Incidence of sexually transmitted hepatitis C virus infection in HIV-positive MSM: a systematic review and meta-analysis

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Objective: The epidemiology of the incidence of sexually transmitted hepatitis C virus (HCV) infection in HIV-positive MSM is only partially understood. In the presence of HIV, HCV infection is more likely to become chronic and liver fibrosis progression is accelerated.

Design: A systematic review and meta-analysis was used to synthesize data characterizing sexually transmitted HCV in HIV-positive MSM.

Methods: Electronic and other searches of medical literature (including unpublished reports) were conducted. Eligible studies reported on HCV seroconversion or on reinfection postsuccessful HCV treatment in HIV-positive MSM who were not injecting drugs. Pooled incidence rates were calculated using random-effects meta-analysis, and meta-regression was used to assess study-level moderators. Attributable risk measures were calculated from statistically significant associations between exposures and HCV seroconversion.

Results: More than 13 000 HIV-positive MSM in 17 studies were followed for more than 91 000 person-years between 1984 and 2012; the pooled seroconversion rate was 0.53/100 person-years. Calendar time was a significant moderator of HCV seroconversion, increasing from an estimated rate of 0.42/100 person-years in 1991 to 1.09/100 person-years in 2010, and 1.34/100 person-years in 2012. Reinfection postsuccessful HCV treatment ($n = 2$ studies) was 20 times higher than initial seroconversion rates. Among the seroconverters, a large proportion of infections were attributable to high-risk behaviours including mucosally traumatic sex and sex while high on methamphetamine.

Conclusion: The high reinfection rates and the attributable risk analysis suggest the existence of a subset of HIV-positive MSM with recurring sexual exposure to HCV. Approaches to HCV control in this population will need to consider the changing epidemiology of HCV infection in MSM.

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Keywords: epidemiology, hepatitis C, HIV, homosexuality, incidence, male, meta-analysis, sexually transmitted diseases

Introduction

Since 2000, there have been multiple reports of outbreaks of sexually transmitted acute hepatitis C virus (HCV) infection in HIV-positive MSM in urban areas of North America, Europe, Australia and Asia [1,2]. Acute HCV infection is more likely to become persistent in the presence of HIV, and liver fibrosis progression in chronic HCV infection is more rapid even in patients with undetectable HIV viral loads [3]. The evidence points to blood as the medium of sexual HCV exposure in these cases [4–9]. Several factors facilitate excess HCV

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transmission in HIV-positive MSM compared with other populations in which sexual transmission is very rare [10]. HCV viral loads are higher in semen and blood in the presence of HIV, and this may increase the likelihood that infectious carriers will transmit HCV infection [11,12]. Mucosally traumatic sexual practices, erosive genital lesions associated with sexually transmitted infections (STIs) and increased sexual disinhibition and prolonged periods of sexual activity related to the use of stimulant drugs may cause blood exposure during sex [8,10,13].

The purpose of this systematic review and meta-analysis was to synthesize data characterizing the incidence of sexual HCV transmission in HIV-positive MSM and to examine study-level influences on HCV seroconversion rates including calendar time and risk of selection bias. In addition, data on individual risk behaviours were assessed in terms of the strength of the association with HCV seroconversion and the factor's contribution to new HCV infections in the HIV-positive MSM population. Rates of HCV reinfection following successful treatment were also synthesized. Extensive knowledge exists regarding HCV transmission via illicit drug use related exposures, so the examination of drug use in the cause of HCV infection in HIV-positive MSM was limited to its role as a facilitator of transmission via sex-related exposures.

Materials and methods

A detailed description of the methods for this systematic review and meta-analysis has been published [14], so a summary is provided here; in general, the methods followed published guidelines [15,16]. The study protocol was also registered with the International Register of Prospective Systematic Reviews (PROSPERO; registration number CRD42013006462).

Search strategy

The search strategy was developed in consultation with a medical librarian. PubMed, EMBASE and BIOSIS databases were searched using terms that covered the themes HCV, HIV/AIDS, MSM, epidemiology, reinfection and transmission. Unpublished reports were located by searching conference proceedings (e.g. American Association for the Study of Liver Diseases, European Association for the Study of the Liver, International Conference on HIV/AIDS and Conference on Retroviruses and Opportunistic Infections), investigators' personal files and reference lists of reviews and related articles. Those conducting the search, screening and data coding had graduate training in research methodology and additional training in HCV epidemiology and systematic review and meta-analysis methods. The search encompassed English-language reports published or made available from January 1990 (after the HCV agent was discovered) through 28 February 2015. Of note, no potentially eligible, non-English language reports were encountered. In eight cases wherein reports were missing, key data and authors were contacted, and four (50%) responded and provided data.

