Risk of hepatitis C reinfection following successful therapy among people living with HIV: a global systematic review, meta-analysis, and meta-regression

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Summary

Background The benefits of direct-acting antivirals towards the elimination of hepatitis C virus (HCV) in people living with HIV are decreased when individuals are reinfected with HCV following treatment. We aimed to systematically review the existing evidence of HCV reinfection risk after treatment among people living with HIV, including people who inject drugs and men who have sex with men (MSM), and to identify the factors that explain heterogeneity in the incidence of HCV reinfection.

Methods For this systematic review and meta-analysis, we searched PubMed, Scopus, Web of Science, Cochrane, PsycINFO, and conference presentations from date of database inception to Jan 10, 2022, for clinical trials and cohort studies providing data that could be used to calculate the incidence of HCV reinfection following HCV treatment. Random-effect meta-analysis models were used to calculate rate estimates. Study-level factors contributing to heterogeneity of reinfection estimates were assessed using meta-regression. This study is registered with PROSPERO, CRD42019146973.

Findings 41 studies, predominantly conducted in Europe, were included, with a total of 9024 participants. The incidence of reinfection was 3·76 cases per 100 person-years of follow-up (95% CI 2·80–5·05; I^2 85·9%) among people living with HIV overall, 6·01 (4·54–7·95; 74·1%) among MSM, and 3·29 (2·01–5·39; 83·9%) among people who inject drugs. A similar incidence of reinfection was observed following interferon-based therapy (4·92 cases per 100 person-years of follow-up, 3·30–7·32; I^2 78·3%) and direct-acting antiviral therapy (3·88, 2·51–6·01; 85·4%). A higher proportion (≥85%) of MSM in the study population (adjusted rate ratio 2·66, 95% CI 1·37–5·15) and recent HCV infection (2·22, 1·09–4·55) were associated with an increased incidence of reinfection; a longer duration of follow-up after treatment (0·97, 0·96–0·99) was associated with a decreased incidence.

Interpretation Risk of HCV reinfection following treatment in people living with HIV was highest among MSM and those with recent HCV infection. Continued scale-up of HCV treatment and ongoing HCV screening and treatment of infection in this patient population should reduce viraemic burden and risk of reinfection.

Funding None.

Introduction

Globally, an estimated 2·3 million people living with HIV are co-infected with hepatitis C virus (HCV), with a higher HCV prevalence among those who inject drugs (82%) than among men who have sex with men (MSM; 6%).[1,2] The availability of highly curative, direct-acting antivirals[1] provides the opportunity to control the HCV epidemic among people living with HIV.[3,4] However, both the individual-level and population-level benefits of treatment scale-up could be affected by reinfection due to ongoing risk behaviours, such as injecting drug use and high-risk sexual practices.[3]

There are substantial differences in the reported incidence of HCV reinfection after treatment among people living with HIV, with individual studies often limited by small sample sizes, few cases of reinfection, and heterogeneous study populations with respect to their risk behaviours. Additionally, previous systematic reviews of reinfection following interferon-based therapy have included few studies among people living with HIV,[4] or have focused on HIV-positive MSM.[5] A comparison of reinfection risk following sustained virological response between interferon-based therapy and direct-acting antivirals will help to address the concerns expressed by some clinicians regarding the increased risk of reinfection after treatment with direct-acting antivirals.[6] Robust comprehensive data are needed to better understand the magnitude of HCV reinfection risk and associated factors in the era of direct-acting antivirals. We aimed to systematically review the existing evidence of HCV reinfection incidence after treatment among people living with HIV, including MSM and people who inject drugs. Additionally, we aimed to identify the factors that explain

Research in context

Evidence before this study

We conducted a systematic review, meta-analysis, and meta-regression of publications in any language listed in MEDLINE (PubMed), Scopus, Web of Science, Cochrane Central Register of Controlled Trials, and PsycINFO, as well as key conferences on HIV or AIDS and viral hepatitis, from date of database inception to Jan 10, 2022, using combinations of search terms relating to HIV or AIDS, hepatitis C virus (HCV), men who have sex with men (MSM), HCV treatment, and reinfection or recurrent viraemia. Studies were eligible if they reported data on reinfection incidence, including person-years of follow-up (stated or calculable) after HCV treatment (interferon-based therapy or direct-acting antiviral therapy) among people living with HIV. To date, systematic reviews of reinfection risk following treatment among people living with HIV have been carried out when interferon-based therapies were the standard of care, and included few studies among people living with HIV or HIV-positive MSM.

Added value of this study

Our study highlighted a higher incidence of HCV reinfection following successful therapy in HIV-positive MSM than in the overall population of people living with HIV and in HIV-positive people who inject drugs. Among HIV-positive MSM, a similar incidence of HCV reinfection was observed in those with and without a history of injecting drug use. Incidence of HCV reinfection among people treated for recent HCV infection was higher than among those treated for chronic HCV infection. Furthermore, incidence of HCV reinfection was similar between interferon-based therapies and direct-acting antiviral therapies. In the meta-regression, a higher proportion of MSM (ie, ≥85%) in the study population and recent HCV infection were associated with an increased risk of reinfection, whereas a longer duration of follow-up following treatment was associated with a decreased risk.

Implications of all the available evidence

HCV reinfection occurs following successful treatment among people living with HIV, with no evidence of increasing reinfection incidence in the era of direct-acting antigen therapy. Incidence of reinfection is highest among HIV-positive MSM and among those with recent HCV infection, highlighting the importance of addressing ongoing high-risk sexual and drug use behaviours. Screening for and treatment of HCV reinfection, education focused on reinfection prevention, and access to harm reduction services are essential.

heterogeneity in the incidence of HCV reinfection across studies.

Methods

Search strategy and selection criteria

This systematic review, meta-analysis, and meta-regression was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.[7] We systematically searched the following electronic bibliographic databases: MEDLINE (PubMed), Scopus, Web of Science, Cochrane Central Register of Controlled Trials, and PsycINFO. Presentations at key conferences on HIV or AIDS and viral hepatitis were also searched. We carried out the initial search on Nov 25, 2019, and updated it on Aug 31, 2020, and again on Jan 10, 2022. No time or language restrictions were applied for the search results. Full details of the search strategies are provided in the appendix (pp 1–2). In brief, combinations of search terms were applied, relating to HIV or AIDS, HCV, MSM, HCV treatment, and reinfection or recurrent viraemia.

To be included in this systematic review, clinical trials and prospective or retrospective cohort studies had to meet all of the following criteria: the study population included people with HIV who had received HCV treatment and were at risk of HCV reinfection following treatment-induced HCV viral clearance; the study population was followed up for reinfection following HCV treatment (interferon-based therapy or direct-acting antiviral therapy); and the reinfection rate, including person-years of follow-up, was either reported or calculable. Studies with less than 10 person-years of follow-up were excluded.

MSM were defined as men who self-identified as gay and bisexual, men reporting having sex with other men, and men for whom having sex with men had been documented as the mode of transmission of HIV, HCV, or both. People who inject drugs were defined as those with a history of injecting drug use (including recent injection) and those for whom injecting drug use had been documented as the mode of transmission of HIV, HCV, or both. Recent injection was considered to be injecting drug use within the past 12 months, including during or following HCV treatment. Active or ongoing drug use at the time of study entry was also accepted for inclusion.

Study subpopulations were categorised where possible into HIV-positive MSM (regardless of injecting drug use history) and HIV-positive people who inject drugs (regardless of gender or sexual orientation). These subpopulations were not mutually exclusive. Among HIV-positive MSM, additional categorisation was based on their history of injecting drug use according to the following criteria: a history, no history, or unknown history of injecting drug use. Among HIV-positive people who inject drugs, additional categorisation was based on a recent history of injecting drug use (ie, within the past 12 months).

