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ORIGINAL ARTICLE

Determining reinfection rates by hepatitis C testing interval among key populations: A systematic review and meta-analysis

Stephanie C. Munari[1] | Michael W. Traeger[1,2] | Vinay Menon[1] | Ned H. Latham[1] | Lakshmi Manoharan[1] | Niklas Luhmann[3] | Rachel Baggaley[3] | Virginia MacDonald[3] | Annette Verster[3] | Nandi Siegfried[4] | Brian Conway[5] | Marina Klein[6] | Julie Bruneau[7] | Mark A. Stoové[1] | Margaret E. Hellard[1,2,8] | Joseph S. Doyle[1,8]

[1]Disease Elimination Program, Burnet Institute, Melbourne, Australia

[2]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

[3]World Health Organization, Global HIV, Hepatitis and Sexually Transmitted Infections Programmes, Geneva, Switzerland

[4]Independent Clinical Epidemiologist, Cape Town, South Africa

[5]Vancouver Infectious Diseases Centre & Simon Fraser University Vancouver, Canada

[6]Department of Medicine, Faculty of Medicine and Health Sciences, McGill University, Montreal, Canada

[7]Department of Family and Emergency Medicine, Université de Montréal, Montreal, Canada

[8]Department of Infectious Diseases, The Alfred Hospital and Monash University, Melbourne, Australia

Correspondence
Stephanie C. Munari and Michael W. Traeger, Disease Elimination Program, Burnet Institute, Melbourne, Australia.
85 Commercial Rd, Melbourne 3004, Australia.
Email: stephanie.munari@burnet.edu.au and michael.traeger@burnet.edu.au

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Abstract

Background & Aims: Detecting hepatitis C virus (HCV) reinfection among key populations helps prevent ongoing transmission. This systematic review aims to determine the association between different testing intervals during post-SVR follow-up on the detection of HCV reinfection among highest risk populations.

Methods: We searched electronic databases between January 2014 and February 2023 for studies that tested individuals at risk for HCV reinfection at discrete testing intervals and reported HCV reinfection incidence among key populations. Pooled estimates of reinfection incidence were calculated by population and testing frequency using random-effects meta-analysis.

Results: Forty-one single-armed observational studies (9453 individuals) were included. Thirty-eight studies (8931 individuals) reported HCV reinfection incidence rate and were included in meta-analyses. The overall pooled estimate of HCV reinfection incidence rate was 4.13 per 100 per person-years (py) (95% confidence interval [CI]: 3.45–4.81). The pooled incidence estimate among people who inject drugs (PWID) was 2.84 per 100 py (95% CI: 2.19–3.50), among men who have sex with

Abbreviations: AASLD, American Association for the Study of Liver Diseases; cAg, core antigen; DAA, direct-acting antiviral; EASL, European Association for the Study of the Liver; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; HCV, hepatitis C virus; MSM, men who have sex with men; OAT, opioid agonist therapy; PrEP, pre-exposure prophylaxis; PWID, people who inject drugs; PYFU, person-years of follow-up; RCTs, Randomised controlled trials; RNA, ribonucleic acid; SVR, sustained virologic response; TasP, treatment-as-prevention; WHO, World Health Organisation.

Stephanie C. Munari and Michael W. Traeger should be considered joint first author.

men (MSM) 7.37 per 100 py (95% CI: 5.09–9.65) and among people in custodial settings 7.23 per 100 py (95% CI: 2.13–16.59). The pooled incidence estimate for studies reporting a testing interval of ≤6 months (4.26 per 100 py; 95% CI: 2.86–5.65) was higher than studies reporting testing intervals >6 months (5.19 per 100 py; 95% CI: 3.92–6.46).

Conclusions: HCV reinfection incidence was highest in studies of MSM and did not appear to change with retesting interval. Shorter testing intervals are likely to identify more reinfections, help prevent onward transmission where treatment is available and enable progress towards global HCV elimination, but additional comparative studies are required.

KEYWORDS
hepatitis C, incidence, key populations, reinfection, testing interval

1 | INTRODUCTION

Global elimination targets set by the World Health Organisation (WHO) aim for the elimination of viral hepatitis as a public health concern by 2030. To achieve elimination, targets call for the treatment of 80% of those eligible and a 90% reduction in incidence of new hepatitis B and C infections by 2030 compared with 2015 levels.[1] Only 12 of 194 countries are reported to be on track to meet the targets,[2] perhaps even fewer at the time of writing with a significant reduction in hepatitis C virus (HCV) testing and treatment rates during the COVID-19 pandemic.[3] Worldwide, HCV was responsible for over a quarter of the 1.1 million deaths caused by viral hepatitis in 2019, due largely to chronic liver disease and liver cancer.[1] Incidence of HCV infection is highest among key populations, with 39% of the 1-year global population attributable fraction of HCV transmission in 2018–19 associated with intravenous drug use.[4] High incidence of HCV has also been observed in studies of men who have sex with men (MSM) living with HIV and those using HIV pre-exposure prophylaxis (PrEP).[5] Microelimination programmes targeting key populations suggest that it may be possible to reduce HCV incidence by improving linkage post-diagnosis to care and treatment, to reduce the risk of reinfection or diagnose and treat it at the earliest possible time.[6–11]

Treatment-as-prevention (TasP), where risk of onward HCV transmission is lowered through high treatment coverage and reduced prevalence, is a key pillar of global elimination efforts and associated reductions in chronic liver disease-related morbidity and mortality.[12] Modelling has suggested that to achieve the WHO HCV incidence reduction targets, more frequent testing is needed in high-prevalence settings.[13] While the advent of highly effective and tolerable treatments, known as direct-acting antiviral (DAA) medication, has led to approximately 9.4 million people with HCV infection being treated between 2015 and 2019 worldwide,[1] individuals may remain at risk of reinfection following cure. Reinfection is defined as recurrent viraemia after its clearance either spontaneously or as a result of treatment.[14] People who inject drugs (PWID), MSM and people in custodial settings are among those at highest risk of recurrent viremia.[15–17] Guidelines recommend 'focused' testing in these populations, along with ongoing linkage to prevention and care services, and suggest targeted testing among these populations is likely to be cost-effective.[15] Following SVR, the European Association for the Study of the Liver (EASL) recommend at least annual, preferably biannual monitoring for HCV reinfection among PWID and MSM[18] and the American Association for the Study of Liver Diseases (AASLD) recommend annual RNA testing among patients with ongoing risk including intravenous drug use or MSM engaging in unprotected sex.[17] This systematic review was commissioned by the WHO

Key points

- Thirty-eight studies (8931 individuals) reported HCV reinfection incidence rate and were included in meta-analyses.
- The overall pooled estimate of HCV reinfection incidence rate was 4.13 per 100 per person-years (py).
- HCV reinfection incidence was highest in studies of MSM (7.37 per 100py) compared with PWID (2.84 per 100py) and people in custodial settings (7.23 per 100 py).
- HCV reinfection incidence was similar among studies that tested at >6-month intervals (5.19 per 100 py) compared with studies reporting testing at ≤6-month intervals (4.26 per 100 py) though findings were not statistically significant.
- HCV reinfection incidence did not appear to change with retesting interval. Longitudinal studies comparing annual HCV retesting with more frequent retesting among key populations are required.

to inform their 'Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations', where key populations included MSM, PWID, people in prisons and closed settings, sex workers and trans and gender diverse people. We aimed to provide specific additional evidence on the association between different reinfection testing intervals and the detection of HCV in the post-SVR follow-up period among highest risk populations.

2 | MATERIALS AND METHODS

This systematic review was commissioned and guided by the WHO Global Hepatitis Programme. The review protocol was prospectively registered with PROSPERO (CRD42021249863).

2.1 | Study identification

Three electronic databases (MEDLINE, Embase and Web of Science) were searched for studies published between 1 January 2014 and 1 February 2023 in preparation for the 2022 WHO global testing recommendations for key populations. Search terms included 'hepatitis C', 'HCV', 'test', 'screen', 'antigen', 'RNA', 'cAg', 'reinfection' and 'infection'. The full search strategy is outlined in Appendix A. Abstract repositories from relevant international conferences, including The International Liver Congress, The Liver Meeting, The International Conference on Hepatitis Care in Substance Users, The International Symposium on Viral Hepatitis and Liver Disease, The International AIDS Conference, The International AIDS Society Conference on HIV Science and Conference on Retroviruses and Opportunistic Infections, from 2014 to 2020 were also searched. Citation lists of included articles were manually reviewed to identify additional articles that met inclusion criteria.

