless anal intercourse [21]) is likely to partly

14 explain the observed trends. Furthermore, although recreational drug use is common

15 among MSM [25], recent studies have reported a low percentage of IDU among HIV-

16 positive MSM with acute HCV infection (5.8% and 12.2%) [6,9]. To the best of our

17 knowledge, evidence of an increase in IDU is scarce as only one study assessed

18 trends in recent years; an increase in IDU, from 45.1% in 2005 to 53.8% in 2014,

19 was observed among HIV-positive MSM reporting methamphetamine use in

20 Australia [31]. Further research is needed to assess changes over time in HCV-

21 related risk factors and the proportion of HCV acquisition attributable to sexual

22 practices and drug use among MSM. Despite the lack of behavioural data, the main

23 focus of our study was to assess temporal trends in HCV incidence, irrespective of

24 the mode of HCV transmission. Furthermore, it is important to bear in mind that

25 clinicians may have monitored patients at risk for HCV infection better over time,

1 leading to more HCV-positive test results in recent years. To account for this

2 possible bias we performed additional HCV testing and we only included data from

3 the date of routine testing onwards. However, the median and mean number of tests

4 was 3 and 4, respectively, over a median follow-up time of 4 years, suggesting that

5 current guidelines [32] might not be followed consistently. This is in line with results

6 from EuroSida where only a median of 3 tests were performed per patient between

7 2002 and 2013 [19]. In addition, due to a lack of country specific HCV testing

8 guidelines (e.g., Italy), HCV testing practices may not be systematic.

9

10 The strengths of our study are that we had data from HIV seroconversion onwards

11 for a large group of MSM, and extensive follow-up that enabled us to assess

12 temporal changes in time from HIV seroconversion to HCV infection and the

13 association between HCV incidence and HIV infection stage. We also applied

14 different estimating methods to calculate HCV incidence and various sensitivity

15 analyses. All methods showed comparable results suggesting that our results are

16 robust.

17

18 To conclude, no decline in HCV incidence was observed in recent years, although

19 trends seem to differ by geographical region. Hence, HCV screening among HIV-

20 positive MSM should be continued and routinely and frequently offered. Furthermore,

21 targeted preventive measures should be implemented and/or scaled-up to decrease

22 the risk of HCV acquisition. Other than recent calendar year, younger age, recent

23 HIV infection and high HIV RNA levels were all associated with HCV incidence.

24

1   Reference List

2

3   Author names **in bold** designate shared co-first authorship

4

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1 **Figures titles and legends**

2 **Fig. 1: Flow diagram of the study population selection for method 1 and 2 of**

3 **the HCV incidence analyses**

4 * Becoming at risk being the latest of: enrolment in the cohort, routine HCV testing

5 date per cohort or HIV seroconversion.

6 ** MSM from the French Primo cohort were censored at the 31st of December 2005

7 as HCV testing was only systematically recorded until that year.

8 The grey boxes depict MSM whose data were excluded from the analyses.

9

10 **Fig. 2: HCV incidence among HIV-positive MSM using two methods to estimate**

11 **follow-up in the CASCADE Collaboration; 1990-2014**

12 Method 1: dashed line, 95%CI: dashed area. Method 2: solid line, 95%CI: grey solid

13 area.

14 Poisson regression was used to test the overall effect of calendar year on HCV

15 incidence between 1990 and 2014.

16

17 **Fig. 3: HCV incidence among HIV-positive MSM by European UN geographical**

18 **region in the CASCADE Collaboration; 1997-2013**

19 *Abbreviations:* m1= method 1; m2= method 2

20 Method 1: dashed line, 95%CI: dashed area. Method 2: solid line, 95%CI: grey solid

21 area.

22 P-values: overall effect of calendar year on HCV incidence between 1997 and 2013

23 obtained from Poisson regression models.

1 **Fig. 4. HCV incidence by age, CD4 cell count and HIV RNA among HIV-positive**

2 **MSM from the CASCADE Collaboration, in year 2007 in Western Europe**[a]

3

4 4(A). Incidence by age <u>in years </u>(model 2)[b]

5 4(B). Incidence by CD4 count for an individual with a HIV RNA = 1000, aged 35

6 (model 3)

7 4(C). Incidence by HIV RNA for an individual with a CD4 cell count = 500, aged 35

8 (model 3)

9 <u>4(D). Incidence by HIV RNA for an individual with a HIV RNA = 1000, aged 35, in the</u>

10 <u>chronic HIV infection stage (model 3)</u>

11

12 [a] The relative hazards obtained from the regression models were translated into the

13 predicted incidence and this is illustrated for certain values of the covariates (e.g.,

14 only for Western Europe).

15 [b] Obtained from model 2 without the interaction term between age and region.