Eligibility criteria and screening

Published and unpublished quantitative studies reporting incidence of HCV seroconversion and re-infection post-SVR (in the form of either incidence density or cumulative incidence rates) in male individuals who were HIV-positive and reported having sex with other men (HIV-positive MSM) were included. Studies reporting on factors associated with seroconversion in this population without incidence estimates, that is case–control studies, were also included. Reports that did not explicitly state that they excluded participants who practiced injection drug use during the period when infection likely occurred or did not provide separate estimates on noninjecting MSM were ineligible, because transmission via parenteral exposure is far more efficient and inclusion of these participants would have led to error in estimates of sexual transmission, towards higher rates [17,18].

All reports must have used laboratory tests to ascertain HCV infection. Studies must have also met the European AIDS Treatment Network (European NEAT) Acute Hepatitis C Infection Consensus Panel preferred criteria for determining acute HCV or seroconversion [19], that is seroconversion or positive HCV RNA following a documented negative HCV RNA or negative HCV antibody test in the previous 12 months. Reinfection following treatment of HCV and SVR was defined as a change in genotype or to a different HCV clade as determined by phylogenetic analysis.

Data coding and quality ratings

The number of reports retrieved via the search, the number eligible and reasons for ineligibility were recorded (Fig. 1). Study years and location, features of the study design and characteristics of the sample were abstracted from each report. In addition to cumulative incidence and incidence density estimates of HCV infection and re-infection, crude and adjusted measures of associations between infection and relevant exposures were also collected.

Screening and data collection protocols were pilot-tested until there was perfect agreement in determination of eligibility and data abstraction among the principal investigator, project director and research assistant. In addition, all screening and coding was reviewed for accuracy and completeness by the project director.

Studies were assigned quality ratings on the basis of the Newcastle-Ottawa Scale, which assesses the likelihood of bias due to selection of study participants, misclassification and the likelihood of confounding in measures of