2.2 | Study selection

Search results were uploaded to Covidence and study titles and abstracts were each independently assessed by at least two reviewers (SM, MT, VM).

2.3 | Eligibility criteria

Studies were included if they sampled people with evidence of cleared previous HCV infection (spontaneous clearance or cured) and who were tested for reinfection with a HCV ribonucleic acid (RNA) or core antigen (cAg) test. Studies were included if participants were according to the following key populations: MSM, PWID, transgender people and people in custodial settings, as these populations are among those at highest risk of HCV reinfection. For this review, studies of PWID were those which included participants reporting to be currently or recently injecting drugs, as well as those receiving opioid agonist therapy (OAT). Studies were included if testing for HCV reinfection were scheduled to occur at discrete intervals of up to every 12 months. Studies that tested individuals at variable testing intervals or at clinician's discretion were not included. Randomised controlled trials (RCTs), comparative observational studies and one-armed observational studies published in English from any country were eligible for inclusion. Studies were included if they reported on the primary outcome: detection of new HCV infections. Data for a range of secondary outcomes related to test uptake, linkage to treatment following reinfection and adverse events were also extracted from included studies.

The following criteria were used to exclude studies:

- Studies with less than 15 participants in total.
- Studies that included children (defined as persons under 18 years of age).
- Review studies and case study papers.
- Studies whose observation period ended before January 2014 as studies prior to this year were not within the direct-acting antiviral (DAA) era.
- Studies that did not perform HCV testing at discrete time intervals.

2.4 | Data extraction

Two independent reviewers extracted data from each study using a standardised spreadsheet and discrepancies were reviewed through discussion and involvement of a third reviewer. Where outcome data were missing or incomplete, study authors were contacted for additional data, with a minimum of two attempts. Where a study resulted in multiple publications, the most up-to-date and comprehensive data were included. The following data were extracted: country, study cohort or setting, study design, sample size, definition and proportion of PWID, MSM, transgender people and people in custodial settings, proportion of cohort with HIV coinfection, treatment regime for post-treatment studies, start and end date of follow-up, testing frequency, number of reinfection cases, person-years of follow-up for reinfection, and incidence of HCV reinfection per 100 person-years and upper and lower confidence intervals were reported.

2.5 | Data synthesis and analysis

Studies which reported the HCV reinfection as an incidence rate per 100 person-year were included in the meta-analysis. Random-effects meta-analysis was used to estimate a pooled HCV reinfection incidence rate. Where incidence rates or confidence intervals were not reported, they were calculated when sufficient data were reported. Statistical heterogeneity between studies was quantified by calculating an I^2 statistic and χ^2 value, with an $I^2 > 50\%$ considered as moderate/high heterogeneity.

Pooled estimates were disaggregated by cohort risk group (PWID, MSM and people in custodial settings) and testing interval (testing intervals less than or equal to 6 months versus longer than 6 months) to investigate sources of heterogeneity and compare differences in pooled incidence rates between groups. The ≤6 month and >6 month testing interval dichotomy was decided post-hoc based on the observed variation of testing intervals of included studies. Studies with testing intervals that changed over time were allocated to the testing category that most closely resembled most tests performed. All statistical analyses were performed with Stata 15 (StataCorp).

2.6 | Risk of bias of individual studies

A modified Newcastle-Ottawa Scale (Appendix B) was used to assess the risk of bias in the included one-armed observational studies. Risk of bias in individual studies was assessed based on selection and outcome characteristics and was classified using a numerical scale from zero to two for each criterion, with a maximum total score of nine. A score of seven or greater was classified as low risk of bias.

3 | RESULTS

3.1 | Search results

A total of 14408 citations were identified from the search strategy, of which 8140 were duplicates. Of the 6268 unique citations screened for eligibility, 220 were eligible for full-text review (Figure 1). A further 11 studies were identified for full-text review by searching conference abstracts and reference lists of included studies. Of the 231 full texts screened, 190 were excluded (study exclusion reasons outlined in Figure 1). The most common reasons for exclusion related to study design, including studies which did not test individuals at discrete testing intervals (n = 91) and studies that sampled populations other than the populations in our inclusion criteria ($n = 14$).

3.2 | Included Studies

Forty-one studies were included in the review, all of which were one-armed observational studies; no RCTs or comparative observational studies were identified. Characteristics of included studies

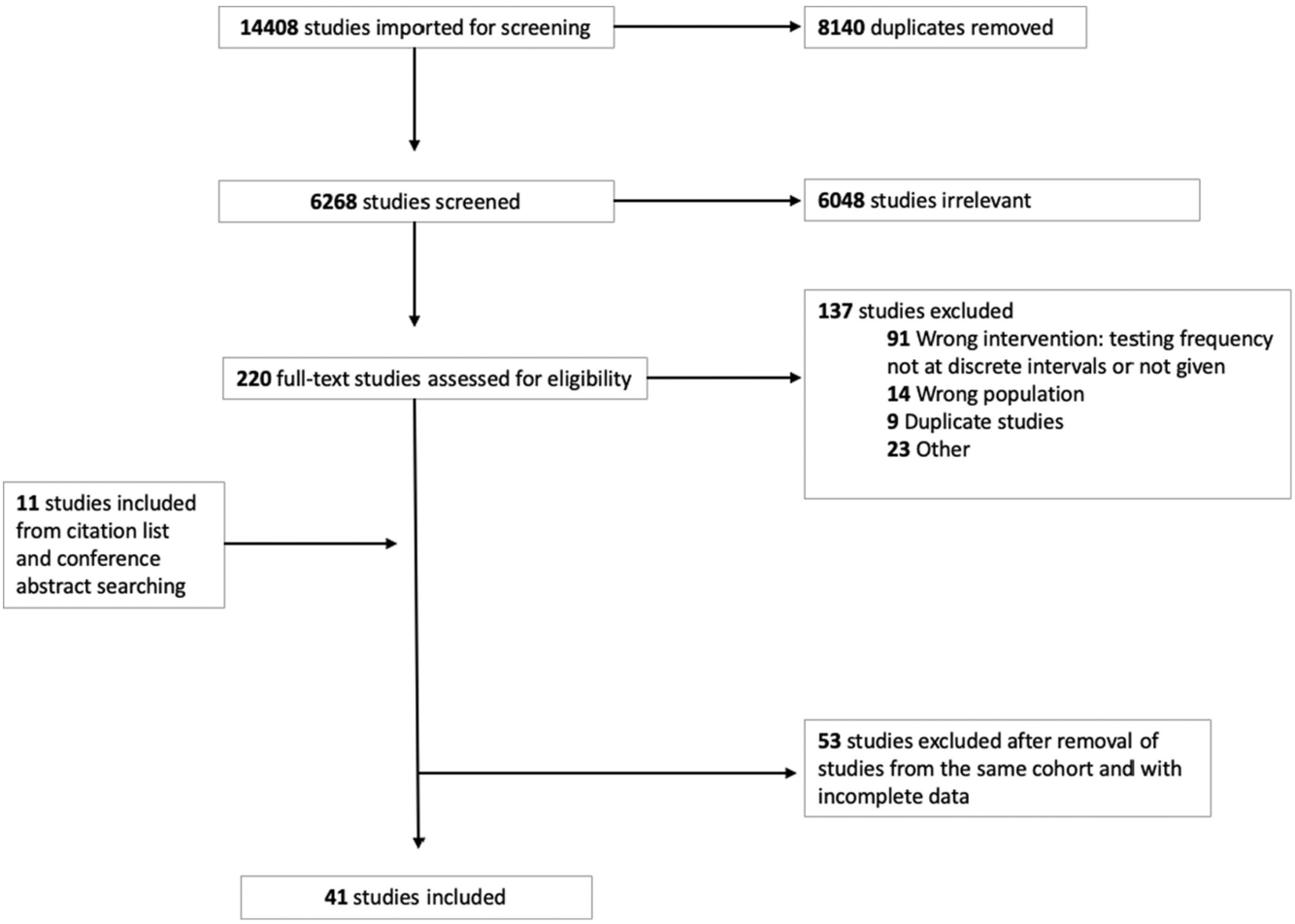

FIGURE 1 PRISMA diagram of search results and screening process.

are outlined in Table 1. The 41 observational studies included 8931 participants at risk of HCV reinfection. Thirty-five studies were from high-income countries, five from upper-middle income countries and one from both upper middle- and high-income countries as a multicentre cohort. All 41 studies reported the detection of new HCV reinfections and no studies reported on the secondary outcomes of test uptake, linkage to treatment following reinfection or adverse events.