16

17 **Fig. 5: Time from HIV seroconversion until HCV infection over time: Kaplan-**

18 **Meier curves by calendar period of HIV seroconversion in the CASCADE**

19 **Collaboration (1990-2014)**[a]

20 [a] Curves were truncated when less than 10 individuals were at risk for HCV infection.

21 <u>The log-rank test was used to assess changes in the time from HIV seroconversion</u>

22 <u>to HCV infection among calendar periods.</u>

23

Cohorts	At least one HCV test result	MSM with follow-up[a] & at least one HCV test result	At-risk set[b]			Method 2			Start routine testing date
			HCV+[d]	HCV-[e]	Method 1				
N[c]	n (%)	Total, n (%)	n (%)	n (%)	n	HCVsc - Pys	n	HCVsc - Pys	
Southern Europe									
AMA; n=177	172 (97.2%)	167 (94.4%)	2 (1.2%)	165 (98.8%)	128	0 - 526.3	87	0 - 347.2	1-1-1991
COR; n=365	353 (97.7%)	310 (84.9%)	5 (1.6%)	302 (97.4%)	184	3 - 246.2	68	3 - 87.7	1-1-2005[f]
ICO; n=1018	914 (89.8%)	848 (83.3%)	49 (5.8%)	770 (90.8%)	497	29 - 1926.3	411	29 - 1705.7	AT
MAD; n=342	308 (90.1%)	293 (85.7%)	16 (5.5%)	274 (93.5%)	213	3 - 1047.9	30	3 - 56.8	1-1-1993
VAL; n=165	89 (53.9%)	85 (51.5%)	13 (15.3%)	71 (83.5%)	65	1 - 66.9	2	1 - 2.9	1-1-1998
Total; n=2067	**1,836 (88.8%)**	**1,703 (82.4%)**	**85 (5.0%)**	**1,582 (92.9%)**	**1,087**	**36 - 3813.6**	**598**	**36 - 2200.4**	
Western Europe									
AQU; n=788	730 (92.6%)	707 (89.7%)	29 (4.1%)	657 (92.9%)	486	21 - 3053.1	360	19 - 2389.3	1-1-1991
AUS; n=212	206 (97.2%)	201 (94.8%)	3 (1.5%)	193 (96.0%)	181	5 - 682.3	150	4 - 575.7	1-1-2006
GER; n=1912	1,848 (96.7%)	1,543 (80.7%)	63 (4.1%)	1,393 (90.3%)	1,025	87 - 4557.0	764	51 - 2665.5	RT
LYO; n=62	60 (96.8%)	59 (95.2%)	1 (1.7%)	57 (96.6%)	11	1 - 40.2	0	0 - 0	1-1-1999[f]
NEM; n=239	239 (100%)	239 (100%)	2 (0.8%)	215 (90.0%)	224	22 - 1841.6	144	21 - 1098.1	RT
PRI; n=966	894 (92.5%)	401 (41.5%)	15 (3.7%)	381 (95.0%)	211	6 - 791.8	190	5 - 748.5	1-1-1996[f]
SWI; n=343	338 (98.5%)	320 (93.3%)	4 (1.3%)	294 (91.9%)	274	22 - 1532.6	236	17 - 1210.2	1-1-2000
Total; n=4522	**4,315 (95.4%)**	**3,470 (76.7%)**	**117 (3.1%)**	**3,190 (91.9%)**	**2,412**	**164 - 12498.5**	**1,844**	**117 - 8687.4**	
Northern Europe									
NOR; n=383	378 (98.7%)	349 (91.1%)	10 (2.9%)	328 (94.0%)	305	11 - 2165.9	258	11 - 1489.6	1-1-1995
UKR; n=2714	2,209 (81.4%)	2,073 (76.4%)	50 (2.4%)	1,903 (91.8%)	1,937	120 - 9395.2	1,582	110 - 6871.6	1-1-2004
Total; n=3097	**2,587 (83.5%)**	**2,422 (78.2%)**	**60 (2.5%)**	**2,231 (92.1%)**	**2,242**	**131 - 11561.1**	**1,840**	**121 - 8361.2**	
North America									
SAL; n=138	**138 (100%)**	**131 (94.9%)**	**4 (3.1%)**	**122 (93.1%)**	**67**	**5 - 327.2**	**43**	**4 - 230.0**	1-1-2000
Australia									
PHA; n=145	**138 (95.2%)**	**138 (95.2%)**	**5 (3.6%)**	**132 (95.7%)**	**133**	**1 - 399.4**	**1**	**1- 0.8**	1-1-2002
Total; n=9,969	**9,014 (90.4%)**	**7,864 (78.9%)**	**271 (3.4%)**	**7,257 (92.3%)**	**5,941**	**337- 28599.9**	**4,326**	**279 - 19479.8**	

Table 1: Number of MSM per cohort with and without HCV test results in the CASCADE Collaboration