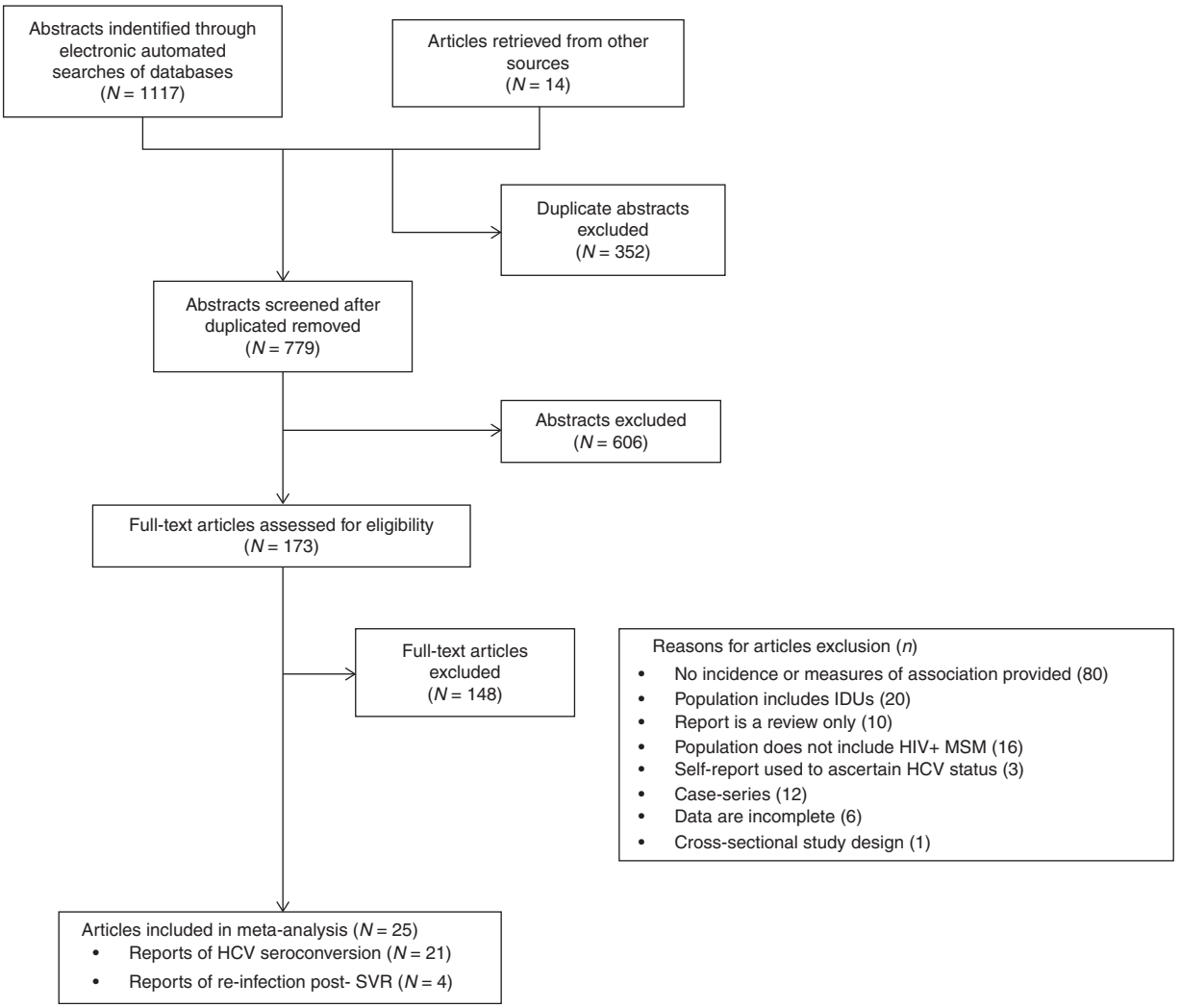

Fig. 1. PRISMA flow diagram of included studies.

association [20]. For this analysis, emphasis was placed on assessment of selection bias, to understand the extent to which the data may over or underestimate incidence rates by virtue of individual-recruitment procedures. In assessing comparability, that is the validity of associations between exposures and HCV infection, higher quality ratings were given to reports that adjusted for confounding, in particular those that used data-based criteria to select covariates for adjustment [21,22]. Misclassification of exposure and outcome was addressed primarily by the exclusion of IDUs and by the use of the European NEAT criteria.

Data analysis

Pooled hepatitis C virus seroconversion rates and study-level moderators

Cumulative incidence measures were included in tables but not in the pooled estimates. In some cases, raw data in the reports were used to calculate the number of person-years and the 95% confidence intervals (95% CIs) around the rates (using Poisson estimation). Cochrane's Q statistic was used to determine whether observed heterogeneity in rates was compatible with chance, and inconsistency was quantified using the I^2 statistic [23]. Pooled incidence rates and 95% CIs were calculated using random-effects meta-analysis calculated via linear mixed-effects model in the *metafor* package of R [24,25]. The same method was used to calculate pooled rates of re-infection post-HCV treatment and SVR. A forest plot was created using the *ggplot2* package [26] of the R statistical computing environment [27].

Study-level covariates were defined by available information from each study; covariate selection was ultimately limited by lack of homogeneous subsets across studies and low reporting of covariates in the studies. However, some data were available for examination. Calendar time was examined as a potential moderator of seroconversion rates. Six reports included HCV incidence rates for individual years. Other reports gave

incidence rates for intervals spanning fewer than 4 years; we assigned the midpoint study year to these rates to permit the inclusion of additional data points in the analysis of incidence trends over time. One study [28] included a plot of incidence over time for individual years as well as numerical incidence rates for the first and last study years (1998 and 2011); observing essentially no change from 1998 to 2008 and then a linear increase to the 2011 incidence rate, we held the incidence rate constant from 1998 to 2008 and then interpolated (i.e. constructed intermediate data points) incidence rates between 2008 and 2011 to estimate annual rates. Degree of precision for interpolated incidence estimates was held constant across study years based on the confidence bands in the plot and the Swiss HIV Cohort Study methodology. Selection bias was also examined as a study-level moderator of incidence. Selection method was categorized as convenience vs. consecutive sampling, under the assumption that convenience sampling may have led to over-representation of those at an elevated risk of HCV.

In a separate analysis, selection bias and year of data collection were included as incidence rate moderators in a meta-regression analysis. Convenience sampling was dummy coded with consecutive sampling as the reference category, making the intercept an estimate of incidence among studies with potentially less-biased sampling, and the coefficient for sampling bias an estimate of the increase in incidence rate due to convenience sampling. To allow for curvature in the trend of incidence rates over time, linear and quadratic polynomial terms were included in the meta-regression analysis of year of data collection. Year of data collection was centred at 2010, making the intercept an estimate of incidence in 2010 and the linear term an estimate of the slope in 2010. Fitted values (predictions) of HCV incidence were calculated from the fixed-effects coefficients of meta-regression results, with standard errors and 95% CIs of predictions taking into account sampling error within and across studies [24].

Individual risk behaviours

Several studies, including the case–control studies, reported the association between HCV seroconversion and behavioural factors. However, there was little consistency across studies in the way factors were analysed, which precluded pooling effect size estimates. Therefore, behavioural risk data were summarized in a table showing adjusted estimates of their association with HCV seroconversion. Using standard formulas, attributable risk measures were calculated for factors with a statistically significant association with HCV seroconversion after adjustment, because it was reasonable to conclude that some fraction of disease could be attributed to them [29]. The attributable risk percentage in the underlying HIV-positive MSM population (population attributable risk percentage, PAR%) was also calculated by standard methodology, using the prevalence of exposure to the factor in question among the control (nonseroconverter) participants to estimate population prevalence [29].

