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HCV micro-elimination in HIV-positive individuals in the Netherlands 4 years after universal access to direct-acting antivirals: a retrospective cohort analysis

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SUMMARY

Background: In the Netherlands, access to direct-acting antivirals (DAA) against hepatitis C virus (HCV) has been unrestricted for chronic infection since 2015. We evaluated whether the nationwide incidence of HCV infections among HIV-positive individuals has changed after 2015.
Methods: In this retrospective study, we used data from the ATHENA cohort in people with HIV aged ≥18 years attending all HIV treatment centres in the Netherlands between 2000-2019. We used parametric proportional hazards models with an exponential survival function to model incidence rates (IR) per 1000 person-years of observation (PYO) of HCV primary infection and re-infection.
Findings: Among 23,590 individuals without prior HCV, 1269 cases of HCV primary infection were documented (IR=5·2/1,000PYO, 95%CI=5·0-5·5). The highest IR was observed in men who have sex with men (MSM) (7·7/1,000PYO, 95%CI=7·3-8·2) and lower among people who inject drugs (PWID) (1·7/1,000PYO, 95%CI=0·7-4·1) and other key populations (1·0/1,000PYO, 95%CI=0·8-1·2). In MSM, IR increased in 2007 (IR=14·3/1,000PYO) and fluctuated between 8·6-14·3/1,000PYO from 2008-2015. In 2016, IR declined to 6·1 cases/1,000PYO and remained steady between ·4·1-4·9/1000PYO from 2017-2019. Among 1866 individuals with a previous HCV infection, 274 re-infections were documented (IR=26·9/1,000PYO, 95%CI=23·9-30·3). The highest IR was observed in MSM (38·5/1,000PYO, 95%CI=33·9-43·7) and was lower among PWID (10·9/1,000PYO, 95%CI=3·5-33·8) and other key populations (8·9/1,000PYO, 95%CI=6·3-12·8). In MSM, re-infection IRs fluctuated until 2015, reaching 55·6/1,000PYO. In 2016, re-infection incidence declined to 41·4/1,000PYO, followed by further decreases of 24·4 in 2017 and 11·4/1,000PYO in 2019.
Interpretation: The sharp decline in HCV incidence among HIV-positive MSM shortly after unrestricted DAA access suggests a “treatment-as-prevention” effect. HCV incidence was already low in PWID and other groups prior to unrestricted access. Ongoing HCV transmission is occurring in MSM, as illustrated by a declining but nonetheless high rate of reinfection, stressing the need for additional preventive measures.
Funding: Dutch Ministry of Health, Welfare and Sport

KEYWORDS: hepatitis C incidence; hepatitis C re-infection, DAA, human immunodeficiency virus; antiviral treatment; men who have sex with men; epidemiology.

RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed and conference databases [International AIDS Society Conference (2018-2020) and Conference on Retroviruses and Opportunistic Infections (2018-2020)] without language restrictions from database inception to 23 April 2020, for articles or abstracts, using the search terms “HCV”, “incidence”, “HIV”, “direct acting antivirals” and “DAA”. Our initial search yielded 120 articles. We selected studies that included individuals living with HIV and provided HCV incidence rate estimates before and after a specific timepoint when DAA access was broadened. Studies focusing on primary HCV incidence after universal DAA access reported stable or decreasing number of incident HCV cases (in MSM and PWID, respectively, Switzerland), immediate decreases in HCV incidence (in MSM, the Netherlands), decreases in HCV incidence rates even prior to universal access (in MSM, London, Bristol, United Kingdom), or even increases in HCV incidence rates (France). Studies focusing on HCV re-infection after universal DAA access reported low infection rates overall (mostly MSM, Australia), low prevalence of viraemic individuals (HIV-positive and HIV-negative PWID, Australia), and no change in re-infection rates between interferon and DAA-eras (Germany, France). Differences in treatment uptake could partly explain these discrepancies. Most studies assumed that HCV testing rates were yearly.

Added value of this study

In the Netherlands, we report that although the incidence rate of both HCV primary and re-infection has drastically decreased in HIV-positive MSM within the first year after unrestricted access to DAA treatment, it has remained steady four years from then on. HCV incidence was already low in PWID and other groups prior to unrestricted access. These changes in incidence were not due to changes in age structure and HIV RNA/CD4 levels, or possibly HCV testing frequency. Meanwhile, the high and rapid uptake of DAAs and increased sustained virological response points towards a “treatment-as-prevention” effect. Importantly, two decades worth of prospective data indicate that 2016-2019 incidence rates of primary HCV infection are similar to those pre-2007.

Implications of all the available evidence

There is a consistent effect of decreasing HCV incidence following high DAA uptake during universal access to DAA. However, infections are still occurring suggesting that other means of preventing HCV infection, possibly including increased HCV testing and/or reducing behaviours associated with HCV acquisition, are needed.

INTRODUCTION

During the 2000s, the incidence rate of hepatitis C virus (HCV) infections rapidly increased among HIV-positive individuals for most of Europe (1). Treatment at the time was limited to interferon-based regimens with suboptimal sustained virologic response (SVR) rates (2). Coupled with the low rates of spontaneous clearance after infection (3) and a prolonged, clinically asymptomatic course of disease, a substantial proportion of HIV-HCV co-infected individuals had active HCV replication and were thereby causing onward transmission of HCV (4).

With the advent of potent direct-acting antivirals (DAA), SVR has become attainable for almost all individuals infected with HCV (5). This has led the World Health Organization to set targets to eliminate HCV as a public health threat by 2030, including 80% reduction in HCV incidence rates (IR) from 2015 (6). Considering that HCV infection is more prevalent in some individuals living with HIV, such as people who inject drugs (PWID) and men who have sex with men (MSM), elimination targets need to be urgently met for these key populations, that is, micro-elimination. Importantly, treatment uptake must be widespread for HCV micro-elimination to occur. Modelling studies specific to HIV-positive PWID and MSM have shown that reductions in incident and prevalent cases of HCV could be obtained for most settings when treatment coverage substantially increases (7,8). Data from observational studies confirming these reports are, however, either lacking or limited in follow-up.

In the Netherlands, DAAs were initially made available in 2014 for HIV-positive individuals with HCV infection under the condition that they had advanced liver fibrosis or cirrhosis. In 2015, these restrictions were removed and rapid uptake of DAAs was observed in this group, particularly among MSM (9). Initial data from a large subset of HIV-treatment centres in the Netherlands have reported that HCV IRs have almost halved directly after unrestricted access of DAAs (10). In other countries without treatment restrictions, e.g. United Kingdom Switzerland, and Australia, similar findings among HIV-positive individuals have been reported (11-13), while in France, no such decrease has been observed (14).

The aim of the current study is to determine the IRs of both primary HCV infection and, in those with previous infection, HCV re-infection over the past two decades using comprehensive data of nearly all HIV-positive individuals actively followed in care in the Netherlands. Particular attention will be focused on key populations and the years prior to and directly after unrestricted access to DAAs.

METHODS

Study design and participants

HIV care in the Netherlands is provided by 24 treatment centres. As an integral part of HIV care, the HIV Monitoring Foundation (https://www.hiv-monitoring.nl/en) is responsible for prospectively collecting demographic data and relevant HIV and treatment data, as well as data on viral hepatitis coinfection, from HIV-positive persons living in the Netherlands and receiving care in one of these treatment centres.

This data collection is known as the ATHENA cohort (15), which was initiated in 1998 and captures data from >98% of all patients with diagnosed HIV infection who are in care in the Netherlands. Data collection is continuous, and the database of the ATHENA cohort is locked and updated twice a year. This article includes data from 1 January 2000 until 31 December 2019 (database lock June 2020).

At its inception, the ATHENA cohort was approved by the institutional review boards of all participating centres. Individuals can opt out after being informed by their treating physician of the purpose of data and sample collection. Data are pseudonymized and made available to investigators in a coded form. Coded data may be used for scientific purposes without further consent. For the purpose of our analysis, only existing data have been used and therefore no additional review or consent was required.

Procedures

Included patients were assessed at first visit for age, sex, and HIV transmission route. We assigned each patient to an HCV key population based on their HIV transmission route. We considered any MSM who ever injected drugs as part of the MSM key population. CD4 T-cell count and HIV-1 RNA measurements were obtained during follow-up visits. Date of initiation and discontinuation for each HIV and HCV treatment, and data on HCV treatment response were also collected during follow-up.

Physicians were recommended to conduct HCV testing according to European AIDS Clinical Society (EACS) guidelines. We used ELISA-based assays to test for HCV antibodies and PCR-based assays to test for HCV-RNA (range of detection thresholds: 15-615 copies/mL). If an HCV test was not performed at a given visit, we assumed that the HCV status did not change since the most recent test (i.e. last observation carried forward).

Primary HCV infection was evaluated in individuals with no evidence of prior HCV infection, which was defined as never having had a previous positive anti-HCV antibody or HCV-RNA test, with testing being a requirement for inclusion. We defined HCV infection by either (i) seroconversion from anti-HCV antibody negative to positive or (ii) change from undetectable HCV-RNA to detectable HCV-RNA. Date of primary HCV infection was defined as the date of first anti-HCV antibody or HCV-RNA test.

HCV re-infection was evaluated in individuals with treatment-induced SVR or spontaneous clearance of HCV and was defined by detectable HCV-RNA at any visit after HCV clearance. Date of HCV re-infection was the date of first positive HCV-RNA test. SVR was defined as a negative HCV-RNA test result ≥24-34 weeks after the end of HCV treatment with an interferon-based regimen or a negative HCV-RNA test result ≥12-34 weeks after the end of treatment with DAAs. If there was no HCV-RNA test result within this timeframe, we used the treatment outcome reported in the patient file. Spontaneous clearance was defined by having a positive test result for HCV antibody or HCV-RNA, a subsequent negative HCV-RNA test result after ≥2 weeks and no prior history of HCV treatment. Similar to a previous study (18), spontaneous clearance was distinguished as either ‘definitive’ (i.e. two consecutive negative HCV-RNA test results after a positive HCV antibody or RNA test result) and ‘possible’ (one negative HCV-RNA test result following an earlier positive HCV antibody or RNA test result, or only two HCV-RNA negative results within <2 weeks).