See Online for appendix

Management of the search results was carried out in Covidence Systematic Review Software. Duplicates were identified and removed in the first stage. The titles and

For more on Covidence Systematic Review software see https://www.covidence.org

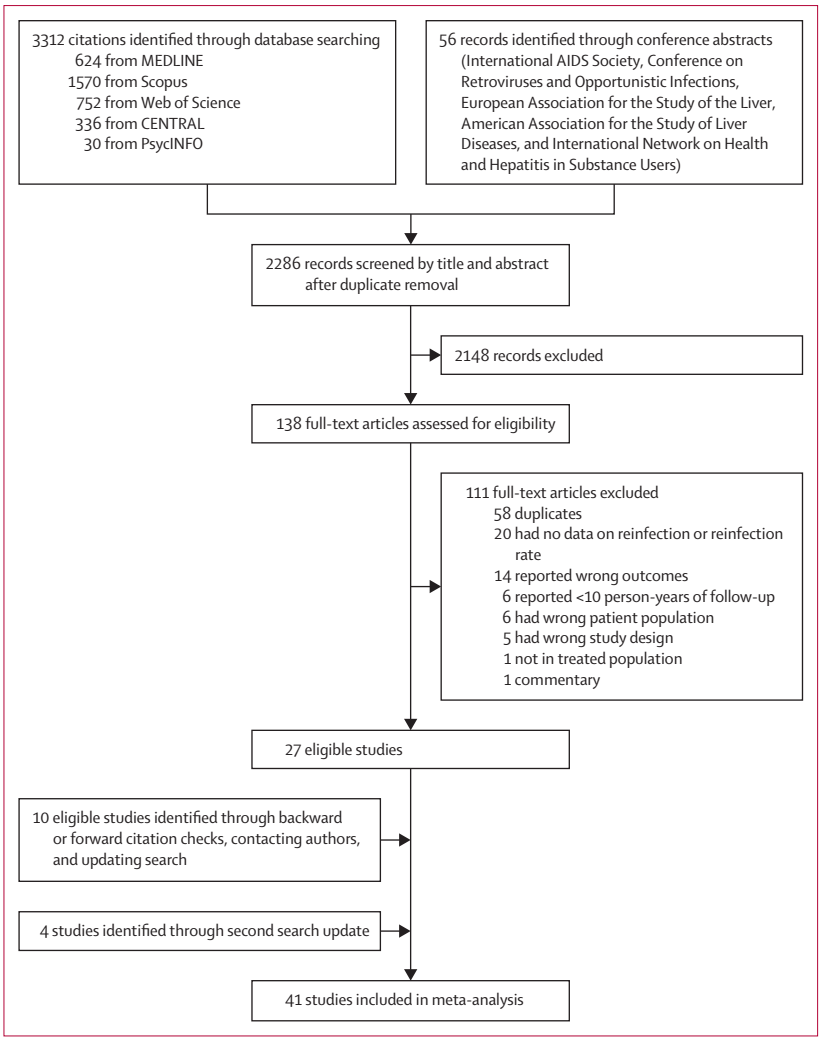


Figure 1: **Study selection**
CENTRAL=Cochrane Central Register of Controlled Trials.

abstracts of all retrieved studies were reviewed (by SH-H, SB, and MM). The full texts of potentially eligible records were reviewed independently by two reviewers (SH-H and SB), and eligible studies were selected for inclusion. In the case of multiple publications of one study or cohort, the publication with the most up-to-date data was included.

Data extraction of study summary estimates from the eligible studies was performed using a standardised spreadsheet. The extracted data included the items related to study design and setting, definition of MSM and people who inject drugs, study participant characteristics, HCV infection type, HCV treatment, follow-up after treatment, and HCV reinfection. Corresponding authors were contacted if data were missing or if supplementary data were required; the authors of 36 included publications were contacted and additional data were provided for 26 studies. The data were extracted by the first reviewer (SH-H) and double-checked by the second reviewer (SB). Disagreement between the two reviewers was resolved by discussion with the third reviewer (MM).

The study protocol is registered with PROSPERO, CRD42019146973.

Data analysis

The risk of bias for the included studies was assessed using a modified scale derived from the Newcastle-Ottawa quality assessment scale for cohort studies,[8] including nine questions in three domains: selection (three questions), exposure (two questions), and outcome (four questions), with a total score of 10 (appendix pp 3–5). For each domain, loss of one point was considered to be moderate risk of bias and loss of more than one point was considered to be high risk of bias. Critical appraisal was carried out by three reviewers (SH-H, SB, and MM), with discrepancies discussed in the group to reach consensus.

The primary outcome was the incidence of HCV reinfection. HCV reinfection was defined as the detection of HCV RNA following the end of treatment response (ie, non-quantifiable HCV RNA at the end of treatment) or following sustained virological response (ie, non-quantifiable HCV RNA at 12 weeks or 24 weeks after the end of treatment). In studies using end of treatment to indicate the beginning of the time at risk of HCV reinfection, HCV RNA recurrence was considered to be reinfection if HCV sequencing or genotype data were used to confirm detection of infection with an HCV strain, subtype, or genotype distinct from the virus before treatment. In the studies using sustained virological response to indicate the beginning of the time at risk of HCV reinfection, any HCV RNA recurrence was considered to be reinfection, given the low likelihood of viral relapse after sustained virological response.[9,10] For each included study, the incidence of HCV reinfection was calculated using the reported number of reinfection cases and person-years of follow-up. A fixed continuity correction of 0·5 was applied in studies with no cases of reinfection. Log-transformed rates were used in all analyses and back transformed for reporting. Heterogeneity across studies was assessed using the I^2 statistic (ie, low heterogeneity <25%, moderate heterogeneity 25–75%, and high heterogeneity >75%).[11] Random-effect meta-analysis models using the metan command in Stata were used to cumulate the rate estimates. Meta-analyses were performed among all people living with HIV and key subpopulations, including MSM and people who inject drugs (ever and recent). Furthermore, stratified analyses were carried out by HCV infection type (recent *vs* chronic), HCV treatment (interferon-based therapy *vs* direct-acting antivirals *vs* a combination of both therapies), and exclusive risk groups among MSM (MSM with no history *vs* a history *vs* unknown history of injecting drug use).

Study-level factors contributing to heterogeneity of reinfection estimates were assessed by meta-regression