Twenty-seven studies reported reinfection among PWID, 9 among MSM and 3 among people in custodial settings (two studies reported on both PWID and MSM[19,20]). No studies reporting reinfection among transgender people were identified. The interval between testing events for reinfection varied across included studies, ranging from as often as every 3 months to once 12 months post-sustained virological response (SVR) (Table 1).

Thirty-eight studies reported the number of HCV reinfections and the amount of person-time accrued, allowing for a calculation of a pooled HCV incidence rate estimate (Table S1). Three studies were identified that reported the proportion of participants diagnosed with a HCV reinfection, but reinfection incidence rate was not reported or could not be calculated from the available data. Gonzalez-Serna et al.[21] tested for recently acquired HCV infection among HIV-infected participants in Spain and reported four cases of reinfection among 42 participants at risk (9.5%). Farley et al.[22] measured reinfection post-SVR among Canadian correctional institutions and found 11 cases of reinfection among 132 participants. Schutz et al.[23] reported two cases of HCV reinfection among 40 PWID participants between week 12 and 24 of follow-up post-SVR.

3.3 | Pooled incidence estimates of HCV reinfection

The 38 studies included in the pooled HCV reinfection incidence estimate comprised 8931 participants at risk of reinfection (Table S1). Berenguer et al,[19] and Chen et al[20] included two study population arms (PWID and MSM) and HCV reinfection incidence rates were extracted for each arm and assigned to each key population meta-analysis separately. The pooled incidence estimate from all included studies was 4.13 per 100 py (95% confidence interval [CI]: 3.45–4.81) with HCV reinfection incidence ranging from 0.00 per 100 py to 31.00 per 100 py across studies. Heterogeneity was high among all included studies ($I^2 = 93.6\%$) (Figure 2).

3.3.1 | By key population groups

Among 27 studies comprising 4899 participants, where the primary study population were PWID, the pooled HCV reinfection incidence estimate was 2.84 per 100 py (95% CI: 2.19–3.50). Among the nine studies comprising 3269 participants whose primary population were MSM, the pooled incidence estimate was 7.37 per 100 py (95% CI: 5.09–9.65). Among the two studies comprising 763 participants who examined people in custodial settings, the pooled HCV reinfection incidence estimate was 7.23 per 100 py (95% CI: −2.13-16.59). Heterogeneity remained high across each subgroup estimate (Figure 3 and Table S2).

3.3.2 | By testing interval

Twenty-three studies comprising 5058 participants were categorised as having testing intervals ≤6 months, with a pooled estimate of 4.26 per 100 py [95% CI: 2.86–5.65). Fifteen studies comprising 3873 participants were categorised as having testing intervals >6 months, with a pooled estimate of 5.19 per 100 py [95% CI: 3.92–6.46). High heterogeneity was observed across both testing interval groups (Figure 4 and Table S2).

3.3.3 | By key population groups and testing interval

Among PWID, 17 studies comprising 3520 participants reported testing intervals of ≤6 months with HCV reinfection incidence rates ranging from 0.00 per 100 py to 21.50 per 100 py. Eleven studies comprising 1663 participants reported testing intervals >6 months, with incidence rates ranging from 0.00 per 100 py to 31.00 per 100 py. The pooled HCV reinfection incidence rate estimate was lower among PWID populations with testing intervals ≤6 months (2.97 per 100 py [95% CI: 1.55–4.39]) compared with those with testing intervals >6 months (3.96 per 100 py [95% CI: 2.64–5.29), though noting the presence of overlapping confidence intervals (Figure 5).

Among MSM, seven studies comprising 1945 participants reported a testing interval of ≤6 months with HCV reinfection rates ranging from 5.93 per 100 py to 27.80 per 100 py. Three studies comprising 1608 participants reported testing intervals >6 months, with HCV reinfection rates ranging from 3.46 per 100 py to 17.00 per 100 py. The pooled HCV reinfection incidence rate estimate among MSM populations was higher among studies with testing intervals ≤6 months (7.94 per 100 py [95% CI: 3.30–12.57]) compared with those with testing intervals >6 months (6.86 per 100 py [95% CI: 4.66–9.05]), though noting the presence of overlapping confidence intervals. Moderate-to-high heterogeneity was observed across all PWID and MSM groups (Figure 6). Among people in custodial settings, low study numbers limited the ability to compare testing frequencies.

3.4 | Risk of bias

Thirty-one of the 41 observational studies were considered at low risk of bias (score ≥ 7) when graded using a modified Newcastle Ottawa Scale for cohort studies. The main biases identified were in determining the representativeness of the cohort, confirmation of

TABLE 1 Study characteristics of included studies, $n = 41$ studies.

Study	Study cohort and setting	World Bank income group (2020)[1]	Study design	Study population
Aitken et al 2017[36]	MIX—Melbourne Injecting Drug Users Cohort Study, Melbourne, Australia	High income	Prospective	PWID
Akiyama et al 2020[37]	PREVAIL Montefiore General clinical Research Centres or 1 of 3 OAT clinics, Bronx, New York	High income	Prospective	PWUD 75% PWID
Baxter et al 2018[38]	North Manchester Hospital database, Manchester, UK	High income	Prospective	PWID 100%
Berenguer et al 2019[19] (MSM)	Madrid Coinfection Registry (Madrid-CoRe), Madrid, Spain	High income	Prospective	MSM 7%
Berenguer et al 2019[19] (PWID)	Madrid Coinfection Registry (Madrid-CoRe), Madrid, Spain	High income	Prospective	PWID 62%
Bregenzer et al 2022[39]	Outpatient Centre for Opioid Agonist Therapy, and Department of Infectious Diseases and Hospital Hygiene, Cantonal Hospital, Switzerland	High income	Prospective	PWID
Buscillao et al 2018[40]	Needle Syringe Program, Tbilisi, Georgia	Upper middle income	Prospective	PWID 100% 57% recent drug use 56.8% use in last 6 months
Byrne et al 2020[41]	NHS Tayside, Scotland	High income	Retrospective	PLWHIV 80% PWID 10% Sexual transmission
Byrne et al 2022[42]	NHS Tayside, Scotland	High income	High income	PWID
Carson et al 2022[43]	STOP-C study Australia	High income	Prospective	Prisoners
Chen et al 2022[20]	National Taiwan University Hospital, Taiwan	Upper middle income	Retrospective	PLWHIV 83.5% MSM 10.6% IDUs
Cheng et al 2022[44]	HIV care hospital, Taiwan	Upper middle income	Retrospective	PLWHIV 78.9% PWID 20.3% MSM
Coffin et al 2019[45]	BYE-C, US	High income	Prospective	PWID
Cotte et al 2018[46]	Dat'AIDS, France	High income	Prospective	MSM
Cunningham et al 2021[47]	SIMPLIFY and D3FEAT, 8 countries	High income	Prospective	PWID All recent IDU or current OAT
Doyle et al 2019[48]	TAP, Australia	High income	Prospective	100% PWID within last 6 months
Farley et al 2018[49]	Community-based clinic that also services correctional institutions, Canada	High income	Retrospective	Prisoners
Forns et al 2020[50]	Harm reduction and addiction centres, Catalonia, Spain	High income	Retrospective	PWID
Foschi et al 2021[51]	6 outpatient clinics in Emilia-Romagna, Italy	High income	Prospective	PWID
Grebely et al 2022[52]	CO-STAR, Multi-country	Upper middle and high income	Prospective	PWID – people receiving OAT
Gonzalez-Serna et al 2020[21]	Four hospitals, Southern Spain	High income	Prospective	MSM
Holeksa et al 2019[53]	Vancouver Infectious Diseases Centre, Vancouver, Canada	High income	Retrospective	PWID