Statistical analysis

We evaluated primary HCV infection and HCV re-infection. For primary infection, analysis was restricted to HIV-positive patients whose first documented anti-HCV antibody result was negative. The individual observation period began at first cohort visit after 1 January 2000 and continued until incident primary HCV infection, death, loss to follow-up, last visit, or 31 December 2019, whichever occurred first. For re-infection, analysis was restricted to HIV-positive patients with a positive anti-HCV antibody test or positive HCV-RNA and who had achieved SVR or spontaneous clearance. The individual observation period began at the first visit >6 months following end of treatment (for SVR) or following spontaneous clearance after 1 January 2000 and continued until HCV re-infection, death, loss to follow-up, last visit, or 31 December 2019, whichever occurred first. Individuals re-started follow-up after SVR or spontaneous clearance of their re-infection until the next censoring event. For both primary infection and re-infection, we included patients who had one visit at the beginning of the observation period and at least one visit during follow-up.

We first examined the yearly testing rate across calendar years within key populations. We then described the numbers of primary HCV infections and HCV reinfection and the proportion of these infections according to key population. Given the preponderance of primary infection and re-infection among MSM, we restricted all further analysis to this group. IRs of both primary HCV infection and HCV re-infection and their 95% confidence intervals (CI) were estimated over calendar years using a piecewise exponential survival regression model. We also evaluated IRs with respect to age, CD4+ cell count and HIV-RNA levels (Appendix, p2). The proportion initiating treatment <12 and <6 months after first anti-HCV antibody positive or HCV-RNA-positive test for primary infection and first HCV-RNA-positive test for re-infection (i.e. treatment uptake) and proportion of those treated reaching SVR were estimated across calendar years (Appendix, p2). We did not include 2019 in this analysis as follow-up was too short to confirm SVR for individuals starting treatment in 2018.

We carried out analysis using STATA (v15.1, College Station, TX) and significance was determined using a *p*-value <0.05. Statistical codes are provided at https://github.com/boyd0094/SHM_HCV_incidence.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Of the 31,070 HIV-1 positive individuals ever registered in the ATHENA cohort, the numbers included for the analysis of primary HCV infection and HCV reinfection are shown in Supplementary Figure S1 (Appendix, p3). The majority of individuals were MSM; the percentage of PWID was low and decreased from 3% in 2000 to <1% in 2015 (Table 1).

23,590 individuals were susceptible to primary HCV infection. Of them, 30% had only one HCV test (23% MSM, 31% PWID, 44% heterosexual/other groups). The percentage with an HCV test at least once during the calendar year increased mainly in MSM (Figure 1A) with stable testing at 31·5-43.1% per year from 2008-2019. PWID and heterosexual/other groups remained stable at 14·7-21·2% and 10·4-23·1% per year over time, respectively (Figure 1A).

During a median follow-up of 9·8 years (IQR=4·8-15·6), 1269 incident primary infections were observed and the highest number of primary infections was observed in 2015 (*n*=116) (Figure 2A). Across calendar years, HIV-positive MSM constituted 92·7% of all primary HCV infections in comparison to 0·4% in PWID or 6·9% in heterosexuals/other (Figure 2B). Of those with genotyped sequences, 696 (70·4%) infections involved genotype 1, 214 (21·6%) genotype 4, 55 (5·6%) genotype 2, and 24 (2·4%) genotype 3.

A total of 1,866 individuals were susceptible to HCV re-infection following SVR during follow-up (Supplementary Figure S1, Appendix, p3). Of the HIV-positive individuals susceptible to re-infection, the percentage of MSM with an HCV test at least once during the calendar year was 53·4-64·6% between 2006-2016 (Figure 1B), followed by noticeable declines from 2017-2019 (43·8%). Yearly HCV testing rates averaged 25·1% for PWID and 30·0% for heterosexuals/other with substantial variation over the years due to small numbers.

During a median follow-up of 4·0 years (IQR=2·8-8·1), 274 cases of HCV re-infection were observed and the highest number of re-infections occurred in 2018 (*n*=32) (Figure 1A). HIV-positive MSM constituted 86·9% of HCV re-infections in comparison to 1·1% in PWID or 12·0% in heterosexuals/other (Figure 1C).

As the majority of HCV infections occurred in MSM, we restricted further analysis to this group. Over 152,671 person-years of observation, 1176 cases of HCV primary infections occurred in MSM (IR=7·7/1000 person-years). IR of primary HCV infection (Figure 2A) substantially increased in 2007 and continued to fluctuate at elevated levels until 2015. After 2015, a large decline in IR occurred in 2016 (versus 2015, $p<0·001$) with a slight decline further (versus 2016: 2017, $p=0·26$; 2018, $p=0·06$; 2019, $p=0·05$).

Over 7,238 person-years of observation, 238 cases of HCV re-infection occurred in MSM (IR=38·5/1000 person-years). Of these cases, 134 occurred after previous treatment-induced SVR and 104 after previous spontaneous clearance (probable, *n*=40; definitive, *n*=64). IR of re-infection was lower after DAA-induced SVR (IR=29·8/1000 person-years) or interferon- or interferon/DAA-induced SVR (IR=34·2/1000 person-years) versus after spontaneous clearance (IR=55·2/1000 person-years) (IRR=0·54, 95%CI=0·38- 0·77 and IRR=0·62, 95%CI=0·46-0·83, respectively). The distribution of total HCV re-infections per MSM was as follows: 1, *n*=186; 2, *n*=20; 3, *n*=4. IR of HCV re-infection (Figure 2B) was variable over calendar time between 2006 and 2015. Nevertheless, substantial declines were observed in 2016 (versus 2015, $p=0·26$) followed by steady declines (versus 2015: 2017, $p=0·003$; 2018, $p=0·02$; 2019, $p<0·001$).

Mean age at primary HCV diagnosis in MSM was 42 years (SD=9) and did not substantially vary during follow-up (Supplementary Figure 2A, Appendix p4), while IR of primary HCV infection was highest between the ages of 30-50 (Supplementary Figure 2B). Proportion of MSM with undetectable HIV-RNA at primary HCV diagnosis increased over calendar period,

from 69·6% in 2005 to 89·7% in 2019 (Supplementary Figure 2C), yet no discernible variation was observed in IR with respect to HIV-RNA viral load (Supplementary Figure 2D). Similarly, mean CD4+ T-cell count at primary HCV diagnosis in MSM increased over calendar period, from 559 per µL in 2005 to 677 per µL in 2019 (Figure Supplementary 2E), with IR slightly increasing until 200 cells per µL and plateauing thereafter (Supplementary Figure 2F). Similar findings were observed in MSM with HCV re-infection (Supplementary Figure S3, Appendix, p5).

For primary infections in MSM, the median time taken to treat HCV infection from HCV-diagnosis declined over the years (p<0·001) from 21 months (IQR=6-86) between 2005-2008 to 5 months (IQR=3-8) between 2015-2018 (Figure 4A). Accordingly, treatment uptake within 6- and 12-months, respectively, after diagnosis increased from 24·1% and 34·4% between 2005-2008 to 48·2% and 67·8% in 2015-2018 (Figure 4B).

All individuals treated for primary HCV infection received peg-IFN until 2011 (Figure 4C). From then, individuals received peg-IFN and/or DAA and by 2016 all individuals received DAAs. SVR also substantially increased from 74·6% in 2005-2008 to 98·0% in 2015-2018 (Figure 4D). Similar findings were observed in MSM with HCV re-infection (Supplementary Figure S4, Appendix, p6).

DISCUSSION

Based on a nationwide database of HIV-positive individuals, we have observed that the HCV-epidemic has disproportionally affected MSM with very few cases of primary HCV infection or re-infection in PWID or heterosexuals even before universal access to DAAs. As indicated in modelling studies (4,8,16), an increase in SVR with highly effective DAAs would decrease the pool of HCV-infected individuals and consequently prevent further transmission. In MSM living with HIV, we observed a 58% overall drop in primary HCV incidence and 79% drop in HCV reinfection incidence when comparing 2015 to 2019 – four years after the introduction of universal access to DAAs for all HCV-infected individuals in the Netherlands. These data provide further epidemiological evidence that the unrestricted availability of potent antiviral therapy is contributing to reductions in HCV incidence among MSM. However, this reduction currently falls short of the WHO's goal for micro-elimination and given the stable or fluctuating IRs between 2016-2019, the WHO target might not be met in 2030.

Other conditions could have explained the decrease in incidence. First, the increased awareness among treating physicians of the ongoing HCV-epidemic among HIV-positive MSM might have resulted in more frequent HCV testing of MSM from 2007 onwards. IRs could have simply been a reflection of identifying all those unaware of their infection. Yearly testing has remained mostly stable since 2008.

Second, sexual risk behaviour necessary for HCV transmission could have decreased, resulting in decreases of further spread of HCV. These behaviours are varied and are not routinely measured in ATHENA. The yearly prevalence of more common STIs, such as chlamydia, gonorrhoea, and infectious syphilis, has either remained unchanged or has slightly increased in HIV-positive MSM over the past decade (17), possibly implying that the

proportion engaging in condomless anal sex, bearing an increased risk of HCV transmission, has also been steady. Fisting without gloves and sharing sex toys have also been strongly linked to HCV re-infection and the frequency of which has remained static in the Netherlands from 2010-2018 (18). Cocaine use (involving the sharing of snorting straws) and “chemsex” (occasionally involving shared injecting equipment), factors also associated with HCV infection, are still frequent in HIV-positive MSM (19) and have been reportedly increasing over the past decade (20).

Finally, higher SVR rates for patients with HCV infection were able to be achieved in the period shortly prior to DAA, when compared to results from clinical trials (2), possibly due to earlier initiation of pegylated-interferon (21). There were also several studies actively recruiting HIV-positive MSM with early HCV infection [Dutch Acute HCV in HIV study (DAHHS1) in 2013-2015 (22), DAHHS2 in 2016-2018 (23) and Randomised Study of Interferon-free Treatment for Recently Acquired Hepatitis C in PWID and People With HIV Coinfection (REACT) in 2017-2019]. However, the only large decrease in HCV infection incidence was observed with the DAHHS2 study and a modelling study has demonstrated that no difference in HCV incidence would be observed with immediate compared to 6-month delayed initiation of DAA therapy (16). Given these aspects discussed above, factors other than DAAs do not seem to explain the drop in incidence in 2016.

