

Incidence of HIV and hepatitis C virus among people who inject drugs, and associations with age and sex or gender: a global systematic review and meta-analysis

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Summary

Background Measuring the incidence of HIV and hepatitis C virus (HCV) infection among people who inject drugs (PWID) is key to track progress towards elimination. We aimed to summarise global data on HIV and primary HCV incidence among PWID and associations with age and sex or gender.

Methods In this systematic review and meta-analysis, we updated an existing database of HIV and HCV incidence studies among PWID by searching MEDLINE, Embase, and PsycINFO, capturing studies published between Jan 1, 2000, and Dec 12, 2022, with no language or study design restrictions. We contacted authors of identified studies for unpublished or updated data. We included studies that estimated incidence by longitudinally re-testing people at risk of infection or by using assays for recent infection. We pooled incidence and relative risk (RR; young [generally defined as ≤ 25 years] vs older PWID; women vs men) estimates using random-effects meta-analysis and assessed risk of bias with a modified Newcastle–Ottawa scale. This study is registered with PROSPERO, CRD42020220884.

Findings Our updated search identified 9493 publications, of which 211 were eligible for full-text review. An additional 377 full-text records from our existing database and five records identified through cross-referencing were assessed. Including 28 unpublished records, 125 records met the inclusion criteria. We identified 64 estimates of HIV incidence (30 from high-income countries [HICs] and 34 from low-income or middle-income countries [LMICs]) and 66 estimates of HCV incidence (52 from HICs and 14 from LMICs). 41 (64%) of 64 HIV and 42 (64%) of 66 HCV estimates were from single cities rather than being multi-city or nationwide. Estimates were measured over 1987–2021 for HIV and 1992–2021 for HCV. Pooled HIV incidence was 1.7 per 100 person-years (95% CI 1.3–2.3; $I^2=98.4\%$) and pooled HCV incidence was 12.1 per 100 person-years (10.0–14.6; $I^2=97.2\%$). Young PWID had a greater risk of HIV (RR 1.5, 95% CI 1.2–1.8; $I^2=66.9\%$) and HCV (1.5, 1.3–1.8; $I^2=70.6\%$) acquisition than older PWID. Women had a greater risk of HIV (RR 1.4, 95% CI 1.1–1.6; $I^2=55.3\%$) and HCV (1.2, 1.1–1.3; $I^2=43.3\%$) acquisition than men. For both HIV and HCV, the median risk-of-bias score was 6 (IQR 6–7), indicating moderate risk.

Interpretation Although sparse, available HIV and HCV incidence estimates offer insights into global levels of HIV and HCV transmission among PWID. Intensified efforts are needed to keep track of the HIV and HCV epidemics among PWID and to expand access to age-appropriate and gender-appropriate prevention services that serve young PWID and women who inject drugs.

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Introduction

Globally, around 18% of people who inject drugs (PWID) are living with HIV and more than 50% have been infected with hepatitis C virus (HCV).¹ Given that effective interventions are available, UNAIDS and WHO have recommended policies and targets for ending the HIV/AIDS epidemic and eliminating HCV as a public health threat by 2030.^{2,3}

Monitoring HIV and HCV incidence is key to understanding the scale of these epidemics, tracking progress towards achieving the 2030 UNAIDS and WHO targets, and evaluating the effect of interventions.^{4,5} Over the past two decades, the incidence rates of HIV and HCV have declined among PWID in some high-income countries (HICs)^{6–12} due to the scale up of harm reduction interventions and, more

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Research in context

Evidence before this study

We did a global systematic review and meta-analysis of studies presenting data on HIV or primary hepatitis C virus (HCV) incidence among people who inject drugs (PWID) published between Jan 1, 2000, and Dec 12, 2022. We searched MEDLINE, Embase, and PsycINFO, without language restrictions, using terms related to HIV infection, HCV infection, injecting drug use, and study designs that could be used to evaluate HIV or HCV incidence (eg, cohort studies and longitudinal studies). We also contacted authors of identified studies to request unpublished or updated data. We included studies that estimated incidence by longitudinally re-testing people at risk of infection or by using assays for recent infection. No previous study has synthesised global incidence data for either of these two outcomes among PWID. One systematic review gathered data on HCV incidence among PWID in Europe from studies published between 2000 and 2012. This review found data from eight countries, where the incidence of HCV was high and variable, ranging from 2.7 per 100 person-years in one UK study to 66 per 100 person-years in an Irish study, with a median of 13 per 100 person-years; no meta-analysis was done. One systematic review and meta-analysis also synthesised data on the association between sex and HCV incidence among PWID and found that the incidence rate ratio for risk of infection in women who inject drugs compared with men who inject drugs was 1.36 (95% CI 1.13–1.64).

Added value of this study

We identified 64 estimates for HIV incidence and 66 for HCV incidence. Estimates ranged from 0.1 per 100 person-years to 31.8 per 100 person-years for HIV (pooled estimate 1.7 per 100 person-years, 95% CI 1.3–2.3) and from 0.2 per 100 person-years to 72.5 per 100 person-years for HCV (pooled estimate 12.1 per 100 person-years, 10.0–14.6). There

was considerable heterogeneity across geographical regions and study and participant characteristics, and there were substantial data gaps. Estimates were found for 31 countries overall, which were mostly high-income and middle-income countries for HIV and high-income countries for HCV. Estimates were available from 27 (14%) of 195 countries for HIV and from 24 (12%) countries for HCV, with 20 (10%) countries having estimates for both HIV and HCV. Approximately two-thirds of estimates were limited to small geographies (eg, a single city). Based on a subset of studies with HIV and HCV incidence data, the incidence of HCV was around 17-times higher than the incidence of HIV. Young PWID (generally defined as ≤ 25 years) had a greater risk of HIV and HCV acquisition than older PWID, and women who inject drugs had a greater risk of HIV and HCV acquisition than men who inject drugs.

Implications of all the available evidence

Our study highlights the sparse empirical data on HIV and HCV incidence available among PWID, particularly in low-income and middle-income countries. Given that HIV and HCV incidence rates are considered key for monitoring the trajectory of these epidemics, evaluating programmatic effect, and tracking progress towards elimination, our findings suggest that intensified efforts are needed to keep track of these outcomes among PWID. Efforts could include the use of indirect methods for estimating HIV and HCV incidence and alternative indicators, such as changes in HCV viraemic prevalence. In most settings, a range of data and indicators might have to be triangulated to adequately monitor the HIV and HCV epidemics among PWID. Given that young PWID and women who inject drugs have a higher risk of both HIV and HCV acquisition, age-appropriate and gender-appropriate prevention measures are urgently needed to reach and engage these higher risk subgroups.

recently, treatment. Meanwhile, persistently high levels or outbreaks of HIV and HCV among PWID have been reported in other HICs and low-income or middle-income countries (LMICs).^{13–18} A better understanding of these shifting epidemiological patterns and the availability of data globally are needed to orient surveillance and programming efforts. However, no global study has summarised HIV and HCV incidence among PWID, except for a modelling study that estimated HCV incidence to be 8.6 per 100 person-years (95% credible interval 5.4–14.4) in 2015.¹⁹

Equally important to informing prevention strategies is a better understanding of age and sex or gender differences in the risks of HIV and HCV acquisition among PWID. However, no study has synthesised data on the relationship between age and incident HIV or HCV infection, despite several studies^{20–23} finding higher risk behaviours among younger versus older PWID. These higher risks are attributed to lower engagement

in harm-reduction programmes,^{22,24,25} a reliance on others to inject,^{26,27} and greater exposure to structural determinants of harm (eg, homelessness or incarceration).^{20,28}

Studies have also highlighted differences in injection and sexual practices that potentially place women who inject drugs at higher HIV or HCV risk than men who inject drugs.^{29,30} Women face greater stigma and criminalisation linked to sex work and gender-role stereotypes (eg, primary caregiver), which can reduce their ability to adopt safer practices.³¹ Three systematic reviews^{32–34} have explored the relationship between gender and prevalent HIV or HCV infection among PWID, and found either similar prevalence^{32,33} or slightly higher prevalence in women than in men.³⁴ Only one review has evaluated the association of sex with incident HCV infection, finding a 1.36-times greater average risk in women than in men.³⁵ No similar study has been done for HIV incidence.

We aimed to summarise global HIV and HCV incidence among PWID, to characterise geographical and temporal differences in pooled HIV and HCV incidence, and to estimate the associations between age and sex or gender and the risks of HIV and HCV acquisition.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis is reported in accordance with PRISMA guidelines.³⁶ We updated an existing database produced for two previous systematic reviews,^{37,38} which included studies published in any language reporting HIV incidence, HCV incidence, or both, among PWID published between Jan 1, 2000, and Sept 14, 2020. Using the same search strategy, AA and DS did a systematic literature search of MEDLINE, Embase, and PsycINFO for studies, including conference abstracts, published between Sept 14, 2020, and Dec 12, 2022. They searched these databases without language restrictions using terms related to HIV infection, HCV infection, injecting drug use, and study designs that could be used to evaluate HIV or HCV incidence (appendix pp 7–8). They also searched the reference lists of review articles published during the same period.

Eligible studies reported summary estimates of HIV or HCV incidence among people with a history of ever injecting drugs, measured either through repeat testing of people at risk or using assays of recent infection (eg, markers of antibody avidity or detection of HCV RNA positivity among anti-HCV antibody-negative participants).^{39–41} Only primary HCV infection was considered. We excluded studies that estimated HIV or HCV incidence among PWID who were incarcerated.