Total cohort sample size	Start date of follow-up	Duration of follow-up	Testing frequency	Assigned testing interval category
757	November 2008	—	12 months	>6
141	April 2017	Median 20.5 months	6 months	≤6
45		Mean 50 months (range 11–95 months)	2 visits in total at least 1 year apart	>6
177	November 2014	Median 15 weeks post-SVR[b]	One-off 3 months, and then every 6–12 months	>6
1459	November 2014	Median 15 weeks post-SVR	One-off 3 months, and then every 6–12 months	>6
19	April 2018	Median 1.8 years	Monthly	≤6
169	July 2015	Median 12.3 months	At month 6 and month 12	≤6
44	January 2001	Median 7 years (IQR[a] 2–12)	12 monthly or ad hoc if raised ALT	>6
227	January 2017	256.57py	12 monthly	>6
161	October 2014	145py	3–6 monthly	≤6
284	January 2018	Median 2.32 years	3–6 monthly	≤6
516	June 2009	Median 63.6 weeks	12 monthly	>6
31	2015	—	Week 2, 4, 8 of Tx. Week 1, 12, 36 post-Tx (= at 3 months, 9 months)	≤6
11467	January 2016	—	3–6 months	≤6
190	March 2016	Median 1.8 years	SVR 12, SVR24, 60w, 84w, 108w (= at 3, 6, 15, 21, 27 months)	≤6
241	—	—	3 monthly	≤6
132	January 2000	>/=10 years	6 months	≤6
20822	—	—	12 weeks, 36 weeks and 60 weeks after end of therapy.	≤6
338	May 2015	Median 53 weeks	6 monthly	≤6
286	July 2015	604py	6 monthly	≤6
350	January 2016	Median 34.9 months (20.7–37.7 IQR)	12 months	>6
243	March 2014	Median 714 days (range 134–1841 days)	6 months	≤6

(Continues)

TABLE 1 (Continued)

Study	Study cohort and setting	World Bank income group (2020)[1]	Study design	Study population
Hoorenborg et a 2020[54]	Amsterdam PrEP study, Netherlands	High income	Prospective	MSM 99% TGW 1%
Huang et al 2019[55]	National Taiwan University Hospital, Taiwan	Upper middle income	Retrospective	MSM 90%
Ingiliz et al 2020[56]	GECCO & NEAT, Germany	High income	Retrospective	MSM
Johannesson et al 2020[57]	TraP Hep C, Iceland	High income	Prospective	PWID 85%
Kaberg et al 2020[58]	Needle Syringe Program, Stockholm, Sweden	High income	Prospective	PWID
Kattakuzy et al 2020[59]	ANCHOR, US	High income	Prospective	PWID 100%
Lens et al 2022[60]	Urban Harm Reduction Clinic, Spain	High income	Prospective	PWID
Liu et al 2022[61]	RECUR study, Taiwan	Upper middle income	Prospective	PLWHIV 92% MSM 5% PWID
Marco et al 2019[62]	Prisons, Catalonia, Spain	High income	Retrospective	Prisoners 100% PWID 74.1%
Martinello et al 2016[63]	ATAHC I, ATAHC II, DARE-C I and DARE-C II, Australia and New Zealand	High income	Prospective	HIV+ MSM 53% PWID (49% current, 69% ever used)
Martinez-Rebollar et al 2021[64]	Hospital clinic, Spain	High income	Prospective	PLWHIV 94% MSM
Midgard et al 2021[65]	Clinic Oslo, Norway	High income	Prospective	PWID
Minoyan et al 2018[66]	HEPCO, Montreal, Canada	High income	Prospective	PWID
O'Sullivan et al 2020[67]	ITTREAT, UK	High income	Prospective	PWUD PWID 92%
Schulkind et al 2019[68]	Eradicate, Dundee, Scotland	High income	Prospective	PWID
Schutz et al 2018[23]	Drug treatment facility Vienna, Austria	High income	Prospective	PWID 58% ongoing IDU
Sylvestre et al 2017[69]	OASIS (urban) methadone clinic, Oakland, California	High income	Prospective	PWID—63% active IDU
Valencia et al 2019[70]	Harm Reduction Centre, Madrid, Spain	High income	Prospective	PWUD 73.8% IDU in last 6 month 52.5% IDU at last month
Wyles et al 2017[71]	V-HICS, US	High income	Prospective	PLWHIV 56.6% PWID 44.9% prior IDU 0.49% current IDU
Young et al 2017[72]	Canadian Co-infection Cohort, Canada	High income	Prospective	PWID and MSM 74% ever IDU 33% recent MSM activity

[a]IQR Interquartile range.

[b]SVR sustained virological response.

[c]EOT end of treatment.

Total cohort sample size	Start date of follow-up	Duration of follow-up	Testing frequency	Assigned testing interval category
350	August 2015	653.6 days	6–12 months	>6
225	January 2011	Median 4.4 years (IQR 2.8–6.6) for reinfection 3.1 years (IQR 2.1–5.2) for no reinfection	Median 5.7 months (IQR 2.7–9.6)	>6
2298	January 2014	Median 604 days (range 16–1353)	MSM 3–6 months	≤6
597	January 2016	—	3-monthly for active injectors, 6 monthly for others	≤6
124	January 2018	—	EOT[c], SVR12 (at 3 months), then every 6 months	≤6
82		Median 96 weeks (24–96)	Post-SVR week 48, 72, 96 (= at 12, 18 and 24 months)	>6
168	November 2018	—	6 monthly	≤6
2016	January 2005	Median 3 years	6 monthly	≤6
602	January 2002	Mean 4.35 ± 2.7 years/reinfected participant	12 months (or upon reincarceration)	>6
120	2004	135py at risk	EOT, at post-treatment weeks 12, 24 and 48 (=at 3, 6 and 12 months)	≤6
290	January 2010	—	6–24 monthly	≤6
488	June 2013	Median 6 months	3 months	≤6
269	January 2010	—	3-monthly in 2010, 6-monthly 2011–2017	≤6
109 achieved SVR; 76 retested	December 2013	—	One off test 12 m post-SVR (48–60 weeks)	>6
105	December 2012	42 months	At EOT, 3 m, 6 m then 18 m post-treatment = 3, 3 then 12 month intervals	>6
40	—	Mean 30.8 ± 13.4 months	Measured at SVR 12 and 24 (= at 3 months then 6 months)	≤6
35	—	—	One off test 12 months post-SVR	>6
160	January 2016	Median 0.6 years (IQR 0.3–1.3)	3–6 months + when high-risk behaviours suspected	≤6
205	March 2015	≥52 weeks	12 months	>6
257	January 2003	Median 1.5 years (IQR 0.6–3.2)	6 months	≤6