The IR of re-infection in MSM continued to slightly decrease from 2016 to 2019, and although it was still high at 11 per 1000 person-years in 2019, it was much lower compared to other European settings (18,24). From 2010-2015, re-infection IRs were variable and although the recent decrease in IR is encouraging, it could be an artefact of the variation normally seen across Europe (24). Furthermore, individuals at-risk of HCV re-infection, particularly MSM, witnessed a rather dramatic decline in yearly HCV testing of 64% in 2016 and 38% in 2019. This could have been due to preferential HCV-RNA testing when ALT levels were elevated, the physicians’ view that the HCV epidemic is no longer of concern and hence HCV testing for re-infection is no longer a priority, and/or reduction in numbers of individuals at high risk of reinfection. This observation might also partially explain the decrease in HCV re-infection IRs observed in our cohort.

Albeit significantly reduced, the source of onwards transmission of HCV in the DAA era is unclear. HCV transmission among HIV-positive MSM is known to occur in widespread networks across Europe (25). However, other research from Switzerland has indicated a shift towards more domestic transmission of HCV infection (26). HIV-negative MSM using pre-exposure prophylaxis (PrEP) against HIV have also witnessed high incidence of HCV infection (27). Phylogenetic evidence suggests clustering of these HCV strains with those from HIV-positive MSM, but specific risk behaviours are known to be inconsistent within clusters (28). Studies are needed to find out whether HIV-negative MSM are a relevant source of undiagnosed HCV. Testing for HCV is currently not standard practise at most sexual health centres in the Netherlands. Of the HIV-positive MSM in care in 2019, only 43·2% of those susceptible to primary infection and a much lower 38·2% susceptible to re-infection were tested for HCV, illustrating that case finding of HCV (re)infections could also be improved in HIV care.

The major question is then how to buttress micro-elimination in a population with already high DAA uptake and fairly regular HCV testing. As the modelling studies would suggest

(8,16), some improvement could be made in even earlier DAA treatment, such as during very early infection, and more frequent or facilitated access to HCV testing, including in individuals with prior spontaneous clearance or treatment-associated SVR who are susceptible to re-infection. For some settings, behavioural interventions aimed at educating and helping to reduce activities associated with HCV acquisition are essential for reducing HCV incidence (29). Improvement in contact tracing and communication with the community should also be considered. Given that HCV infections are more commonly being observed in HIV-negative MSM, particularly those undergoing PrEP (27), these public health tools will have to focus on the broader MSM population engaging in high risk behaviours (30).

Several study limitations should be addressed. First, HCV key populations were determined from HIV transmission and could have been misclassified, particularly for those who acquired HIV via 'heterosexual/other' routes. Second, we depended on laboratory data collected during routine visits to define HCV infections and assess HCV testing frequency. HIV physicians were recommended to follow HCV testing guidelines from the EACS; however, we were unable to ascertain the adherence to these guidelines. Some cases could be missed by failure to test unsuspected or asymptomatic HCV infections and only a few cases of definitive spontaneous clearance were not able to be confirmed with two consecutive HCV-RNA negative tests at least 4 weeks apart (i.e. EACS definition of spontaneous clearance). Finally, the period to determine SVR may have been too short and thus some of the HCV re-infections could have been late relapses, particularly during the interferon-era. The testing interval after spontaneous clearance could have also been too short to differentiate re-infection from recrudescence. Nevertheless, the median time until first HCV-RNA test to detect HCV re-infection after spontaneous seroclearance was 13 months (IQR=4-37), with 85% of these tests being negative, and 33% of reinfections had been confirmed by genotype switches, both of which would limit this error.

In conclusion, a decline in primary HCV infection and HCV re-infection was observed among MSM living with HIV in the years following unrestricted access to DAAs in the Netherlands, suggesting a "treatment as prevention" effect. Our results provide evidence that widespread DAA use is helping curb the HCV epidemic in this key population. At the same time, the persisting IRs of primary HCV infection and to a lesser extent HCV re-infection in 2016-2019 exemplify the difficulty in HCV micro-elimination. Increased testing and behavioural interventions for those at risk could assist in meeting this public health challenge.

CONTRIBUTORS

CS, ABoy and PR contributed to study concept and design. CS and ABoy performed study analysis. BJAR, EML, WFB, KB, MAC, JdH, JA and MvdV contributed to data collection and interpretation of the data. TJWvdL, ABoe, AN, JS, MP and EodC contributed to interpretation of the data. CS and ABoy wrote the first draft of the report. All authors critically revised and approved the final version for publication. CS and ABoy have accessed and verified the underlying data.

DECLARATIONS OF INTEREST

BJAR reports grants from MSD and Gilead, all outside the submitted work; he has participated in advisory boards organized by MSD, Gilead, Pfizer, ViiV Healthcare, Janssen-Cilag, and Abbvie. EMM reports participating an advisory board of Gilead. WB reports other funds from GSK and non-financial support from Janssen, all outside the submitted work. KB reports participating in advisory boards of ViiV, Gilead, MSD and Janssen; he has received research grants form ViiV and Gilead. JS reports grants from Gilead Sciences, outside the submitted work. MP reports grants, personal fees and other funds from Gilead Sciences, Roche, MSD and Abbvie, all outside the submitted work. JA reports other funding from Gilead Sciences, Janssen-Cilag, Abbvie, BSM, and MSD, all outside the submitted work. MvdV reports grants and personal fees from Abbvie, Gilead, Johnson & Johnson, MSD, ViiV Healthcare, all outside the submitted work. PR reports grants from Gilead Sciences, ViiV Healthcare, and Merck & Co, and other funds from Gilead Sciences, ViiV Healthcare, Merck & Co, and Teva Pharmaceutical Industries, all outside the submitted work. All other authors report no conflicts of interest.

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FIGURE LEGENDS

Figure 1. Yearly Hepatitis C virus (HCV) testing across calendar years in HIV-positive individuals

Proportion of HIV-positive individuals who were susceptible to primary HCV infection and who had a yearly HCV test (i.e. anti-HCV antibody and/or HCV-RNA) is depicted in (**A**). Proportion of HIV-positive individuals who were susceptible to HCV re-infection and who had a yearly HCV test (i.e. HCV-RNA) is depicted in (**B**). Fitted lines are represented as solid lines and 95% confidence intervals as dashed lines. We stratified analysis by groups: men who have sex with men (MSM), heterosexual or other (hetero/other) and persons who inject drugs (PWID).

Figure 2. HCV primary infection and re-infection in HIV-positive individuals

Data are from the ATHENA cohort among HIV-positive individuals in care from 2000-2019. Total numbers of primary infection and re-infection with hepatitis C virus (HCV) are provided over calendar years (**A**). The proportion of cases in men who have sex with men (MSM), heterosexual or other (hetero/other) and persons who inject drugs (PWID) are given across calendar years for HCV primary infection (**B**) and HCV re-infection (**C**).

Figure 3. Incidence rate of HCV primary infection and re-infection in HIV-positive men who have sex with men (MSM)

The incidence rate per 1000 person-years (py) for hepatitis C virus (HCV) primary infection (**A**) and HCV re-infection (**B**) is estimated among MSM.

Figure 4. Treatment of primary infections across calendar years in HIV-positive men who have sex with men (MSM)

Data include only HIV-positive MSM with primary hepatitis C virus (HCV) infection. Box-plots of time from HCV diagnosis to anti-HCV treatment are depicted across years at which treatment began in (**A**). The proportion with treatment uptake (i.e. treatment initiation within 6- or 12-months after HCV diagnosis) is depicted across year of HCV-diagnosis in (**B**). The numbers of primary HCV infection treated with only interferon (IFN), combined IFN and direct-acting antivirals (DAA) (boceprevir or telaprevir for this category), or only DAAs are depicted across years at which treatment began (**C**), along with the proportion of treated individuals achieving sustained virological response (SVR) (**D**). Fitted lines (solid) along with 95% confidence intervals (dashed lines) are given for proportion with treatment uptake and with SVR.

Table 1. Description of the study population at specific years

	1 Jan 2000 (*n*=4,916)	1 Jan 2005 (*n*=8,763)	1 Jan 2010 (*n*=13,308)	1 Jan 2015 (*n*=16,858)
Median (IQR) age, years	39 (34-46)	41 (35-48)	44 (37-51)	47 (39-55)
Gender				
Male	4139 (84)	6961 (79)	10,706 (80)	13,808 (82)
Female	777 (16)	1801 (21)	2597 (20)	3039 (18)
HIV/HCV mode of transmission				
MSM	3312 (67)	5249 (60)	8183 (61)	10,814 (64)
PWID	47 (1)	90 (1)	139 (1)	132 (1)
Heterosexual/other	1557 (32)	3424 (39)	4986 (37)	5912 (35)
Region of origin				
Netherlands	2948 (60)	4846 (55)	7583 (57)	9976 (59)
Europe	406 (8)	613 (7)	848 (6)	937 (6)
Sub-Saharan Africa	500 (10)	1428 (16)	1993 (15)	2188 (13)
Caribbean/South America	592 (12)	1074 (12)	1640 (12)	2038 (12)
South-east Asia	148 (3)	289 (3)	451 (3)	605 (4)
Other	322 (7)	513 (6)	793 (6)	1114 (7)
Ever AIDS	1945 (40)	2966 (34)	3770 (28)	4145 (25)
AIDS at diagnosis	708 (14)	1290 (15)	1834 (14)	2223 (13)
Median (IQR) CD4+ T cells per µL	460 (290-650)	470 (330-655)	530 (390-700)	640 (480-830)
Median (IQR) CD8+ T cells per µL	1040 (730-1420)	960 (690-1300)	880 (640-1200)	850 (620-1150)
HIV-RNA <200 copies/mL	2451 (50)	6032 (69)	10,097 (76)	15,663 (93)
Current HIV treatment				
On combined ART	3170(65)	5900(68)	10,007(76)	15,205 (91)
Not on combined ART	11,719 (35)	2806 (32)	3223 (24)	1566 (9)
Never initiated combined ART	11,320 (27)	2092(25)	2547 (19)	960 (6)
HCV infection risk				
At risk of primary infection	4883 (99)	8621 (98)	12,944 (97)	15,989 (95)
At risk of re-infection	34 (1)	143 (2)	366 (3)	754 (4)

All statistics are *n* (%) unless indicated otherwise. Median calendar year of inclusion was 2007 (IQR=2001-2012).