	Participants								Follow-up after treatment				
	Mean or median age, years	Total	Men	MSM	People who inject drugs	Receiving ART	Suppressed HIV viral load	Cirrhosis	Start point	HCV testing schedule	Mean or median duration, months	Loss to follow-up	Person-years of follow-up
Adekunle et al, 2020 (USA)[14]	60	108	108 (100·0%)	NR	NR	108 (100·0%)	89 (82·4%)	43 (39·8%)	ETR	NR	3	0	25
Adu et al, 2021 (Canada)[36]	45	112	112 (100·0%)	112 (100·0%)	47 (42·0%)	NR	NR	NR	SVR at 12 weeks	NR	44	NR	460
Akiyama et al, 2020 (USA)[15]	55	19	14 (73·7%)	NR	16 (84·2%)	NR	NR	2 (10·5%)	ETR	Every 6 months	24	NR	39
Alessio et al, 2020 (Italy)[48]	52	235	180 (76·6%)	13 (5·5%)	147 (62·6%)	235 (100·0%)	222 (94·5%)	84 (35·7%)	ETR	Variable	12	0	54
Beiser et al, 2019 (USA)[16]	53	39	34 (87·2%)	0	39 (100·0%)	37 (94·9%)	36 (92·3%)	12 (30·8%)	ETR	Variable	23	0	68
Berenguer et al, 2019 (Spain)[17]	NR	2359	NR	177 (7·5%)	1459 (61·8%)	NR	NR	NR	SVR at 12 weeks	Variable	18	NR	3546
Boerekamps et al, 2019 (Belgium and Netherlands)[18]	47	72	72 (100·0%)	72 (100·0%)	NR	72 (100·0%)	70 (97·2%)	0	ETR	NR	3	0	17
Boyd et al, 2020 (France)[19]	45	28	28 (100·0%)	28 (100·0%)	5 (17·9%)	28 (100·0%)	26 (92·9%)	0	ETR	NR	3	NR	13
Busschots et al, 2021 (Belgium)[49]	NR	180	NR	NR	NR	NR	NR	NR	SVR at 12 or 24 weeks	NR	23	NR	349
Byrne et al, 2020 (Scotland [UK])[50]	NR	44	30 (68·2%)	NR	39 (88·6%)	44 (100·0%)	NR	16 (36·4%)	SVR at 12 weeks	Every 12 months	136	2 (4·1%)	500
Cachay et al, 2019 (Italy, Spain, and USA)[20]	50	730	546 (74·8%)	69 (9·5%)	56 (7·7%)	NR	645 (88·4%)	226 (31·0%)	ETR	NR	3	0	168
Centeno et al, 2021 (Spain)[51]	41	47	47 (100·0%)	47 (100·0%)	NR	47 (100·0%)	47 (100·0%)	NR	SVR at 12 weeks	Variable	11	NR	44
Chaillon et al, 2019 (USA)[21]	50	43	43 (100·0%)	43 (100·0%)	NR	NR	NR	9 (20·9%)	SVR at 12 or 24 weeks	Variable	29	0	104
Chkhartishvili et al, 2020 (Georgia [USA])[22]	46	274	242 (88·3%)	14 (5·1%)	201 (73·4%)	274 (100·0%)	239 (87·2%)	NR	SVR at 12 weeks	Variable	22	0	507
Chromy et al, 2019 (Austria)[23]	41	72	70 (97·2%)	66 (91·7%)	6 (8·3%)	70 (97·2%)	53 (73·6%)	6 (8·3%)	SVR at 12 weeks	Every 3 months	8	0	154
Domínguez-Domínguez et al, 2019 (Spain)[24]	51	397	297 (74·8%)	19 (4·8%)	335 (84·4%)	391 (98·5%)	376 (94·7%)	120 (30·2%)	ETR	Variable	6	10 (2·5%)	183
Factor et al, 2020 (USA)[25]	48	218	218 (100·0%)	218 (100·0%)	70 (32·1%)	NR	146 (67·0%)	NR	ETR	Variable	24	NR	433
Garcia-Retortillo et al, 2020 (Spain)[26]	48	31	20 (64·5%)	0	31 (100·0%)	29 (93·5%)	27 (87·1%)	2 (6·5%)	SVR at 12 weeks	Every 6 months	5	NR	14
Girometti et al, 2019 (UK)[27]	44	29	29 (100·0%)	29 (100·0%)	11 (37·9%)	29 (100·0%)	28 (96·6%)	0	SVR at 12 weeks	Variable	38	2 (6·9%)	91
Hill et al, 2020 (USA)[28]	52	200	170 (85·0%)	112 (56·0%)	118 (59·0%)	NR	184 (92·0%)	NR	SVR at 12 weeks	NR	20	NR	328
Hosseini-Hooshyar et al, 2020 (Australia)[29]	49	268	254 (94·8%)	223 (83·2%)	96 (35·8%)	251 (93·7%)	229 (85·4%)	40 (14·9%)	ETR	NR	21	NR	461
Huang et al, 2019 (Taiwan)[30]	34	103	103 (100·0%)	103 (100·0%)	0	103 (100·0%)	88 (85·4%)	0	ETR	Variable	20	0	174
Huhn et al, 2020 (USA)[31]	53	140	104 (74·3%)	NR	NR	140 (100·0%)	140 (100·0%)	16 (11·4%)	ETR	NR	3	2 (1·4%)	32
Hullegie et al, 2016 (Netherlands)[53]	40	49	49 (100·0%)	49 (100·0%)	NR	NR	NR	NR	ETR	NR	3	0	11

(Table 1 continues on next page)

	Participants								Follow-up after treatment				
	Mean or median age, years	Total	Men	MSM	People who inject drugs	Receiving ART	Suppressed HIV viral load	Cirrhosis	Start point	HCV testing schedule	Mean or median duration, months	Loss to follow-up	Person-years of follow-up
(Continued from previous page)													
Ingiliz et al, 2017 (Austria, France, Germany, and UK)[32]	39	451	451 (100·0%)	451 (100·0%)	NR	NR	NR	NR	ETR	Variable	35	0	1587
Ingiliz et al, 2020 (Germany)[33]	47	509	442 (86·3%)	245 (48·1%)	152 (30·0%)	NR	432 (84·9%)	86 (16·9%)	ETR	Variable	20	NR	830
Marco et al, 2019 (Spain)[34]	41	173	164 (94·8%)	NR	159 (91·9%)	NR	NR	NR	SVR at 24 weeks	Every 12 months	32	0	464
Martinello et al, 2017 (Australia and New Zealand)[35]	44	64	64 (100·0%)	64 (100·0%)	39 (60·9%)	52 (81·3%)	32 (50·0%)	0	ETR	Variable	13	0	68
Newsum et al, 2021 (Netherlands)[37]	45	112	112 (100·0%)	112 (100·0%)	8 (7·1%)	103 (92·0%)	91 (81·3%)	NR	ETR	Every 6 months	27	NR	248
Pineda et al, 2015 (Spain)[38]	44	84	68 (81·0%)	NR	72 (85·7%)	NR	73 (86·9%)	NR	SVR at 24 weeks	Every 12 months	34	NR	331
Rockstroh et al, 2015 (Australia, Canada, Denmark, France, Germany, Israel, Spain, UK, and USA)[39]	49	212	175 (82·5%)	NR	NR	211 (99·5%)	211 (99·5%)	35 (16·5%)	ETR	Variable	3	2 (1·0%)	49
Rockstroh et al, 2017 (Canada, France, Germany, Italy, New Zealand, Puerto Rico, Russia, Spain, UK, and USA)[40]	49	221	175 (79·2%)	NR	105 (47·5%)	221 (100·0%)	215 (97·3%)	21 (9·5%)	ETR	Variable	3	NR	51
Rossi et al, 2018 (Canada)[41]	52	573	439 (76·6%)	212 (37·0%)	500 (87·3%)	NR	NR	NR	SVR at 12 weeks	NR	12	NR	716
Selfridge et al, 2019 (Canada)[42]	54	50	40 (80·0%)	0	50 (100·0%)	37 (74·0%)	37 (74·0%)	15 (30·0%)	ETR	Variable	24	1 (2·0%)	98
Soriano et al, 2004 (Spain)[43]	34	77	68 (88·3%)	NR	NR	53 (68·8%)	NR	NR	SVR at 24 weeks	NR	58	NR	372
Sulkowski et al, 2015 (Puerto Rico and USA)[44]	51	60	55 (91·7%)	NR	21 (35·0%)	60 (100·0%)	58 (96·7%)	10 (16·7%)	ETR	Variable	3	NR	14
Swain et al, 2010 (country NR)[10]	NR	100	82 (82·0%)	NR	NR	NR	NR	NR	SVR at 24 weeks	NR	48	NR	398
Valencia et al, 2019 (Spain)[45]	46	53	41 (77·4%)	NR	53 (100·0%)	52 (98·1%)	50 (94·3%)	11 (20·8%)	SVR at 12 weeks	Variable	12	2 (3·8%)	54
Ward et al, 2019 (USA)[46]	55	101	62 (61·4%)	NR	NR	98 (97·0%)	81 (80·2%)	NR	ETR	Variable	3	0	23
Wyles et al, 2021 (USA)[52]	53	130	105 (80·8%)	NR	56 (43·1%)	130 (100·0%)	124 (95·4%)	NR	ETR	Every 12 months	66	0	593
Young et al, 2017 (Canada)[47]	49	257	212 (82·5%)	70 (27·2%)	190 (73·9%)	236 (91·8%)	224 (87·2%)	54 (21·0%)	SVR at 12 weeks	Every 6 months	18	45 (17·5%)	589

Data are n (%), mean (SD), or median (IQR). MSM=men who have sex with men. ART=antiretroviral therapy. HCV=hepatitis C virus. NR=not reported. ETR=end of treatment. SVR=sustained virological response.