In our two previous systematic reviews,^{37,38} we contacted authors of published studies that reported HIV or HCV incidence estimates among PWID but did not report on the association with incarceration or housing (focus of those studies), and studies in which HIV or HCV incidence among PWID was measured, but not yet published (166 authors). We re-contacted authors who responded to previous requests (29 authors) to ask for up-to-date HIV or HCV incidence estimates and, if not published, the associations between HIV or HCV acquisition risks with age and sex or gender. We also contacted two additional authors because we needed further information⁴² or because the study was unpublished at the time of writing (Wisse E, *Medécins du Monde France*, McNaughton A, University of Bristol, personal communication—now published⁴³). We use the term “unpublished” for estimates that were calculated for this study. However, most unpublished estimates were based on data from published studies, for which we cite the most recently published article.

We created an Endnote library to catalogue search results. The titles and abstracts of each record were first

screened by one author (AA or DS), with 10% being checked by another (AA, DS, AT, JS, or ZW). If inconsistencies arose between two authors, all their records were double-screened, with disagreements resolved by discussion. Full-text review of records deemed potentially eligible was completed in duplicate (AA, DS, HF, ZW, and JGW). We used Google Translate to read non-English language papers.

Contrary to the protocol, we included incidence data from the intervention arm of trials when data were unavailable for the control arm or when both arms received some form of intervention (appendix pp 18–19); this decision was implemented at the data extraction stage. No other protocol deviations occurred. The study protocol can be found online.

Data analysis

Eligible records were extracted into Microsoft Excel (version 16.7) by AA and double-checked by CA, HF, AGL, ALM, DS, AT, and ZW. We extracted HIV and HCV incidence rates; the associations between HIV and HCV acquisition risks and age and sex or gender; and incidence data disaggregated by age and sex or gender, where available. For some studies, particularly long-term studies and those for which several publications were available, several estimates of HIV and HCV incidence measured over different time periods were available. In these cases, we extracted the most recent HIV or HCV incidence estimate and, if available, the least recent without temporal overlap to explore temporal trends. Few studies had multiple non-overlapping incidence estimates, and, therefore, we extracted, at most, two estimates per study. Less recent HIV and HCV incidence estimates that overlapped temporally with estimates that were extracted were marked as duplicates.

For each record, we extracted the number of incident cases, the total person-years at-risk, incidence, and 95% CIs. Where available, we also extracted the incidence rate ratio (IRR), hazard ratio, or risk ratio (collectively referred to as the relative risk [RR]) comparing HIV and HCV acquisition risks among young and older PWID and among women and men who inject drugs. We only extracted unadjusted RR estimates, as our aim was to synthesise the total effects of age and sex or gender on HIV and HCV acquisition risks. Extraction of adjusted RRs was deemed unnecessary, as the individual-level factors included in adjusted estimates are likely to reflect mediators of these associations rather than confounders. Because studies used different age groupings, we defined young as the most frequently reported threshold (≤ 25 years) and allowed for variations in this definition across studies. We included sex or gender, as reported, when comparing women and men; other gender identities were not extracted as they were rarely reported. We also extracted several study (eg, design, sampling strategy, and recruitment sources) and participant

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For the study protocol see
https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=220884

See Online for appendix

characteristics (eg, mean or median age and whether $\geq 80\%$ had injected within the past year [denoted as having injected recently]); all characteristics are listed in the appendix (p 9). For studies that reported both mean and median, we prioritised using the median as it is a better measure for summarising non-normally distributed data.

Records with duplicate data were excluded from the analysis. We assessed the risk of bias for each record using a modified Newcastle–Ottawa Scale,⁴⁴ which allocates up to 9 points on criteria related to the selection of participants and assessment of the outcome (appendix p 10). We penalised all interventional studies in the risk-of-bias assessment on the sample representativeness criterion (ie, we did not allocate these studies a point for this criterion). Risk of bias was assessed by AA and reviewed by HF, AGL, ALM, DS, AT, and ZW. We classified risk of bias as high if a study scored 3 or less, moderate if they scored between 4 and 6, and low if they scored 7 or more.

We used random-effects meta-analysis (inverse-variance method) to estimate pooled HIV and HCV incidence rates (primary outcome) on the basis of the number of incident cases and duration at risk. Between-study variance was estimated by use of the DerSimonian–Laird method and 95% CIs were estimated by use of the formula by Rothman and Greenland.⁴⁵ For HIV or HCV incidence measured by use of assays for recent infection, total duration at risk was imputed from the number of incident cases and incidence rate. A fixed value (0.5) was applied to all cells of studies with no infection cases. Rates were log-transformed in analyses and back-transformed for reporting. We explored heterogeneity in HIV or HCV incidence through a-priori-defined subgroup analyses, including of study characteristics (eg, sampling strategy and recruitment venues) and participant characteristics (eg, whether $\geq 80\%$ injected recently and mean or median age). Variables used in the subgroup analyses were defined in the protocol (appendix pp 5–6) and are outlined in the appendix (p 11). Heterogeneity was quantified by use of the I^2 statistic and differences between groups tested by use of the Q test.⁴⁶ We similarly synthesised the IRR of HCV to HIV incidence when both were available through the same study and explored heterogeneity in the pooled estimate by WHO region.

To investigate geographical and temporal differences in pooled HIV and HCV incidence, we did univariable and multivariable random-effects meta-regression (linear mixed-effects) analyses using the inverse-variance method and log-transformed incidence rates. Models assume that the random-error and random-effect terms are normally distributed and that the relationship between the continuous moderators and the outcome is linear.⁴⁷ Model assumptions were inspected by use of normal Q-Q plots, the Kolmogorov–Smirnov test, and

residuals-versus-fitted plots. Geographical differences were explored by use of the World Bank income classification because data were sparse for some WHO regions. Temporal differences were explored by use of the midpoint of each study period as the time variable. Because only the most recent estimate per study was used in this analysis, we estimated temporal differences by comparing data between studies. We adjusted our meta-regression models for recruitment sources, study duration, and whether at least 80% of participants had injected recently. The multivariable model was fitted by use of a theory-led approach and the number of variables was minimised to avoid over-fitting and multi-collinearity. Variables were selected a priori on the basis of their potential to confound the relationship between geographical or temporal differences and HIV and HCV incidence. Results are presented as unadjusted or adjusted IRRs with 95% CIs.

We used random-effects meta-analysis to pool RRs and their corresponding 95% CIs comparing HIV or HCV acquisition risk among young versus older PWID and among women versus men who inject drugs. Similar meta-analytical methods were used to quantify between-study variance and to conduct subgroup analyses by several study characteristics, including WHO region, World Bank income classification, and publication status (appendix p 11). Where available, we also synthesised age-disaggregated and sex-disaggregated or gender-disaggregated absolute HIV and HCV incidence rates.

We did two sensitivity analyses to assess the robustness of the pooled HIV and HCV incidence estimates, excluding (1) studies that used assays for recent infection, for which we imputed the duration of follow-up, potentially leading to differences in the estimated 95% CIs relative to those reported in the original study and (2) intervention studies. Because there is some evidence that Poisson-normal models via generalised linear mixed-effects models could perform better than the conventional inverse-variance method in meta-analyses involving sparse data,⁴⁸ we did an additional sensitivity analysis to explore the robustness of our results to the use of different methods.

We also did several sensitivity analyses for our meta-regression models. First, because use of the study period midpoint as the time variable can bias measures of temporal change in incidence when estimates are based on long follow-up periods, we excluded those estimates with follow-up exceeding 10 years. Second, we included non-recent incidence estimates derived from the same study, when available, and accounted for their nested structure using a multi-level meta-regression model.⁴⁹ This analysis estimated temporal differences in pooled HIV and HCV incidence rates by comparing data between and within studies. Finally, three additional sensitivity analyses were done to assess the robustness of results to the assumptions of the meta-regression

For the World Bank income classification see <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>

models. These comprised log-transforming continuous moderators for which we observed potential departures from the linearity assumption; excluding estimates that appeared to be outliers and demonstrated potential departures from the normality assumptions; and using Poisson-normal models rather than the conventional inverse-variance method to synthesise estimates for the

same reason as before (ie, potentially better suitability for sparse data).⁴⁸

Publication bias in measures of RR was explored by use of funnel plots and Egger's test. The effects of publication bias on measures of incidence rates and approaches to explore them are not well established, so we did not do such analyses. We did all analyses in R