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; MSM, men who have sex with men; PWID, person who injects drugs.

Figure 1A

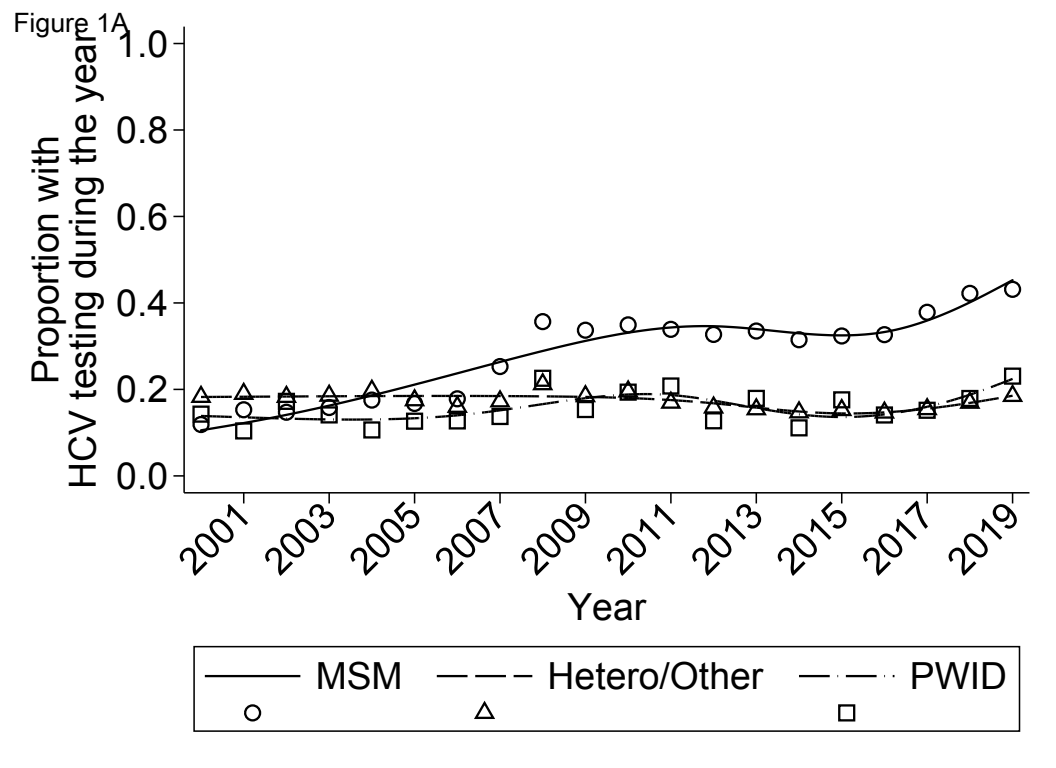

Proportion with HCV testing during the year
1.0
0.8
0.6
0.4
0.2
0.0
2001
2003
2005
2007
2009
2011
2013
2015
2017
2019
Year
MSM
Hetero/Other
PWID

Figure 1B

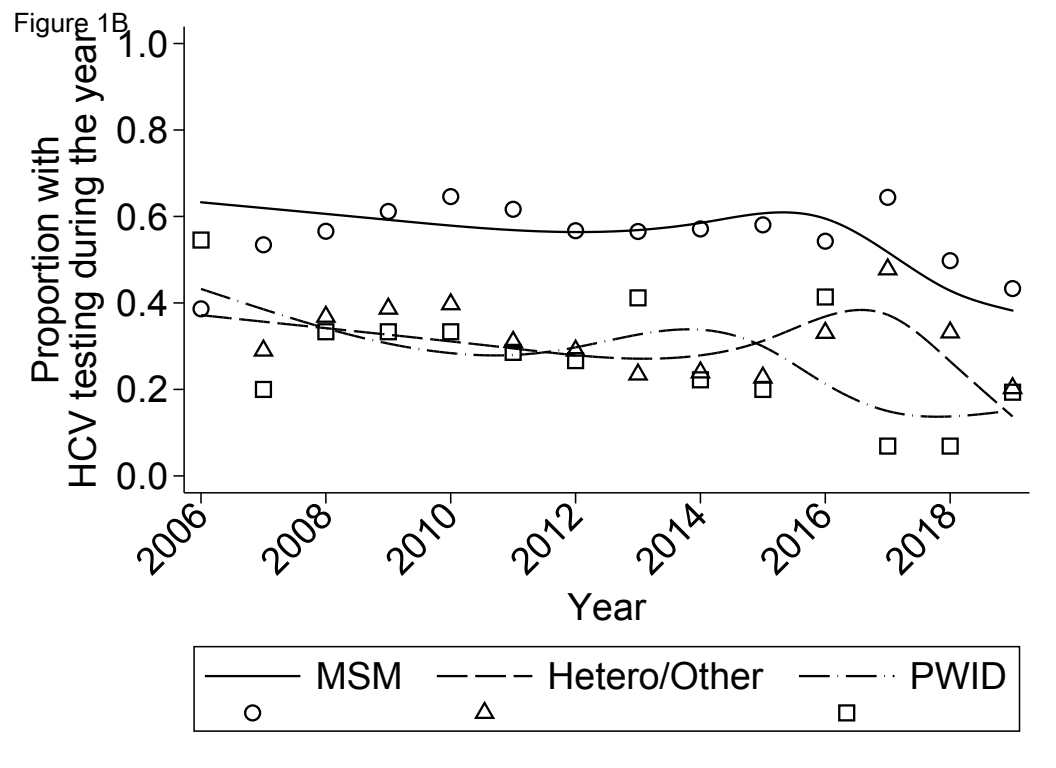

Proportion with HCV testing during the year
1.0
0.8
0.6
0.4
0.2
0.0
2006
2008
2010
2012
2014
2016
2018
Year
MSM
Hetero/Other
PWID

Figure 2A

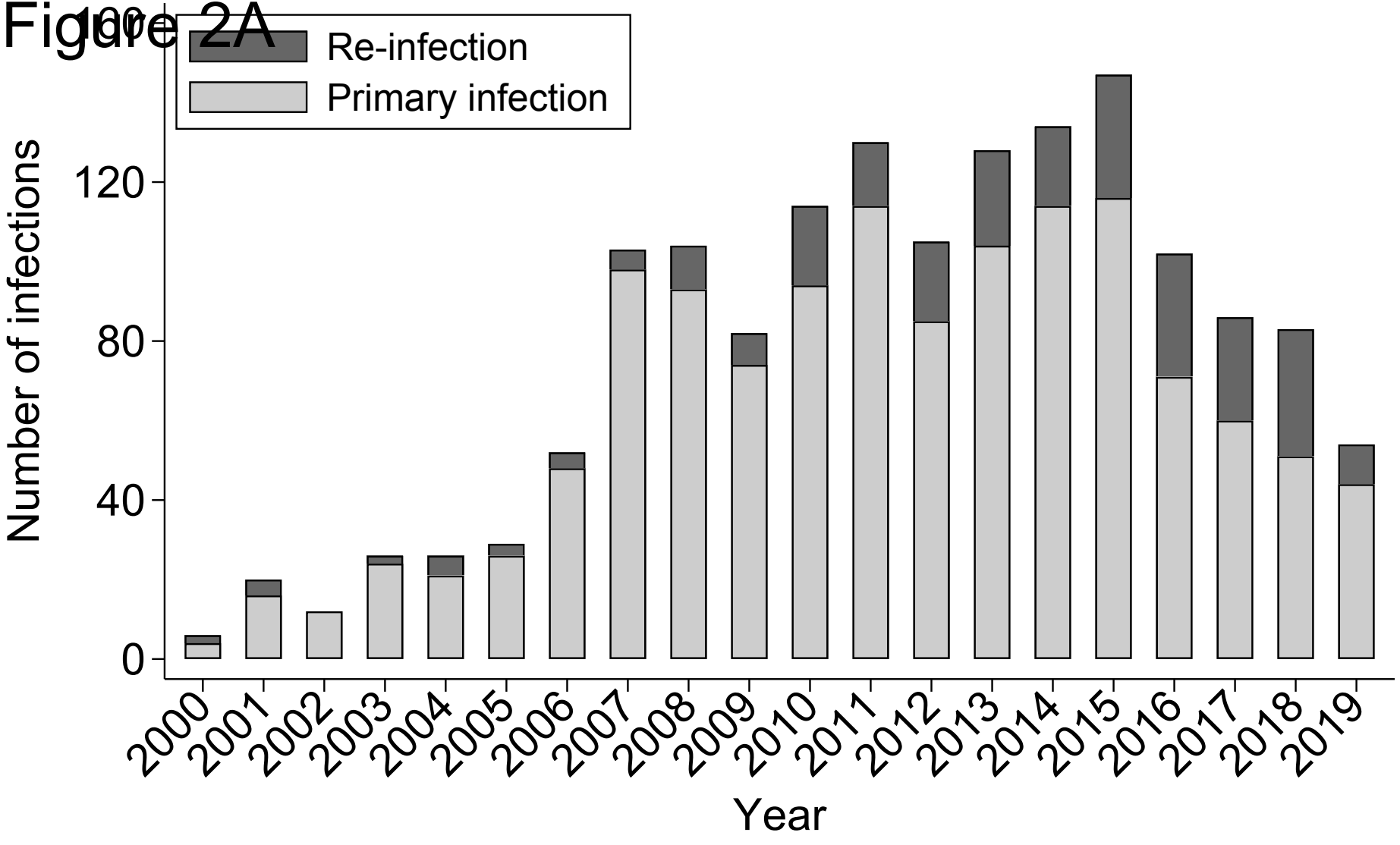

Re-infection
Primary infection
Number of infections
0
40
80
120
160
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
Year

