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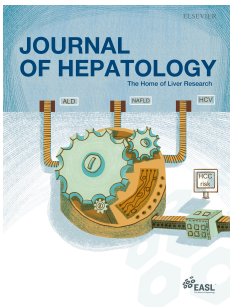

Hepatitis C reinfection after successful antiviral treatment among people who inject drugs: A meta-analysis

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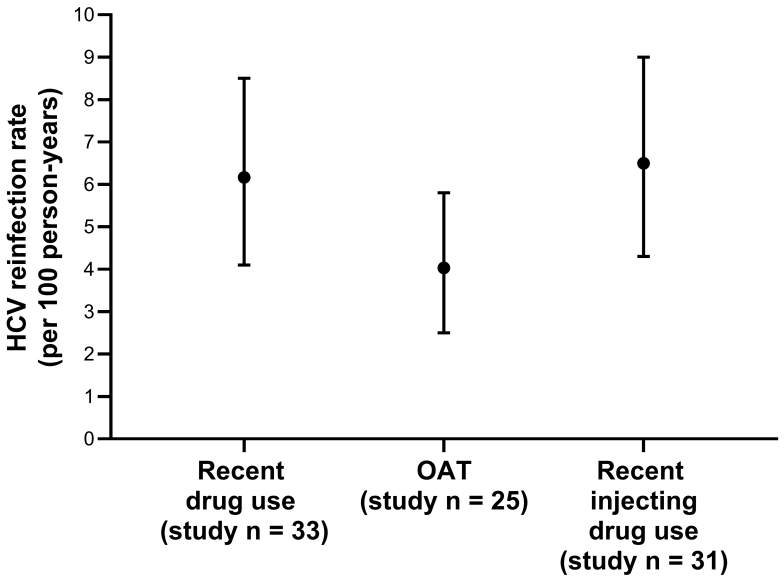
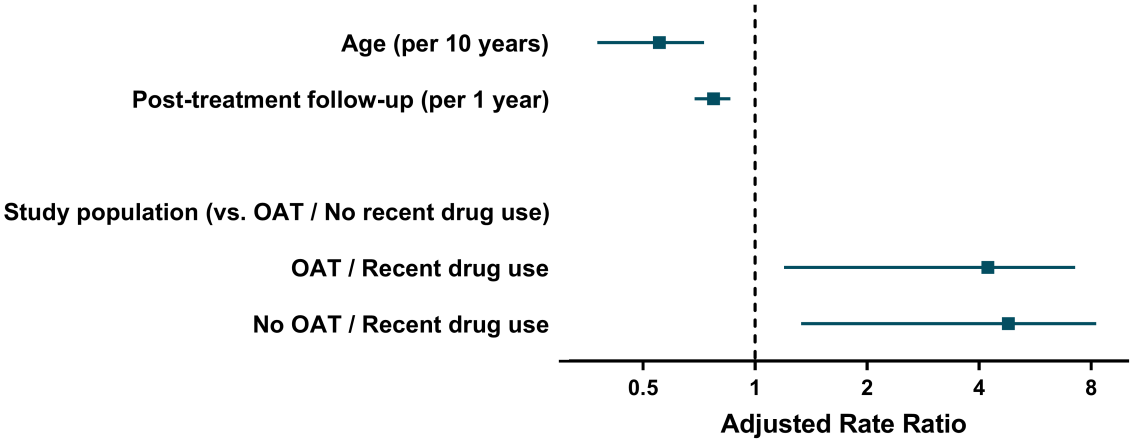


HCV reinfection rate in various study populations, based on recent drug use and OAT status



Study-level study-level factors associated with HCV reinfection rate

TITLE PAGE

Title:

Hepatitis C reinfection after successful antiviral treatment among people who inject drugs: A meta-analysis

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Authors contributions:

BH, GD, and JG conceived the scope of the review which was critically revised by all coauthors. Screening, review, data extraction and verification was done by BH, EC, HV and JG. Data analysis was done by BH which was reviewed by ML. BH and JG drafted the first iteration of manuscript. All authors made substantial contributions to the critical review, editing, and revision of the manuscript. All authors approved the final version of the manuscript.

ABSTRACT

Background/Aims: HCV reinfection following successful treatment can compromise treatment outcome. This systematic review assessed the rate of HCV reinfection following treatment among people with recent drug use and those receiving opioid agonist therapy (OAT).

Methods: Bibliographic databases and conference abstracts were searched for studies assessing post-treatment HCV reinfection rate among people with recent drug use (injecting or non-injecting) or those receiving OAT. Meta-analysis was used to cumulate reinfection rates and meta-regression to explore heterogeneity.

Results: Thirty-six studies were included (person-years follow-up=6,311). The overall rate of HCV reinfection was 5.9/100 person-years (95%CI: 4.1-8.5) among people with recent drug use (injecting or non-injecting), 6.2/100 person-years (95%CI: 4.3-9.0) among people recently injecting drugs, and 3.8/100 person-years (95%CI: 2.5-5.8) among those receiving OAT. Reinfection rates were comparable following interferon-based (5.4/100 person-years; 95%CI: 3.1-9.5), and direct-acting antiviral therapy (3.9/100 person-years; 95%CI: 2.5-5.9). In stratified analysis, reinfection rate was 1.4/100 person-years (95%CI: 0.8-2.6) among people receiving OAT with no recent drug use, 5.9/100 person-years (95%CI: 4.0-8.6) among people receiving OAT with recent drug use, and 6.6/100 person-years (95%CI: 3.4-12.7) among people with recent drug use, not receiving OAT. In meta-regression analysis, longer follow-up was associated with lower reinfection rate [adjusted Rate Ratio (aRR) per year increase in mean/median follow-up: 0.77, 95%CI: 0.69-0.86]. Compared with people receiving OAT with no recent drug use, those with recent drug use, receiving OAT (aRR: 3.50, 95%CI: 1.62-7.53), and those with recent drug use, not receiving OAT (aRR: 3.96, 95%CI: 1.82-8.59) had higher reinfection rates.

Conclusion: HCV reinfection risk following treatment increased among people with recent drug use compared to those receiving OAT. Lower rates in studies with longer follow-up suggested higher reinfection risk early post-treatment.

Word counts: 275 words

Lay summary

Our findings demonstrate that although reinfection by hepatitis C virus following successful treatment occurs among people with recent drug use, the rate of hepatitis C reinfection is lower than rates of primary infection that have been reported in the literature in this population and it should not be used as a reason to withhold therapy from people with ongoing injecting drug use. The rate of hepatitis C reinfection was lowest among people receiving opioid agonist therapy with no recent drug use, compared to people with recent drug use. These data illustrate that harm reduction services are required to reduce the reinfection risk, while regular post-treatment hepatitis C assessment is required for early detection and retreatment.

INTRODUCTION

Globally, among the 71 million people living with hepatitis C virus (HCV) [1], 6.1 million (8.6%) injected drugs during the previous year [2]. HCV transmission continues to occur among people who have recently injected drugs [3-6]. Increasing access to HCV prevention services and HCV treatment among people who inject drugs will be critical to achieve the World Health Organization goal of eliminating HCV as a major global public health threat by 2030 [7].

Direct-acting antiviral (DAA) therapy for HCV infection is effective among people who have recently injected drugs [8]. In many countries, people who have not ceased injecting drug use are ineligible to receive HCV treatment, either because of clinical guidelines or due to restrictions for government reimbursement of therapy [9, 10]. A major concern is that ongoing injecting risk behaviours following DAA therapy may lead to HCV reinfection, reversing the benefit of cure [11]. Given that DAA therapy is expensive, data on the magnitude of post-treatment HCV reinfection risk is crucial to guide clinical decision making and policy in this area.

Although there have been three systematic reviews evaluating the rate of HCV reinfection among people who inject drugs [12-14], there is only one performed in the DAA era (included five studies) [13]. These systematic reviews are limited by the inclusion of studies with heterogeneous study populations, small numbers of identified studies, limited sub-group analysis, and lack of data on persistent HCV reinfection. To our knowledge, there has been no published meta-regression analysis to assess the study-level factors associated with HCV reinfection rate.

The aim of this systematic review was to evaluate the rate of HCV reinfection following successful HCV treatment (interferon-based and DAA) among well-defined populations of individuals with recent drug use, including those with recent injecting drug use, and individuals receiving OAT. Factors explaining heterogeneity across studies were also assessed.

METHODS

This study is reported based on the PRISMA statement [15]. Study protocol was registered with PROSPERO (PROSPERO 2018 CRD42018114765).

Eligibility criteria

We included prospective and retrospective studies, investigating HCV reinfection following HCV treatment, if they met all the following criteria:

a) Study population included defined populations of people with recent drug use or people receiving OAT
b) Reinfection following treatment-induced HCV clearance (interferon-based or DAA therapy) was assessed
c) Reinfection rate, including person-years follow-up was reported.

Studies including participants with former or current drug use were included when the data specifically for those with recent drug use were available. “Recent drug use” was considered as injecting or non-injecting drug use within six months prior to treatment initiation, during treatment, at the end of treatment, or during post-treatment follow-up. Other definitions referring to active drug use at the time of study entry were also accepted for inclusion. Studies with <10 person-years follow-up were excluded.