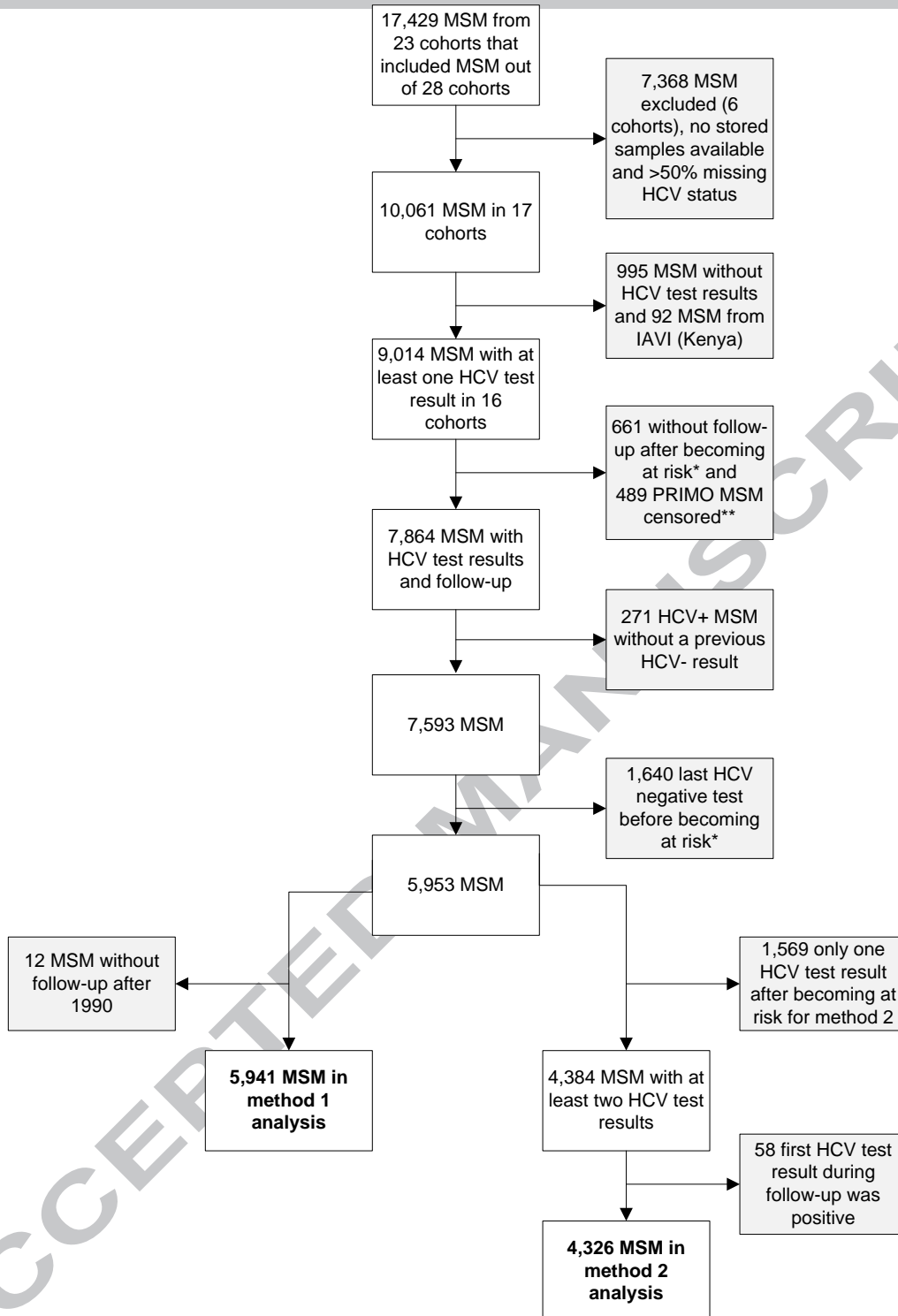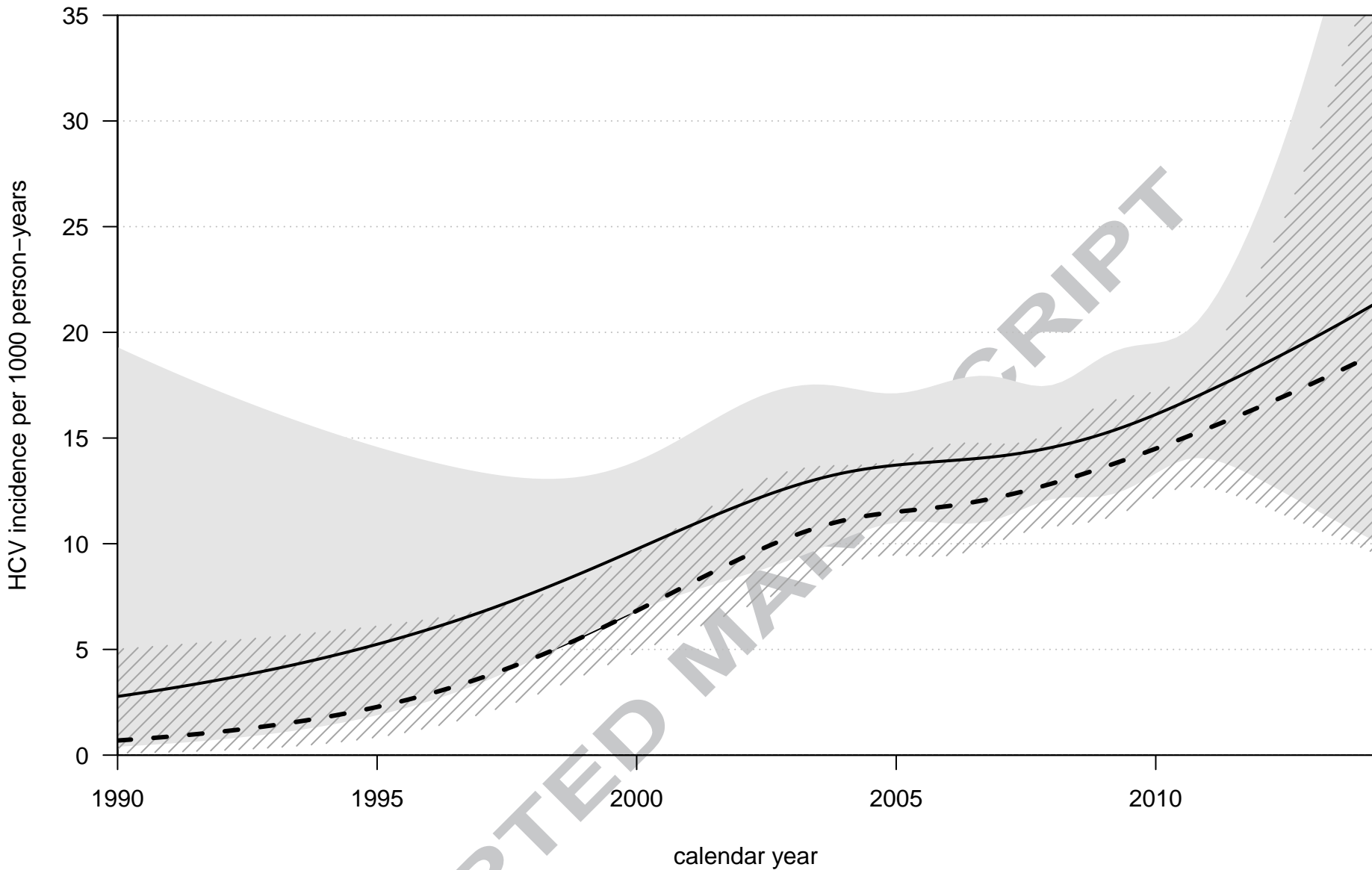Abbreviations: N=number; n=number; HCVsc=HCV seroconverters; PYs=person years of