Figure 2B

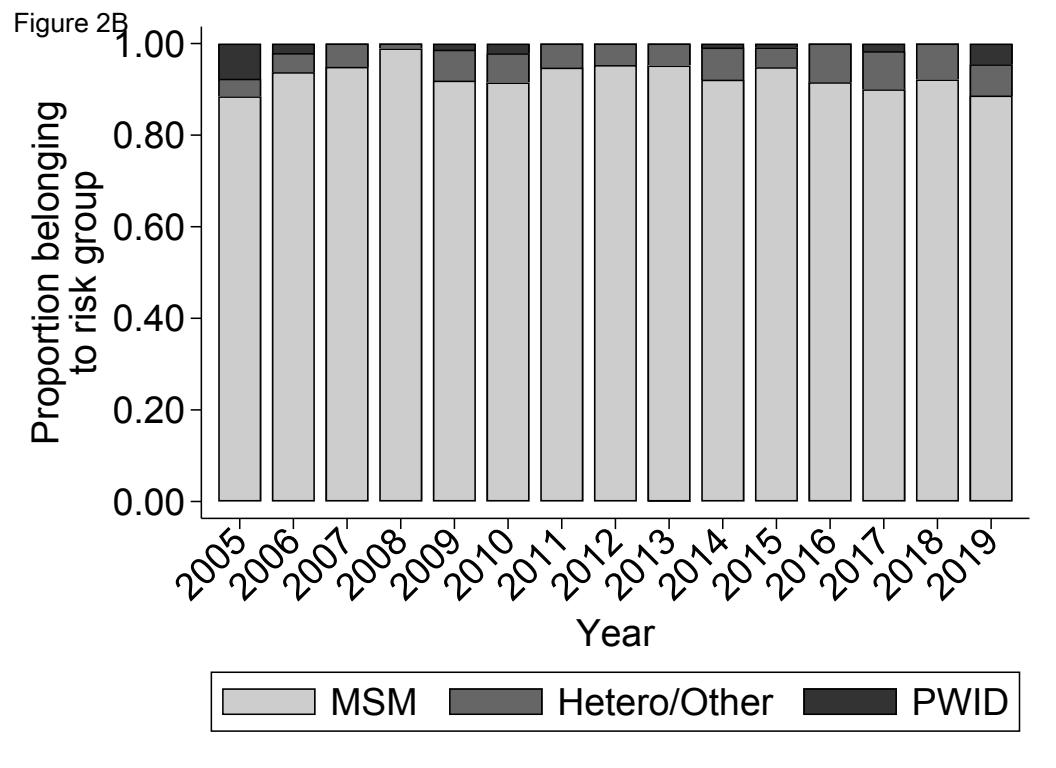

Proportion belonging to risk group
1.00
0.80
0.60
0.40
0.20
0.00
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
Year
MSM
Hetero/Other
PWID

Figure 2C

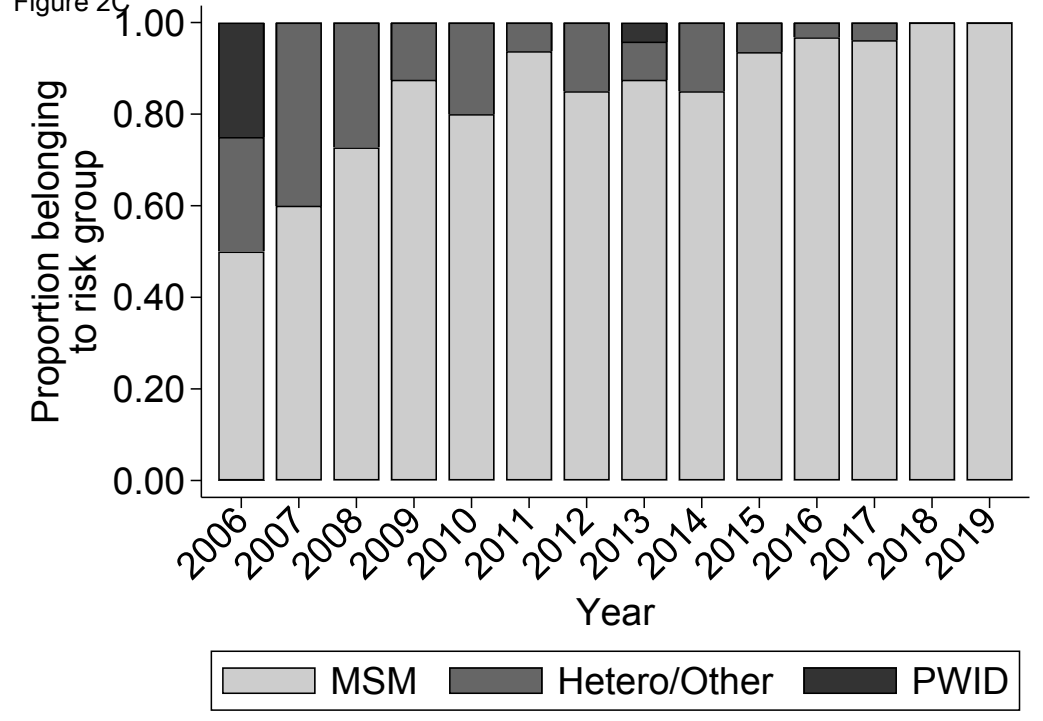

Proportion belonging to risk group
1.00
0.80
0.60
0.40
0.20
0.00
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
Year
MSM
Hetero/Other
PWID

Figure 3A

Incidence (per 1000 py)
20.0
15.0
10.0
5.0
0.0
Year 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019
PYO 3430 3781 4176 4540 4925 5410 5956 6495 7097 7684 8263 8819 9343 9766 10150 10467 10743 10991 11107 9527

Figure 3B

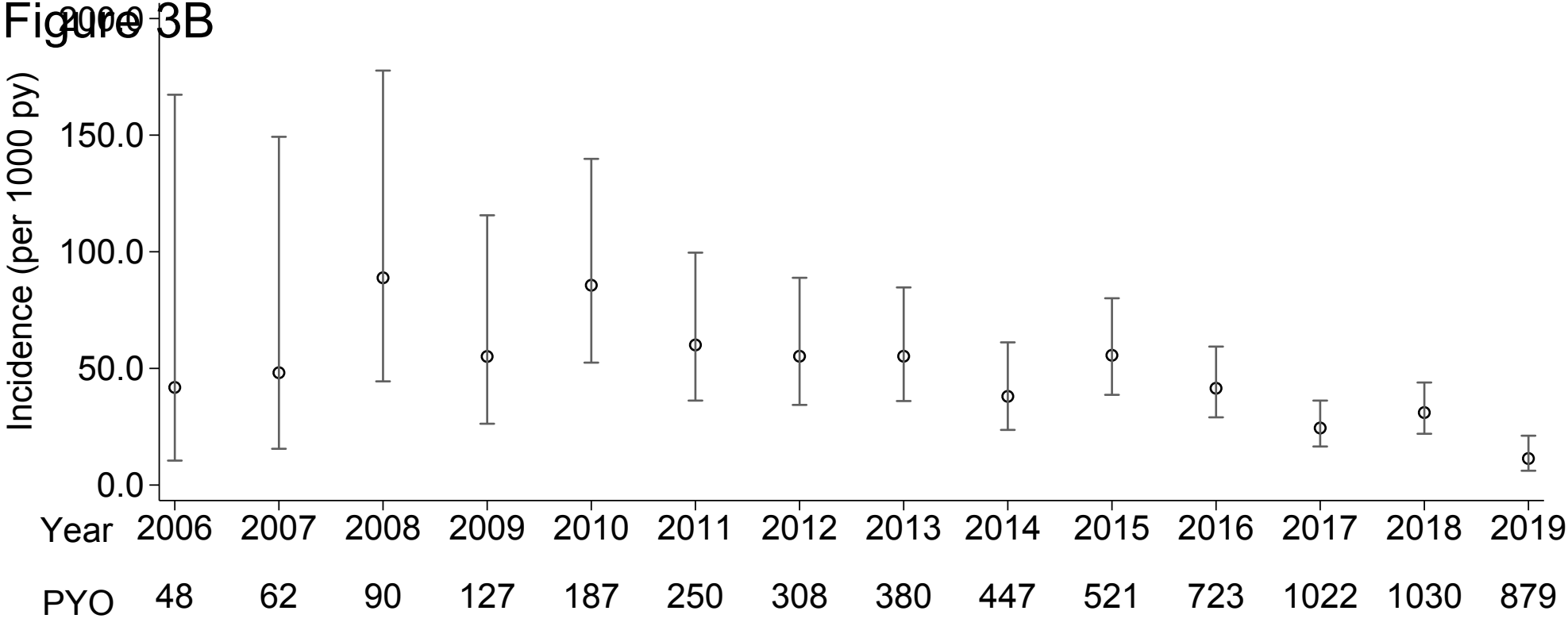

Incidence (per 1000 py)
200.0
150.0
100.0
50.0
0.0
Year 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019
PYO 48 62 90 127 187 250 308 380 447 521 723 1022 1030 879