Table 1: **Participant and follow-up characteristics of the studies included in the meta-analysis**

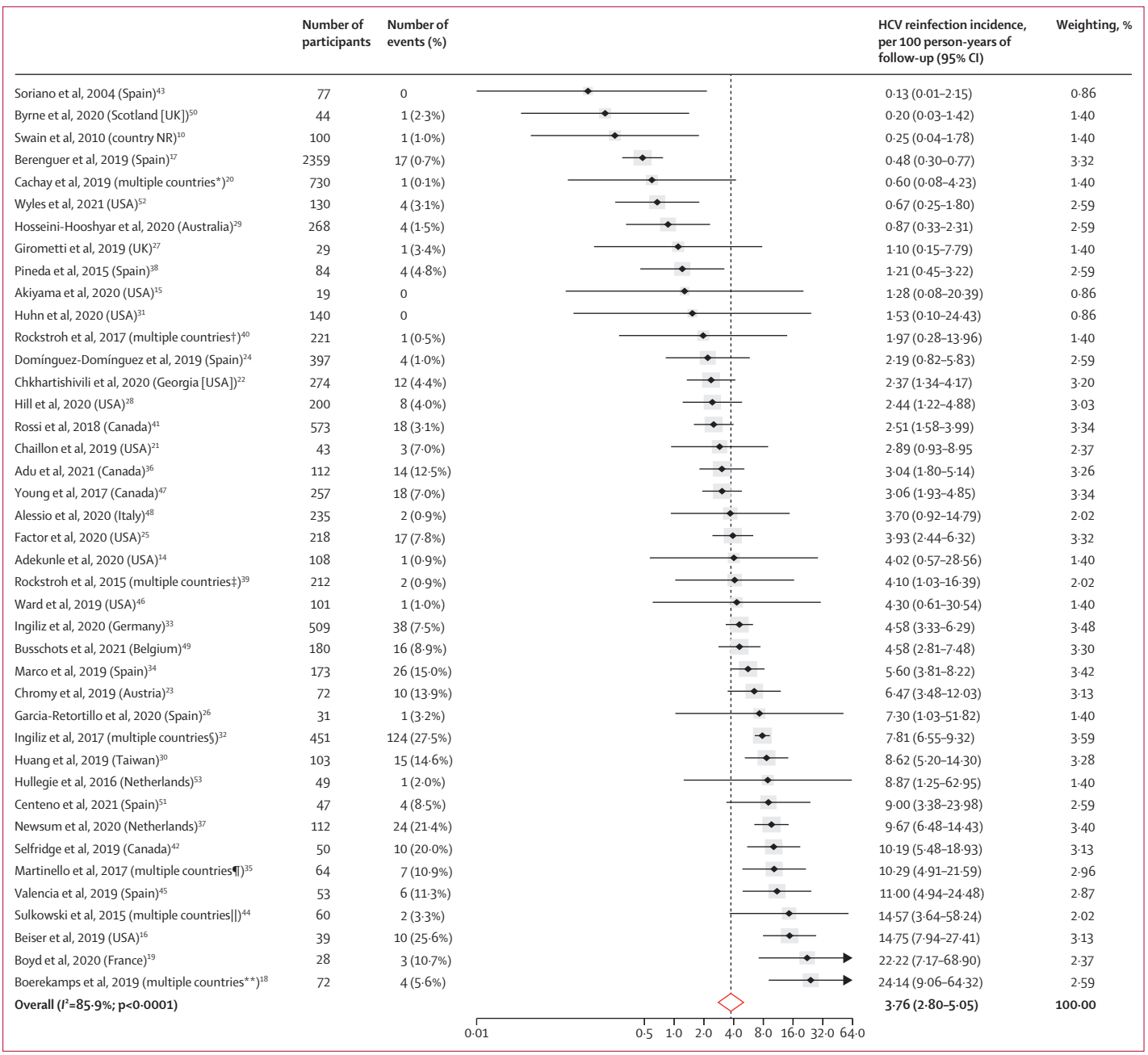
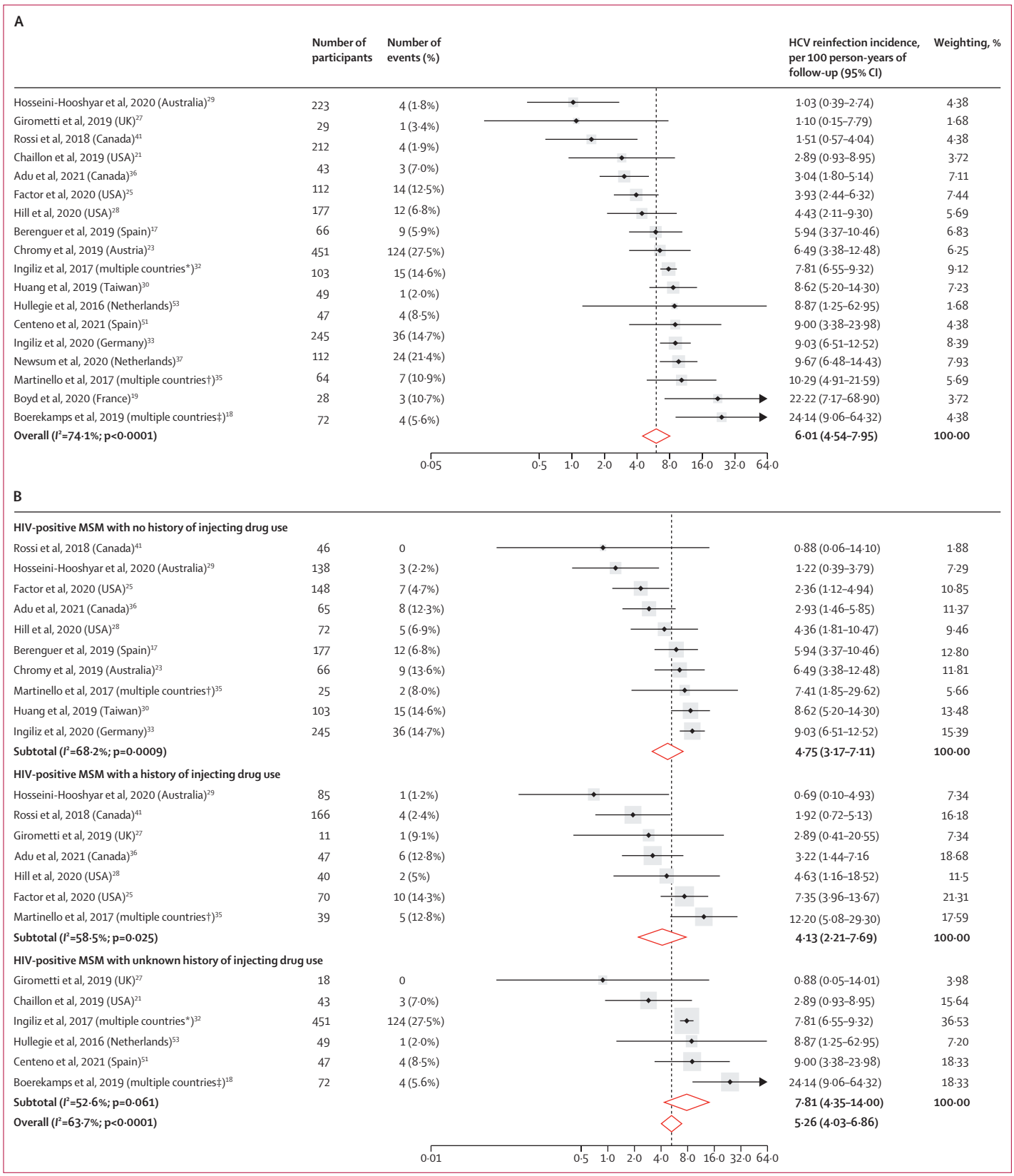