observation; HCV+=HCV-positive; HCV-=HCV-negative; RT=retrospective testing; AT=additional

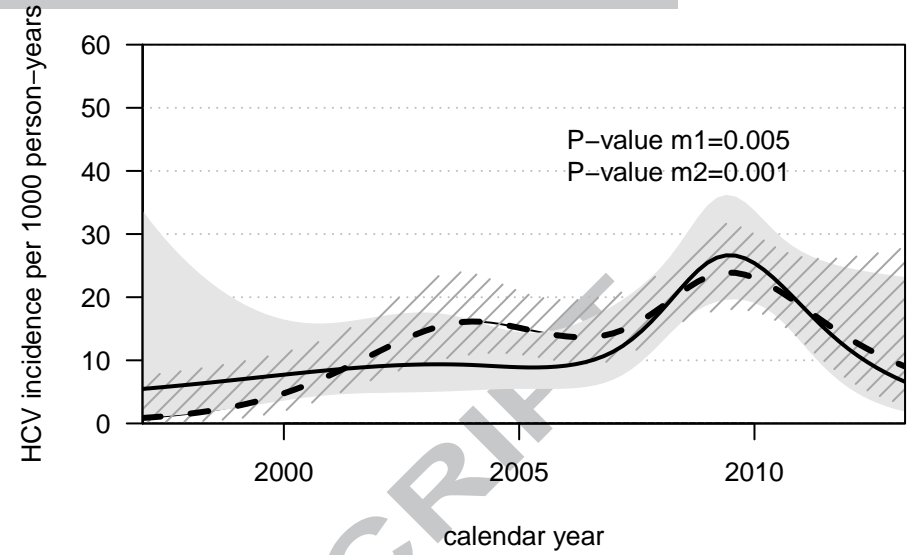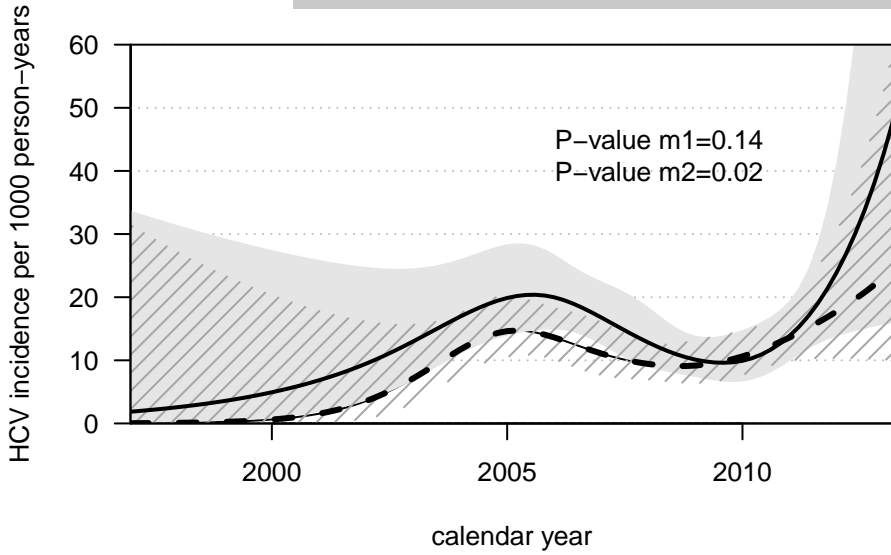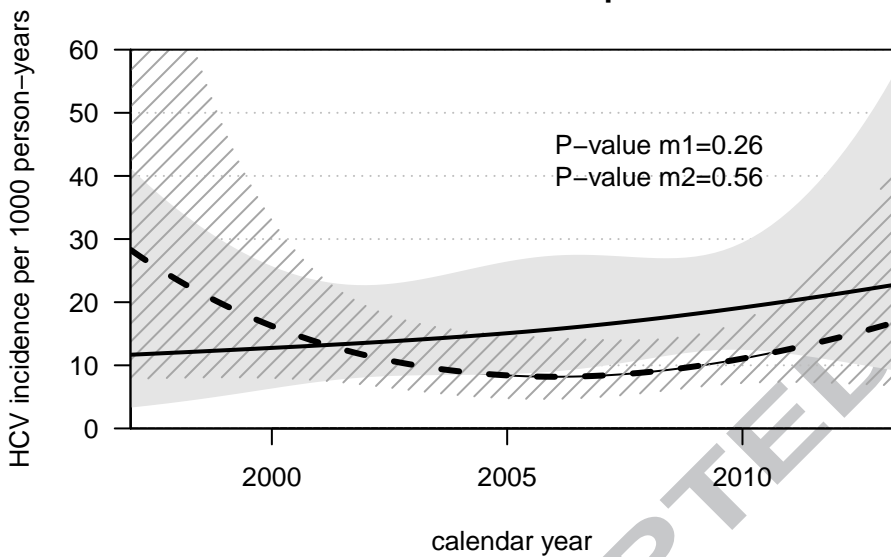testing only (no routine testing); AMA= AMACS cohort, Greece; AQU: Aquitaine cohort, France; AUS:

1   Austrian HIV cohort study, Austria; COR=CoRis cohort, Spain; GER=German cohort, Germany;

2   IAV=IAVI, Kenya; ICO=ICONA cohort, Italy; LYO= Lyon cohort, France; MAD=Madrid cohort, Spain;

3   NEM=Amsterdam Cohort Study among MSM, the Netherlands; NOR=Oslo and Ulleval hospital

4   cohorts, Norway; PHA=PHAEDRA cohort, Australia; PRI=PRIMO cohort, France; SAL=Southern

5   Alberta Clinic, Canada; SWI=Swiss HIV cohort, Switzerland; UKR=UK Register of HIV

6   seroconverters, UK; VAL=Valencia cohort, Spain; NA=not applicable.

7   [a] MSM with a clinic visit, and thus follow-up, after becoming at risk, being the latest of: enrolment in

8   the cohort, HIV seroconversion or routine testing per cohort. HCV test results irrespective of the

9   moment of becoming at risk.

10   [b] MSM included in the analyses from 1990 until 2014.

11   [c] Number of MSM per cohort irrespective of the moment of becoming at risk, HCV test, year and

12   length of follow-up.

13   [d] HCV-positive MSM without a previous HCV negative test result (i.e., excluding HCV seroconverters).

14   [e] MSM who remained HCV negative throughout follow-up (from becoming at risk until last clinic visit).

15   [d,e] Out of all MSM with follow-up & at least one HCV test result (third column).