Figure 4A

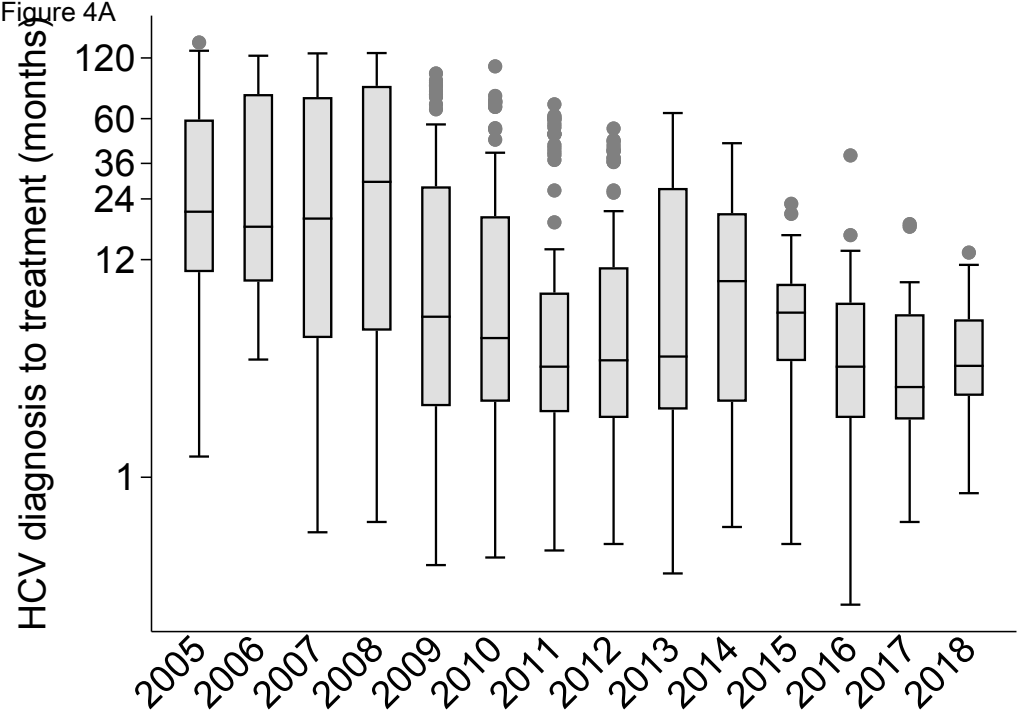

HCV diagnosis to treatment (months)
120
60
36
24
12
1
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018

Figure 4B

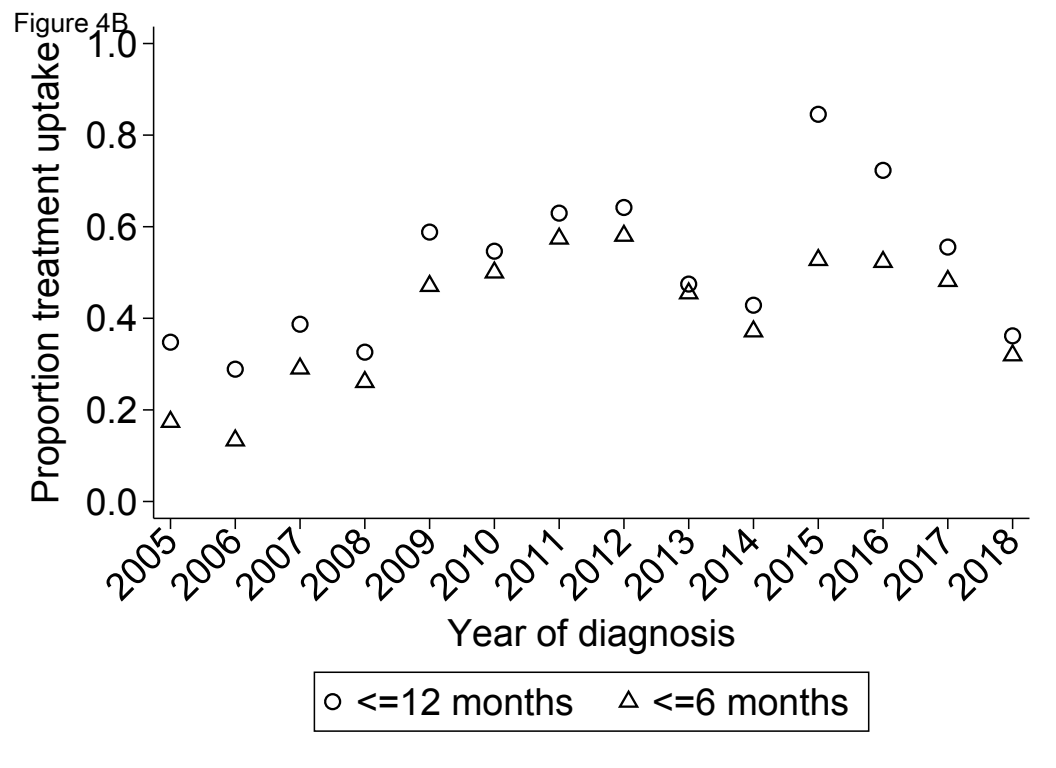

Proportion treatment uptake
0.0
0.2
0.4
0.6
0.8
1.0
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
Year of diagnosis
<=12 months
<=6 months

Figure 4C

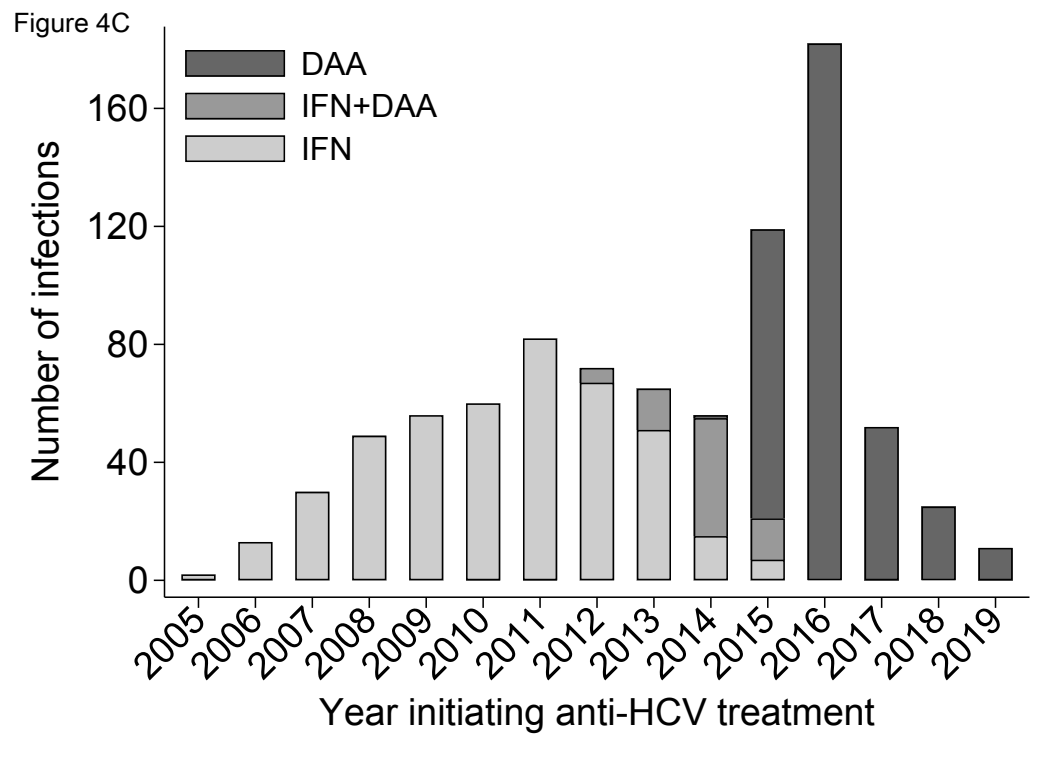
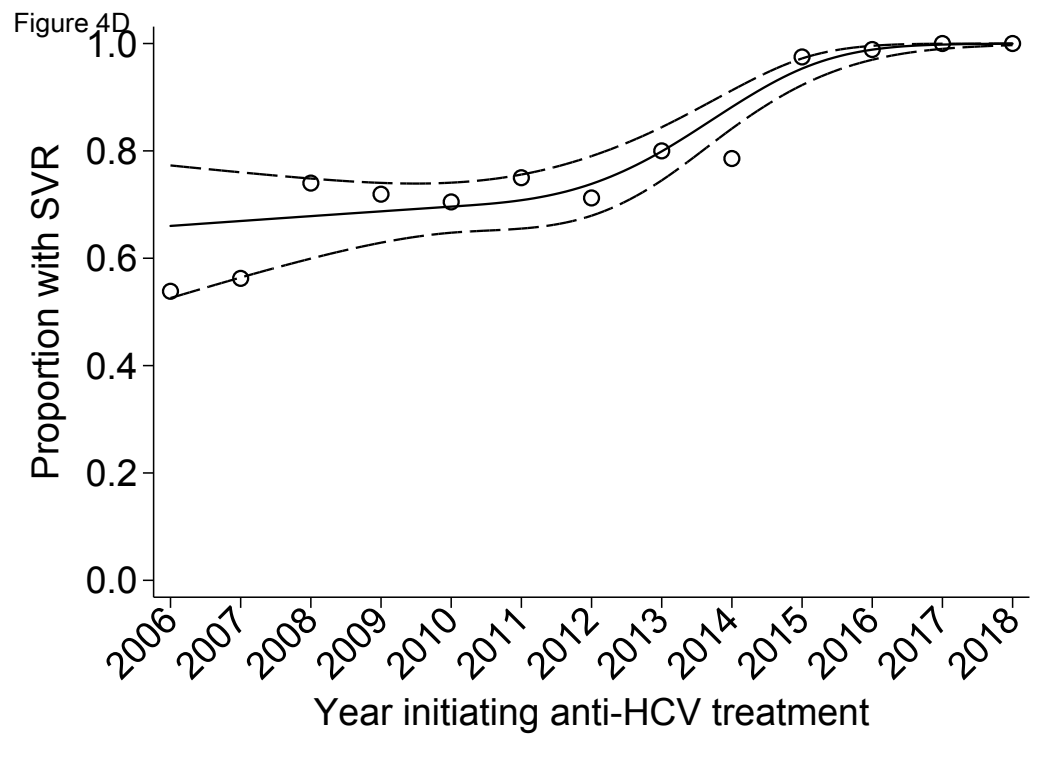

DAA
IFN+DAA
IFN
Number of infections
0
40
80
120
160
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
Year initiating anti-HCV treatment

Figure 4D


Proportion with SVR
0.0
0.2
0.4
0.6
0.8
1.0
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
Year initiating anti-HCV treatment

SUPPLEMENTARY MATERIALS

Supplement to: Smit C, Boyd A, Rijnders BJA, et al. HCV micro-elimination in HIV-positive individuals in the Netherlands 4 years after universal access to direct-acting antivirals: a retrospective cohort analysis