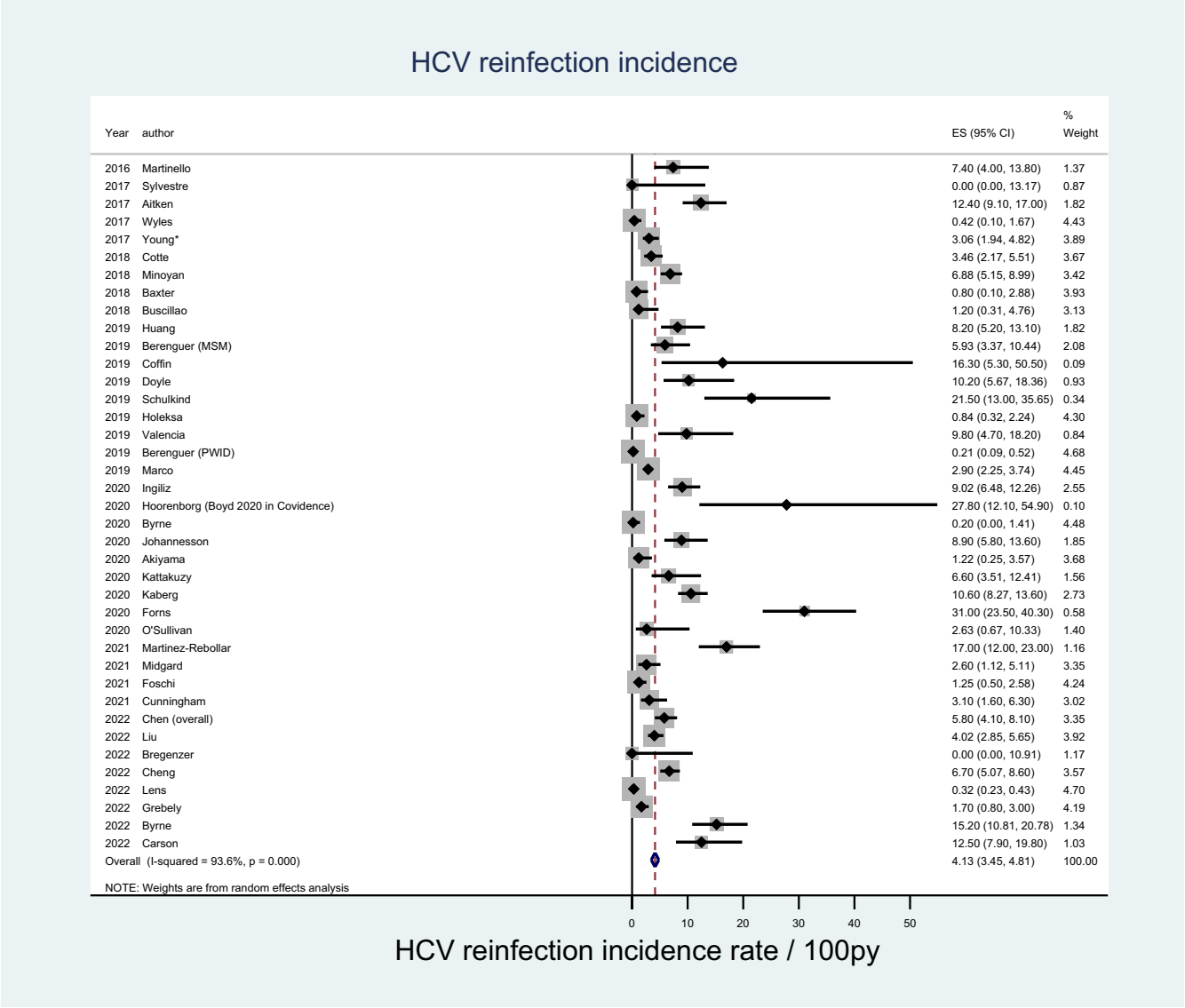

FIGURE 2 Forest plot of pooled HCV reinfection incidence rate from all studies included in meta-analysis.

the outcome and adequacy of follow up. The modified Newcastle Ottawa Scale for cohort studies and assessment scores are outlined in Appendices B and C, respectively.

4 | DISCUSSION

In this systematic review of HCV reinfection intervals, we observed higher HCV reinfection incidence rates among studies including MSM compared with PWID. We detected no difference in HCV reinfection incidence based on retesting intervals. There has been interest globally in WHO guidelines development[24] to determine optimal testing intervals for people at risk of HCV reinfection. A greater detection of HCV reinfection in studies with shorter testing intervals has been noted and explained previously, in part, due to less time for infections to spontaneously clear.[25] Conversely, partial protective immunity from the primary infection may lead to a more rapid resolution of reinfection.[26] It is also likely that higher incidence rates in studies which tested more frequently is biased by higher frequency testing protocols in studies of cohorts at greater risk of reinfection. This large meta-analysis has been able to explore both hypotheses and demonstrate no clear difference in very frequent (less than 6 months) or less frequent (more than 6 months) retesting.

Previous systematic reviews have estimated comparative pooled incidence rates of HCV reinfection among key populations and different HCV testing intervals. An earlier review found that rates of HCV reinfection were lower in studies of HCV mono-infected PWID, MSM and prisoners (1.91/100py) compared with HIV/HCV co-infected individuals (3.20/100py).[27] Multiple reviews have reported a lower HCV reinfection incidence among individuals receiving opioid agonist therapy (OAT) (ranging from 0.55 to 1.4/100py) compared with those not receiving OAT.[28,29] Another meta-analysis among people living with HIV found that HCV reinfection was higher among MSM (5.89/100py) compared with people with recent

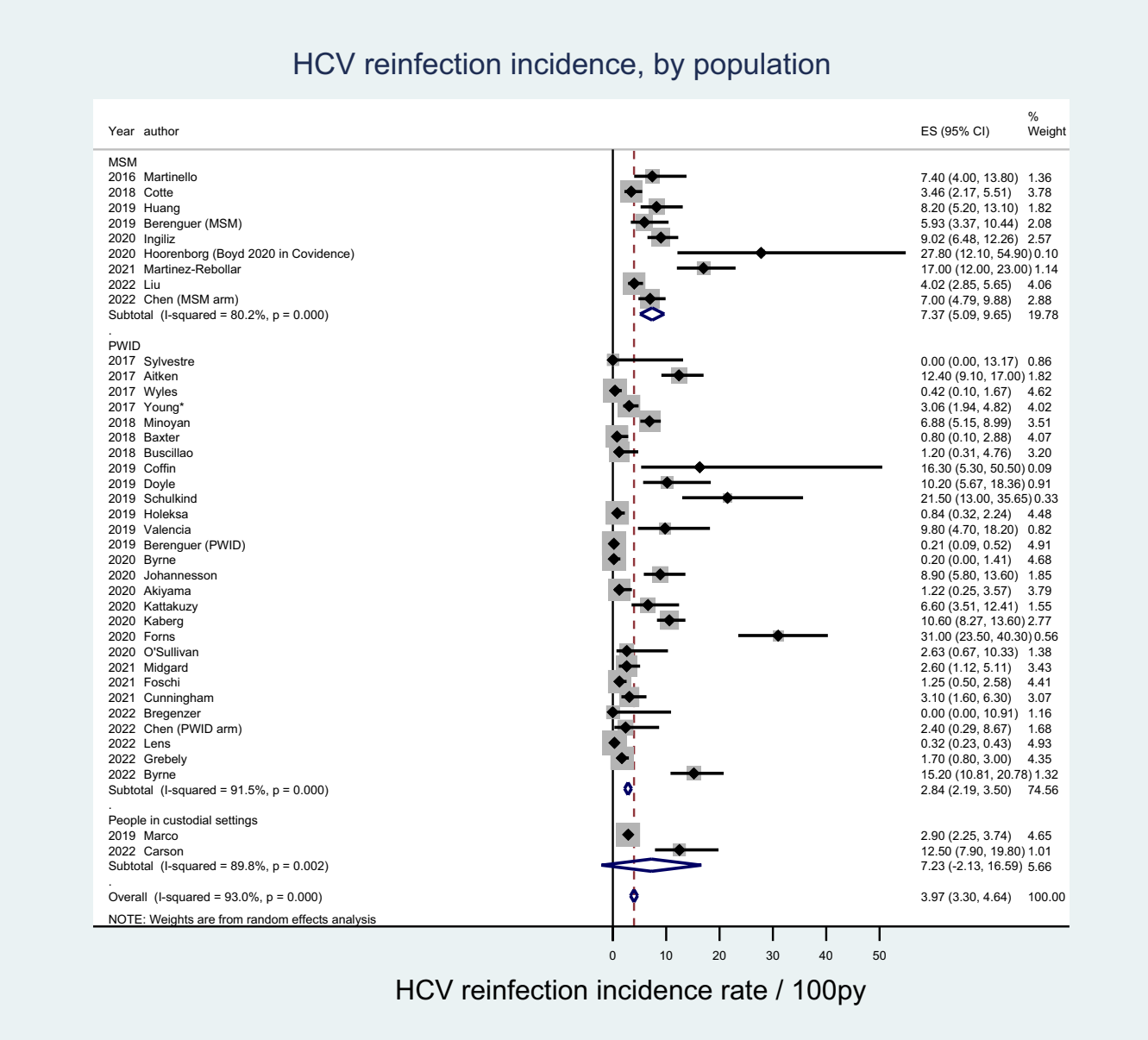

FIGURE 3 Forest plot of pooled HCV reinfection incidence rates by key populations included in meta-analysis.

injection drug use (5.49/100py).[30] Another meta-analysis among HIV-infected MSM estimated an overall HCV reinfection rate of 5.27/100 py and found a higher reinfection rate among people with HCV test intervals of less than 6 months (7.59/100py) compared with those tested at greater than 6 month intervals (2.88/100 py).[31] Among PWID populations, our findings are consistent with previously reported estimates in this group and are higher compared with studies examining HCV reinfection among MSM. A strength of this review is that all individuals at risk were compared using the same methodical approach allowing for better understanding of relative risks in these key populations.