Figure 2: **Forest plot of HCV reinfection incidence among people living with HIV**
Weights are from random-effects analyses. HCV=hepatitis C virus. NR=not reported. *Italy, Spain, and the USA. †Canada, France, Germany, Italy, New Zealand, Puerto Rico, Russia, Spain, the UK, and the USA. ‡Australia, Canada, Denmark, France, Germany, Israel, Spain, the UK, and the USA. §Austria, France, Germany, and the UK. ¶Australia and New Zealand. ||Puerto Rico and the USA. **Belgium and the Netherlands.

using the metareg command in Stata. Covariates were determined a priori and included age (mean and median), study design (clinical trial, prospective observational, retrospective observational, and retrospective linkage observational), risk population (proportion of MSM, proportion of people who inject drugs, or both), CD4 cell count (mean and median), HIV viral load (proportion suppressed), HCV infection type (recent or chronic), HCV treatment (interferon-based therapy, direct-acting antivirals, or a combination of both therapies), months of follow-up after treatment (mean and median), visit when HCV reinfection risk assessment began (end of treatment or sustained virological response), and study quality assessment (risk of bias) score. The final adjusted model included variables with p<0·10 in unadjusted analyses (0·10 was used as the p value cutoff to avoid model


A
Number of participants
Number of events (%)
HCV reinfection incidence, per 100 person-years of follow-up (95% CI)
Weighting, %
Hosseini-Hooshyar et al, 2020 (Australia)[29] 223 4 (1·8%) 1·03 (0·39–2·74) 4·38
Girometti et al, 2019 (UK)[27] 29 1 (3·4%) 1·10 (0·15–7·79) 1·68
Rossi et al, 2018 (Canada)[41] 212 4 (1·9%) 1·51 (0·57–4·04) 4·38
Chaillon et al, 2019 (USA)[21] 43 3 (7·0%) 2·89 (0·93–8·95) 3·72
Adu et al, 2021 (Canada)[36] 112 14 (12·5%) 3·04 (1·80–5·14) 7·11
Factor et al, 2020 (USA)[25] 177 12 (6·8%) 3·93 (2·44–6·32) 7·44
Hill et al, 2020 (USA)[28] 66 9 (5·9%) 4·43 (2·11–9·30) 5·69
Berenguer et al, 2019 (Spain)[17] 451 124 (27·5%) 5·94 (3·37–10·46) 6·83
Chromy et al, 2019 (Austria)[23] 103 15 (14·6%) 6·49 (3·38–12·48) 6·25
Ingiliz et al, 2017 (multiple countries*)[32] 49 1 (2·0%) 7·81 (6·55–9·32) 9·12
Huang et al, 2019 (Taiwan)[30] 47 4 (8·5%) 8·62 (5·20–14·30) 7·23
Hullegie et al, 2016 (Netherlands)[53] 245 36 (14·7%) 8·87 (1·25–62·95) 1·68
Centeno et al, 2021 (Spain)[51] 112 24 (21·4%) 9·00 (3·38–23·98) 4·38
Ingiliz et al, 2020 (Germany)[33] 64 7 (10·9%) 9·03 (6·51–12·52) 8·39
Newsum et al, 2020 (Netherlands)[37] 28 3 (10·7%) 9·67 (6·48–14·43) 7·93
Martinello et al, 2017 (multiple countries†)[35] 72 4 (5·6%) 10·29 (4·91–21·59) 5·69
Boyd et al, 2020 (France)[19] 22·22 (7·17–68·90) 3·72
Boerekamps et al, 2019 (multiple countries‡)[18] 24·14 (9·06–64·32) 4·38
Overall (I²=74·1%; p<0·0001) 6·01 (4·54–7·95) 100·00
0·05 0·5 1·0 2·0 4·0 8·0 16·0 32·0 64·0
B
HIV-positive MSM with no history of injecting drug use
Rossi et al, 2018 (Canada)[41] 46 0 0·88 (0·06–14·10) 1·88
Hosseini-Hooshyar et al, 2020 (Australia)[29] 138 3 (2·2%) 1·22 (0·39–3·79) 7·29
Factor et al, 2020 (USA)[25] 148 7 (4·7%) 2·36 (1·12–4·94) 10·85
Adu et al, 2021 (Canada)[36] 65 8 (12·3%) 2·93 (1·46–5·85) 11·37
Hill et al, 2020 (USA)[28] 72 5 (6·9%) 4·36 (1·81–10·47) 9·46
Berenguer et al, 2019 (Spain)[17] 177 12 (6·8%) 5·94 (3·37–10·46) 12·80
Chromy et al, 2019 (Australia)[23] 66 9 (13·6%) 6·49 (3·38–12·48) 11·81
Martinello et al, 2017 (multiple countries†)[35] 25 2 (8·0%) 7·41 (1·85–29·62) 5·66
Huang et al, 2019 (Taiwan)[30] 103 15 (14·6%) 8·62 (5·20–14·30) 13·48
Ingiliz et al, 2020 (Germany)[33] 245 36 (14·7%) 9·03 (6·51–12·52) 15·39
Subtotal (I²=68·2%; p=0·0009) 4·75 (3·17–7·11) 100·00
HIV-positive MSM with a history of injecting drug use
Hosseini-Hooshyar et al, 2020 (Australia)[29] 85 1 (1·2%) 0·69 (0·10–4·93) 7·34
Rossi et al, 2018 (Canada)[41] 166 4 (2·4%) 1·92 (0·72–5·13) 16·18
Girometti et al, 2019 (UK)[27] 11 1 (9·1%) 2·89 (0·41–20·55) 7·34
Adu et al, 2021 (Canada)[36] 47 6 (12·8%) 3·22 (1·44–7·16 18·68
Hill et al, 2020 (USA)[28] 40 2 (5%) 4·63 (1·16–18·52) 11·5
Factor et al, 2020 (USA)[25] 70 10 (14·3%) 7·35 (3·96–13·67) 21·31
Martinello et al, 2017 (multiple countries†)[35] 39 5 (12·8%) 12·20 (5·08–29·30) 17·59
Subtotal (I²=58·5%; p=0·025) 4·13 (2·21–7·69) 100·00
HIV-positive MSM with unknown history of injecting drug use
Girometti et al, 2019 (UK)[27] 18 0 0·88 (0·05–14·01) 3·98
Chaillon et al, 2019 (USA)[21] 43 3 (7·0%) 2·89 (0·93–8·95) 15·64
Ingiliz et al, 2017 (multiple countries*)[32] 451 124 (27·5%) 7·81 (6·55–9·32) 36·53
Hullegie et al, 2016 (Netherlands)[53] 49 1 (2·0%) 8·87 (1·25–62·95) 7·20
Centeno et al, 2021 (Spain)[51] 47 4 (8·5%) 9·00 (3·38–23·98) 18·33
Boerekamps et al, 2019 (multiple countries‡)[18] 72 4 (5·6%) 24·14 (9·06–64·32) 18·33
Subtotal (I²=52·6%; p=0·061) 7·81 (4·35–14·00) 100·00
Overall (I²=63·7%; p<0·0001) 5·26 (4·03–6·86)
0·01 0·5 1·0 2·0 4·0 8·0 16·0 32·0 64·0

instability). Statistical significance was assessed at p<0·05 (two-sided p values). Publication bias was explored by constructing the funnelplots[12] and computing the Egger's test[13] using the metafunnel and metabias commands in Stata. Stata (version 14.2) was used for all statistical analyses.