TABLE OF CONTENTS

SUPPLEMENTARY METHODS

Incidence rates with respect to determinants

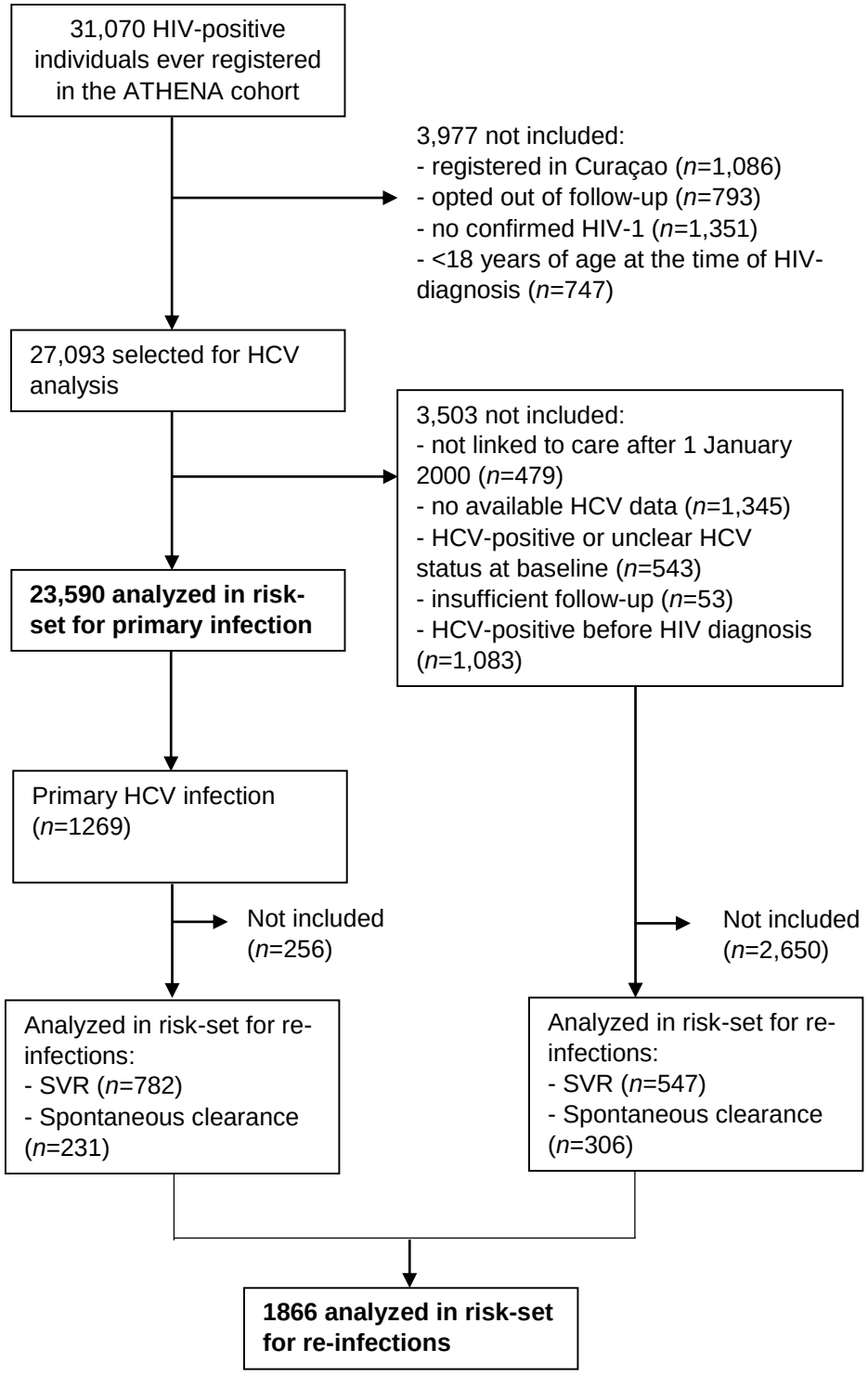
In individuals with primary HCV infection or HCV re-infection, mean age, HIV-RNA viral load, and CD4+ cell count, along with their 95%CI, were estimated across calendar years using linear regression. In additional models, we estimated IR as a function of calendar year and age (as a restricted cubic spline with 5 knots) to obtain predicted IR across age, and as a function of calendar year, HIV-RNA (log10 copies per mL) and CD4+ (squared-root cells per μL) to obtain predicted IR across levels of HIV-RNA and CD4+ cell count.

Model for treatment outcomes

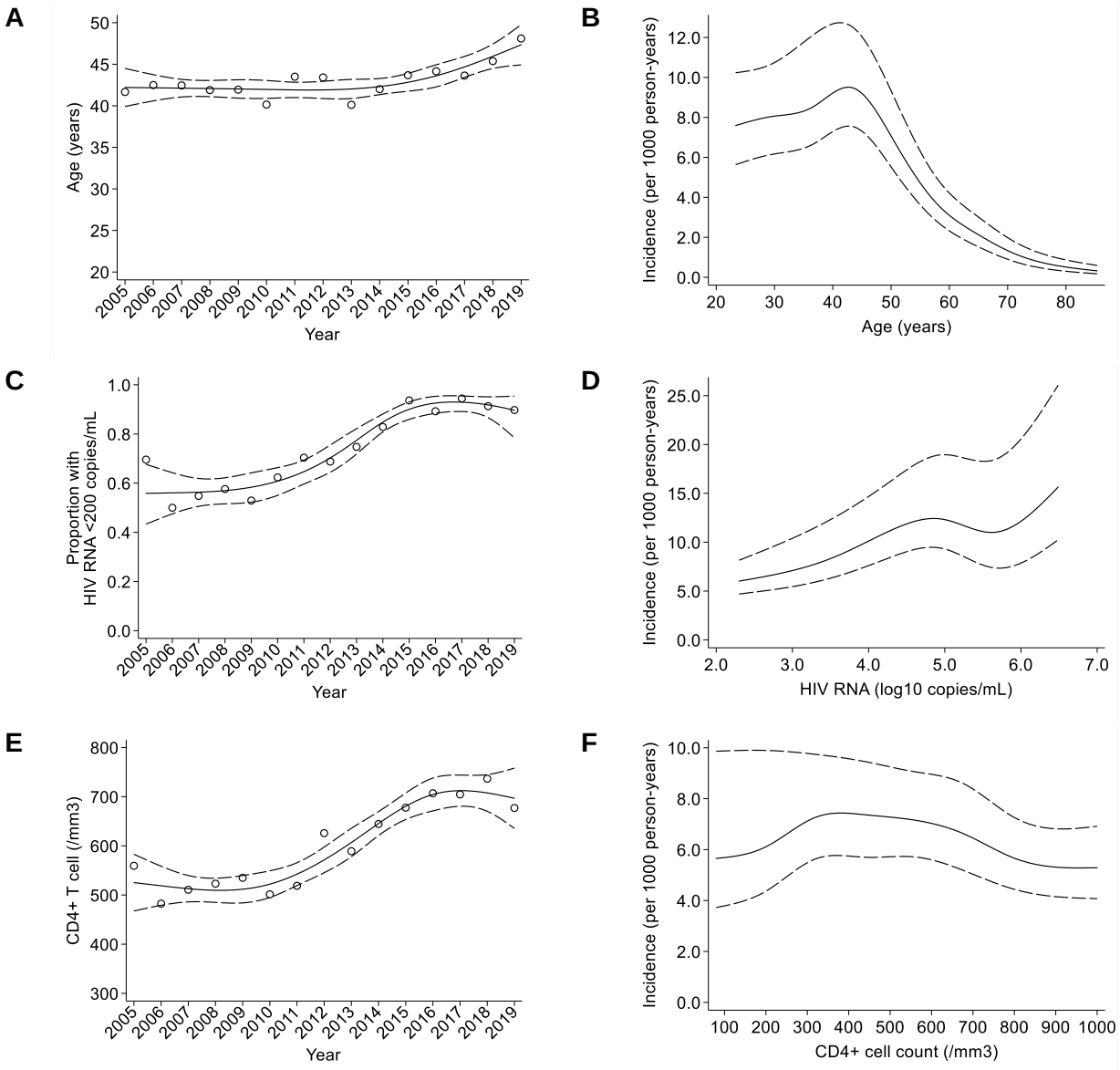
The proportion initiating treatment <12 and <6 months after first anti-HCV-positive antibody test for primary infection and first HCV-RNA-positive test for re-infection (i.e. treatment uptake) and proportion of those treated reaching SVR were estimated across calendar years using logistic regression model. For these models, calendar year was modelled using restricted cubic splines with 3 knots.