Information sources and search

Literature searches of five bibliographic databases, including MEDLINE (Pubmed), Scopus, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and PsycINFO were performed. Presentations at the key viral hepatitis conferences were searched, including International Liver Congress™, The Liver Meeting®, Annual Conference on Retroviruses

and Opportunistic Infections (CROI), and International Symposium on Hepatitis Care in Substance Users (INHSU). ClinicalTrials.gov was searched for unpublished or ongoing studies. Reference lists of the articles included in the analysis, and relevant review articles were hand searched. Forward citation tracking was carried out, using Scopus. Searches were performed in October 2018, and updated in June 2019. No time restriction was applied for the search results.

The details of the search strategies are provided in Supplementary Table 1. In brief, combinations of search terms were used, relating to HCV, drug use, OAT, HCV treatment, and reinfection/reviraemia.

Study selection

The records found through primary search were initially screened by title and abstract. The full-text of potentially eligible records were reviewed, and eligible studies were selected for inclusion (Figure 1). In the case of multiple publications of one study, the one with the most updated data was included.

Data collection process and data items

Required data were extracted into a standardized spreadsheet. The extracted data included the items related to study design and setting, definition of recent drug use and OAT, study participant characteristics, HCV treatment, post-treatment follow-up, and HCV reinfection (Table 1). Authors were contacted if supplementary data were required.

Risk of bias in individual studies

The risk of bias for the included studies was assessed using a modified scale derived from Newcastle-Ottawa quality assessment scale for cohort studies [16], including eight items with a total score of nine (Supplementary Table 2). Studies with a score of <6, 6–7, and >7 were considered as having high, moderate, and low risk of bias, respectively.

Two or more reviewers independently carried out title/abstract screening (EC, HV), full text review (BH, EC, JG), data extraction (BH, EC, HV), and critical appraisal (BH, EC, HV, JG), with discrepancies discussed in the group to reach consensus.

Synthesis of results

The primary outcome was the rate of HCV reinfection. The secondary outcome was the rate of persistent HCV reinfection. HCV reinfection was defined as the detection of HCV RNA following an end of treatment response (i.e., non-quantifiable HCV RNA at the end of treatment) or following sustained virologic response [SVR, i.e., non-quantifiable HCV RNA at 12 (SVR12) or 24 (SVR24) weeks after the end of treatment]. In studies using end of treatment to indicate the beginning of the time at risk for HCV reinfection, HCV RNA recurrence was considered as 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 prior to treatment. In the studies using SVR to indicate the beginning of the time at risk for HCV reinfection, any HCV RNA recurrence was considered as reinfection, given the low likelihood of viral relapse after SVR [17, 18]. Persistent HCV reinfection refers to the detection of HCV RNA at least 24 weeks following reinfection. For each included study, the rate of HCV reinfection was calculated, using the reported number of reinfection cases and person-years 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-square statistic, with an I-square <25%, 25%-75%, and >75% considered as low, moderate, and high heterogeneity, respectively [19]. Random effect meta-analysis models were used to cumulate the rate estimates.

Study-level factors contributing to heterogeneity of the outcome were assessed using stratified analysis and meta-regression. Stratified analyses were performed by HCV treatment (interferon-based, versus DAA therapy), risk of bias, and exclusive study population risk groups (based on recent drug use and OAT status). In studies combining populations of people with recent drug use and people receiving OAT, sub-population data were used in the risk group analyses.

In meta-regression, the covariates were determined *a priori* and included study design, study setting, study population risk groups, participants' mean/median age, proportion of men, proportion with HIV co-infection, HCV treatment, mean/median post-treatment follow-up, visit when HCV reinfection risk assessment began (e.g. end of treatment or SVR), HCV testing interval during follow-up, and study quality assessment score. The final adjusted model included variables with P<0.10 in unadjusted analyses (0.10 was used as the P value cut-off to avoid model instability). Publication bias was assessed using funnel plots and Begg's test. Statistical significances were assessed at P<0.05 (P-values are two sided). All analyses were performed using Stata 14.2 (StataCorp, College Station, TX, USA).

RESULTS

Study selection

A total of 1,160 records in bibliographic databases and 43 records from other sources were identified in the initial search, while 36 eligible studies were eventually included in the analysis (Figure 1).

Study characteristics

Thirty-six studies [20-55] with a total 6,311 person-years follow-up were included (Tables 1 and 2). Twenty-two studies (61%) reported the proportion of participants with no post-treatment follow-up assessment (loss to follow-up), which was between zero and 38% (median: 10%). In most studies, recent drug use and receiving OAT were defined as drug use (n=19) and OAT (n=17) during HCV treatment or post-treatment follow-up. Drug use referred to “injecting or non-injecting” drug use in three studies and “injecting only” drug use in 32 studies. HCV treatment was interferon-based therapy in 17 studies, including one study for acute HCV infection [41], and DAA therapy in 19 studies. In most studies, HCV reinfection assessment started from end of treatment (n=14), or SVR12 (n=11). Diagnosis of reinfection was often based on HCV RNA detection following SVR (n=14), or detection of different HCV strain using viral sequencing (n=10).

Risk of bias within studies

The risk of bias assessment scores is shown in Supplementary Table 3. Risk of bias was high in four studies (score <6), moderate in 23 studies (score: 6–7), and low in nine studies (score >7).

Synthesis of results

Data on the rate of HCV reinfection were available for people with recent drug use (injecting or non-injecting) in 33 studies (5,061 person-years follow-up) [20-25, 27-37, 39-53, 55], for people with injecting drug use in 31 studies (4,648 person-years follow-up) [20-25, 27-36, 39-44, 46-53, 55], and for those receiving OAT in 25 studies (2,507 person-years follow-up) [20, 22, 24-26, 28, 29, 31-35, 38-42, 44-49, 51, 54]. The pooled estimates of reinfection rates were 5.9 per 100 person-years (95%CI: 4.1, 8.5) among people with recent injecting or non-injecting drug use, 6.2 per 100 person-years (95%CI: 4.3, 9.0) among people with recent injecting drug use, and 3.8 per 100 person-years (95%CI: 2.5, 5.8) among those receiving OAT (Figure 2). High heterogeneity was observed across studies, although lower across studies among people receiving OAT (I-square=56.9%), than studies among people with recent drug use (I-square=81.4%) and studies among those with recent injecting drug use (I-square=81.2%; Figure 2). In a sensitivity analysis, excluding two linkage-based Canadian studies contributing the largest person-years follow-up [39, 47], the pooled reinfection rates slightly increased while heterogeneity decreased (Supplementary Table 4). The funnel plots of reinfection rates and the Begg's test showed no significant evidence of publication bias (Supplementary Figure 1).

Twenty-four studies with 3,381 person-years follow-up provided data on the rate of persistent HCV reinfection [20, 22, 24-26, 28, 31, 32, 34, 37, 38, 41-49, 51, 52, 54, 55]. The pooled rate estimates were 5.1 per 100 person-years (95%CI: 3.6, 7.1; I-square=58.2%) among people with recent drug use, 5.4 per 100 person-years (95% CI: 3.9, 7.5; I-square=51.2%) among people with recent injecting drug use, and 3.4 per 100 person-years (95%CI: 2.5, 4.6; I-square=15.0%), among those receiving OAT.

None of the studies reported any case of fulminant hepatitis or acute-on-chronic liver failure following HCV reinfection.

Stratified analysis

Sub-populations of people with recent drug use and those receiving OAT have overlaps given that many participants with recent drug use were also receiving OAT. For stratified analysis, data of exclusive study population/sub-populations, based on recent drug use and OAT status (no overlap) were extracted. For 30 studies, supplementary data were provided by the authors. HCV reinfection rates by study population risk groups are illustrated in Figure 3. The lowest rate was identified among people receiving OAT, with no recent drug use (1.4 per 100 person-years; 95%CI: 0.8, 2.6). Increased reinfection rates were identified among people with recent drug use who were or were not receiving OAT, with the highest rate identified among people with recent drug use, not receiving OAT (6.6 per 100 person-years; 95%CI: 3.4, 12.7; Figure 3A). Restricting the analysis to studies providing data on injecting drug use, the results were similar (Figure 3B).

Stratified analysis by HCV treatment regimen indicated comparable rates of reinfection following interferon-based therapy (5.4 per 100 person-years; 95%CI: 3.1, 9.5) and DAA therapy (3.9 per 100 person-years; 95%CI: 2.5, 5.9; Figure 4).

In stratified analysis by risk of bias, no significant difference was observed in rates of reinfection across different groups although studies with low risk of bias reported relatively higher rates (Supplementary Table 5).

Meta-regression

In the adjusted meta-regression model, having a study population with recent drug use was associated with a higher rate of reinfection, while higher mean/median age of participants and longer mean/median post-treatment follow-up were associated with lower rate of reinfection. Compared to people receiving OAT, with no recent drug use, those with recent drug use who also received OAT had 3.5 times higher risk of reinfection [adjusted Rate Ratio (RR): 3.50, 95%CI: 1.62, 7.53; P=0.002), and those with recent drug use, not receiving OAT had four times higher risk of reinfection (adjusted RR: 3.96; 95%CI: 1.82, 8.59; P=0.001). Risk of reinfection was decreased by 6% for each year increase in mean/median age of study participants (adjusted RR: 0.94; 95%CI: 0.91, 0.97; P<0.001), and decreased by 23% by each year increase in mean/median post-treatment follow-up (adjusted RR: 0.77; 95%CI: 0.69, 0.86; P<0.001) (Table 3). Restricting the meta-regression analysis to the studies providing data on injecting drug use, no major difference was observed in the results. The residual I-square of the adjusted model was 9%, indicating that the factors included in the model explained a large proportion of heterogeneity across studies (Table 4).