Results

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [30]) flow diagram describes each phase of this study's systematic review of HCV incidence among HIV-positive MSM (Fig. 1). A total of 1117 potentially eligible reports were identified through the search of electronic databases; another 14 were located through searches of conference abstracts and other sources. After excluding 352 duplicates, the remaining 779 abstracts were screened and a subset (173) was reviewed as full-text articles. After this screening step, 21 reports of HCV seroconversion [4,7,28,31–48] and four reinfection reports [49–52] were eligible. Reasons for ineligibility are also shown in Fig. 1.

Seventeen of the 21 eligible studies of HCV seroconversion (81%) provided incidence density data (*n* seroconversions, *n* person-years) that could be used to calculate pooled rates; three out of 17 were conference abstracts. Two were case–control studies that reported on the association between HCV seroconversion and exposures. Two reports [28,41] were from the Swiss HIV Cohort Study (http://www.shcs.ch/) and two were from the Amsterdam Cohort Study (https://www.amsterdamcohortstudies.org/acsc/index.asp) and so only one estimate of incidence from each cohort [28,47] was included in the calculation of the pooled rate, leaving 15 unique estimates of incidence density. As summarized in Table 1, cohort study periods spanned 1984–2012; this included the testing of stored sera after HCV screening tests became available [53]. Half of the studies were from Europe, four from the USA, three from Asia and two from Australia. All took place in high-income countries and in urban settings. In the majority of studies, convenience sampling was used to select study participants; consecutive sampling was used in six cases. In 55% of reports, participants were recruited from HIV clinics. Other recruitment locations included hospitals, STI clinics, 'social venues for MSM' and community-based organizations. Each study's inclusion criteria are described in Table 1.

Pooled hepatitis C virus seroconversion rates and study-level moderators

More than 13 000 individuals were followed in 15 unique studies to observe 497 cases of HCV seroconversion over 93 100 person-years using incidence density estimation (Fig. 2). HCV incidence rates ranged from 0.00/100 to 1.40/100 person-years. The pooled incidence rate was 0.53/100 person-years (95% CI 0.49–0.58). In a

Table 1. Studies reporting hepatitis C virus incidence among HIV-positive MSM and men do not inject drugs.

Ref.	Location	Selection method/ Study design	Recruitment setting	Inclusion/exclusion criteria; All: HIV-positive MSM, noninjector	No. of individuals	Study dates	Total person-years	HCV incidence/100 PY (95% CI)
Barfod *et al.*, Danish HIV Cohort Study [31]	Copenhagen, Denmark	Consecutive sampling/ Prospective cohort	HIV clinics	Aged 16 years or older Excluded all who used drugs except marijuana	871	2006–2009	3513.51	0.37 (0.22–0.63)
Brooks *et al.*, 2010 HIV Outpatient Study [32]	Multisite, USA	Convenience sampling/ Prospective cohort	HIV clinics		Not specified	2000–2008	3902	1.23 (0.53–1.93)
Coffin *et al.* [33]	Seattle, USA	Consecutive sampling/ Cross-sectional	HIV clinic		477	Prior to 2012	2921	0.89 (0.61–1.30)
Fox *et al.* [34]	London, United Kingdom	Not specified	Hospital	Evidence of HIV acquisition within previous 6 months	155	1999–2006	unspecified	7% cumulative incidence/8 years
Gamage *et al.* [35]	Melbourne, Australia	Consecutive sampling/ Retrospective cohort	HIV clinic	Anti-HCV negative >6 months after HIV diagnosis	581	2002–2010	4018	0.60 (0.40–0.80)
Jin *et al.*, Health in Men Study [36]	Sydney, Australia	Convenience sampling/ Prospective cohort	Gay community events and venues, HIV clinics, referrals and so on	Sex with at least 1 man in previous 5 years	129	2005–2007	202.1	0.00 (0.00–0.02)
Lin *et al.* [37]	Hong Kong, China	Consecutive sampling/ Prospective cohort	HIV clinic		1311	1999–13	6295	0.22 (0.12–0.37)
						1999–2002		0.13
						2002–2007		0.19
						2008–2013		0.47
Nishijima *et al.* [38]	Tokyo, Japan	Convenience sampling/ Prospective cohort	HIV clinic	Aged 18 years or older Excluded patients who visited the clinic for a second opinion	716	2005–2012	2146	0.792 (0.49–1.26)
						2005–2006	258	0
						2007–2008	650	0.15 (0.03–0.86)
						2009–2010	747	0.80 (0.37–1.74)
						2011–2012	495	2.02 (1.10–3.68)
Palacios *et al.* [39]	Andalusia, Spain	Consecutive sampling/ Cross-sectional	Infectious disease or internal medicine clinics in 7 hospitals	Excluded those with history of blood transfusion since 1992	727	2006	5263.16	0.19 (0.13–0.47)
Puoti *et al.*, Icona Cohort Study [40]	Multisite, Italy	Convenience sampling/Not specified	71 infectious disease wards		Not specified	1997–2012	6020	1.40 (1.1–1.7)
						1997	45	6.67 (2.29–17.86)
						1998	265.6	1.13 (0.39–3.27)