Frequent testing is likely to increase case finding and be beneficial in reducing HCV disease burden for both the individual and community through early detection, treatment and cure as part of a TasP approach, and can be combined with other testing strategies, such as HIV and STI testing. This could potentially improve linkage to care and harm reduction support through increased engagement with healthcare services.[15,32] Although a person's risk of reinfection may decline over time, it is difficult to determine when in the post-SVR period any reinfection occurs, and thus if different testing intervals should be offered at different years. Routine HCV testing among people actively using drugs has been shown to be cost-effective in multiple settings, even when repeat testing leads to the need for repeat treatment, due to both the low cost of HCV testing and effective treatment.[33] However, implementing testing for reinfection at regular intervals for all PWID may not be feasible in many settings. As testing for HCV reinfection relies on RNA or antigen testing, limited availability of these testing strategies may pose an additional challenge in certain settings. Further, in resource-constrained settings without universal healthcare or

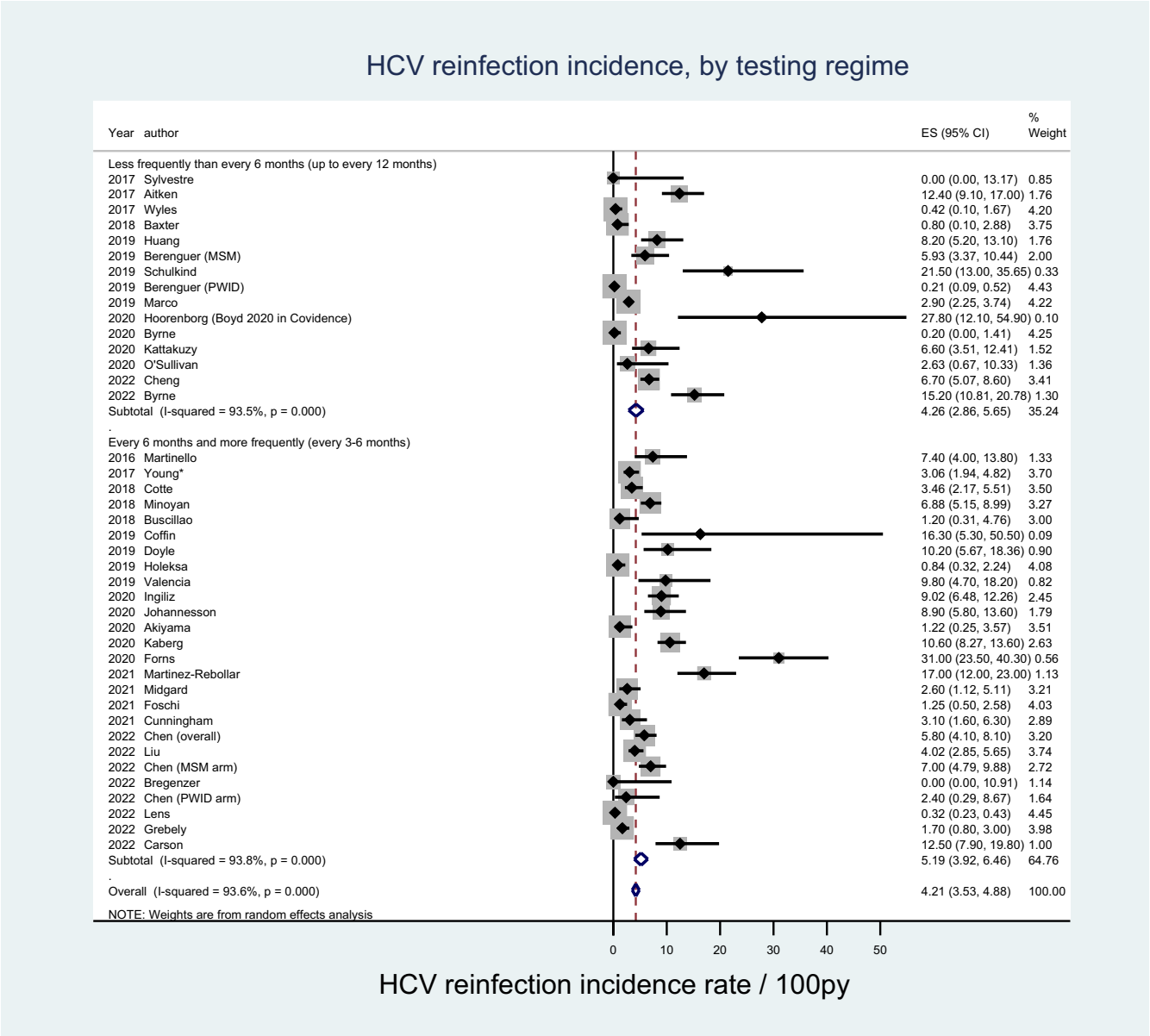

FIGURE 4 Forest plot of pooled HCV reinfection incidence by testing frequency included in meta-analysis.

where systems that can deliver effective care post-diagnosis are not available, increased screening may not be cost-effective. Consideration should be given to higher short-term costs of tests, outpatient visits including healthcare personnel, the opportunity cost for time and resources diverted by healthcare staff, and if more re-infections are identified, the short-term costs of increased treatment. Furthermore, while frequent testing may diagnose individuals during the acute HCV phase, many DAAs are only approved for confirmed chronic HCV infection. Additionally, testing must be voluntary and offered alongside counselling to minimise the risk of stigma, discrimination and adverse psychological impacts.[32,34] While our analyses show no difference in the reinfection incidence rate based on retesting interval, recommendations for screening frequency should consider country-level or setting-specific contexts, including the availability of appropriate linkage to treatment following diagnosis.

There are important limitations to note when interpreting our findings. First, the purpose of our systematic review was to find RCTs and other comparative studies to determine the association between HCV testing frequency and HCV reinfection among key populations in the post-SVR period; however, only single-arm observational studies were identified. We have thus explored HCV reinfection between pooled estimates of observational studies, limiting our ability to determine the effectiveness of different testing regimes on HCV detection. Second, only studies that tested at discrete time intervals were included, and as such results were more representative of studies from high-income countries. Studies where clinicians self-selected when to offer testing were not included to reduce the influence of higher risk individuals being tested more often. Third, only nine studies were included among MSM and two among people in custodial settings, limiting our ability to discern meaningful differences between testing frequencies for these key populations.