DISCUSSION

This study provides estimates of the rate of reinfection following successful HCV treatment among people with recent drug use (5.9 per 100 person-years), people with recent injecting drug use (6.2 per 100 person-years), and those receiving OAT (3.8 per 100 person-years). Among people with recent drug use, not receiving OAT, the reinfection rate was 6.6 per 100 person-years. In meta-regression analysis, recent drug use was associated with higher risk of reinfection, while older age and longer follow-up was associated with lower risk. This study provides robust data on the magnitude of HCV reinfection risk following treatment, important to inform HCV clinical guidelines globally and public health policy decisions around treatment access and national strategies to guide HCV elimination efforts.

The estimated HCV reinfection rate of 6.2 per 100 person-years among people who have recently injected drugs is higher than previous systematic reviews (1.9 to 2.4 per 100 person-years) [12-14], but consistent with an estimate among people with ongoing injecting drug use in the interferon era (6.4 per 100 person-years) [12]. Given the small number of studies, and person-years follow-up, this previous estimate is limited by a wide uncertainty range (95% CI, 2.5 to 16.7) [12]. Previous systematic reviews have also been limited by inclusion of heterogenous study populations with former or current drug use [12, 14], and the small number of studies identified (particularly in the DAA era) [12-14]. The large number of included studies, and person-years follow-up, and well-defined study populations in this study provide a more precise estimate of the rate of HCV reinfection among people with recent drug use and those receiving OAT. Moreover, the considerable efforts made to contact the authors to collect supplementary data is a major strength of the current study, enabling sub-group and meta-regression analyses.

The pooled rate of HCV reinfection among people with recent injecting drug use in this study (6.2 per 100 person-years) is lower than reported rates of primary HCV infection in the community. In a pooled analysis of seven studies of people who inject drugs from four countries, HCV incidence was 23 per 100 person-years, ranging from 7 to 33 per 100 person-years [3]. The lower rate of HCV reinfection compared to primary infection could be related to various factors, including reduced risk behaviors among people who have received HCV treatment and a difference in the risk profiles among people at risk of primary infection and reinfection, with low-risk individuals more probably engaged in care.

Our finding of significantly lower reinfection risk among people receiving OAT who did not use drugs, indicates the importance of enhancing access to OAT as a strategy to prevent reinfection. One study demonstrated that lower OAT dose is associated with higher HCV incidence [56], suggesting that in addition to improving OAT access, ensuring appropriate OAT dosing may also be important for HCV prevention.

This study demonstrated a higher rate of HCV reinfection in studies with shorter follow-up. One explanation of this finding is that there is a higher risk of reinfection in the early period following treatment completion. Alternatively, this finding may be due to bias resulting from a cohort effect, with high-risk individuals contributing shorter person-years of follow-up due to becoming reinfected early post-treatment or loss to follow-up. Future studies of HCV reinfection require strategies to enhance study follow-up and ensure there is adequate person-years of post-treatment follow-up to minimize the potential for bias.

Comparable rates of HCV reinfection were observed following interferon-based and DAA therapy in this study. There have been concerns from some practitioners that the broadening

of HCV DAA therapy to more marginalized populations might lead to increased rates of reinfection. Further, it has been suggested that the ease and high cure rates of DAA therapy might lead to increased risk behaviours among people who inject drugs as compared to interferon-based therapies. However, there are now several studies demonstrating that injecting risk behaviours remain stable or decrease during and following interferon-based and DAA therapy [57-60]. Collectively, these data suggest that there is no difference in the rate of reinfection following interferon or DAA therapy.

It should be acknowledged that early stages of HCV treatment scale-up among high-risk populations will result in increased HCV reinfection [61]. Rapid scale-up of treatment will lead to a greater number of people clearing the virus, thereby increasing the pool of people who are susceptible to reinfection and potentially increasing the number of people with reinfection. As the prevalence of HCV infection decreases, the numbers with HCV reinfection should also decrease. Slow scale-up of treatment has a more limited effect on the reservoir of HCV infection, so the numbers with reinfection will continue to increase. Increased numbers of HCV reinfection cases in the context of treatment scale-up should be viewed as a marker of high treatment uptake among at-risk populations, but also an indication that other harm reduction interventions may need to be intensified [62].

It should be acknowledged that HCV reinfection following successful treatment can increase the overall health system costs within an HCV elimination program since people with HCV reinfection require multiple courses of treatment. As such, it is critical to have complementary strategies to prevent and manage HCV reinfection [63, 64]. At an individual level, prior to initiating DAA therapy, an assessment of HCV reinfection risk should be performed by the treating clinician. Management options include identifying populations with

potential reinfection risk, education and counselling regarding HCV transmission and drug use (particularly the importance of using sterile needles/syringes), optimising access to harm reduction services [39, 63, 65, 66], treating the individual, their injecting (or sexual) partner and people in their injecting network [67], management of medical and psychiatric co-morbidities [39], post-treatment surveillance [68], and rapid retreatment of reinfection. At a population-level, appropriate healthcare provision with universal access to HCV treatment and harm reduction services, adequate funding (for both DAA therapy and harm reduction programs), and alleviation of the stigma associated with HCV infection and drug use should assist in efforts to reduce HCV primary and reinfection incidence. If HCV reinfection does occur, retreatment for reinfection should be offered, without stigma or discrimination, to reduce further potential transmission.

This study provides the most comprehensive review of HCV reinfection following successful treatment among people who inject drugs performed to date, but has several limitations. A high heterogeneity in rates of HCV reinfection was observed across studies. The residual I-square in adjusted meta-regression models were 21% and 9%, indicating that the factors included in the model explained a large proportion of heterogeneity across studies. The residual heterogeneity may be explained by other factors not considered in our analysis due to lack of data, including 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. In most studies, all cases of recurrent viraemia following SVR were considered as reinfection. Although post-SVR HCV relapse is rare [17, 18], this method without using HCV sequencing cannot fully distinguish reinfection from late relapse. In several studies, reinfection was diagnosed on the basis of detection of recurrent viraemia with different HCV genotype/subtype. In rare occasions, genotype-specific HCV treatment among

people with mixed HCV infection (infection with multiple viruses) can result in the eradication of one genotype, but not another [69]. Although uncommon, the presence of mixed infection in studies defining reinfection based on HCV genotype switch may result in a misclassification bias and overestimate the reinfection rate. Several studies conducted interventions to reduce risk behaviours following treatment, such as education of safe injection and other preventions, peer-support, counselling, social support, and provision of sterile injecting equipment [22-25, 35, 37, 46, 49, 51, 52]. Given the wide heterogeneity between interventions, we were not able to assess the impact of these interventions on reinfection risk. Although assessment of HCV reinfection requires having at least one post-treatment HCV assessment, several studies did not report or reported a relatively high proportion of people lost to follow-up. It is possible that people lost to follow-up and not included in analyses had higher risk behaviours for HCV reinfection, leading to a potential risk of selection bias towards including people at lower risk of reinfection. Lastly, it is also possible that there was a selection bias among people treated for HCV infection in these studies representing a less marginalized population, which would underestimate the rate of HCV reinfection.

In conclusion, this study demonstrated that post-treatment HCV reinfection occurred, but the rate of reinfection in the DAA era was similar to rates observed in the interferon era. Although the rate of reinfection was higher in people with recent injecting drug use, it was lower than rates of primary infection reported in the community. Monitoring HCV reinfection following successful HCV treatment in people who inject drugs will be crucial to HCV elimination efforts. Further studies are required to evaluate innovative strategies and models of care to enhance engagement in post-treatment care and prevent HCV reinfection among people who inject drugs.