Table 1 (*continued*)

Ref.	Location	Selection method/ Study design	Recruitment setting	Inclusion/exclusion criteria; All: HIV-positive MSM, noninjector	No. of individuals	Study dates	Total person-years	HCV incidence/100 PY (95% CI)
						1999	315.5	1.27 (0.50–3.21)
						2000	339.7	2.06 (1.00–4.19)
						2001	400	0.50 (0.14–1.80)
						2002	429.9	1.86 (0.95–3.63)
						2003	454.1	1.54 (0.75–3.15)
						2004	475.6	0.84 (0.33–2.14)
						2005	460.8	2.17 (1.18–3.95)
						2006	414.8	0.96 (0.37–2.45)
						2007	415.9	0.72 (0.24–2.10)
						2008	441.6	0.68 (0.23–1.98)
						2009	462.1	0.87 (0.34–2.21)
						2010	474	3.38 (2.09–5.42)
						2011	438.5	1.60 (0.77–3.25)
						2012	187	0
Rauch *et al.* [41]	Multisite, Switzerland	Not specified	Hospitals and clinics		1571	2000–2004	4142	0.338 (0.20–0.57)
Richardson *et al.* [42]	Brighton, United Kingdom	Consecutive sampling/ Cross-sectional	Sexual health clinics		Not specified	2000–2006	1361	1.18 (0.73–1.91)
						2000–2003	not specified	0.59
						2004	not specified	1.11
						2005	not specified	1.14
						2006	not specified	1.75
Sobrino-Vegas *et al.*, CoRIS Study [43]	Multisite, Spain	Not specified/ Prospective cohort	Healthcare centres	Excluded patients with <2 years follow-up	3621	2004–2011	3620.7	0.58 (0.36–0.89)
						2004–2005	263.2	1.14 (0.24–3.33)
						2006–2007	882.4	0.68 (0.25–1.48)
						2008–2009	1363.6	0.66 (0.30–1.25)
						2010–2011	1071.4	0.28 (0.06–0.82)
Sun *et al.* [44]	Taipei, Taiwan	Not specified	Hospital (inpatient and outpatient clinics)		731	1994–2010	3025.9	0.925 (0.64–1.34)
						1994–2000	137.73	0
						2001–2005	858.8	0.349 (0.07–1.02)
						2006–2010	2029.4	1.23 (0.80–1.82)
Van de Laar *et al.*, Amsterdam Cohort Study [7]	Amsterdam, Netherlands	Convenience sampling/ Prospective cohort	STD clinic, 'social venues for MSM', chain referral, hospital case reports	At least one male sex partner in 6 months preceding enrolment	491	1984–2003	4408	0.18 (0.08–0.36)
						1984–1999	3836	0.08 (0.02–0.23)
						2000–2003	572	0.87 (0.28–2.03)
Van der Helm *et al.*, CASCADE Cohorts [45]	Europe, Australia, Canada	Not specified/ Prospective cohort	HIV seroconverter cohort studies	Acquired HCV after HIV diagnosis	1354			

Table 1 (*continued*)

Ref.	Location	Selection method/ Study design	Recruitment setting	Inclusion/exclusion criteria; All: HIV-positive MSM, noninjector	No. of individuals	Study dates	Total person-years	HCV incidence/100 PY (95% CI)
						1990	not specified	0.09 (0.005–1.52)
						1995	not specified	0.55 (0.27–1.30)
						2000	not specified	0.80 (0.60–1.88)
						2005	not specified	1.68 (1.03–2.74)
						2007	not specified	2.34 (0.82–6.69)
Vanhommerig *et al.* [47], Amsterdam Cohort Study	Amsterdam, Netherlands	Convenience sampling/ Prospective cohort	STD clinic, 'social venues for MSM', chain referral, hospital case reports	At least one male sex partner in 6 months preceding enrolment	761	1984–2011[a]	6205.38	0.47 (0.33–0.67)
Wandeler *et al.*, Swiss Cohort Study [28]	Multisite, Switzerland	Convenience sampling/ Prospective cohort	Hospitals and clinics		3333	1998–2011	23707	0.43 (0.35–0.52)
						1998	not specified	0.23 (0.08–0.54)
						2011	not specified	4.09 (2.57–6.18)
Witt *et al.*, MACS Study [46]	Multisite, USA	Convenience sampling/ Prospective cohort	Multicentre, various		Not specified	1984–2011	20900	0.34 (0.27–0.43)

CI, confidence interval; HCV, hepatitis C virus; PY, person-years.
[a]The authors provided annual incidence density rates, but these are not shown because the data are unpublished and provided via personal communication.

meta-analysis, selection bias was not a significant moderator of seroconversion rates. Reports using convenience sampling had a pooled rate of 0.65/100 vs. 0.47/100 person-years in reports using consecutive sampling [QM(df = 1) = 0.68, $P = 0.41$]. Significant residual heterogeneity in incidence remained after taking selection bias into account [QE(df = 11) = 153.5597, $P < 0.0001$; $I^2 = 92.60$, 95% CI 83.82–97.51].