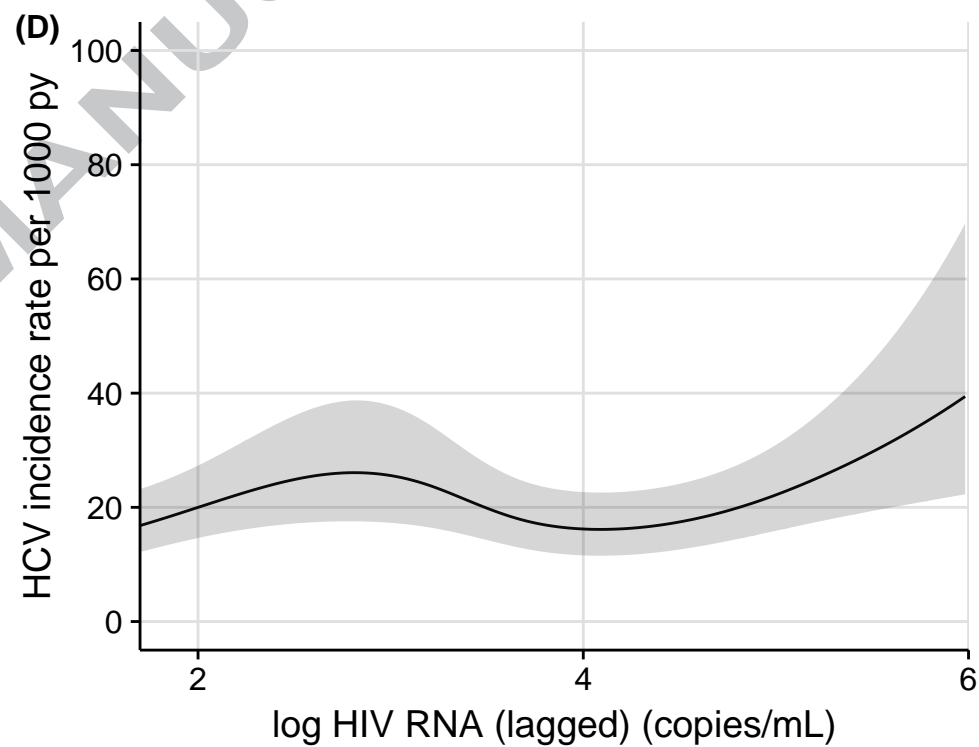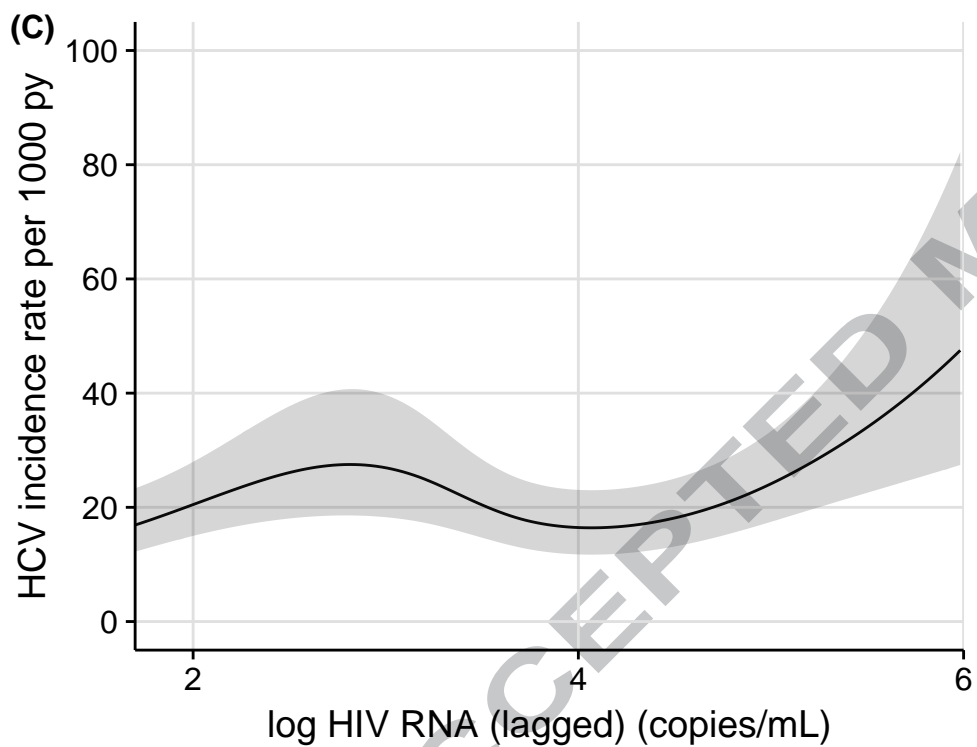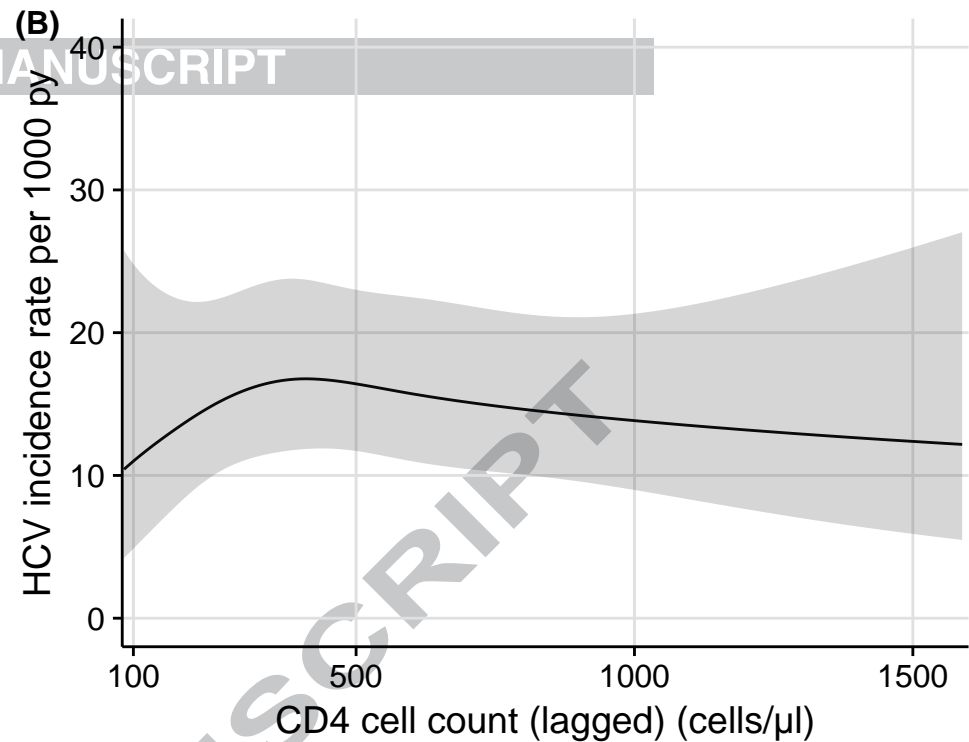16   [f] Start of routine testing date before individuals were enrolled in the cohort.