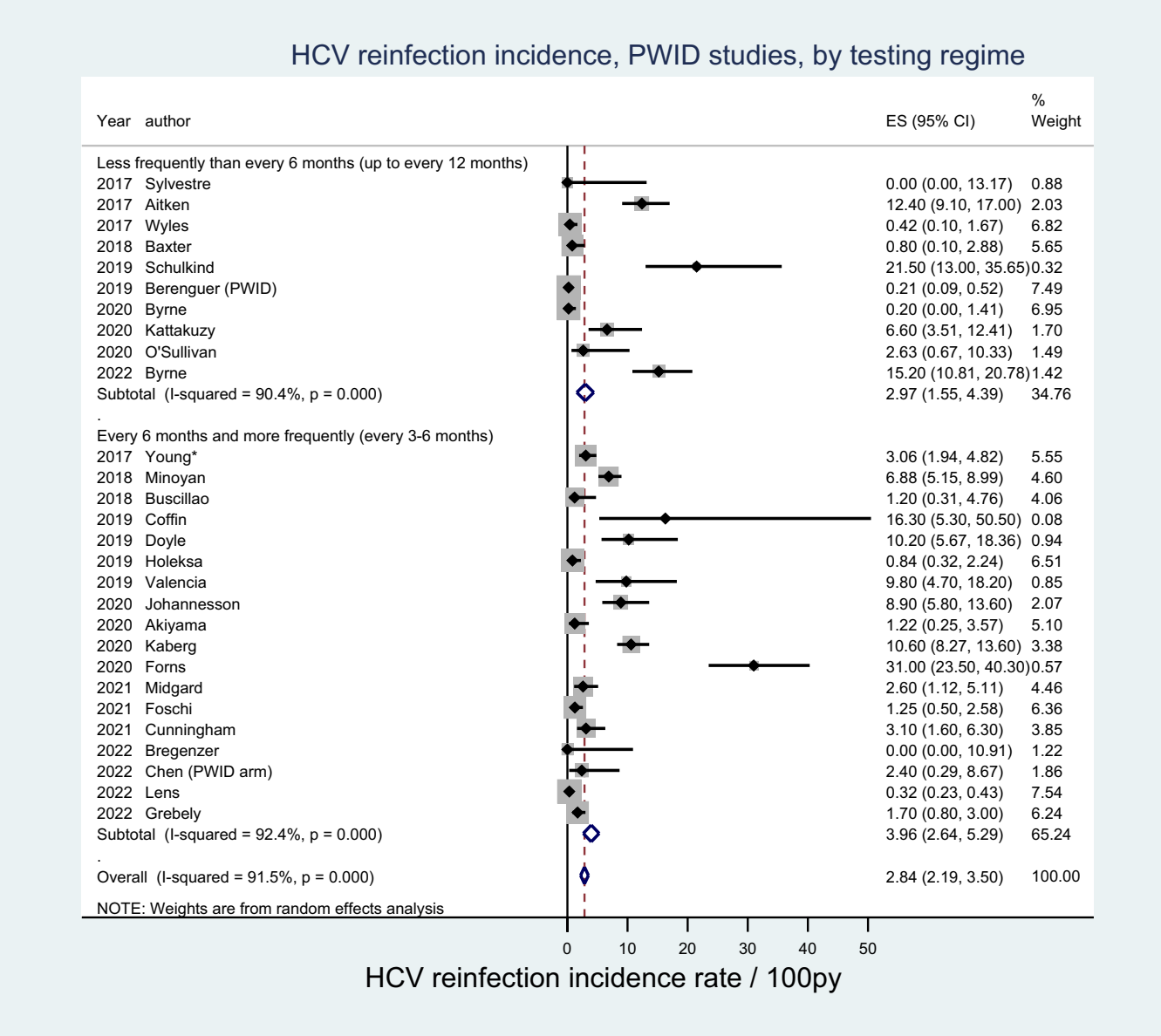

FIGURE 5 Forest plot of pooled HCV reinfection incidence among PWID by testing frequency included in meta-analysis.

Fourth, our analysis could not account for confounding factors, such as age, gender and socioeconomic status since it was inconsistently reported within studies. Fifth, the studies included in this review contain significant heterogeneity among population characteristics, where some studies included participants with life-time drug use, those with only recent drug use or injecting drug use or those on opioid substitution therapy or other risk reduction measures. Due to this heterogeneity, along with incomplete reporting by study authors, we were unable to disaggregate the PWID sub-population by recent and ever injecting drug use, limiting the ability to confidently detect differences between these groups. This heterogeneity has also been observed in previous systematic reviews including the ones described above. Additionally, the inclusion of both recent and past injecting exposure within the PWID cohorts, and the fact that testing frequency within study protocols may have been influenced by the risk profile of included participants (i.e. less frequent testing for those without recent injecting exposure) is likely to be a significant factor altering estimates of incidence of reinfection among this key population. Sixth, our review did not find any studies examining HCV reinfection among transgender people. While it is possible that transgender people were included in our studies, often as part of MSM cohorts, this finding is most likely reflective of deficiencies in the collection and reporting of gender identity in health records and research. The adoption of a gender lens to HCV care and research to explore the impacts of gender disparities on HCV elimination is required.[35] Finally, as nearly all included studies were from high-income country settings, any consideration of HCV testing frequency recommendations should be applied to high-income settings only due to differences in HCV risk context including local drivers of HCV transmission and availability of resources. This highlights the crucial need for more context-specific HCV elimination research from low- and middle-income countries.

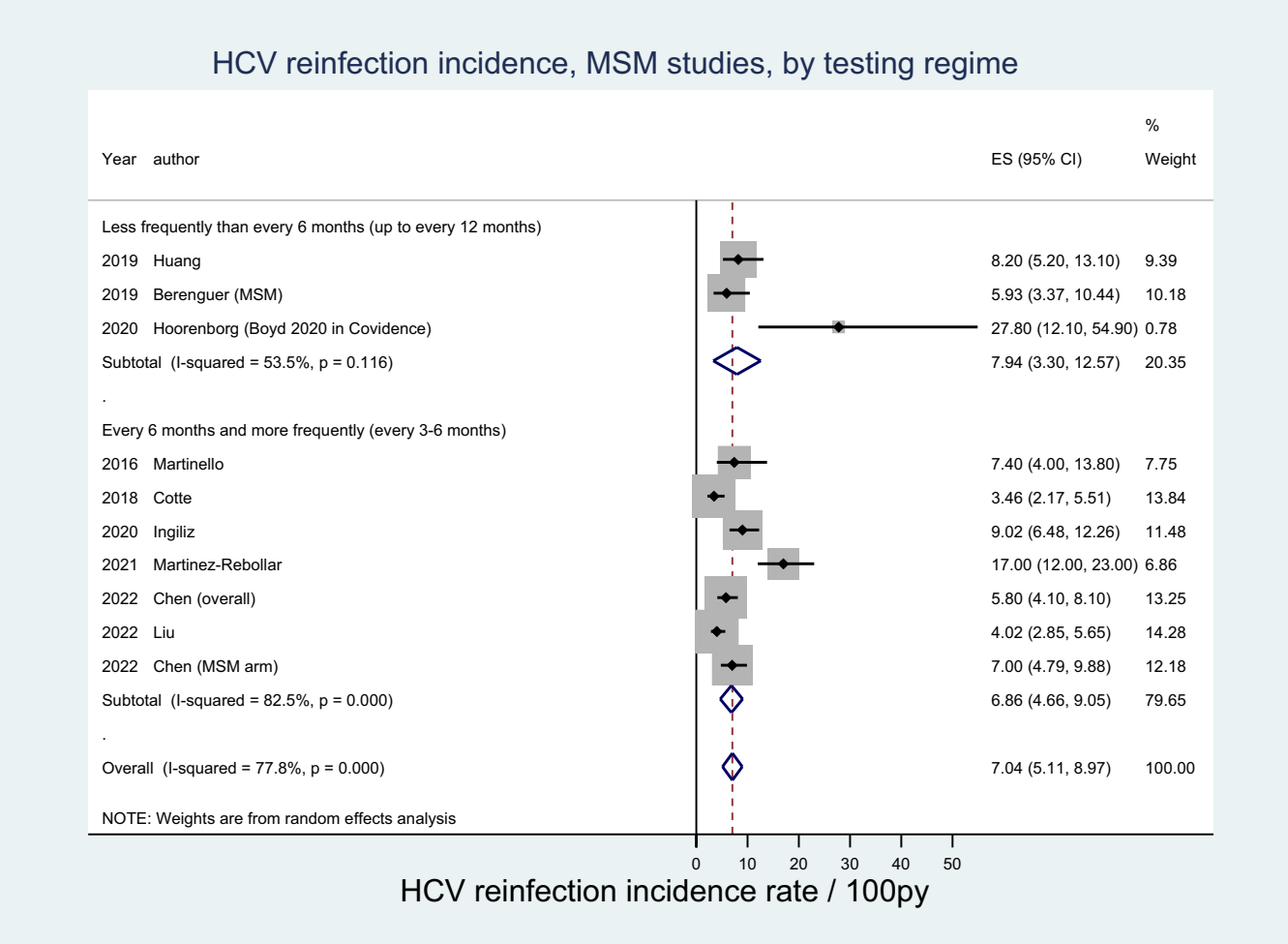

FIGURE 6 Forest plot of pooled HCV reinfection incidence among MSM by testing frequency included in meta-analysis.

This systematic review advances our understanding of how different testing intervals influence HCV detection among PWID, MSM, and people in custodial settings. Furthermore, this review updates the HCV reinfection incidence estimates among these key populations. Our findings have highlighted the absence of high-quality trial or cohort data to make direct comparisons on testing frequency, and suggest that future longitudinal studies comparing annual testing with more frequent testing (i.e. 3–6 monthly) among key populations are needed. Our findings have direct implications for clinical practice and have contributed to WHO global testing recommendations for key populations, where people at ongoing risk and a history of previous HCV infection may be offered 3–6 monthly HCV testing where appropriate and available.[24] Increasing voluntary testing frequency coupled with offers of HCV treatment among people at ongoing risk could have significant individual and population level benefits, enabling further progress towards global HCV elimination.