Calendar time, however, was a significant moderator of HCV seroconversion rates [QM(df = 2) = 7.50, $P = 0.02$]. Figure 3 includes predictions of HCV incidence on the basis of the meta-regression with calendar time as a moderator, including up to the present year. Estimated annual incidence rates ranged from a low of 0.42/100 person-years in 1991 (95% CI 0.23–0.77) to 1.34/100 person-years in 2012 (95% CI 0.76–2.36). Incidence in 2010 (centred) was 1.09/100 person-years (95% CI 0.73–1.61), and the instantaneous rate of increase in log incidence in 2010 was 0.10 per year (95% CI 0.003–0.197). The quadratic term showed no significant degree of curvature in the log incidence trend ($P = 0.27$). Significant residual heterogeneity in incidence remained after taking calendar time into account [QE(df = 76) = 257.85, $P < 0.0001$; $I^2 = 68.9$, 95% CI 50.53–74.16].

Reinfection following SVR

Four studies reported on HCV reinfection in HIV-positive MSM following HCV treatment and SVR. Two studies provided incidence density estimates of reinfection, 15.2/100 person-years in Amsterdam [50], and 9.6/100 person-years in London [49]. The pooled rate for these two studies was 11.41/100 person-years (95% CI 7.36–17.68). Both of these studies also reported high 2-year cumulative rates of reinfection (25–33%). Two other studies estimated that 16–28% were reinfected post-SVR, but the amount of observation time was not given [51,52].

Risk factors for hepatitis C virus seroconversion

Only 10 of the 21 studies of HCV seroconversion reported on associations with potentially causal exposures (sexual risk behaviour, sex while using noninjection drugs, recent sexually transmitted infection or an HIV-related factor such as whether on antiretroviral therapy, $CD4^+$ cell count or HIV viral load). However, six of the 10 either did not provide adjusted estimates or included IDUs or non-MSM in the risk factor analysis. This left four studies reporting adjusted associations between the potentially causal exposures and HCV seroconversion in HIV-positive MSM [4,28,41,48]. As summarized in Table 2, in the New York City case–control study [48], the adjusted odds ratio (AOR) for receptive anal intercourse without a condom, with ejaculation was 23.0 (95% CI 2.2–243.8) and the proportion of HCV infections in the cases that were attributable to this behaviour was 95.7%

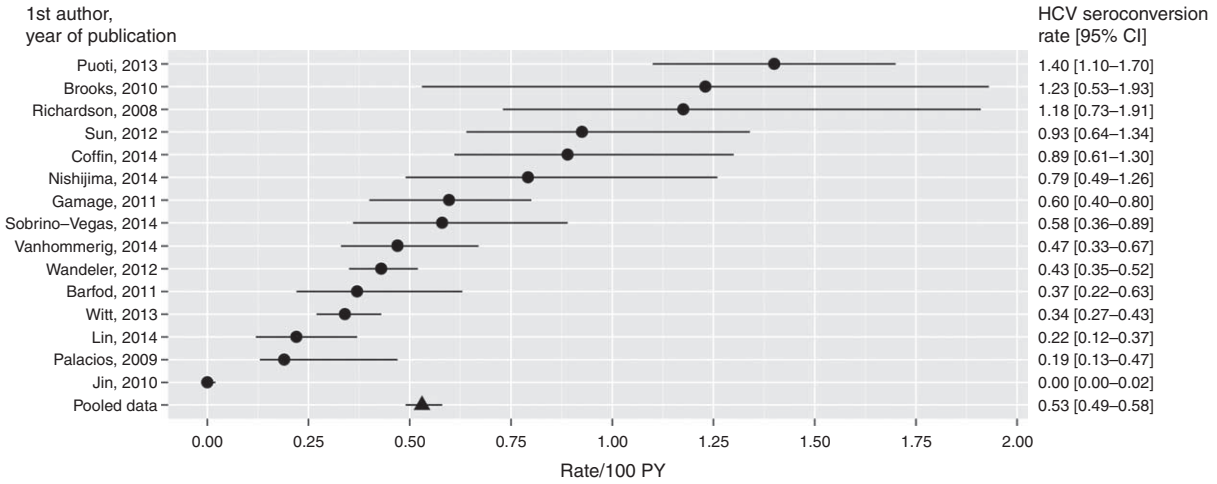

Fig. 2. Forest plot of hepatitis C virus seroconversion in HIV-positive MSM in 15 studies.