Role of the funding source

There was no funding source for this study.

Results

Our search retrieved a total of 3368 citations. After several stages of reviews, 41 eligible studies were included in the analysis (figure 1), with a total of 9024 participants and 14263 person-years of follow-up (appendix pp 6–10). The study designs of the included studies were retrospective observational (17 studies), clinical trial (13 studies), prospective observational (nine studies), and retrospective linkage observational (two studies). Included studies were conducted in the European region (33 studies), region of the Americas (20 studies), and Western Pacific region (six studies). Studies were mostly conducted in tertiary care (24 studies) or mixed settings (11 studies), with 31 multicentre studies and ten in single-centre locations.

Most studies included individuals with chronic HCV infection (32 studies), compared with recent HCV infection (nine studies). HCV treatment was direct-acting antiviral therapy (24 studies), interferon-based therapy (eight studies), or a combination of both (nine studies). In most studies, assessment of HCV reinfection started from end of treatment (23 studies) or from non-quantifiable HCV RNA at 12 weeks (12 studies). Diagnosis of reinfection was mostly based on only recurrent viraemia following sustained virological response (15 studies) or incorporated HCV sequencing, or genotype or subtype switch (11 studies).

The risk of bias assessment is shown in the appendix (pp 4–5). Three studies had low risk of bias in all three domains, 21 studies had moderate or high risk of bias in one domain, and 13 studies had moderate or high risk of bias in two domains. No study had moderate or high risk of bias in all three domains.

Data on the incidence of HCV reinfection were available in 41 studies (14263 person-years of follow-up) for people living with HIV,[10,14–52] in 18 studies (4802 person-years follow-up) for HIV-positive MSM,[17–19,21,23,25,27–30,32,33,35–37,41,51,53] in 19 studies (5511 person-years of follow-up) for HIV-positive people who inject drugs,[15–17,22–29,33–36,38,41,42,45] and in four studies (402 person-years of follow-up) for HIV-positive people who inject drugs with recent injecting drug use (table 1).[25,27,29,42]

The pooled estimates of reinfection incidence were 3·76 cases per 100 person-years of follow-up (95% CI 2·80–5·05; I^2 85·9%) among people living with HIV overall (figure 2), 6·01 (4·54–7·95; 74·1%) among HIV-positive MSM (figure 3A), 3·29 (2·01–5·39; 83·9%) among HIV-positive people who inject drugs (figure 4A), and 5·49 (2·08–14·48; 72·1%) among HIV-positive people who inject drugs with recent injecting drug use (figure 4B).

Among HIV-positive MSM, pooled estimates of reinfection incidence were 4·75 cases per 100 person-years of follow-up (95% CI 3·17–7·11; 68·2%) among those with no history of injecting drug use (ten studies with 1927 person-years of follow-up), 4·13 (2·21–7·69; 58·5%) among those with a history of injecting drug use (seven studies with 793 person-years of follow-up), and 7·81 (4·35–14·00; 52·6%) among those with an unknown history of injecting drug use (six studies with 1820 person-years of follow-up; figure 3B).

Stratified analysis by HCV treatment indicated a similar incidence of reinfection in participants following interferon-based therapy (4·92 cases per 100 person-years of follow-up, 95% CI 3·30–7·32; I^2 78·3%), direct-acting antiviral therapy (3·88, 2·51–6·01; 85·4%), and a combination of interferon-based and direct-acting antiviral therapy (3·41, 1·77–6·59; 74·5%; appendix p 11).

Stratified analysis by HCV infection type indicated a higher incidence of reinfection among participants with recent HCV infection (8·16 cases per 100 person-years of follow-up, 95% CI 5·77–11·54; 64·1%) than among those with chronic HCV infection (2·89, 2·03–4·12; 83·8%; appendix p 12).

In the unadjusted meta-regression, a higher proportion of MSM (ie, ≥85%) in the study population, recent HCV infection, and starting reinfection follow-up from end of treatment were associated with an increased incidence of reinfection, whereas a longer duration of follow-up after treatment was associated with a decreased incidence of reinfection (table 2).

Given that all the studies among individuals with recent HCV infection had included HIV-positive MSM as their main study population, we conducted two adjusted meta-regression models. In the first adjusted model, we included the proportion of MSM in the study population, duration of follow-up after treatment, and the start point for reinfection assessment, and we excluded HCV infection status. Compared with a lower proportion of MSM in the study population (ie, <85%), a higher proportion of MSM was associated with a higher incidence of reinfection (adjusted rate ratio [RR] 2·66, 95% CI 1·37–5·15; p=0·0049). No association was found between studies with an unknown proportion of MSM and incidence of reinfection (1·28, 0·62–2·64; p=0·50). A longer duration of follow-up

Figure 3: **Forest plot of HCV reinfection incidence among HIV-positive MSM**
HCV reinfection incidence among HIV-positive MSM overall (A) and among HIV-positive MSM with no history, a history, or unknown history of injecting drug use (B). HCV=hepatitis C virus. MSM=men who have sex with men. *Austria, France, Germany, and the UK. †Australia and New Zealand. ‡Belgium and the Netherlands.