17

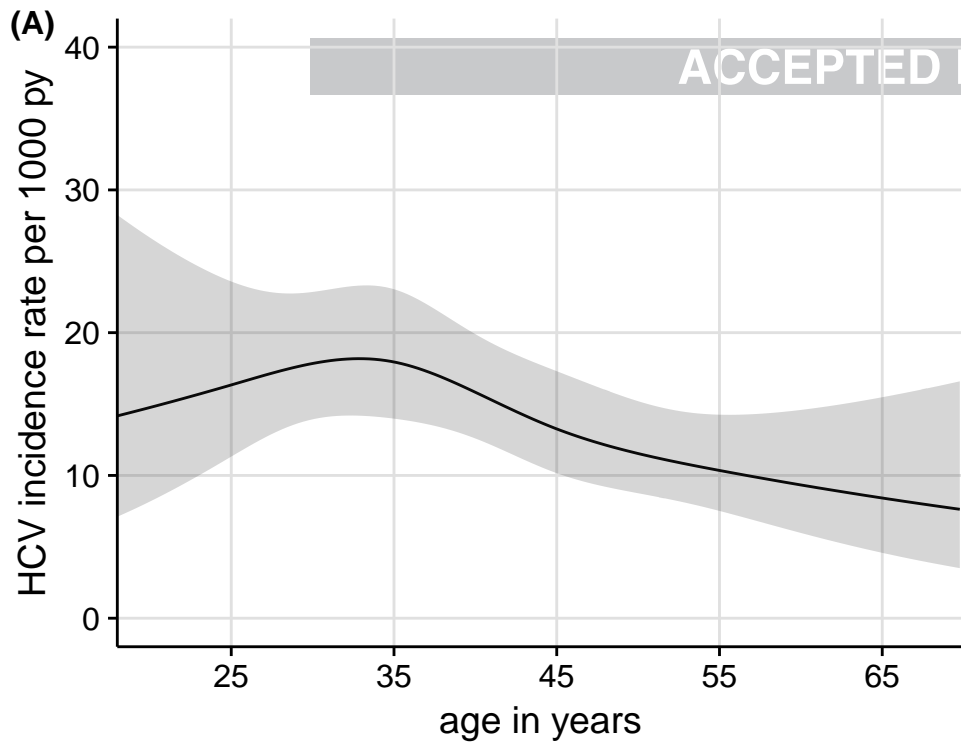17,429 MSM from 23 cohorts that included MSM out of 28 cohorts

7,368 MSM excluded (6 cohorts), no stored samples available and >50% missing HCV status