(the AR%). The proportion of infections in the underlying HIV-positive MSM population attributable to receptive anal intercourse without a condom, with ejaculation (the PAR%) was 22%. In the German study [4], the AOR for rectal trauma during sex with bleeding was 6.2 (95% CI 1.2–32.8), the AR% was 71% and (owing to a low prevalence of this exposure in the underlying population) the PAR% was 3.8%. Frequent receptive fisting without gloves (or gloves shared) was associated with a six-fold excess risk of HCV seroconversion (95% CI 1.5–21.7), the AR% was 83% and the PAR% was also relatively low at 5%.

Two studies examined noninjection drug use. These include Fierer *et al.* [48], wherein sex while high on methamphetamine was associated with a 28.6-fold elevated risk of HCV infection, but the PAR% was only 4% because of low prevalence of this exposure in controls. The use of inhaled drugs was associated with HCV infection in study in Germany, and because half of the controls reported this exposure, the PAR% was 36%. None of the included studies reported statistically significant adjusted estimates of the association between HIV-related factors ($CD4^+$, HIV viral load or antiretroviral therapy) and seroconversion.

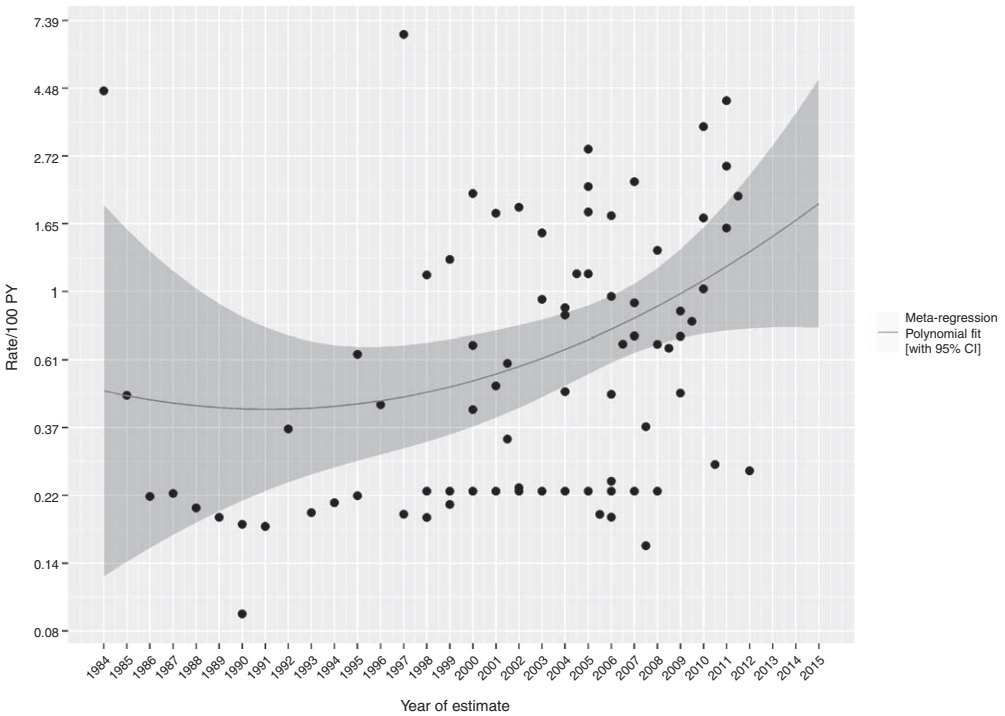

Fig. 3. Hepatitis C virus incidence in HIV-positive MSM in relation to calendar time.

Table 2. Factors associated with hepatitis C virus seroconversion (after adjustment) in studies of HIV-positive MSM, with attributable risk measures.

Ref.	Behaviour	Adjusted measure of association (95% confidence interval)	AR%	pr (exposure) in controls)	PAR%
Fierer *et al.* [48]	Receptive anal intercourse without a condom, with ejaculation	23 (2.2–243.8)	95.7%	23.0%	22.0%
Schmidt *et al.* [4]	Rectal trauma with bleeding	6.2 (1.2–32.8)	83.9%	4.5%	3.8%
	Frequent receptive fisting without gloves (or gloves shared)	5.7 (1.5–21.7)	82.5%	6.0%	4.9%
Wandeler *et al.* [28]	Inconsistent condom use	2.1 (1.3–3.3)	52.4%	51.0%	26.7%
Fierer *et al.* [48]	Sex while high on methamphetamine	28.6 (1.8–443.0)	96.5%	4.0%	3.9%
Schmidt *et al.* [4]	Use of nasally administered drugs (cocaine, amphetamine, ketamine and so on)	3.25 (1.1–9.9)	69.2%	52.2%	36.1%

PAR%, population attributable risk percentage.

Discussion/Conclusion

In this systematic review and meta-analysis that included 13 000 HIV-positive MSM enrolled in 15 studies in urban areas of Europe, the USA, Australia and Asia, the pooled rate of HCV seroconversion was 0.5/100 person-years. The data show an upward trend beginning in about 1995. If the trend identified in the meta-regression has continued to the present, current incidence may be as high as 1.92/100 person-years, but the predictions also show increasing uncertainty over the past several years (95% CI 0.77–4.80). This suggests that additional primary data collection and updated meta-analyses should be a high priority to estimate the current burden of HCV infection.