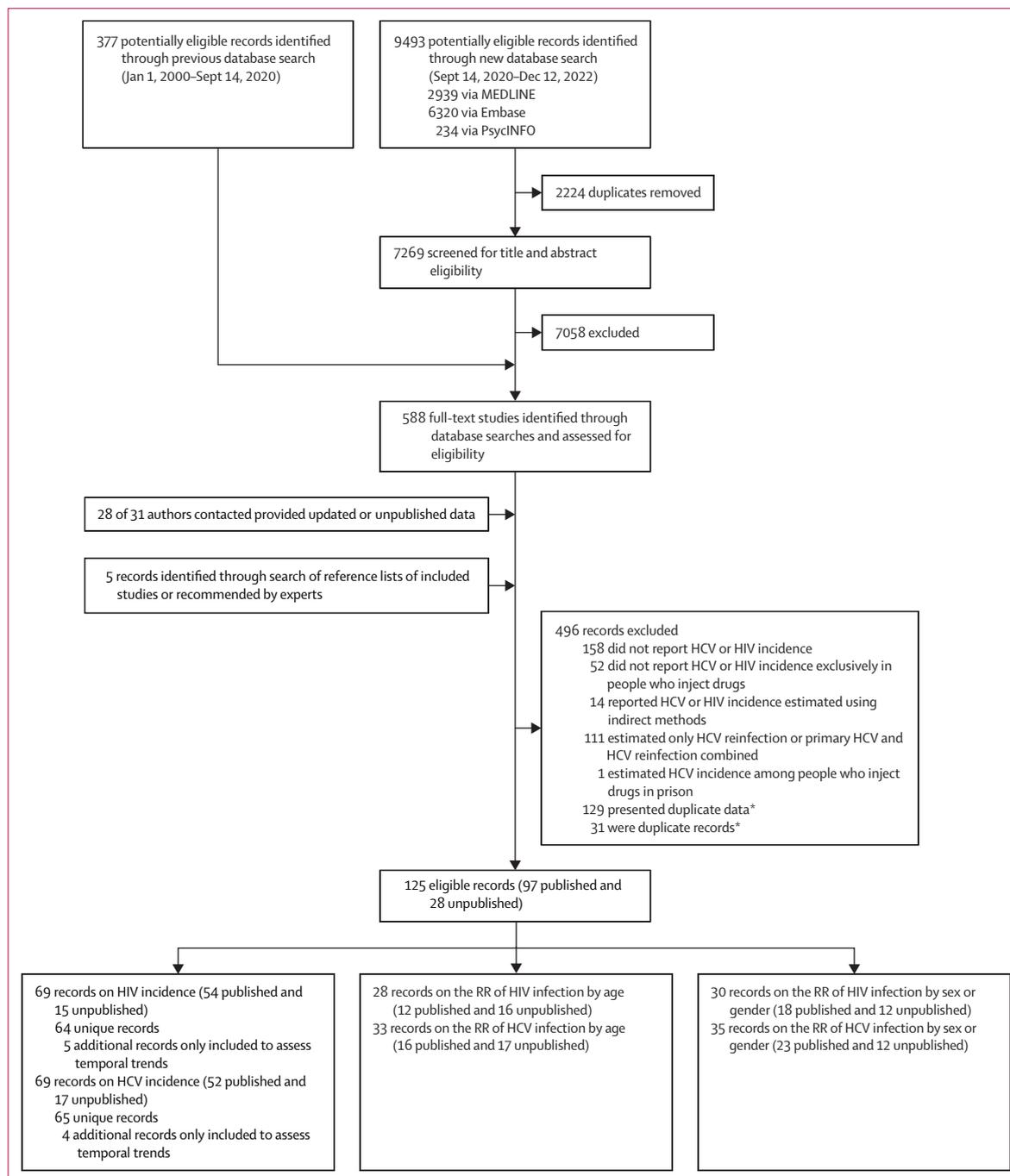


Figure 1: Study selection

HCV=hepatitis C virus. RR=relative risk. *Duplicate data refer to different publications that present data from the same study; duplicate records refer to the same publication.

	Number of estimates	Pooled incidence (95% CI)	I ² (%)	p value*
HIV				
Overall	64	1.7 (1.3-2.3)	98.4	..
WHO region	<0.0001
European	19	2.4 (1.3-4.5)	98.8	..
Western Pacific	10	1.1 (0.4-2.8)	97.2	..
The Americas	19	0.9 (0.6-1.2)	89.3	..
Eastern Mediterranean	4	4.1 (1.2-14.0)	90.6	..
South-East Asia	10	3.6 (2.1-6.3)	98.1	..
African	1	2.6 (1.8-3.7)	NA	..
Mixed regions	1	0.5 (0.3-1.1)	NA	..
World Bank income classification	<0.0001
High-income	30	0.9 (0.6-1.3)	93.9	..
Low-income and middle-income†	34	3.2 (2.2-4.6)	98.5	..
Study start year	0.44
2010 or later	29	2.0 (1.3-3.0)	98.6	..
Before 2010	35	1.6 (1.0-2.4)	97.7	..
Study design	0.24
Prospective cohort	42	1.4 (0.9-2.2)	98.0	..
Retrospective cohort	6	2.0 (1.2-3.3)	98.2	..
Randomised trial	7	2.3 (0.5-10.7)	98.9	..
Linked repeated cross-sectional study	4	0.9 (0.2-3.8)	98.5	..
Cross-sectional study	5	4.1 (1.7-10.0)	97.6	..
Sampling strategy	0.015
Convenience	36	1.4 (1.0-2.0)	97.8	..
Peer referral	12	4.5 (2.3-8.8)	98.7	..
Mixed	10	1.7 (0.8-3.4)	95.5	..
Targeted	5	1.1 (0.7-1.7)	67.1	..
Time-location	1	1.5 (0.7-3.4)	NA	..
Recruitment sources	0.015
Community	25	1.2 (0.8-1.8)	97.6	..
Medical	13	1.6 (0.9-2.8)	96.4	..
Network	12	4.5 (2.3-8.8)	98.7	..
Mixed	14	1.7 (0.9-3.2)	97.2	..
Method of incidence estimation	0.046
Repeated follow-up and re-testing	59	1.6 (1.1-2.2)	98.4	..
Assay for recent infection	5	4.1 (1.7-10.0)	97.6	..
Study duration, years	<0.0001
≤2.0	25	2.9 (1.9-4.4)	96.6	..
>2.0 and ≤3.0	13	3.5 (1.9-6.5)	98.7	..
>3.0 and ≤5.3	10	1.3 (0.7-2.6)	90.2	..
>5.3	16	0.6 (0.4-0.9)	94.9	..

(Table continues in next column)

	Number of estimates	Pooled incidence (95% CI)	I ² (%)	p value*
(Continued from previous column)				
Mean duration of follow-up per person, years	<0.0001
≤1.0	17	4.6 (2.4-9.0)	98.8	..
>1.0 and ≤1.4	13	1.7 (1.1-2.6)	88.5	..
>1.4 and ≤2.5	14	1.0 (0.4-2.4)	98.3	..
>2.5	14	0.7 (0.4-1.2)	98.0	..
Not available	1	3.4 (2.2-5.0)	NA	..
NA‡	5	4.1 (1.7-10.0)	97.6	..
Risk of bias score	0.92
Low	28	1.7 (1.0-2.7)	98.3	..
Moderate or high	36	1.7 (1.1-2.6)	98.5	..
≥80% of participants injected within the past year	0.071
Yes	46	1.6 (1.1-2.5)	98.5	..
No	8	0.9 (0.4-2.3)	96.5	..
Not available	10	2.8 (1.7-4.4)	97.5	..
Median or mean age, years	0.036
≤28.0	13	2.0 (0.8-5.0)	98.9	..
>28.0 and ≤31.7	9	4.5 (2.1-9.8)	99.0	..
>31.7 and ≤35.1	11	1.5 (0.6-3.7)	99.0	..
>35.1	11	1.5 (0.7-3.1)	87.0	..
Not available	20	1.1 (0.7-1.7)	96.1	..
Median or mean duration of injection, years	0.22
≤5.0	5	3.6 (1.4-9.4)	98.4	..
>5.0 and ≤6.9	3	0.7 (0.2-2.1)	43.0	..
>6.9 and ≤9.2	4	1.2 (0.2-8.1)	99.1	..
>9.2	4	3.4 (0.6-20.5)	99.5	..
Not available	48	1.6 (1.2-2.2)	97.3	..
HIV antibody prevalence	<0.0001
≤5.3%	11	0.7 (0.2-2.0)	94.9	..
>5.3% and ≤11.4%	11	1.1 (0.6-1.9)	92.0	..
>11.4% and ≤25.8%	10	1.6 (0.9-2.9)	97.3	..
>25.8%	11	7.9 (4.4-14.0)	97.9	..
Not available	21	1.6 (1.0-2.5)	98.1	..
HCV				
Overall	66	12.1 (10.0-14.6)	97.2	..
WHO region	0.82
European	26	12.8 (9.5-17.2)	97.6	..
Western Pacific	13	12.2 (7.6-19.5)	94.6	..
The Americas	21	12.1 (8.4-17.5)	97.7	..
Eastern Mediterranean	2	16.1 (3.3-78.4)	96.9	..
South-East Asia	4	6.4 (2.1-19.3)	96.9	..