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TABLES

Table 1: Characteristics of the studies included in analysis

First author, year (country)	Study design	Setting	Definition and time point of		Number of participants	Age mean or median, year	Proportion of participants				HCV treatment	Post-treatment follow-up							
			Recent drug use	OAT			With recent drug use	Receiving OAT	Men	With HIV		Start point	HCV testing schedule	Duration mean or median, months	Loss to follow-up	Person-years follow-up	Reinfection diagnosis	Number of HCV reinfection cases	Number of chronic HCV reinfection cases
Akiyama, 2018 (USA)[20]	Clinical trial	Drug treatment service, multicentre	IDU post-treatment	Post-treatment	114	53	19%	100%	61%	10%	DAA	ETR	Every 6 mo	24	19%	230	HCV sequencing	3	2
Alimohammadi, 2016 (Canada)[21]	Observational, retrospective	Community clinic, single centre	IDU during treatment	During treatment	70	53	100%	59%	86%	57%	IFN-based	SVR12	Every 6 mo	66	NR	385	Post-SVR reviraemia	5	NR
Backmund, 2004 (Germany)[22]	Observational, prospective	Drug treatment service, single centre	IDU at the end of treatment	At treatment initiation	18	32	100%	100%	61%	0%	IFN-based	SVR24	Every 12 mo	34	6%	49	Post-SVR reviraemia	2	2
Baxter, 2018 (UK)[23]	Observational, prospective	Community clinic, single centre	IDU post-treatment	NR	19	43	100%	NR	89%	0%	IFN-based	SVR24	Every 12 mo	143	NR	90	Post-SVR reviraemia	2	NR
Bielen, 2019 (Belgium)[24]	Clinical trial	Drug treatment service, single centre	IDU during the 6 mo pre-treatment	During the 6 mo pre-treatment;	36	50	36%	100%	83%	0%	DAA	SVR12	Variable	18	NR	39	HCV genotype switch	1	1
Bouscaillou, 2018 (Georgia)[25]	Observational, prospective	Drug treatment service, single centre	IDU post-treatment	Post-treatment	136	47	100%	21%	96%	0%	DAA	SVR12	Every 6 mo	12	NR	137	Post-SVR reviraemia	2	2
Boyle, 2018 (UK)[26]	Observational, retrospective	Drug treatment service, multicentre	IDU or non-IDU during 3 mo pre-treatment	At treatment initiation	87	45	NR	100%	80%	2%	DAA	ETR	Variable	6	NR	43	NR	1	0
Coffin, 2019 (USA)[27]	Clinical trial	Community clinic, single centre	IDU during 1 month pre-treatment	NR	30	42	100%	NR	81%	0%	DAA	ETR	After 3, and 9 mo	7	3%	18	HCV sequencing	3	NR
Cuadrado, 2018 (Spain)[28]	Clinical trial	Prison, single centre	IDU during or post-treatment	During or post-treatment	27	39	48%	85%	96%	4%	DAA	SVR12	Every 6 mo	21	2%	49	HCV sequencing	0	0
Cunningham, 2018 (Multi-country)[29]	Clinical trial	Mixed, multicentre	IDU post-treatment	At the end of treatment	164	48	76%	68%	72%	0%	DAA	ETR	After 3 mo, then every 6 mo	11	NR	130	HCV sequencing	6	NR
Dalgard, 2002 (Norway)[30]	Clinical trial	Mixed, multicentre	IDU post-treatment	NR	9	30	100%	0%	100%	0%	IFN-based	SVR24	Variable	53	0	40	HCV genotype switch	1	NR
Deshaies, 2016 (Canada)[31]	Observational, prospective	Drug treatment service, single centre	IDU during the 6 mo pre-treatment	At treatment initiation	30	38	100%	33%	60%	10%	IFN-based	ETR	After 3, 6, and 12 mo	31	10%	78	HCV genotype switch for those with reviramemia between ETR and SVR24, and any post-SVR24 reviraemia	10	10
Dore, 2017 (Multi-country)[32]	Clinical trial	Mixed, multicentre	IDU post-treatment	Post-treatment	199	49	60%	100%	76%	8%	DAA	ETR	After 3 mo, then every 6 mo	25	33%	528	HCV sequencing	7	6

First author, year (country)	Study design	Setting	Definition and time point of		Number of participants	Age mean or median, year	Proportion of participants				HCV treatment	Post-treatment follow-up							
			Recent drug use	OAT			With recent drug use	Receiving OAT	Men	With HIV		Start point	HCV testing schedule	Duration mean or median, months	Loss to follow-up	Person-years follow-up	Reinfection diagnosis	Number of HCV reinfection cases	Number of chronic HCV reinfection cases
Eckhardt, 2018 (USA)[33]	Observational, prospective	Drug treatment service, single centre	IDU during 1 month pre-treatment	At treatment initiation	45	45	100%	53%	89%	0%	DAA	SVR12	Every 3 mo	4	NR	16	HCV sequencing	3	NR
Grady, 2012 (Netherlands)[34]	Observational, prospective	Tertiary clinic, single centre	IDU post-treatment	During treatment	11	47	100%	100%	91%	0%	IFN-based	ETR	Variable	29	0	29	HCV sequencing	1	0
Grebely, 2010 (Canada)[35]	Clinical trial	Community clinic, single centre	IDU post-treatment	Post-treatment	16	44	100%	50%	88%	6%	IFN-based	SVR24	Every 12 mo	21	11%	28	HCV sequencing	2	NR
Hilsden, 2013 (Canada)[36]	Clinical trial	Community clinic, multicentre	IDU during 3 mo pre-treatment	At treatment initiation	23	41	100%	NR	75%	0%	IFN-based	SVR24	NR	22	26%	36	Post-SVR reviraemia	1	NR
Holeska, 2019 (Canada)[37]	Observational, retrospective	Community clinic, single centre	IDU or non-IDU post-treatment	NR	195	53	100%	53%	79%	15%	DAA	SVR12	Every 6 mo	24	6%	379	Post-SVR reviraemia	4	4
Ingiliz, 2017 (Germany)[38]	Observational, prospective	Mixed, multicentre	NR	At treatment initiation	267	50	NR	100%	76%	25%	DAA	ETR	After 1, 3, and 6 mo, then variable	6	NR	117	HCV genotype switch for those with reviramemia between ETR and SVR12, and any post-SVR12 reviraemia	2	1
Islam, 2017 (Canada)[39]	Observational, retrospective*	Mixed, multicentre	IDU during 3 yr pre-SVR or anytime post-treatment	Post-treatment	399	43	84%	35%	66%	12%	IFN-based	SVR12	Variable	55	NR	1952	Post-SVR reviraemia	22	NR
Marco, 2013 (Spain)[40]	Observational, prospective	Prison, multicentre	IDU during or post-treatment	During or post-treatment	59	32	20%	80%	97%	19%	IFN-based	SVR24	Every 12 mo	20	2%	76	Post-SVR reviraemia	6	NR
Martinello, 2017 (Australia)[41]	Clinical trial	Mixed, multicentre	IDU at the end or post-treatment	At treatment initiation	45	34	100%	24%	84%	31%	DAA**	ETR	After 1, and 3 mo, then every 6 mo	15	4%	52	HCV sequencing for those with reviramemia between ETR and SVR12/24, and any post-SVR12/24 reviraemia	8	4
Midgard, 2016 (Norway)[43]	Clinical trial	Mixed, multicentre	IDU post-treatment	NR	37	33	100%	NR	62%	0%	IFN-based	SVR24	Variable	82	14%	206	HCV sequencing; If not available any post-SVR24 reviraemia in a patient who had recent IDU	12	10
Midgard, 2018 (Norway)[42]	Observational, prospective	Community clinic, single centre	IDU during 3 mo pre-treatment	At treatment initiation	83	48	100%	22%	78%	0%	DAA	ETR	Every 3 mo	10	NR	71	Post-SVR reviraemia	2	2
Pineda, 2015 (Spain)[45]	Observational, retrospective	Tertiary clinic, multicentre	IDU or non-IDU post-treatment	Post-treatment	11	46	100%	64%	100%	100%	IFN-based	SVR24	Every 6 mo	32	24%	34	HCV sequencing	3	3
Rosenthal, 2018 (USA)[46]	Clinical trial	Tertiary clinic, single centre	IDU during 3 mo pre-treatment	During or post-treatment	79	58	100%	91%	75%	4%	DAA	ETR	After 3 mo, then every 6 mo	9	NR	52	HCV genotype switch for those with reviramemia between ETR and SVR12, and any post-SVR12 reviraemia	3	3
Rossi, 2018 (Canada)[47]	Observational, retrospective*	Mixed, multicentre	IDU during 3 yr pre-SVR	At the end or post-treatment	909	58	96%	7%	67%	19%	DAA	SVR12/24	Variable	6	22%	697	Post-SVR reviraemia	22	18

First author, year (country)	Study design	Setting	Definition and time point of		Number of participants	Age mean or median, year	Proportion of participants				HCV treatment	Post-treatment follow-up							
			Recent drug use	OAT			With recent drug use	Receiving OAT	Men	With HIV		Start point	HCV testing schedule	Duration mean or median, months	Loss to follow-up	Person-years follow-up	Reinfection diagnosis	Number of HCV reinfection cases	Number of chronic HCV reinfection cases
Scherz, 2018 (Switzerland)[48]	Observational, retrospective	Tertiary clinic, single centre	IDU post-treatment	Post-treatment	39	49	31%	100%	82%	10%	DAA	SVR12	Variable	16	NR	45	HCV genotype switch	2	2
Schubert, 2018 (Austria)[49]	Observational, prospective	Tertiary clinic, single centre	IDU during 3 yr pre-SVR	At the end or post-treatment	178	39	75%	100%	82%	10%	DAA	SVR12	Every 3 mo	13	NR	192	HCV genotype switch	11	10
Schulkind, 2018 (UK)[50]	Observational, prospective	Tertiary clinic, single centre	IDU during 1 week pre-treatment	During treatment	77	35	100	72	72%	0%	IFN-based	SVR12	After 3, and 12 mo	11	1%	68	Post-SVR reviraemia	15	NR
Selfridge, 2019 (Canada)[51]	Observational, retrospective	Primary care, single centre	IDU during the 6 mo pre-treatment	At treatment initiation	159	53	78%	74%	68%	24%	DAA	ETR	Variable	10	6%	167	HCV genotype switch for those with reviramemia between ETR and SVR12, and any post-SVR12 reviraemia	8	8
Valencia, 2019 (Spain)[52]	Observational, prospective	Drug treatment service, multicentre	IDU during the 6 mo pre-treatment	NR	87	45	100%	NR	72%	44%	DAA	ETR	Variable	8	24%	60	HCV genotype switch for those with reviramemia between ETR and SVR12, and any post-SVR12 reviraemia	10	8
Weir, 2016 (UK)[53]	Observational, retrospective*	Mixed, multicentre	IDU post-treatment	NR	29	38	100%	NR	79%	7%	IFN-based	1 yr post-treatment	Variable	86	38%	88	Post-SVR reviraemia	5	NR
Xynotroulas, 2015 (Greece)[54]	Observational, retrospective	Tertiary clinic, single centre	IDU during or post-treatment	At the end or post-treatment	30	33	17%	100%	80%	0%	IFN-based	SVR12/ 24	Variable	7	NR	18	Post-SVR reviraemia	1	1
Young, 2017 (Canada)[55]	Observational, prospective	Mixed, multicentre	IDU during or post-treatment	NR	42	47	100%	NR	87%	100%	DAA†	SVR12	Every 6 mo	18	19%	96	Post-SVR reviraemia	9	6
Øvrehus, 2018 (Denmark)[44]	Clinical trial	Drug treatment service, single centre	IDU during 1 month pre-treatment	At treatment initiation	31	39	35%	100%	81%	0%	DAA‡	ETR	After 1, 3, and 6 mo, then variable	6	10%	13	HCV sequencing	1	1