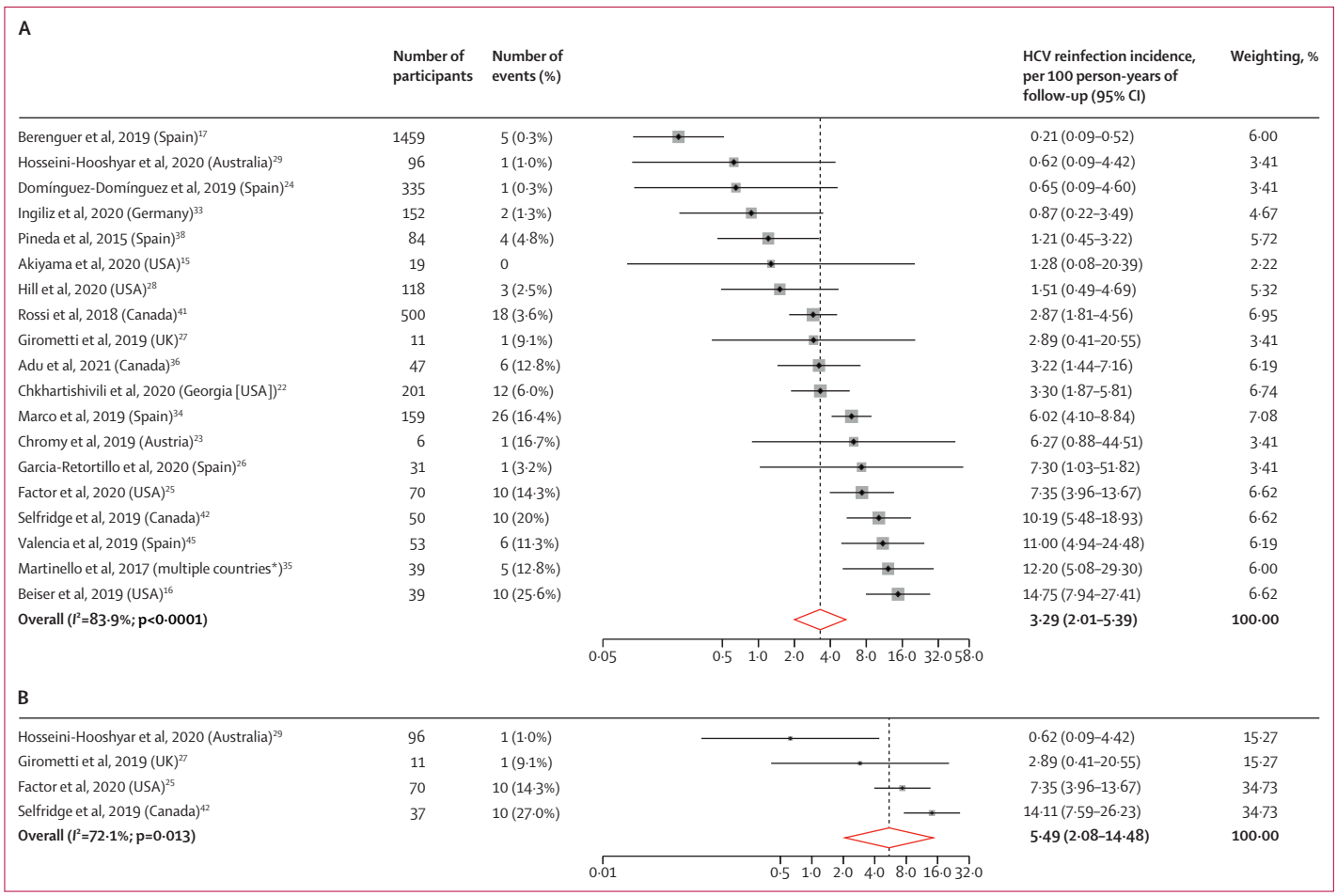


Figure 4: **Forest plot of HCV reinfection incidence among HIV-positive people who inject drugs**
HCV reinfection incidence among HIV-positive people who inject drugs overall (A) and among HIV-positive people who inject drugs with recent injecting drug use (B). HCV=hepatitis C virus. *Australia and New Zealand.

after treatment was associated with a decreased incidence of reinfection (0·97, 0·96–0·99; p=0·0012). Compared with starting reinfection assessments following sustained virological response at 12 weeks or later, starting these assessments at the end of treatment was not associated with a higher incidence of reinfection (1·47, 0·82–2·62; p=0·19).

The second adjusted model included HCV infection status, duration of follow-up following treatment, and the start point for reinfection assessment, and excluded the proportion of MSM in the study population. This model indicated that, compared with individuals with chronic HCV infection, people with recent HCV infection had a higher incidence of reinfection (adjusted RR 2·22, 95% CI 1·09–4·55; p=0·029). Similarly to the first model, longer duration of follow-up after treatment was associated with a lower incidence of reinfection (0·97, 0·96–0·99; p=0·0025). Compared with starting reinfection assessments following sustained virological response at 12 weeks or later, no association was found between starting assessments at the end of treatment studies and incidence of reinfection (1·35, 0·72–2·54; p=0·33).

The residual I^2 values were 77·42% in the first adjusted meta-regression model and 79·61% in the second adjusted model.

The funnel plot analysis of HCV reinfection rate showed asymmetry (p=0·040), indicating that publication bias could have influenced the meta-analysis (appendix p 13).

Discussion

This study presents a comprehensive overview of the incidence of HCV reinfection among people living with HIV, overall and among key populations at risk. The pooled estimates of HCV reinfection incidence following successful therapy were 3·76 cases per 100 person-years follow-up among people living with HIV, 6·01 among HIV-positive MSM, and 3·29 among HIV-positive people who inject drugs. Among HIV-positive MSM, a similar incidence of HCV reinfection was observed in individuals with no history of injecting drug use and in those with a history of injecting drug use. In meta-regression analyses,

a higher proportion of MSM in the study population and recent HCV infection were associated with an increased risk of reinfection, whereas a longer duration of follow-up after treatment was associated with a decreased risk.

Among people living with HIV in this study, the incidence of HCV reinfection following treatment (3·76 cases per 100 person-years of follow-up) was similar to that reported in a previous systematic review conducted in the era of interferon therapy (3·20 cases per 100 person-years of follow-up, 95% CI 0·00–12·35).[4] The incidence in the previous review was derived from four studies with heterogeneous study populations and highly variable reinfection rates, ranging from 0·0 cases per 100 person-years of follow-up in two clinical trials (excluding people who inject drugs)[10,54] to 9·6 among MSM at high risk[55] and 13·4 among people who were incarcerated.[56] The present analysis extends our understanding of contemporary risk of HCV reinfection among people living with HIV, with the inclusion of studies among people with different risk profiles and those receiving direct-acting antiviral therapy.

The pooled estimate of HCV reinfection incidence among HIV-positive MSM (6·01 cases per 100 person-years of follow-up) was higher in our analysis than in reports of primary HCV infection in this population. In a meta-analysis of 39 studies of HIV-positive MSM,[57] incidence of HCV was 0·85 cases per 100 person-years of follow-up, ranging from 0·68 cases to 1·03 cases per 100 person-years of follow-up. Ongoing higher HCV risk behaviour almost certainly explains higher HCV reinfection incidence compared with primary infection among HIV-positive MSM, which is not surprising given that all of this population have previously been infected. These findings are similar to a previous review among HIV-positive MSM, indicating an incidence of reinfection that was 20 times higher than that of primary infection.[5]

Incidence of HCV reinfection was similar among HIV-positive MSM with and without a history of injecting drug use, although higher among MSM with an unknown history of injecting drug use. Reinfection might be related to recurring high-risk sexual exposures, unsafe injecting practices, or both. Changes in sexual behaviour among MSM have been reported following advances in HIV treatment and prevention (eg, pre-exposure prophylaxis), including increases in so-called chemsex and reductions in consistent condom use with casual male partners.[58,59] Behavioural interventions that reduce risk of HCV transmission, in combination with high uptake of direct-acting antivirals, are a central part of continuing efforts to eliminate HCV among MSM.[60] Thus, strategies that enable individuals to form and maintain safe sexual and injecting practices are essential,[61] despite perceived difficulties in enacting behavioural modification.[62] Furthermore, in this study, reinfection incidence was higher among people living with HIV with a recent history of injecting drug use (5·49 cases per 100 person-years of follow-up) than in those with a lifetime history of injecting drug use (3·29 cases per 100 person-years of follow-up), indicating the importance of optimising access to harm reduction for those with ongoing injecting risk behaviours. Little evidence is available on the incidence of HCV reinfection among people living with HIV who inject drugs. However, our estimates of HCV reinfection incidence among those with recent injecting drug use are consistent with those reported among people who have recently injected drugs (6·2 cases per 100 person-years of follow-up).[63]

The incidence of HCV reinfection was higher among people treated for recent HCV infection (8·16 cases per

	Studies with available data (n=41)	Rate ratio (95% CI)	p value
Age, per year increase	37 (90%)	0·97 (0·91–1·03)	0·270
Study design			
Retrospective observational study	19 (46%)	1 (ref)	..
Prospective observational study	9 (22%)	0·67 (0·29–1·55)	0·34
Clinical trial	13 (32%)	1·79 (0·75–4·27)	0·18
Proportion of MSM in study population			
<85%	13 (32%)	1 (ref)	..
≥85%	13 (32%)	2·54 (1·16–5·57)	0·021
Unknown	15 (37%)	0·84 (0·37–1·93)	0·68
Proportion of people who inject drugs in study population			
<60%	14 (34%)	1 (ref)	..
≥60%	15 (37%)	0·91 (0·39–2·15)	0·83
Unknown	12 (29%)	1·14 (0·43–3·00)	0·79
CD4 count, per 100 cell increase in number	29 (71%)	0·93 (0·51–1·69)	0·801
Suppressed viral load, per 10% increase	29 (71%)	0·89 (0·63–1·25)	0·49
HCV status			
Chronic	32 (78%)	1 (ref)	..
Recent	9 (22%)	2·88 (1·33–6·24)	0·0088
HCV treatment			
Direct-acting antiviral therapy	24 (59%)	1 (ref)	..
Interferon-based therapy	8 (20%)	0·75 (0·28–2·01)	0·55
Combination therapy	9 (22%)	1·12 (0·46–2·74)	0·80
Duration of follow-up, per month increase	41 (100%)	0·97 (0·96–0·99)	0·001
Start point for reinfection assessment			
12 weeks after treatment or later	18 (44%)	1 (ref)	..
End of treatment	23 (56%)	2·10 (1·05–4·18)	0·035
Study quality assessment score	41 (100%)	1·00 (0·66–1·51)	0·99

Data are n (%), unless otherwise indicated. HCV=hepatitis C virus. MSM=men who have sex with men.