(Table continues on next page)

	Number of estimates	Pooled incidence (95% CI)	I ² (%)	p value*
(Continued from previous page)				
World Bank income classification	0.44
High-income	52	12.1 (9.7–15.0)	97.4	..
Low-income and middle-income†	14	12.6 (8.7–18.1)	95.0	..
Study start year	0.87
2010 or later	18	12.6 (9.8–16.2)	93.9	..
Before 2010	48	12.2 (9.5–15.7)	97.7	..
Study design	0.056
Prospective cohort	49	13.1 (10.4–16.7)	97.3	..
Retrospective cohort	5	5.6 (2.9–10.7)	95.8	..
Randomised trial	5	11.3 (6.9–18.5)	82.7	..
Linked repeated cross-sectional study	3	19.3 (9.2–40.4)	94.2	..
Cross-sectional study	4	8.8 (5.7–13.7)	84.8	..
Sampling strategy	<0.0001
Convenience	40	9.8 (7.4–13.0)	97.8	..
Peer referral	8	14.9 (10.5–21.1)	90.7	..
Mixed	12	16.9 (11.1–25.6)	95.1	..
Targeted	4	16.9 (10.6–26.9)	86.7	..
Time–location	1	35.5 (28.3–44.6)	NA	..
Probability	1	11.6 (9.8–13.8)	NA	..
Recruitment sources	0.012
Community	22	16.6 (13.0–21.3)	95.2	..
Medical	15	7.6 (5.0–11.4)	96.5	..
Network	8	14.9 (10.5–21.1)	90.7	..
Mixed	21	11.6 (7.5–17.9)	97.7	..
Method of incidence estimation	0.17
Repeated follow-up and re-testing	62	12.4 (10.1–15.1)	97.3	..
Assay for recent infection	4	8.8 (5.7–13.7)	84.8	..
Study duration, years	0.15
<3	16	16.8 (12.1–23.2)	92.7	..
≥3 and <4	14	13.2 (8.6–20.4)	94.9	..
≥4 and <7	17	11.4 (8.6–15.2)	92.1	..
≥7	19	9.7 (6.5–14.2)	98.8	..
Mean duration of follow-up per person, years	<0.0001
≤1.0	14	23.7 (18.1–31.1)	90.4	..
>1.0 and ≤1.3	17	20.3 (15.8–26.0)	92.5	..
>1.3 and ≤2.1	14	9.0 (6.5–12.7)	96.9	..
>2.1	15	5.2 (3.0–9.3)	98.0	..
Not available	2	8.1 (6.2–10.6)	23.7	..
NA‡	4	8.8 (5.7–13.7)	84.8	..

(Table continues in next column)

	Number of estimates	Pooled incidence (95% CI)	I ² (%)	p value*
(Continued from previous column)				
Risk of bias score	0.21
Low	25	10.2 (6.9–14.9)	97.7	..
Moderate or high	41	13.5 (10.8–16.8)	96.8	..
≥80% of participants injected within the past year	0.0060
Yes	47	14.4 (11.4–18.1)	97.1	..
No	5	9.6 (7.2–12.7)	55.3	..
Not available	14	7.7 (5.5–10.9)	95.8	..
Median or mean age, years	0.0003
≤25.0	13	22.6 (16.6–30.6)	95.5	..
>25.0 and ≤29.2	10	14.7 (10.1–21.3)	95.2	..
>29.2 and ≤34.8	11	14.0 (11.4–17.2)	85.7	..
>34.8	13	7.8 (5.2–11.8)	95.6	..
Not available	19	8.3 (4.9–14.1)	97.3	..
Median or mean duration of injection, years	<0.0001
≤2.7	5	38.2 (24.4–59.6)	86.4	..
>2.7 and ≤5.9	5	20.3 (17.0–24.1)	66.8	..
>5.9 and ≤7.9	5	7.0 (3.8–12.9)	90.5	..
>7.9	5	16.8 (11.8–23.9)	93.8	..
Not available	46	10.6 (8.3–13.7)	97.3	..
HCV antibody prevalence	0.67
≤46.6%	12	14.0 (8.3–23.5)	97.0	..
>46.6% and ≤59.3%	12	12.8 (9.5–17.4)	93.5	..
>59.3% and ≤68.3%	11	13.8 (8.7–21.8)	96.7	..
>68.3%	12	12.3 (6.2–24.2)	98.7	..
Not available	19	9.8 (7.0–13.6)	95.6	..

Additional subgroup analyses are presented in the appendix (pp 34–35). Continuous variables have been categorised into quartiles. HCV=hepatitis C virus. NA=not applicable. *Based on the Q test for differences between groups. †For both HIV and HCV, only one estimate was based in low-income countries. ‡Cross-sectional study.

Table: Subgroup analyses

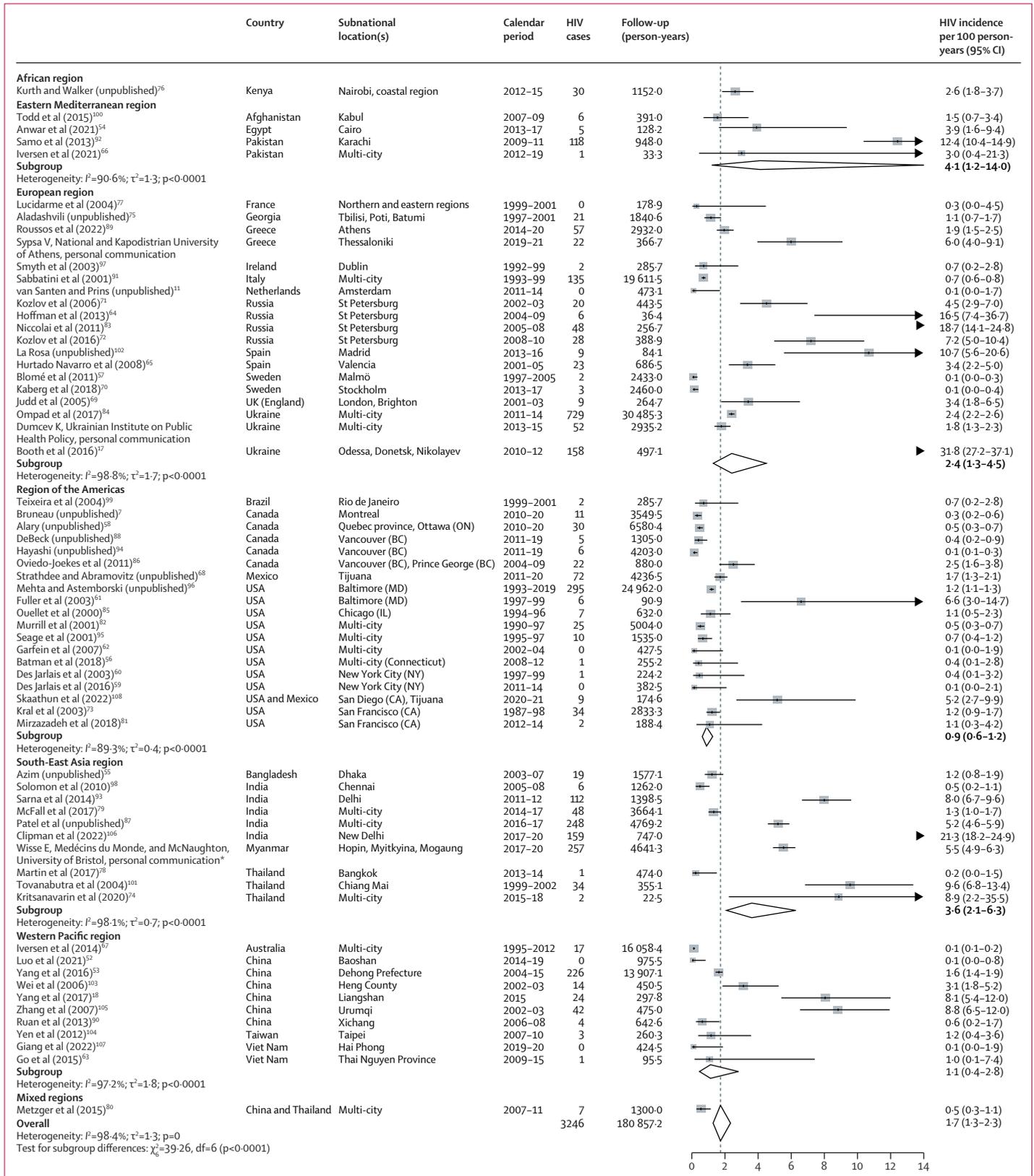
(version 4.0.5) using the “meta” and “metafor” packages.⁵⁰ This systematic review and meta-analysis is registered on PROSPERO, CRD42020220884.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Our new database searches identified 9493 potentially eligible records, of which 2224 were duplicates (figure 1). Initial screening of titles and abstracts resulted in 211 new records eligible for full-text review. We retrieved



377 additional records from our existing database of incidence studies,^{37,38} resulting in 588 records for full-text review. After contacting 31 authors for additional data and retrieving five additional records through searches of reference lists of included studies or recommendations by experts, we identified 125 eligible records (including four not written in English);^{18,51–53} 97 published records and 28 unpublished records. We excluded 129 records for having duplicate data (appendix pp 20–23).

We identified 64 unique records for HIV incidence (Dumcev K, Ukrainian Institute on Public Health Policy, personal communication; Sypsa V, National and Kapodistrian University of Athens, personal communication; Wisse E, *Medécins du Monde*, and McNaughton A, University of Bristol, personal communication)^{7,11,17,18,52–108} and 65 unique records for HCV incidence (Dumcev K, Ukrainian Institute on Public Health Policy, personal communication)^{6,11,13,40,42,51,52,55–57,60,49,70,75,77,88,90,96–98,100,106,107,109–149} among PWID, producing 64 HIV and 66 HCV estimates (one record presented HCV estimates from two countries).¹²⁵ Extracted data are shown in the appendix (pp 24–29). 58 (91%) of 64 HIV estimates originated from the European, American, Western Pacific, and South-East Asia WHO regions, with all except one estimate being from high-income or middle-income countries (table). 60 (91%) of 66 HCV estimates originated from the European, American, and Western Pacific WHO regions, with 52 (79%) estimates being from HICs (table). Estimates were available from 27 (14%) of 195 countries¹⁵⁰ for HIV and from 24 (12%) countries for HCV, with 31 (16%) countries having data for either HIV or HCV and 20 (10%) countries having estimates for both HIV and HCV (appendix p 12). 41 (64%) of 64 HIV and 42 (64%) of 66 HCV estimates came from single cities within a country, rather than being multi-city or nationwide. Estimates were measured over 1987–2021 for HIV and 1992–2021 for HCV. Less than half of HIV and HCV estimates were initiated in 2010 or later (table) and only eight HIV and five HCV estimates were initiated since 2015. Most estimates came from prospective studies with convenience-based recruitment. For both HIV and HCV, the median risk-of-bias score was 6 (IQR 6–7), indicating moderate risk, with most records being penalised on sample representativeness and adequacy of follow-up criteria (appendix pp 30–33).