These HCV incidence rates are still relatively low compared with people who inject drugs (PWID). Indeed, the highest rates of HCV infection in HIV-positive MSM do not reach the lower bound of the range in PWID (5–60/100 person-years) [54]. However, our analysis also showed that the pooled rate of reinfection following successful HCV treatment was 20 times higher than the rate of initial infection in HIV-positive MSM – 11/100 person-years – and 2-year cumulative incidence post-SVR in two studies was 25–33%. Indeed, in one study, five HIV-positive MSM were reinfected more than once following SVR, and multiple reinfections were also observed in men who experienced spontaneous clearance [49]. Another study reported on two cases of HCV super-infection among HIV/HCV-coinfected MSM engaging in high-risk sexual behaviour [55]. These data indicate that there exists a subgroup of HIV-positive MSM with recurring sexual exposure to HCV in whom the rates may begin to approach the risk of HCV infection among PWID.

The attributable risk analysis also supports the notion of a high-risk subset of HIV-positive MSM. A large proportion of infections in the HCV seroconverters were attributable to mucosally traumatic sex and sex while high on methamphetamine. These exposures were infrequent in the nonseroconverters.

Ideally, an HCV prevention programme for HIV-positive MSM engaging in high-risk sexual practices would integrate successful behavioural and biomedical approaches similar to currently recommended HIV prevention strategies that combine behavioural risk reduction interventions with preexposure prophylaxis (PrEP). Unfortunately, chemoprophylaxis for HCV has not been developed and is unlikely to be available in the near future, and HIV-PrEP does not protect against sexually transmitted HCV. In fact, there have been recent reports of acute HCV in HIV-negative men engaging in high-risk practices with many on daily PrEP [56].

One of the main factors contributing to high HCV incidence rates among PWID is the high prevalence of infectious carriers (50–80%) in the underlying PWID population [57]. Increasing HCV transmission in HIV-positive MSM (and HIV-negative MSM) will similarly raise the prevalence of HCV-RNA in MSM communities and facilitate further spread. The observed increase in HCV incidence parallels a number of other trends in MSM communities, including an increased use of social media geosocial sexual networking applications and its association with STIs, the increase in 'seroadaptive' sexual behaviour that includes unprotected sex between men with the same HIV status and rising rates of STIs and use of 'chemsex' drugs, including by injection [13,58–60].

Recommendations for management of acute HCV in HIV-positive MSM centre on detection through screening for elevated liver enzymes every 3–6 months and providing either early or delayed treatment, that is before or after a 12-week period to determine whether the patient has spontaneously cleared infection [62]. Research on the new direct-acting antiviral (DAA) treatments for acute HCV infection suggest that they may be equally effective in curing HCV in monoinfected and HIV-coinfected patients [63]. However, the high rates of reinfection and the cost of treatment with the new DAAs may impact on the feasibility of this approach to HCV control among HIV-positive MSM [64]. The changing epidemiology of HCV in MSM communities, towards

increasing incidence and prevalence, will only add to the cost and scope of the problem.

There were several limitations to this study that must be acknowledged. As with all systematic reviews and meta-analyses, we were limited by the amount and type of data given in the original studies. There was relatively little reporting of exposure risk across the studies, and in many cases, sample sizes were too small to detect significant associations with HCV after adjustment for confounding. Greater reporting of nonsignificant associations would permit the pooling of individuals across studies, increasing power to detect significant covariates. Selection bias was the chief concern in synthesizing the HCV seroconversion rates, and there was limited description of study methods to clearly identify samples that may have over or underestimated HCV risk. Therefore, our meta-regression may have failed to properly adjust for this source of bias. Our analysis of calendar time as a modifier of incidence relied upon interpolation for 12 of 79 incidence estimates, which may have overestimated the precision of observed trends in incidence over time. However, the significant increase in incidence was also observed in the large primary study that required interpolation [28]. In addition, although the seroconversion rates observed in the individual studies were at least an order of magnitude lower than in studies of PWID, it is conceivable that some PWID may have been inadvertently included in the HIV-positive MSM studies. This would have biased the rates upward.

The multifactorial nature of sexually transmitted HCV in HIV-positive MSM will require a combination approach addressing individual sexual and drug use behaviour in the context of a changing epidemiology. A fuller understanding of the causal pathways is needed to identify effective strategies, and lessons learned about HIV prevention in MSM engaging in sexual risk behaviour are a useful starting point. The results of this study suggest that cumulative HCV incidence in HIV-positive MSM – the result of initial and reinfection – is perhaps a useful way to represent disease burden and to identify subgroups for targeted intervention.

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Conflicts of interest

None declared.

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Uncited reference

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