10,061 MSM in 17 cohorts

995 MSM without HCV test results and 92 MSM from IAVI (Kenya)

9,014 MSM with at least one HCV test result in 16 cohorts

661 without follow-up after becoming at risk* and 489 PRIMO MSM censored**

7,864 MSM with HCV test results and follow-up

271 HCV+ MSM without a previous HCV- result

7,593 MSM

1,640 last HCV negative test before becoming at risk*

5,953 MSM

12 MSM without follow-up after 1990

1,569 only one HCV test result after becoming at risk for method 2

5,941 MSM in method 1 analysis

4,384 MSM with at least two HCV test results

58 first HCV test result during follow-up was positive

4,326 MSM in method 2 analysis

Northern Europe   **Western Europe**

Southern Europe
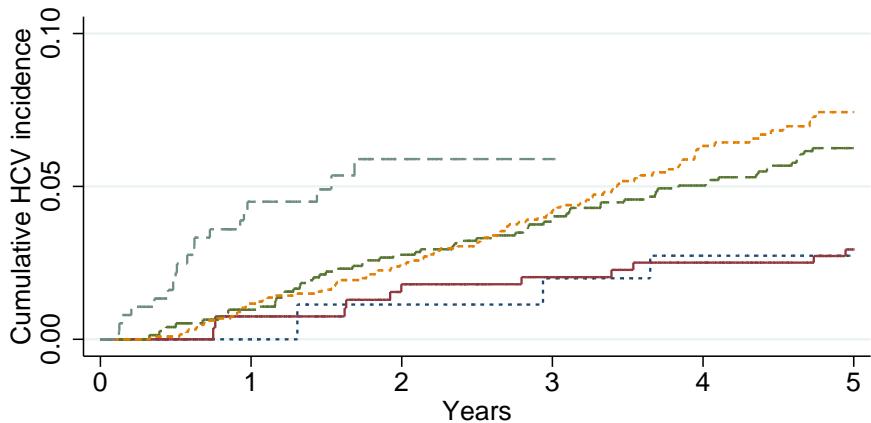
Number at risk						
1990-1994	33	83	104	115	143	177
1995-1999	57	302	388	420	408	455
2000-2004	309	964	1077	1076	1048	955
2005-2009	743	1471	1514	1191	831	529
2010-2014	383	316	113	12	0	0
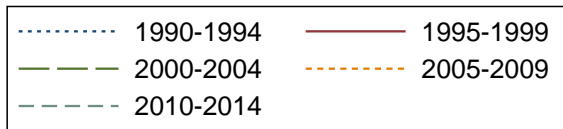
On-going hepatitis C virus transmission among HIV-positive men who have sex with men (MSM)

HCV incidence per 1000 person-years increased over calendar years

2014

2000

1990

0.7/1000

7/1000

18/1000
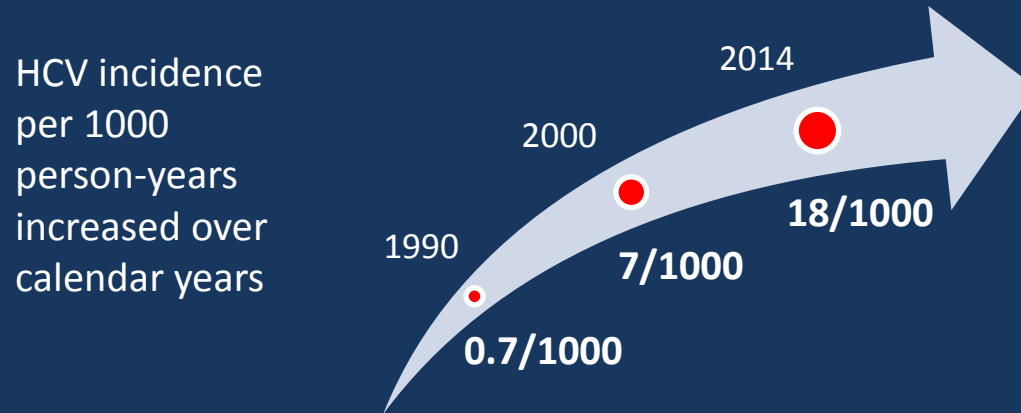
Recent HCV trends differ by European region
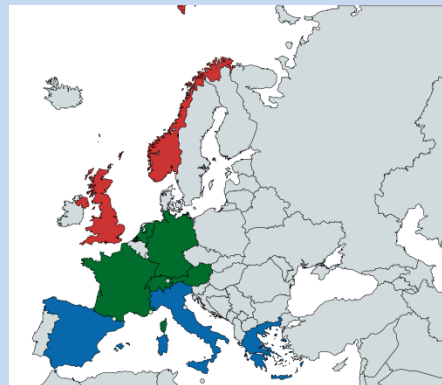
Increasing

Stabilizing

Remained stable

Younger age, recent HIV infection and higher HIV RNA levels were significantly associated with HCV incidence, while CD4 was not