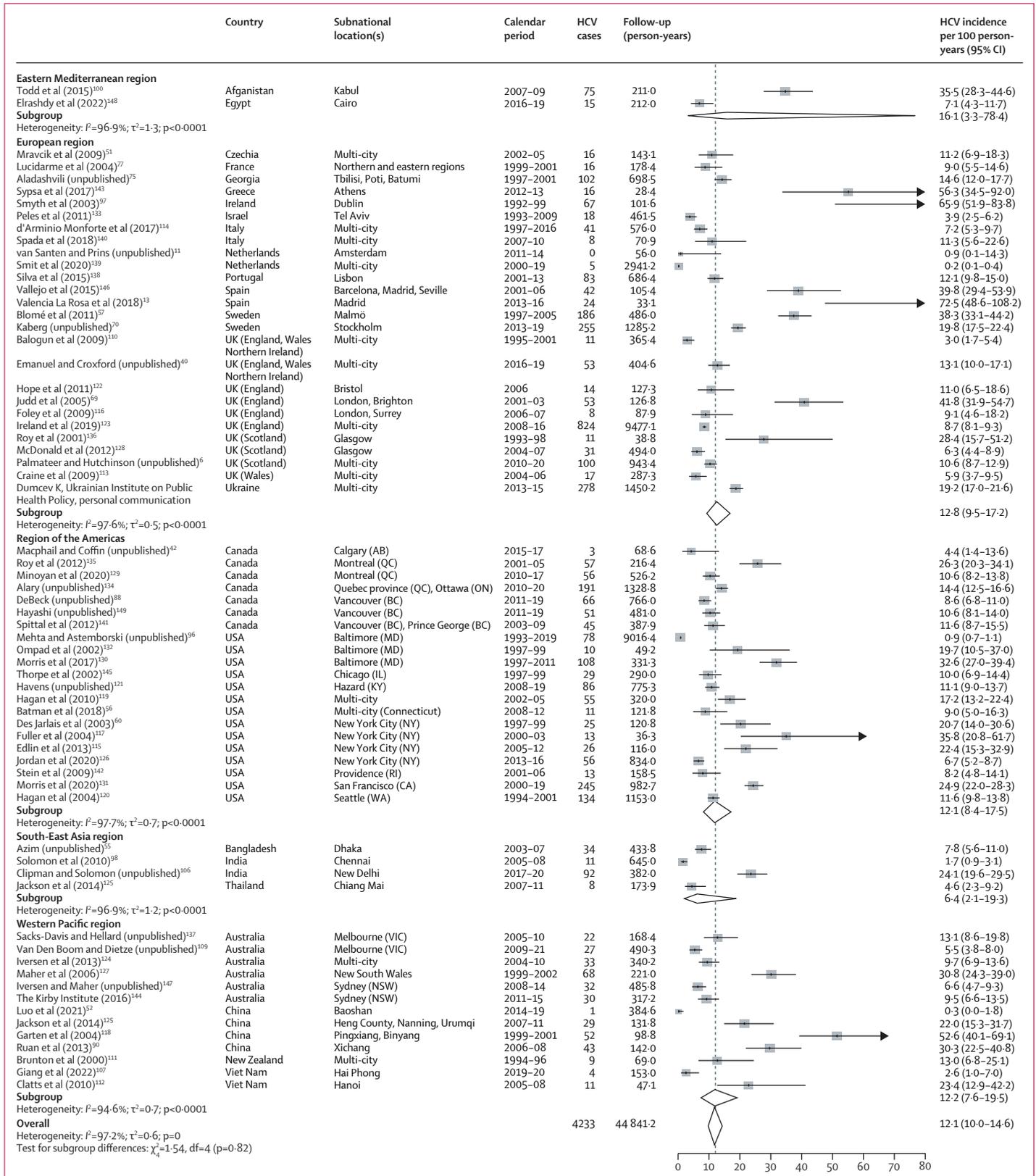
Figure 2: Incidence of HIV among people who inject drugs, stratified by WHO region

For five records (Kral et al, 2003;⁷³ Patel et al, unpublished;⁸⁷ Niccolai et al, 2011;⁸³ Teixeira et al, 2004;³⁹ and Yang et al, 2017¹⁵), the follow-up duration was imputed from the number of HIV cases and the incidence rate, potentially leading to differences in the estimated 95% CIs relative to those reported in the original study (appendix pp 24–26). Box sizes are proportional to the weight of the study in relation to the pooled incidence. Arrow heads represent estimates that fall completely outside of the axis range. *This study has now been published.⁴³

3246 incident cases of HIV were reported during 180 857.2 person-years of follow-up. HIV incidence ranged from 0.1 per 100 person-years in several settings, including Amsterdam (the Netherlands), Vancouver (BC, Canada), and New York (NY, USA), to 31.8 per 100 person-years in a multi-city study in Ukraine (figure 2). Pooled HIV incidence was 1.7 per 100 person-years (95% CI 1.3–2.3), with substantial heterogeneity ($I^2=98.4\%$). This pooled estimate varied by several study and participant characteristics (table). HIV incidence was highest in the Eastern Mediterranean and South-East Asia regions, and lowest in the Western Pacific and American regions (table). HICs had a significantly lower HIV incidence than LMICs. HIV incidence was highest where sampling occurred through peer referral and recruitment through participants' networks compared with other sampling strategies and recruitment sources (table). HIV incidence generally decreased as study duration and mean duration of follow-up per person increased. When stratified by participant characteristics, the incidence of HIV was higher in studies in which the mean or median age of participants and the proportion on opioid agonist treatment were lower and in studies in which HIV prevalence was higher (table; appendix pp 34–35).

4233 incident cases of HCV were reported during 44 841.2 person-years of follow-up (figure 3). HCV incidence ranged from 0.2 per 100 person-years in a multi-city study in the Netherlands to 72.5 per 100 person-years in a study in Madrid (Spain; figure 3). Pooled HCV incidence was 12.1 per 100 person-years (95% CI 10.0–14.6), with substantial heterogeneity ($I^2=97.2\%$). Pooled HCV incidence also varied by several characteristics (table; appendix pp 34–35). When stratified by study design, sampling strategy, and recruitment sources, HCV incidence was lowest in retrospective cohorts, studies in which sampling was convenience based, and studies in which recruitment occurred through medical sources, and, conversely, HCV incidence was highest in linked repeated cross-sectional studies, if sampling was based on time–location, and if recruitment occurred in the community. The incidence of HCV decreased as study duration and mean follow-up duration per person increased. When stratified by participant characteristics, HCV incidence was significantly higher in studies in which at least 80% of participants had injected recently and in studies in which participants were younger or had a shorter duration of injection (table). HCV incidence did not vary by WHO region or World Bank income classification (table).

Excluding intervention trials or studies that used assays for recent infection in our sensitivity analyses had little effect on pooled HIV and HCV incidence estimates (appendix p 36). Sensitivity analyses pooling estimates with the use of Poisson-normal models instead of the inverse-variance method produced similar results (appendix p 50).



The pooled IRR for HCV versus HIV incidence was 17.4 (95% CI 9.0–33.8; 30 estimates; $I^2=96.9\%$; appendix p 14). IRRs varied by WHO region, with the IRR being lowest in South-East Asia (no estimate for the African region).

Results from meta-regression analyses exploring temporal and geographical differences in pooled HIV and HCV incidence rates are shown in the appendix (pp 13, 37). For HIV incidence, results were inconclusive regarding temporal trends, as estimates were imprecise and compatible with a difference in both directions (adjusted IRR per 5-year increase 1.11, 95% CI 0.87–1.41), but LMICs had a significantly higher pooled incidence than HICs (adjusted IRR 2.41, 1.24–4.69). Conversely, for HCV, results were inconclusive regarding a difference between LMICs versus HICs (adjusted IRR 0.67, 0.37–1.23), but we found some evidence for a decrease in incidence with time (adjusted IRR per 5-year increase 0.84, 0.70–1.02), albeit this decrease was not significant. We found no major departures from the normality and linearity assumptions in meta-regression models (appendix pp 15–16) and estimates were robust to sensitivity analyses (appendix pp 40–41).

Overall, young PWID had a greater risk of HIV (RR 1.5, 95% CI 1.2–1.8; 28 estimates;^{7,11,58,65,67–69,72,73,75,76,81–83,85,87–89,91,94,96,100,105,106,151,152} $I^2=66.9\%$) and HCV (1.5, 1.3–1.8; 33 estimates;^{6,31,40,42,51,69,70,75,77,88,96,97,100,106,109,113,119,121,124,127,128,131,134,136,137,146,147,149,152–155} $I^2=70.6\%$) acquisition than older PWID (figure 4; extracted data in appendix pp 43–44). Similarly, women had a greater risk of HIV (RR 1.4, 95% CI 1.1–1.6; 30 estimates;^{7,17,58,65,67–69,72,73,76,79,81–83,85,87–89,91,94–96,101,105,108,151,152,156} $I^2=55.3\%$) and HCV (1.2, 1.1–1.3; 35 estimates;^{6,40,51,57,69,70,77,88,96,97,109,111,113,119–121,124,127,128,131,134–137,141,145–147,149,152–156} $I^2=43.3\%$) acquisition than men (figure 5; appendix pp 45–46). These associations persisted in subgroup analyses (appendix pp 47–48). We found insufficient evidence of publication bias in any of the four RR measures (appendix p 17). Absolute pooled HIV and HCV incidences stratified by age and sex or gender are presented in the appendix (p 49).