OAT: opiod agonist therapy; IDU: injecting drug use; Non-IDU: non-injecting drug use; DAA: direct-acting antiviral agent; SVR: sustained virologic response; NR: Not reported
* Data linkage study
** Acute HCV infection; 4 participants (9%) received DAA therapy
† 4 participants (10%) received DAA therapy
‡ 15 participants (50%) received sofosbuvir/ledipaspir + Pegylated IFN

Table 2: Cumulative summary characteristics of the studies, included in analysis

	Study n (%)	Person-years follow-up
Study design		
Clinical trial	13 (36)	1,421
Observational study, prospective	13 (36)	1,082
Observational study, retrospective	7 (19)	1,071
Observational study, retrospective linkage	3 (8)	2,737
Study setting		
Drug treatment service	13 (36)	1,024
Community clinic	7 (19)	1,007
Tertiary care	3 (8)	82
Prison	2 (6)	125
Primary care	1 (3)	167
Mixed setting	10 (28)	3,907
Single- or multi-centre		
Single-centre	20 (56)	1,925
Multi-centre	16 (44)	4,386
Study population		
All participants had recent drug use and received OAT	2 (6)	78
All participants had recent drug use; some received OAT	15 (42)	1,701
All participants had recent drug use; none received OAT	1 (3)	40
All participants had recent drug use; OAT status not reported	3 (8)	196
All participants received OAT; some had recent drug use	8 (22)	1,107
All participants received OAT; recent drug use status not reported	1 (3)	117
Some participants received OAT; some had recent drug use	6 (17)	3,072
Drug use type		
Injecting drug use	32 (89)	5,738
Injecting or non-injecting drug use	3 (8)	456
Not reported	1 (3)	117
Definition of "recent drug use"		
During HCV treatment or post-treatment follow-up	19 (53)	2,641
At the time of or during the 1-6 months before HCV treatment initiation	14 (39)	904
Other	2 (6)	2,649
Not reported	1 (3)	117
Definition of "receiving OAT"		
During HCV treatment or post-treatment follow-up	17 (47)	4,653
At the time of HCV treatment initiation	10 (28)	642
During the 6 months before HCV treatment initiation	1 (3)	39
Not reported	8 (22)	977
HCV treatment		
Interferon-based therapy	17 (47)	3,327
Direct-acting antiviral therapy	19 (53)	2,984

	Study n (%)	Person-years follow-up
Start point for reinfection assessment		
End of treatment	14 (39)	1,589
12 weeks post-treatment (SVR12)	11 (31)	3,361
12-24 weeks post-treatment (SVR12/24)	2 (6)	715
24 weeks post-treatment (SVR24)	8 (22)	559
Other	1 (3)	88
HCV reinfection diagnosis method		
Recurrent viraemia following SVR	14 (39)	4,144
Detection of different HCV strain using sequencing	10 (28)	1,076
Detection of different HCV genotype/subtype	4 (11)	316
HCV sequencing or genotype switch in recurrent viraemia between end of treatment and SVR + any recurrent viraemia following SVR	6 (17)	526
Other	1 (3)	206
Not reported	1 (3)	43

Table 3: Meta-regression analysis of study-level factors associated with HCV reinfection rate

	Number of studies/sub-studies	Unadjusted models		Adjusted model*	
		Rate Ratio (95% CI)	P	Rate Ratio (95% CI)	P
Proportion of men, per 10% increase	61	1.08 (0.84, 1.39)	0.529		
Median/mean age, per year increase	61	0.95 (0.91, 0.98)	0.002	0.94 (0.91, 0.97)	<0.001
Proportion of participants with HIV co-infection, per 10% increase	61	1.04 (0.93, 1.17)	0.452		
Study design	61				
Observational study, retrospective	18	1.00		1.00	
Observational study, prospective	19	2.62 (1.37, 4.98)	0.004	1.36 (0.76, 2.42)	0.294
Clinical trial	24	2.01 (1.05, 3.85)	0.036	1.28 (0.74, 2.23)	0.371
Study setting	61				
Tertiary care, primary care or community clinic	16	1.00			
Drug treatment service	22	1.73 (0.83, 3.60)	0.141		
Prison	5	1.72 (0.48, 6.22)	0.402		
Mixed setting	18	0.82 (0.39, 1.70)	0.587		
HCV treatment	61				
Interferon-based therapy	24	1.00			
Direct-acting antiviral therapy	37	0.78 (0.44, 1.42)	0.412		
Study population	61				
OAT: yes, DU: no	12	1.00		1.00	
OAT: yes, DU: unknown	3	1.81 (0.37, 8.88)	0.456	1.16 (0.27, 4.90)	0.841
OAT: yes, DU: yes	21	4.03 (1.59, 10.21)	0.004	3.50 (1.62, 7.53)	0.002
OAT: unknown, DU: yes	10	3.99 (1.48, 10.74)	0.007	5.69 (2.53, 12.78)	<0.001
OAT: no DU: yes	15	4.52 (1.71, 11.93)	0.003	3.96 (1.82, 8.59)	0.001
Median/mean follow-up, per year increase	61	0.87 (0.76, 0.99)	0.032	0.77 (0.69, 0.86)	<0.001
Start point for reinfection assessment	61				
12 weeks post-treatment (SVR) or later	36	1.00			
End of treatment	25	1.39 (0.78, 2.51)	0.261		
HCV testing interval, per month increase	48	1.01 (0.98, 1.04)	0.636		
Study quality assessment score	61	1.30 (0.95, 1.78)	0.098	0.99 (0.74, 1.31)	0.926

DU: Injecting or non-injecting drug use; OAT: Opioid agonist therapy; SVR: Sustained virological response
*Includes variables with P<0.1 in unadjusted models (61 studies/substudies included); Residual I-square=20.65%

Table 4: Meta-regression analysis of study-level factors associated with HCV reinfection rate, in studies providing data on injecting drug use among participants

	Number of studies/sub-studies	Unadjusted models		Adjusted model*	
		Rate Ratio (95% CI)	P	Rate Ratio (95% CI)	P
Proportion of men, per 10% increase	55	1.04 (0.80, 1.36)	0.747		
Median/mean age, per year increase	55	0.95 (0.92, 0.99)	0.007	0.95 (0.92, 0.97)	<0.001
Proportion of participants with HIV co-infection, per 10% increase	55	1.03 (0.89, 1.19)	0.699		
Study design	55				
Observational study, retrospective	13	1.00		1.00	
Observational study, prospective	18	3.11 (1.59, 6.11)	0.001	1.36 (0.75, 2.48)	0.303
Clinical trial	24	2.20 (1.12, 4.33)	0.023	1.31 (0.75, 2.26)	0.331
Study setting	55				
Tertiary care, primary care or community clinic	12	1.00			
Drug treatment service	21	1.78 (0.80, 3.98)	0.157		
Prison	5	1.70 (0.45, 6.39)	0.422		
Mixed setting	17	0.84 (0.37, 1.87)	0.660		
HCV treatment	55				
Interferon-based therapy	21	1.00			
Direct-acting antiviral therapy	34	0.91 (0.49, 1.70)	0.775		
Study population	55				
OAT: yes, IDU: no	12	1.00		1.00	
OAT: yes, IDU: yes	20	4.08 (1.62, 10.29)	0.004	3.47 (1.65, 7.32)	0.002
OAT: unknown, IDU: yes	9	4.83 (1.78, 13.07)	0.003	6.81 (3.08, 15.01)	<0.001
OAT: no IDU: yes	14	4.22 (1.60, 11.15)	0.004	3.74 (1.77, 7.89)	0.001
Median/mean follow-up, per year increase	55	0.85 (0.75, 0.97)	0.017	0.76 (0.69, 0.84)	<0.001
Start point for reinfection assessment	55				
12 weeks post-treatment (SVR) or later	32	1.00			
End of treatment	23	1.52 (0.83, 2.79)	0.175		
HCV testing interval, per month increase	43	1.01 (0.97, 1.04)	0.677		
Study quality assessment score	55	1.34 (0.94, 1.92)	0.107		

IDU: Injectiong drug use; OAT: Opioid agonist therapy; SVR: Sustained virological response
*Includes variables with P<0.1 in unadjusted models (61 studies/substudies included); Residual I-square=8.95%

FIGURE LEGENDS

Fig. 1. Flow diagram detailing the review process and study

Fig. 2. Forest plots of studies, evaluating HCV reinfection rate following HCV treatment

(A) Among people with recent injecting or non-injecting drug use; (B) Among people with recent injecting drug use; (C) Among people receiving OAT