Table 2: **Unadjusted meta-regression analysis of study-level factors associated with HCV reinfection incidence among people living with HIV**

100 person-years of follow-up) than among those with chronic HCV infection (2·89 cases per 100 person-years of follow-up). Additionally, our meta-regression findings showed a significantly higher incidence of HCV reinfection in studies enrolling individuals with recent HCV infection than in those enrolling individuals with chronic HCV infection. Recency of HCV acquisition is strongly suggestive of current risk behaviour. However, awareness of recent HCV infection and risk behaviour patterns could influence clinical practice and HCV testing frequency, facilitating diagnosis of reinfection.[64,65] We further observed a lower incidence of HCV reinfection in studies with longer duration of follow-up after treatment. This finding could be explained by an increased risk of reinfection in the early period following treatment completion or by the fact that individuals at high risk tend to contribute shorter person-years of follow-up due to early reinfection after treatment or loss to follow-up.[63] Nevertheless, regular HCV assessment following treatment is required to detect and treat reinfection early, particularly in populations with recent HCV infection because they are at increased risk of reinfection.

In this meta-analysis, the incidence of HCV reinfection in studies of direct-acting antiviral-based therapies (3·88 cases per 100 person-years of follow-up) was similar, although lower, than the incidence in studies of interferon-based therapies (4·92 cases per 100 person-years of follow-up). These findings are in line with a 2020 systematic review and meta-analysis,[63] which evaluated HCV reinfection following treatment among people who inject drugs, and adds to the evidence ameliorating concerns about reinfection risk following direct-acting antiviral therapy. In addition, studies of direct-acting antiviral treatment have indicated that recent injecting (within the past 6 months) and high-risk sexual practices among MSM remain stable following direct-acting antiviral therapy,[29] and injecting risk behaviours among people who inject drugs[66] remain stable or decrease during and following direct-acting antiviral therapy. Furthermore, broad access to direct-acting antivirals should be assured, with decreases in population-level HCV RNA prevalence and a low incidence of reinfection observed in settings with high uptake of direct-acting antivirals.[29,67–69] Continued monitoring following treatment (with a minimum of annual HCV RNA testing[70,71] in the setting of ongoing risk behaviours) and rapid retreatment of reinfection among people living with HIV are required for HCV elimination targets to be met.[60] Optimised strategies, including education on risk reduction, counselling before and during treatment,[60,61,72] and facilitating access to harm reduction services[73,74] among individuals with an increased risk of reinfection, should be adopted.

The main strengths of this meta-analysis were the large number of included studies, overall population sample, and person-years of follow-up; the well defined study population; and precise data collection. Additionally, we made considerable efforts to contact the authors to obtain supplementary data and extra information that enabled us to conduct subgroup analyses of reinfection risk. However, while collecting and analysing data on different subpopulations at risk (ie, MSM and people who inject drugs), we noted that data on both injecting drug use and sexual risk practices were often poorly reported. In particular, recency of risk behaviour relative to HCV reinfection was inconsistently reported. Mode of HIV or HCV transmission, or both, was used to define the MSM population in most studies, with little to no detail on recent sexual behaviour. Data on injecting drug use was not available in various studies, particularly among MSM populations. This paucity in data might explain the higher incidence of reinfection in the studies with unknown injecting drug use among MSM in our study. Among studies of people living with HIV who inject drugs, injecting drug use was often defined as either the history of injecting drug use or the mode of transmission of HIV or HCV, or a combination of both. Few studies included data on recent or ongoing injecting drug use. Future evaluation of HCV reinfection should include more detailed and granular data on ongoing transmission risk behaviours among people living with HIV, to allow further risk analysis and assessment among this population to enable tailored interventions.

This study has several limitations. First, most of the studies included were conducted in high-income countries with predominantly male study populations; future research should ensure broader representation with gender and ethical diversity. Furthermore, this study carries a potential risk of selection bias towards the inclusion of those who are more likely to be engaged in care, leaving out marginalised individuals who might be at an increased risk of reinfection. Additionally, the funnel plot analysis and the Egger test indicated potential publication bias that could have influenced our pooled estimates. Second, reinfection diagnosis methods varied. For several studies, recurrent viraemia following sustained virological response was the only indicator of reinfection. Although HCV relapse following sustained virological response is rare,[9,10] genotyping or sequencing would be needed to precisely distinguish reinfection from late relapse. Third, our results might have been influenced by a scarcity of data on testing frequency, and loss to follow-up. The HCV testing schedule following treatment and the numbers and percentage of individuals lost to follow-up were not reported or well described in many studies. Fourth, there was high heterogeneity of reinfection incidence across studies overall, and by risk groups. The residual I^2 in our meta-regression models indicated that the heterogeneity might be explained by several other factors not considered in our analysis, such as varying risk profiles or inclusion criteria for study populations, the population-level prevalence and incidence of HCV infection, and the coverage of harm reduction services. We were not able to include these

variables in our analyses given unavailable data from most studies.

In conclusion, the observed incidence of HCV reinfection following successful treatment among people living with HIV was highest among HIV-positive MSM and among those with recent HCV infection. These findings highlight the importance of addressing contemporary sexual and drug use risk behaviours. Further evaluation of data on ongoing transmission risk behaviours is suggested for a refined risk assessment among this population. Screening for and treatment of HCV reinfection, education focused on reinfection prevention, and access to safe sex and harm reduction services are essential. Sustained treatment uptake and innovative models of care aimed at preventing infection and reinfection must be assured to achieve HCV elimination among people living with HIV.

Contributors

SH-H, MM, and GVM conceptualised the review project and developed the study protocol. GJD and BH reviewed the study protocol before it was finalised. SH-H did the literature review. SH-H, SB, and MM screened and reviewed all the published literature, including the title, abstract, and full text. SH-H did the data extraction. SB and MM double-checked the extracted data. SH-H, SB, and MM did the risk of bias assessments. SH-H carried out the meta-analyses and meta-regressions under the supervision of BH and drafted the manuscript under the supervision of MM and GVM. SB, ML, NZJ, DSF, DC, JKR, TCSM, PI, C-CH, and GJD critically reviewed the manuscript and provided feedback. All authors contributed to the interpretation of study results, reviewed the draft manuscript, and approved the final version of the manuscript before its submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

ML reports grants from Gilead Sciences, Janssen-Cilag, and ViiV Healthcare, outside the submitted work. DC reports personal fees from Merck; and non-financial support from Merck, Gilead, and GlaxoSmithKline–ViiV, outside the submitted work. JKR reports personal fees from Abivax, Galapagos, Gilead, Janssen, Merck, and ViiV, outside the submitted work. PI reports grants from Gilead and Abbott; and personal fees from Gilead, MYR Pharmaceuticals, AbbVie, and ViiV, outside the submitted work. C-CH reports grants and personal fees from Gilead Sciences and ViiV, outside the submitted work. GJD reports grants from Gilead Sciences, AbbVie, and Merck, outside the submitted work. GVM reports grants from Gilead and AbbVie, outside the submitted work. All other authors declare no competing interests.

Data sharing

Following publication, data sharing requests will be considered by the group upon written request to the corresponding author. The analytical dataset or other prespecified data will be available subject to a written proposal and a signed data sharing agreement.

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