Discussion

In this systematic review and meta-analysis of HIV and HCV incidence among PWID, studies were highly variable in their methodology and participant characteristics and there were substantial data gaps. HIV incidence ranged from 0.1 per 100 person-years to 31.8 per 100 person-years and HCV incidence ranged

from 0.2 per 100 person-years to 72.5 per 100 person-years, with pooled estimates of 1.7 per 100 person-years for HIV and 12.1 per 100 person-years for HCV. Based on a subset of studies with both HIV and HCV incidence data, the incidence of HCV was on average 17.4 times greater than the incidence of HIV. Young PWID had on average a 1.5-times greater risk of HIV and HCV acquisition than older PWID, and women had a 1.4-times greater risk of HIV and a 1.2-times greater risk of HCV than men.

We identified several sources of heterogeneity across pooled HIV and HCV incidence estimates. For example, HIV and HCV incidence estimates were higher in studies in which recruitment occurred through participants' networks rather than through medical sources, possibly reflecting differences in risk profiles. Studies in which participants had a longer mean duration of follow-up had lower HIV and HCV incidence rates, which could reflect reductions in risk behaviour following repeated risk-reduction messaging or better retention of PWID with lower risk of acquisition. Higher HIV and HCV incidence rates were identified if most participants injected recently (albeit non-significant for HIV) and higher HIV incidence if a lower proportion of the sample received opioid agonist treatment. Our review also illustrates the scarcity of HIV and HCV incidence data among PWID globally, which were available in only 14% and 12% of countries, respectively. Moreover, less than half of estimates were from 2010 onwards and only eight (HIV) and five (HCV) estimates were initiated since 2015. We found a considerable geographical skew in the availability of estimates, with few from middle-income countries for HCV, and only one HIV and HCV incidence estimate from low-income countries. Two-thirds of estimates were from single cities and so might not be nationally representative.

This scarce and heterogeneous body of evidence made the evaluation of geographical and temporal differences in HIV and HCV incidence challenging. In several settings, HIV incidence has been shown to have decreased as a result of the implementation of combined prevention and care.^{11,157} However, globally, temporal trend data were scarce and our assessment of the change in incidence with time was mainly based on comparing estimates from different studies. We found no evidence of a decline in HIV incidence with time, which could be due to methodological reasons such as little comparability between estimates, preferential measurement in settings with extreme incidence (very low or very high), and inclusion of estimates averaged over long time periods. However, at least in LMICs, our finding might also reflect a real absence of decline in HIV incidence because of insufficient access to harm reduction interventions.¹⁵⁸ Supporting this theory, we found HIV incidence to be more than two-times higher in LMICs than in HICs. Conversely, there was no

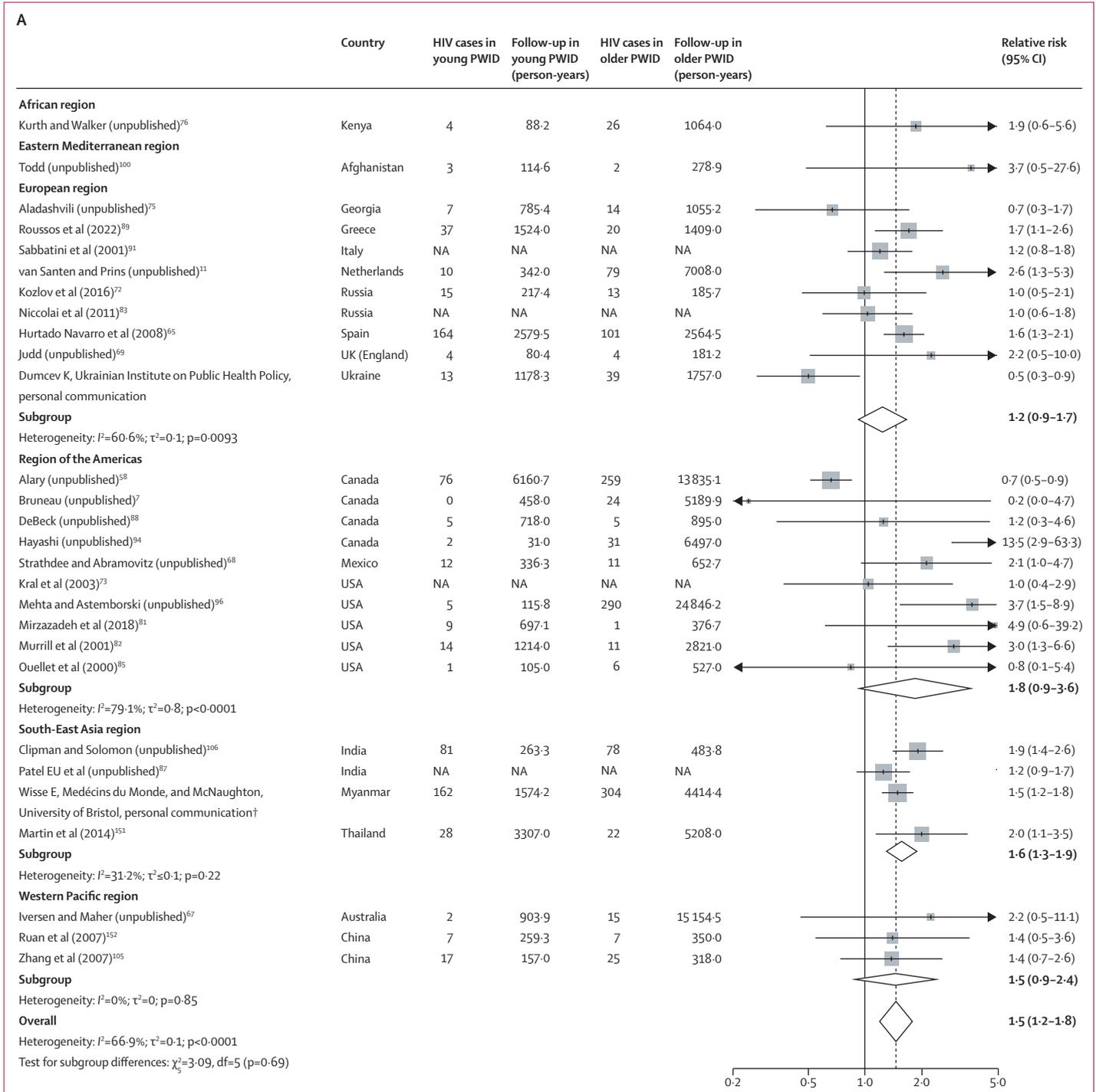
Figure 3: Incidence of HCV among people who inject drugs, stratified by WHO region

For four records (Balogun et al, 2009;¹¹⁰ Emanuel and Croxford, unpublished;⁴⁰ Hope et al, 2011;¹²² and Palmateer and Hutchinson, unpublished⁶), the follow-up duration was imputed from the number of HCV cases and the incidence rate, potentially leading to differences in the estimated 95% CIs relative to those reported in the original study (appendix pp 27–29). Box sizes are proportional to the weight of the study in relation to the pooled incidence. HCV=hepatitis C virus.

evidence that HCV incidence varied between geographical regions, and only some weak evidence that HCV incidence declined with time. As with HIV, the scale-up in HCV treatment in many HICs since 2015 might have led to lower HCV incidence in HICs compared with LMICs. However, data from this period

are scarce, which might be why we found no difference by LMICs versus HICs.

Estimates of HIV and HCV incidence with time among PWID are important for monitoring the trajectory of epidemics, adapting the public health response, and assessing progress towards achieving the UNAIDS and



(Figure 4 continues on next page)

WHO 2030 targets.^{4,159} Although direct methods for measuring HIV and HCV incidence rates are preferred, these methods are not without limitations (eg, high cost and participant attrition) and, in some countries, might not be feasible to implement on a national scale.⁴ In these contexts, indirect methods of estimating incidence