DU: recent drug use (injecting or non-injecting); IDU: recent injecting drug use; OAT: opioid agonist therapy

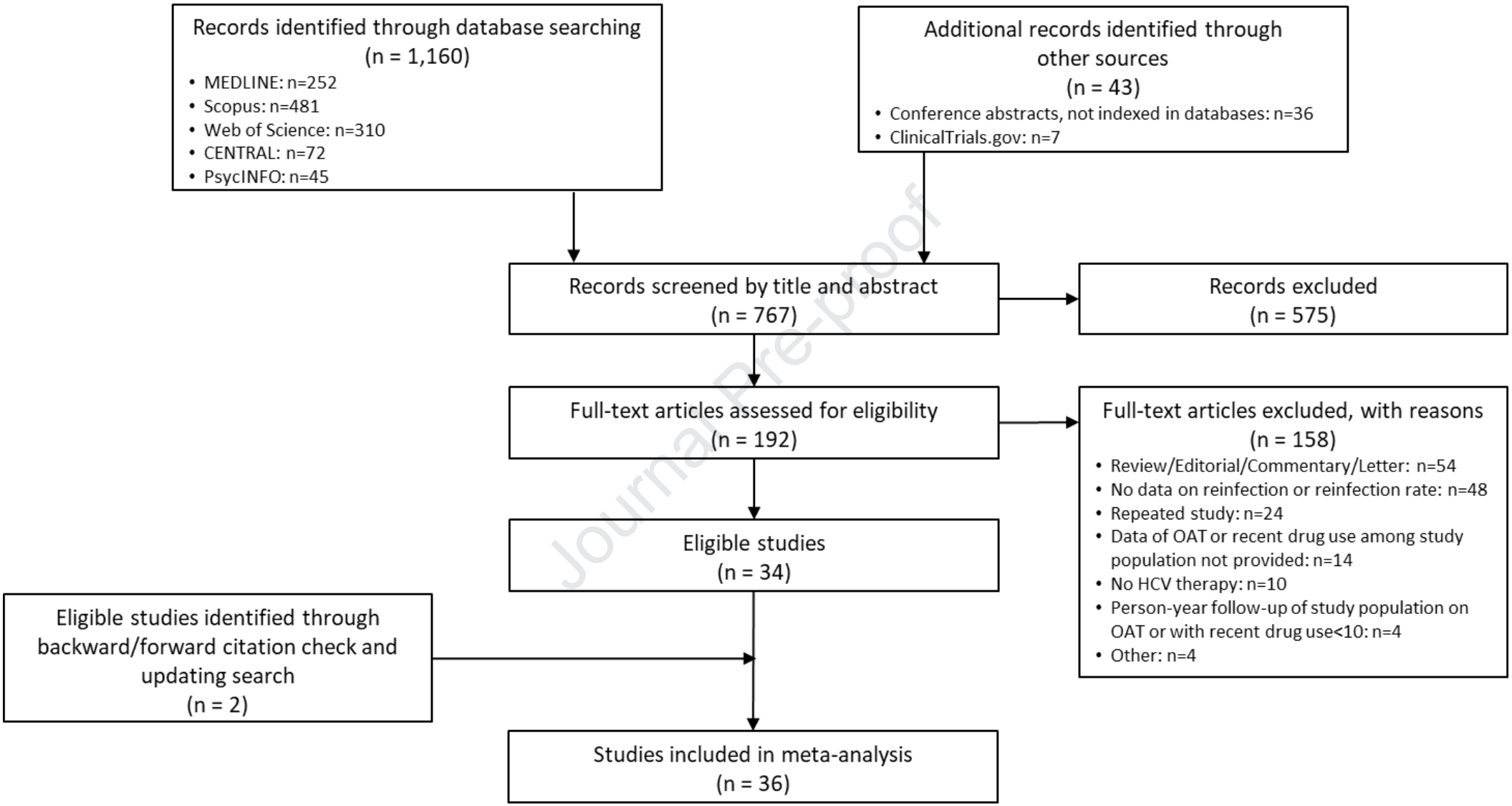
Fig. 3. Forest plots of studies, evaluating HCV reinfection rate following HCV treatment, stratifyed by study population/sub-population

(A) Based on recent drug use (injecting or non-injecting) and OAT status; (B) Based on injecting drug use and OAT status

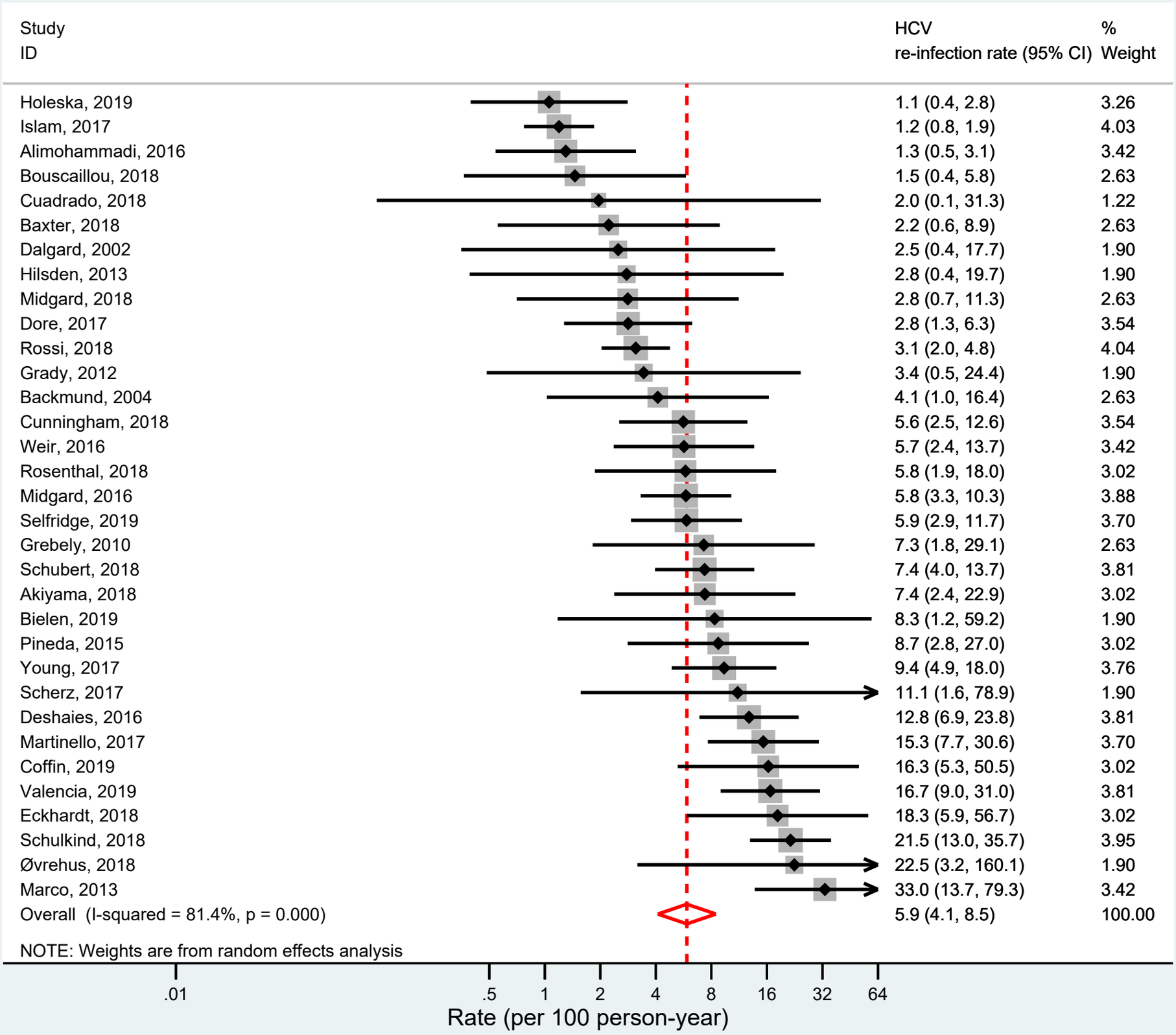
DU: recent drug use (injecting or non-injecting); IDU: recent injecting drug use; OAT: opioid agonist therapy

Fig. 4. Forest plots of studies, evaluating HCV reinfection rate following HCV treatment, stratifyed by HCV treatment regimen