AUTHOR CONTRIBUTIONS

Joseph S. Doyle is the guarantor of this article. Authors Joseph S. Doyle, Margaret E. Hellard, Mark A. Stoové, Ned H. Latham, Rachel Baggaley, Virginia MacDonald, Annette Verster, Nandi Siegfried, Stephanie C. Munari, Michael W. Traeger, Virginia MacDonald, Ned H. Latham and Lakshmi Manoharan contributed to the conceptualisation and design of the research study. Nandi Siegfried provided methodological expertise. Brian Conway, Marina Klein and Julie Bruneau contributed to the acquisition and interpretation of data. Stephanie C. Munari, Michael W. Traeger and Vinay Menon performed the search, data collection and analysis. Stephanie C. Munari, Michael W. Traeger and Joseph S. Doyle prepared the original draft manuscript. All authors were involved in reviewing and revising the manuscript and have approved the final version for publication.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

ORCID

Stephanie C. Munari https://orcid.org/0000-0002-2296-7787
Michael W. Traeger https://orcid.org/0000-0002-3452-350X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

Search strategies

Ovid EMBASE

1. exp *Hepatitis C/* or exp *Hepatitis C, Chronic/*
2. (hepatitis c or hepatitis c virus or hcv).mp
3. 1 or 2
4. (test* or screen*).mp
5. (antigen or RNA).mp
6. 4 or 5
7. re?infection).mp
8. exp *Incidence/* or inciden*.mp
9. 7 or 8
10. 3 and 6 and 9
11. limit 11 to (yr="2014-current")

Yield = 4376

Ovid MEDLINE

1. exp *Hepatitis C/* or exp *Hepatitis C, Chronic/*
2. (hepatitis c or hepatitis c virus or hcv).mp
3. 1 or 2
4. (test* or screen*).mp
5. (antigen or RNA).mp
6. 4 or 5
7. re?infection).mp
8. exp *Incidence/* or inciden*.mp
9. 7 or 8
10. 3 and 6 and 9
11. limit 11 to (yr="2014-current")

Yield = 1011

Web of Science

TS = (hepatitis C or HCV)
TS = (test* or screen*)
TS = (antigen or RNA or ribo$nucleic)
2 or 3
TS = (re$infection or inciden*)
1 and 4 and 5.
Timespan: 2014–2021 to the above terms.
Yield = 1677.

APPENDIX B

Quality appraisal checklist

Modified Newcastle-Ottawa quality assessment scale for cohort studies.

Selection	1. Representativeness of the cohort [1 score if a or b; zero score if c or d] a. Study population are truly representative of the average PWID/MSM/people in custodial settings with a previously cleared HCV infection living in the community* b. Study population are somewhat representative of the average PWID/MSM/people in custodial settings with a previously cleared HCV infection living in the community* c. Study population are selective group of average PWID/MSM/people in custodial settings with a previously cleared HCV infection (e.g. volunteers, specific genotype, HIV-HCV co-infection) d. No description of the derivation of the cohort 2. Clear definition of study population provided (i.e. recent injecting drug use, recent MSM sexual activity, currently in a custodial setting) [1 score if a; zero score if b] a. Yes* b. No 3. Ascertainment of testing frequency interval in study population [1 score if a; zero score if b or c] a. Secure record (e.g. clinical record, record linkage)* b. Self-report c. No description 4. Demonstration that outcome of interest was not present at start of study (all participants' HCV RNA undetectable/unquantifiable at the time of start of follow-up) [1 score if a; zero score if b] a. Yes* b. No
Outcome	5. Assessment of outcome (HCV reinfection) [1 score if a or b; zero score if c or d] a. Independent blind assessment by HCV RNA test results* b. Record linkage* c. Self-report d. No description 6. Confirmation of outcome (HCV reinfection) [2 scores if a; 1 score if b; zero score if c] a. HCV sequencing or any other method to distinguish relapse from reinfection ** b. Only HCV genotype/subtype switch or HCV RNA detection after SVR* c. No description 7. Was follow-up long enough for outcomes to occur [1 score if a; zero score if b or c] a. Yes (mean/median of follow-up longer than six months)* b. No c. Not reported 8. Adequacy of follow-up of cohort [1 score if a or b; zero score if c or d] a. Complete follow-up – all participants accounted for* b. Participants lost to follow-up unlikely to introduce bias (small number lost (<20%), or description provided of those lost)* c. >20% lost to follow-up and no description provided of those lost d. No statement

APPENDIX C

Risk of Bias scores for included observational studies.

Study	1) Representativeness of the cohort	2) Clear definition of study population provided	3) Ascertainment of testing frequency interval in study population	4) Demonstration that outcome of interest was not present at start of study	5) Assessment of outcome	6) Confirmation of outcome	7) Was follow-up long enough for outcomes to occur	8) Adequacy of follow-up of cohort	Total score (/9)
Aitken et al, 2017	1	1	1	1	1	1	1	1	**8**
Akiyama et al, 2020	1	1	1	1	1	2	1	1	**9**
Baxter et al, 2018	1	1	1	1	1	1	1	0	**7**
Berenguer et al, 2019	0	1	1	1	1	1	0	0	**5**
Bouscillao et al, 2018	1	1	1	1	1	1	1	0	**7**
Bregenzer et al, 2022	0	0	1	1	1	1	1	0	**5**
Byrne et al, 2020	0	1	1	1	1	1	1	1	**7**
Byrne et al, 2022	1	1	1	1	1	1	1	1	**8**
Carson et al, 2022	1	1	1	1	1	2	1	1	**9**
Chen et al, 2022	1	1	1	1	1	2	1	0	**8**
Cheng et al, 2022	1	1	1	1	1	1	1	1	**8**
Coffin et al, 2019	1	1	1	1	1	2	1	1	**9**
Cotte et al, 2018	0	1	1	1	1	1	1	1	**7**
Cunningham et al, 2021	1	1	1	1	1	2	1	1	**9**
Doyle et al, 2019	1	1	1	0	0	0	1	1	**5**
Farley et al, 2018	1	1	1	1	1	0	1	1	**7**
Forns et al, 2020	1	1	0	1	0	0	0	0	**3**
Foschi et al, 2021	1	1	1	1	1	1	1	1	**8**
Grebely et al, 2022	1	1	1	1	1	2	1	1	**9**
Gonzalez-Serna et al 2020	0	1	1	1	1	1	1	0	**6**
Holeksa et al, 2019	1	1	1	1	1	2	1	1	**9**
Hoorenborg et al, 2020	0	1	1	1	1	1	1	0	**6**
Huang et al, 2019	0	1	1	1	1	1	1	1	**7**
Ingiliz et al, 2020	1	1	1	1	1	1	1	0	**7**
Johannesson et al, 2020	1	1	1	1	1	2	1	0	**8**
Kaberg et al, 2020	1	1	1	1	1	1	0	1	**7**
Kattakuzy et al, 2020	1	1	0	1	0	1	1	0	**5**
Lens et al, 2022	1	1	1	1	1	2	0	1	**8**
Liu et al, 2022	1	1	1	1	1	1	1	0	**7**

Study	1) Representativeness of the cohort	2) Clear definition of study population provided	3) Ascertainment of testing frequency interval in study population	4) Demonstration that outcome of interest was not present at start of study	5) Assessment of outcome	6) Confirmation of outcome	7) Was follow-up long enough for outcomes to occur	8) Adequacy of follow-up of cohort	Total score (/9)
Marco et al, 2019	1	1	1	1	1	1	1	0	**7**
Martinello et al, 2016	1	1	1	1	1	2	1	1	**9**
Martinez-Rebollar et al, 2021	1	1	1	1	1	1	0	0	**6**
Midgard et al, 2021	1	1	1	1	1	1	1	1	**8**
Minoyan et al, 2018	1	0	1	1	1	1	1	1	**7**
O'Sullivan et al, 2020	1	1	1	1	1	1	1	1	**8**
Schulkind et al, 2019	1	1	1	1	1	1	1	1	**8**
Schutz et al, 2018	1	1	1	1	1	1	1	0	**7**
Sylvestre et al, 2017	1	1	0	1	0	0	1	1	**5**
Valencia et al, 2019	1	1	1	1	1	1	1	0	**7**
Wyles et al, 2017	0	1	1	1	1	1	1	0	**6**
Young* et al, 2017	0	1	1	1	1	1	1	1	**7**