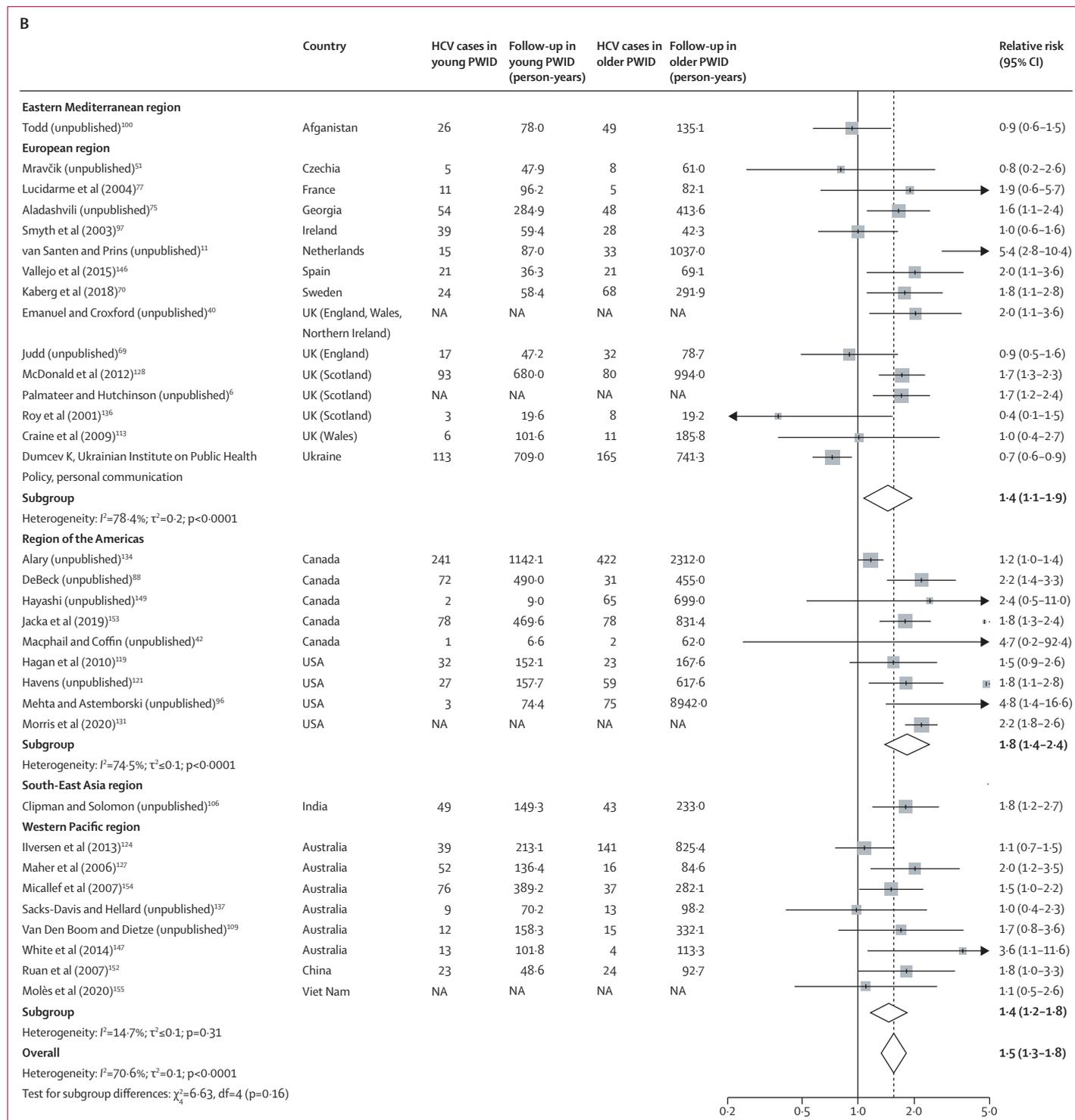
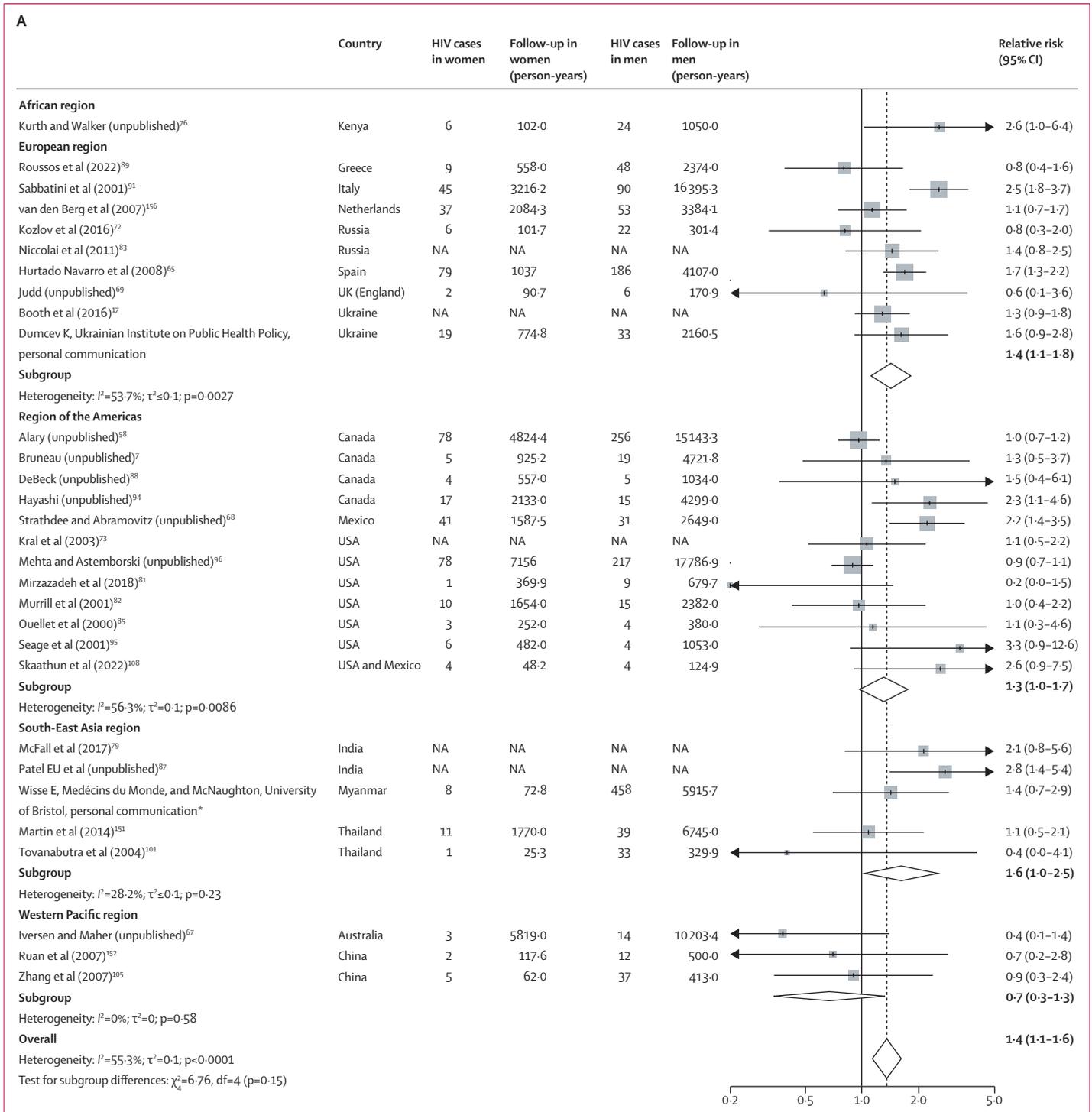


Figure 4: Association between age (young* vs older PWID) and risk of HIV and HCV acquisition
 (A) HIV. (B) HCV. Box sizes are proportional to the weight of the study in relation to the pooled incidence. HCV=hepatitis C virus. NA=not available. PWID=people who inject drugs. *Threshold varied between studies: median value was 25 years (IQR 25–28; range 24–34) for HIV and 25 years (24–25; 20–31) for HCV. †This study has now been published.⁴³



(Figure 5 continues on next page)

from prevalence data or by the use of mathematical modelling could be preferred.^{4,5} Alternatively, our group has shown that changes in chronic HCV prevalence can track changes in HCV incidence when resulting from increases in HCV treatment, and so HCV prevalence

could also be reliably used instead.⁴ Regardless of the options chosen, different data and indicators should be triangulated, including measuring HCV reinfection to keep track of HCV incidence, to adequately monitor these epidemics among PWID.