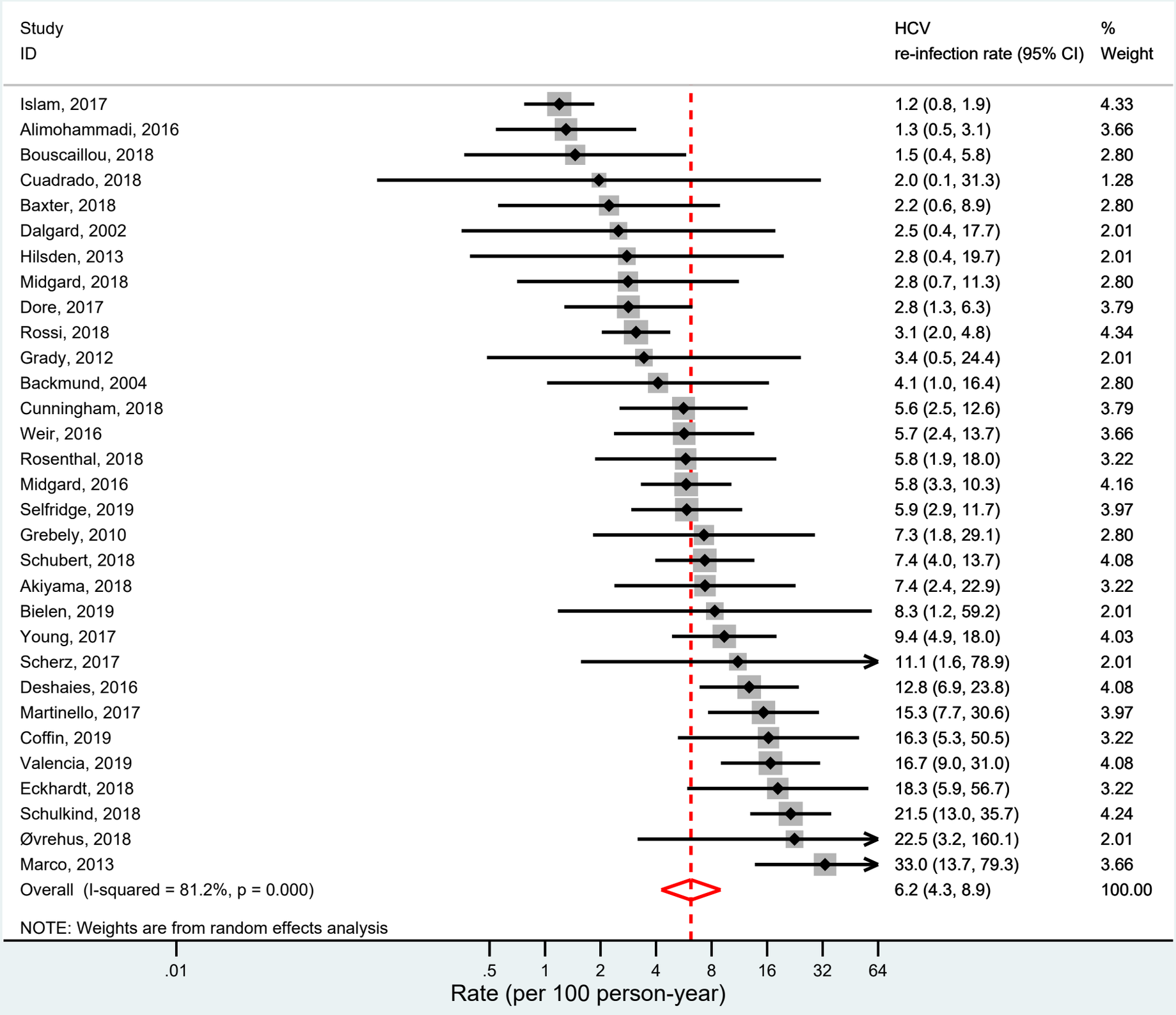
IFN: Interferon; DAA: direct-acting antiviral