SUPPLEMENTARY FIGURES

Supplementary Figure S1. Patient flow

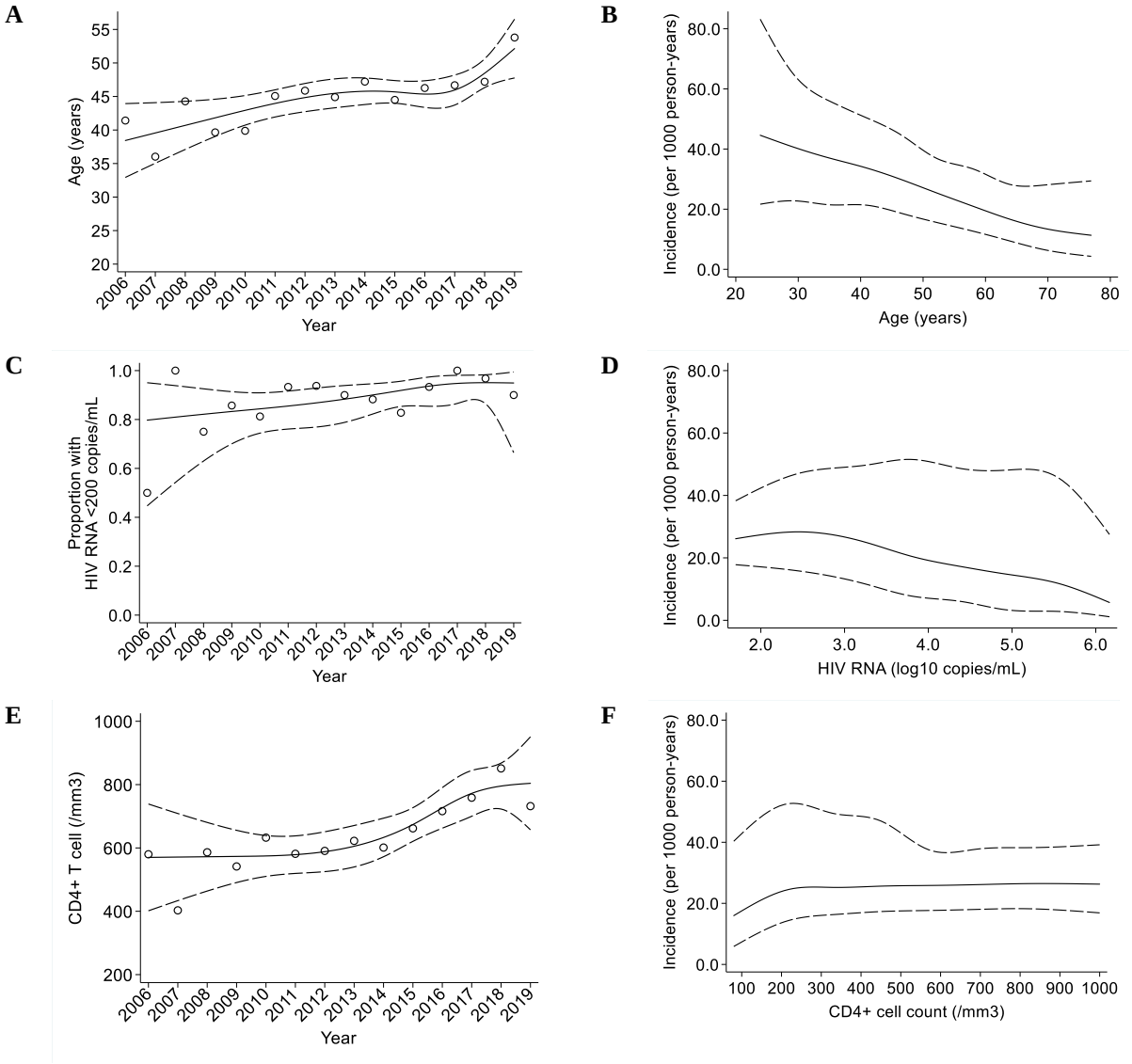


Supplementary Figure S2. Characteristics of men who have sex with men (MSM) with a primary HCV infection across calendar years and incidence of primary infection in relation to age, HIV-RNA and CD4



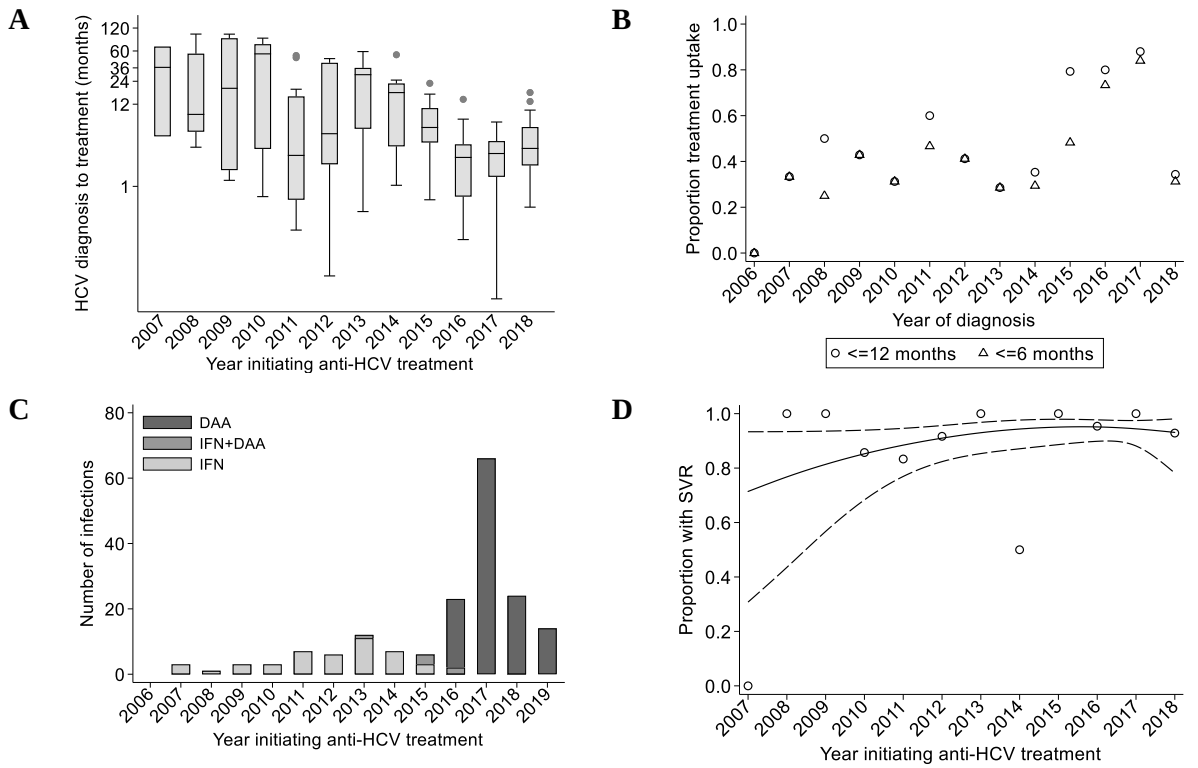
Mean age at primary hepatitis C virus (HCV) infection is given across calendar year (A), while the incidence rate (IR) for all MSM at risk is given as a smoothed function of age (B). Proportion with HIV-RNA <200 copies at primary HCV infection is given across calendar year (C) and IR for all MSM at risk is given according to HIV-RNA levels (D). Mean CD4+ T cell count at primary HCV infection is given across calendar year (E) and IR for all MSM at risk is given according to CD4+ levels (F). For all plots, fitted lines are represented as solid lines and 95% confidence intervals as dashed lines.

Supplementary Figure S3. Characteristics of men who have sex with men (MSM) with an HCV re-infection across calendar years and incidence of re-infection in relation to age, HIV-RNA and CD4



Mean age at hepatitis C virus (HCV) re-infection is given across calendar year (**A**), while the incidence rate (IR) for all at risk individuals is given as a smoothed function of age (**B**). Proportion with HIV RNA <200 copies per mL at HCV re-infection is given across calendar year (**C**) and IR for all at risk individuals is given according to HIV RNA levels (**D**). Mean CD4+ T cell count at HCV re-infection is given across calendar year (**E**) and IR for all at risk individuals is given according to CD4+ levels (**F**). For all plots, fitted lines are represented as solid lines and 95% confidence intervals as dashed lines.

Supplementary Figure S4. Treatment of re-infections across calendar years in HIV-positive men who have sex with men (MSM)



Data include only HIV-positive MSM with hepatitis C virus (HCV) re-infection. Box-plots of time from diagnosis of HCV re-infection to anti-HCV treatment are depicted across years at which treatment began in (**A**). The proportion of treatment uptake (i.e. defined as treatment initiation within 6- or 12-months after diagnosis of HCV re-infection) is depicted across year of HCV-diagnosis in (**B**). The numbers of HCV re-infections treated with only interferon (IFN), combined IFN and the direct-acting antivirals (DAA) (boceprevir or telaprevir for this category), or only DAAs are depicted across years at which treatment began (**C**), along with the proportion of treated individuals achieving sustained virological response (SVR) (**D**). Fitted lines (solid) along with 95% confidence intervals (dashed lines) are given for proportion with treatment uptake and with SVR.

SUPPLEMENTARY INFORMATION

List of ATHENA study group members

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Bax, E.C.M. van Gorp, N.C. de Jong-Peltenburg, M. de Mendonça Melo, E. van Nood, J.L. Nouwen, B.J.A. Rijnders, C. Rokx, C.A.M. Schurink, , L. Slobbe, A. Verbon. HIV nurse consultants: N. Bassant, J.E.A. van Beek, M. Vriesde, L.M. van Zonneveld. Data collection: J. de Groot. HIV clinical virologists/chemists: C.A.B. Boucher, M.P.G Koopmans, J.J.A van Kampen. **Flevoziekenhuis, Almere:** HIV treating physicians: J. Branger*, R.A. Douma. HIV nurse consultant: A.S. Cents-Bosma, C.J.H.M. Duijf-van de Ven. **HagaZiekenhuis, Den Haag:** HIV treating physicians: E.F. Schippers*, C. van Nieuwkoop. HIV nurse consultants: J.M. van IJperen, J. Geilings. Data collection: G. van der Hut. HIV clinical virologist/chemist: N.D. van Burgel. **HMC (Haaglanden Medisch Centrum), Den Haag:** HIV treating physicians: E.M.S. Leyten*, L.B.S. Gelinck, F. Mollema. HIV nurse consultants: S. Davids-Veldhuis, C. Tearno, G.S. Wildenbeest. HIV clinical virologists/chemists: E. Heikens. **Isala, Zwolle:** HIV treating physicians: P.H.P. Groeneveld*, J.W. Bouwhuis, A.J.J. Lammers. HIV nurse consultants: S. Kraan, A.G.W. van Hulzen, M.S.M. Kruiper. Data collection: G.L. van der Bliek, P.C.J. Bor. HIV clinical virologists/chemists: S.B. Debast, G.H.J. Wagenvoort. **Leids Universitair Medisch Centrum, Leiden:** HIV treating physicians: F.P. Kroon*, M.G.J. de Boer, H. Jolink, M.M.C. Lambregts, A.H.E. Roukens, H. Scheper. HIV nurse consultants: W. Dorama, N. van Holten. HIV clinical virologists/chemists: E.C.J. Claas, E. Wessels. **Maasstad Ziekenhuis, Rotterdam:** HIV treating physicians: J.G. den Hollander*, R. El Moussaoui, K. Pogany. HIV nurse consultants: C.J. Brouwer, J.V. Smit, D. Struik-Kalkman. Data collection: T. van Niekerk. HIV clinical virologists/chemists: O. Pontesilli. **Maastricht UMC+, Maastricht:** HIV treating physicians: S.H. Lowe*, A.M.L. Oude Lashof, D. Posthouwer, M.E. van Wolfswinkel. HIV nurse consultants: R.P. Ackens, K. Burgers, J. 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