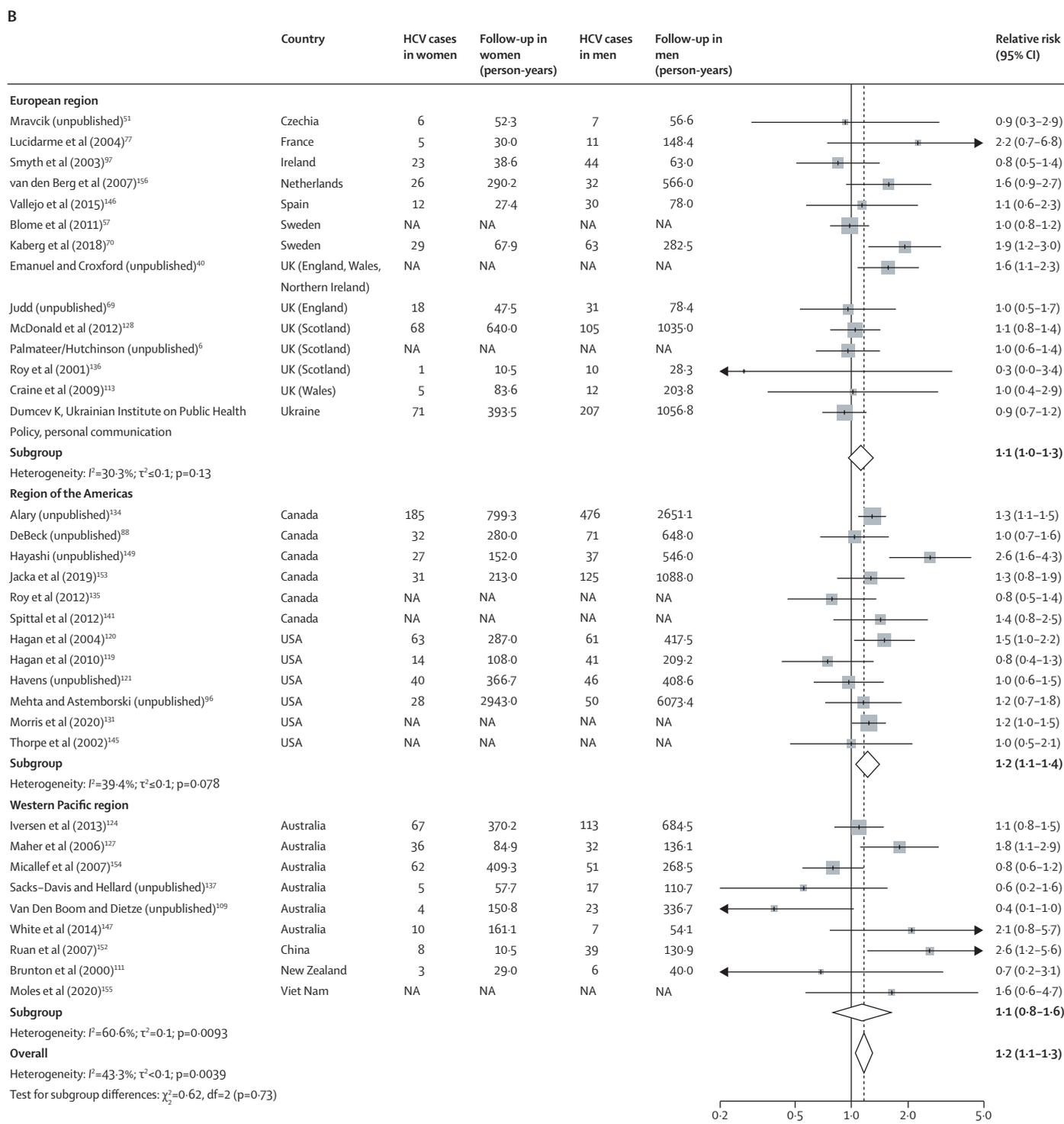


Figure 5: Association between sex or gender and risk of HIV and HCV acquisition in PWID

(A) HIV. (B) HCV. Box sizes are proportional to the weight of the study in relation to the pooled incidence. HCV=hepatitis C virus. NA=not available. PWID=people who inject drugs. *This study has now been published.⁴³

We found the risks of HIV and HCV acquisition to vary by age and sex or gender. Although the magnitude of the associations varied in stratified analyses, HIV and HCV acquisition risks were consistently greater among young PWID compared with older PWID. These findings align with previous studies that report greater injecting and sexual risk behaviours among young compared with older PWID.^{20–23} By contrast, the overall greater risks of HIV and HCV acquisition among women versus men were more modest compared with the age analysis, particularly for HCV. The pooled estimates for sex or gender differences in risk could mask regional differences. We found the magnitude of the association for HIV risk between women and men to be highest in the African and South-East Asia regions and lowest in the Western Pacific region, consistent with findings from a 2019 systematic review focused on prevalence.³² For HCV, there were no estimates for the African and South-East Asia regions to enable a similar comparison. The only other systematic review to have explored the association between gender or sex and incident HCV infection found a 1.36-times greater risk of acquisition in women than in men,³⁵ slightly higher than our pooled estimate, possibly due to methodological differences (eg, including prison samples and adjusted estimates).

Our efforts to include unpublished data increased the number and recency of estimates for all outcomes. Encouragingly, we found no evidence of a difference between published and unpublished estimates. Owing to a preponderance of studies that were more than 10 years old and based in HICs, one of the most important limitations of our review is that our findings provide an incomplete depiction of current global HIV and HCV incidence rates among PWID. The inclusion of data derived through intervention trials and studies that used assays for recent infection might have biased pooled estimates, although results remained largely consistent when these estimates were excluded. Additionally, our assessment of temporal and geographical differences in HIV and HCV incidence rates was exploratory due to sparse data from most global settings, including trend data. Finally, sparse data bias in some studies, owing to a small number of events, small sample sizes, or both, can carry over to the pooled estimates, leading to potentially biased summary estimates and 95% CIs.^{160,161} However, pooled estimates were similar in sensitivity analyses that used meta-analytical approaches that are likely to be more suited for sparse data, which is reassuring.

In conclusion, this systematic review and meta-analysis produced, to our knowledge, the first pooled estimates of HIV and HCV incidence rates derived by use of direct methods among PWID. The low availability of incidence estimates globally, particularly in LMICs, suggests that intensified efforts are urgently needed to keep track of the HIV and HCV epidemics among PWID in these countries. Because PWID often face stigma and discrimination, there is a risk that they will be overlooked in elimination

efforts if national data on HIV and HCV incidence remain absent. This gap needs to be addressed to achieve the global goals of eliminating HIV and HCV. Given the higher risks of HIV and HCV acquisition in young versus older PWID and in women versus men who inject drugs, age-appropriate and gender-appropriate prevention and harm reduction measures are also urgently needed to serve these subgroups at high risk. Factors other than age and sex or gender are also likely to be influencing HIV and HCV acquisition risks (eg, types of drugs injected and the context of injection, identifying as men who have sex with men, and engaging in sex work), and research is also needed to synthesise the role of these other factors to better strengthen HIV and HCV prevention responses. We plan to explore some of these factors in future studies.

HIV and HCV Incidence Review Collaborative Group

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Contributors

AA, JS, HF, and PV conceived the study and drafted the protocol. AA and DS updated the literature search. AA, HF, DS, JS, AT, JGW, and ZW screened the identified records. AA, HF, DS, ZW, and JGW did the full-text review of records deemed potentially eligible. AA extracted and analysed the data and wrote the first draft of the manuscript. JS and CA led the literature search and the screening of studies for eligibility for the previous reviews, which were updated in this study. CA, HF, AGL, ALM, DS, AT, and ZW double-checked the data extraction and risk-of-bias assessment. PV and AA contacted cohorts to request unpublished data. ALM, DA, MA, JA, JB, SJC, CSC, SC, KD, EE, KH, GM, LM, NEP, EUP, RS-D, WVDB, DKvS, JGW, MH, and all members of the HIV and HCV Incidence Review Collaborative Group contributed unpublished data for the study. JS, HF, AGL, ALM, DS, AT, and ZW accessed and verified the data reported in this study. All authors contributed to the interpretation of data and the critical revision of the Article. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. For contributions of the study group members, see the appendix (p 51).

Declaration of interests

AA acknowledges support through postdoctoral fellowships from the Canadian Institute of Health Research (CIHR), Fonds de recherche du Québec – Santé (FRQ-S), and the Canadian Network on Hepatitis C. MA reports grants paid to his institution from the Public Health Agency of Canada and grants from the Ministère de la santé et des services sociaux du Québec, during the conduct of this study, and grants from the CIHR, outside the submitted work. JA reports grants from the National Institutes of Health (NIH), during the conduct of this study. JB reports consulting fees from Gilead Sciences, AbbVie, and Cepheid; payment or honoraria from Gilead Sciences for an educational event; and receipt of equipment, materials, drugs, medical writing, gifts, or other services from Gilead Sciences, as part of an NIH R01 grant, outside of the submitted work. CSC reports grants from Gilead Sciences, Janssen Pharmaceuticals, and GSK (paid to the University of Calgary); consulting fees from Roche Pharmaceuticals, Gilead Sciences, Janssen Pharmaceuticals (paid to the University of Calgary, on behalf of the Canadian Hepatitis B Virus [HBV] Network), and Altimmune (paid to the University of Calgary, on behalf of the Canadian HBV Network); payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events through Gilead Sciences; and patents planned, issued, or pending (PCT/CA2021/050234; international patent application title: polypeptides directed against viral infection and uses thereof; compositions and methodologies for the detection and treatment of HBV infection; USA; 62/982,474; Feb 28, 2020). SC reports payments for chairing or presenting at a European HIV Testing Week webinar from

the Centre of Excellence for Health, Immunity and Infections, outside the submitted work. KH reports financial support for the present manuscript paid to her institution from the US National Institute of Drug Abuse (NIDA; Vancouver Drug Users Study: the impacts of evolving drug use patterns on HIV/AIDS; U01DA038886), the Michael Smith Foundation for Health Research Scholar Award, and St Paul's Foundation, and grants or contracts from the CIHR and the William and Ada Isabelle Steel Fund through Simon Fraser University (paid to institution) and the British Columbia Centre on Substance Use (paid to KH). GM reports grants or contracts from AbbVie (clinic support, advisory board, and speaker fees), the Canadian Network on Hepatitis C (research support), Coverdale (clinic support), Gilead Sciences (clinic support and speakers fees), International Network on Health and Hepatitis in Substance Users (INHSU; speaker fees), and TD Bank (clinic support); payment or honoraria from the Canadian Association for the Study of the Liver (scientific planning committee for web-based learning, conjoint with AbbVie; payment to institution), AbbVie (speakers fees for educational podcasts and brochure; payment partly to institution and partly to GM), Gilead Sciences (speaker fees; payment partly to institution and partly to GM), and ECHO plus (honorarium for speaking); and support for attending meetings or travel, or both, from INHSU and being on the advisory board for AbbVie and Gilead. JGW reports grants and contracts from Gilead Sciences and FIND, The Global Alliance for Diagnostics. MH reports having a leadership or fiduciary role as trustee of the Society for the Study of Addiction. All other authors declare no competing interests. Declaration of interests for the members of the HIV and HCV Incidence Review Collaborative Group are provided in the appendix (p 52).

Data sharing

Extracted data sheets will be shared with researchers who provide a methodologically sound proposal approved by AA and PV. Proposals should be directed to adelina.artenie@bristol.ac.uk and peter.vickerman@bristol.ac.uk; requesters will need to sign a data access agreement. Data can be made available starting with the date of publication of this Article and up to 5 years thereafter.

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