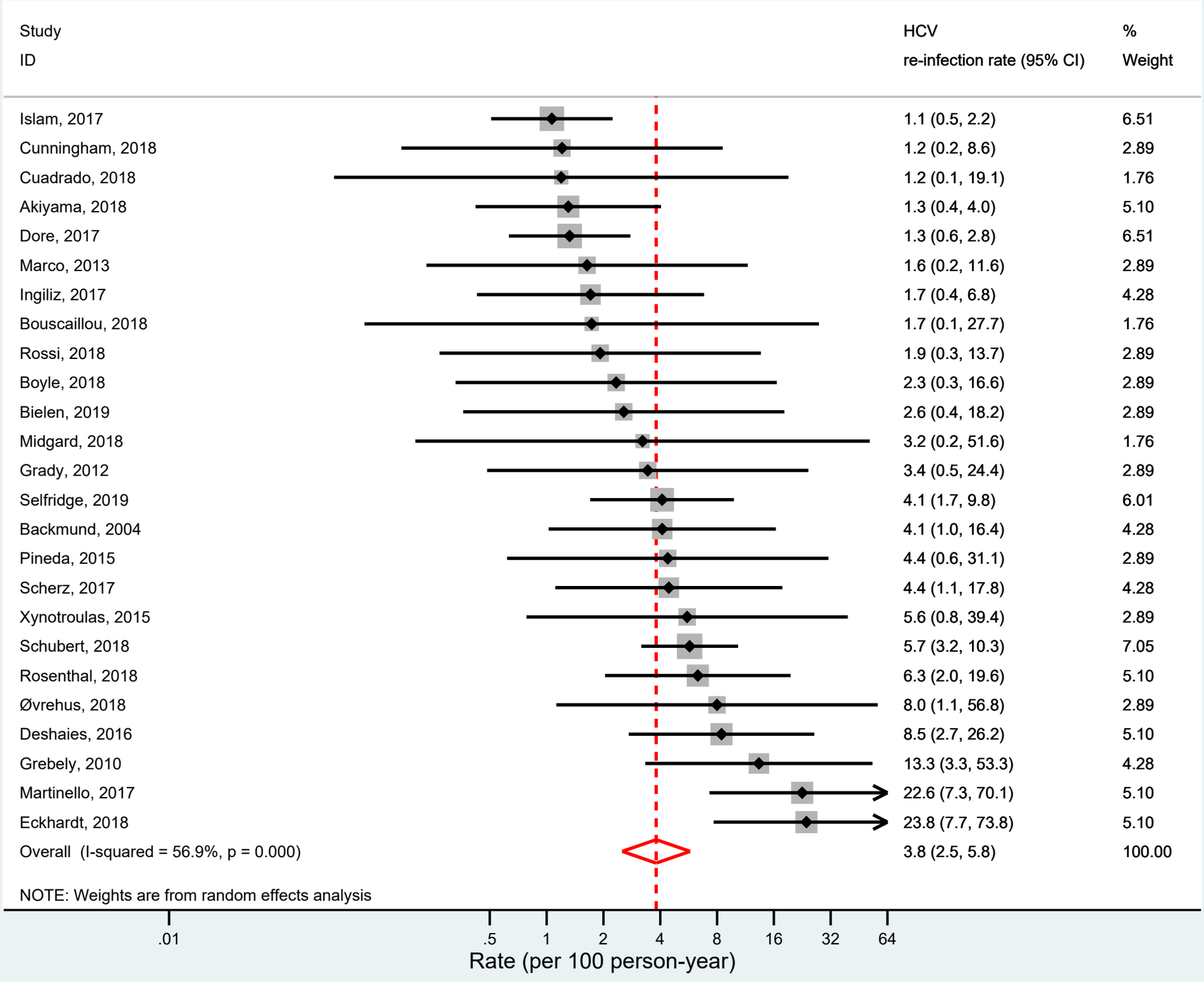
People with recent drug use



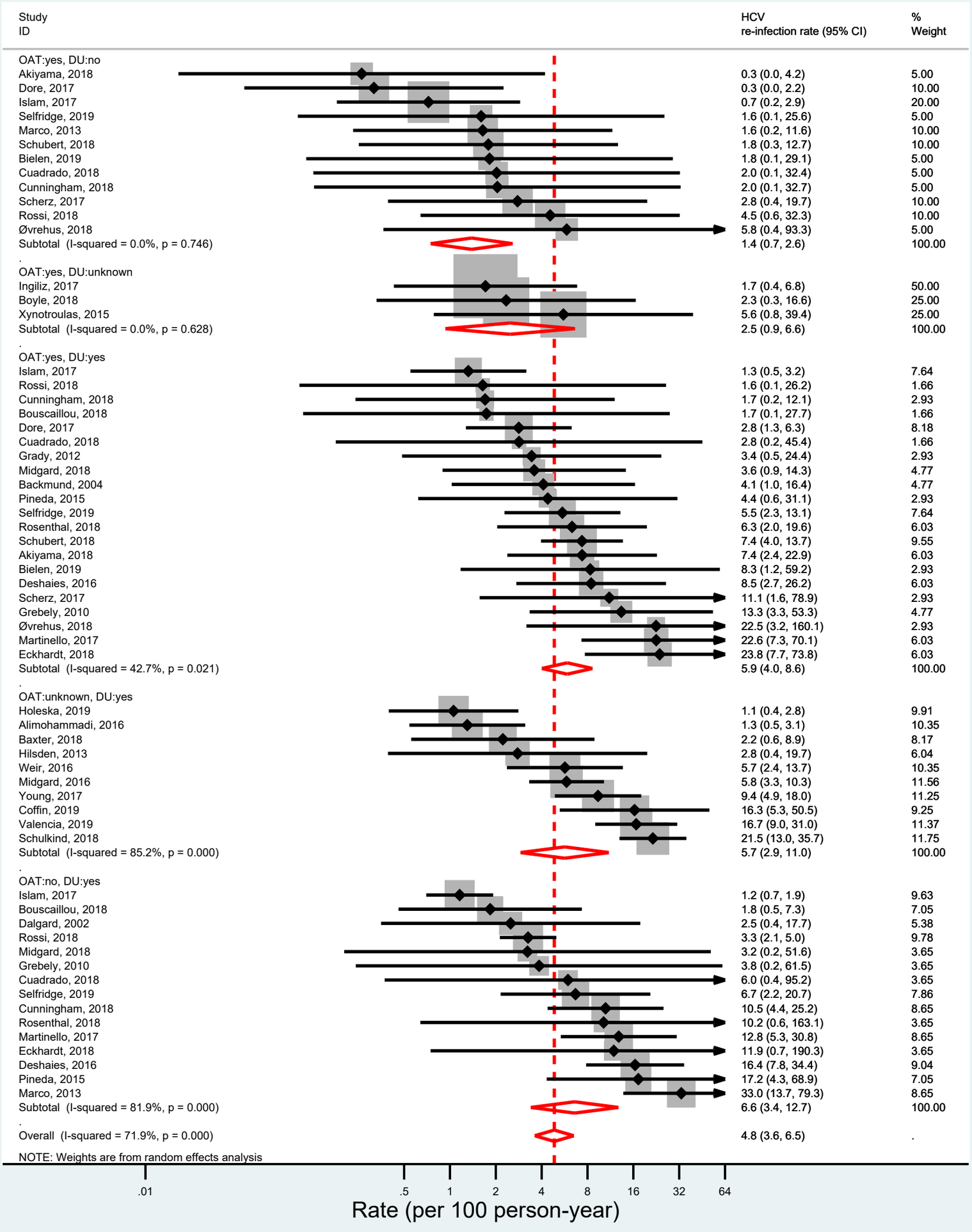
People with recent injecting drug use



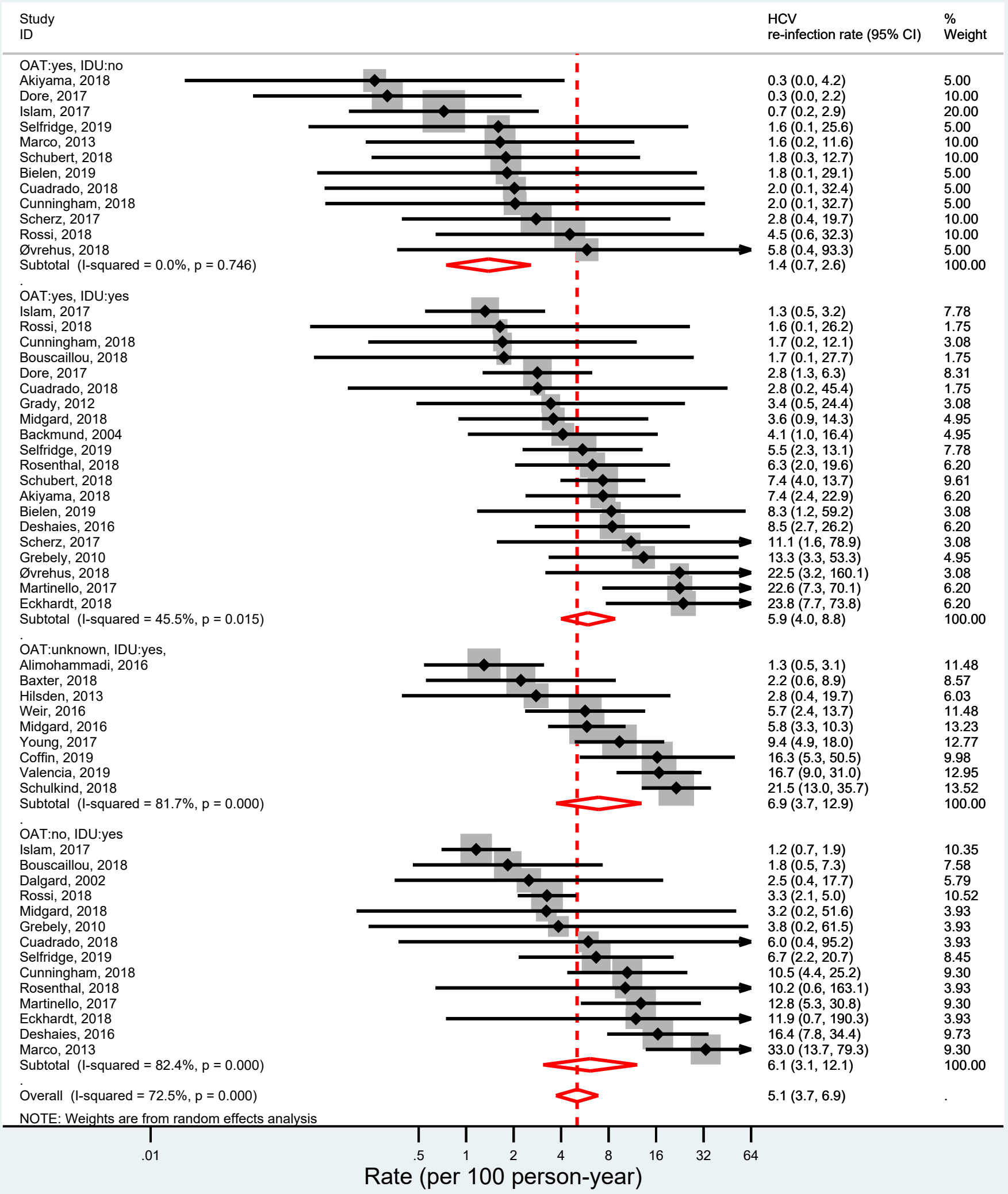
People receiving OAT



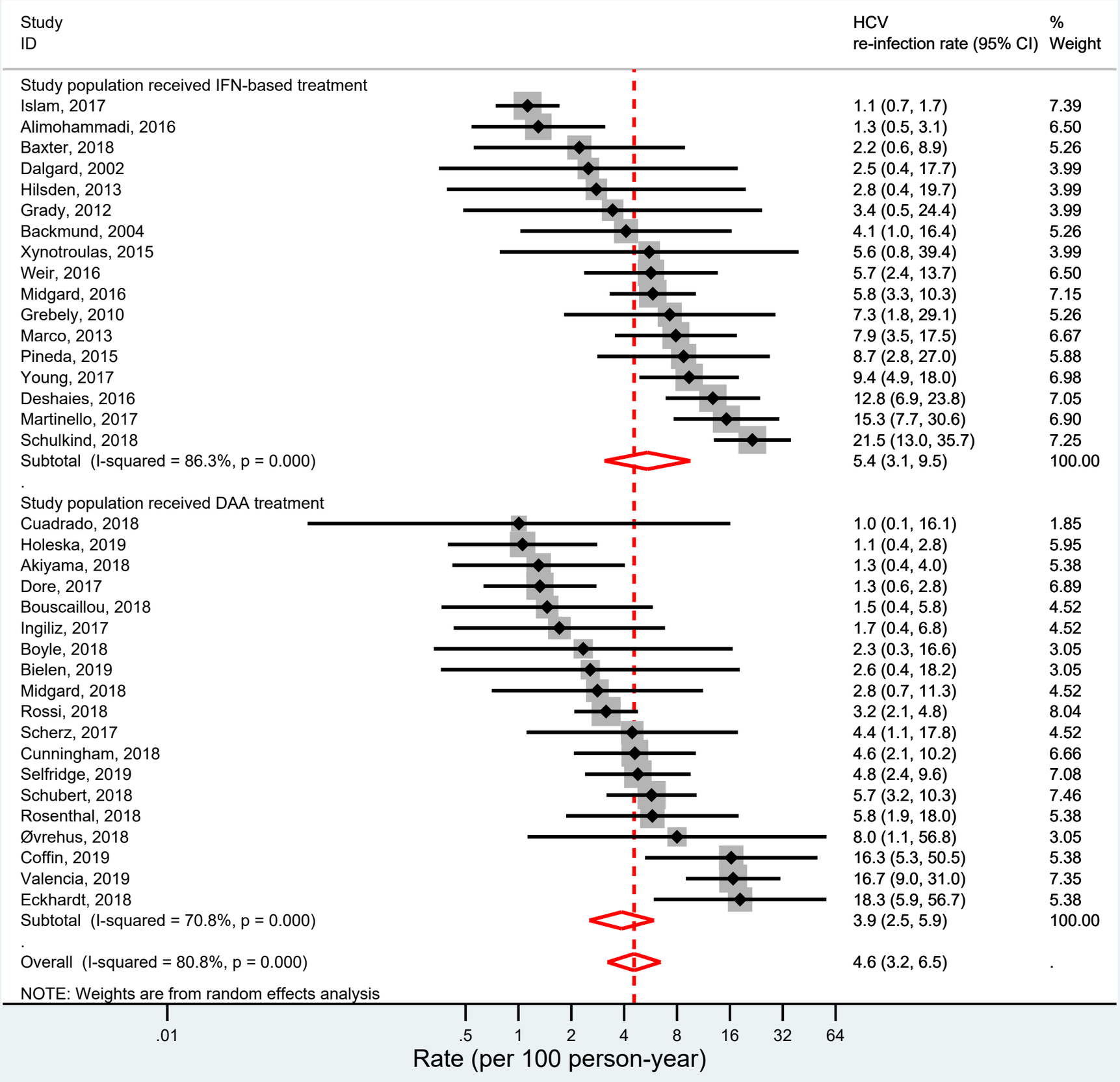
HCV re-infection rate, by drug use/OAT status



HCV re-infection rate, by injecting drug use/OAT status



HCV re-infection rate by HCV treatment regimen



Highlights

- In this systematic review, we assessed the rate of HCV reinfection after treatment among people who recently used drugs or received opioid agonist therapy.
- The rate of reinfection was lowest among people receiving opioid agonist therapy with no recent drug use, compared to people with recent drug use.
- The rate of HCV reinfection was comparable between post-interferon therapy, and post-direct acting antiviral therapy.
- A higher rate of HCV reinfection was observed in studies with shorter follow-up