SUPPLEMENT ARTICLE

# Treatment of Hepatitis C Virus Infection Among People Who Are Actively Injecting Drugs: A Systematic Review and Meta-analysis

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***Background.*** Although guidelines recommend that people who inject drugs (PWID) should not be excluded from hepatitis C (HCV) treatment, some services remain reluctant to treat PWID. The aim of this review was to investigate sustained virologic response (SVR), adherence, discontinuation, and HCV reinfection among PWID.

***Methods.*** A search of Medline, Embase, and Cochrane databases (between 2002 and January 2012) was conducted for primary articles/conference abstracts examining HCV treatment outcomes in PWID. Meta-analysis was used to obtain pooled estimates of SVR, adherence, discontinuation, and HCV reinfection.

***Results.*** Ten primary articles and 1 conference abstract met the inclusion criteria. Across 6 studies (comprising 314 drug users, of whom 141 [45%] were PWID), pooled SVR was 56% (95% confidence interval [CI], 50%–61%) for all genotypes, 37% (95% CI, 26%–48%) for genotypes 1/4, and 67% (95% CI, 56%–78%) for genotypes 2/3. Pooled 80/80/80 adherence was 82% (95% CI, 74%–89%) across 2 studies, and pooled treatment discontinuation was 22% (95% CI, 16%–27%) across 4 studies. Across 5 studies (comprising 131 drug users) examining reinfection, pooled risk was 2.4 (95% CI, .9–6.1) per 100 person-years.

***Conclusions.*** HCV treatment outcomes are acceptable in PWID, supporting treatment guidelines. The pooled estimate of HCV reinfection risk was low, but there was considerable uncertainty around this estimate. Further studies on the risk of reinfection are needed to assess the long-term effectiveness of HCV treatment in PWID.

***Keywords.*** hepatitis C; treatment; people who inject drugs.

Injection drug use is the main mode of hepatitis C virus (HCV) transmission in developed countries, accounting for the majority of new and existing infections [1, 2]. Efforts to tackle HCV infection in people who inject drugs (PWID) are needed to reduce HCV-related morbidity and mortality and prevent onward transmission of HCV [3, 4]. Treatment with pegylated interferon (peg-IFN) and ribavirin (RBV) leads to a sustained virologic response (SVR) in 46%–52% of patients with genotype 1 (GT1) infection, and 76%–80% of those with genotype 2 or 3 (GT2/GT3) infection, although these outcomes have been reported in large clinical trials that excluded patients with a recent history of using drugs [5, 6].

Evidence for treatment outcomes among PWID is currently limited. In a systematic review by Hellard et al, most studies either used receipt of opiate substitution therapy (OST) as a proxy for active drug use, or stipulated a minimum period of abstinence prior to treatment, thus excluding active drug users altogether [7]. Another review reported a pooled SVR of 39% (95% confidence interval [CI], 30%–49%) across 3 studies of active drug users, but 2 of these studies were of patients who reported any type of drug use, rather than specifically injection drug use [8].

Current guidelines recommend that active injection drug use should not exclude patients from HCV

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treatment [9]. However, many services remain reluctant to treat PWID, citing concerns over adherence, increased susceptibility to side effects, and the risk of reinfection through continuing to inject [10]. We carried out a systematic review and meta-analysis of HCV treatment outcomes (including SVR, adherence, discontinuation, and reinfection) among people who are actively injecting drugs.

## METHODS

### Study Identification

A search of Medline, Embase, and Cochrane electronic databases was carried out for English-language articles or conference abstracts published between January 2002 and January 2012, using the search terms in Supplementary Appendix 1. The reference lists of selected studies were examined for relevant articles, and efforts were made to find unpublished or ongoing research presented at international conferences. The review protocol was prospectively registered with PROSPERO (number 2011: CRD42012001923).

### Criteria for Study Selection

The study inclusion criteria are shown in Table 1, and the screening process for study selection is shown in Figure 1.

### Quality Assessment

Articles meeting the inclusion criteria were assessed for quality by 2 independent reviewers (EJA, JSD) using the Newcastle-Ottawa Scale (NOS) [11]. Studies were assigned a score ranging from 1 (poor quality) to 9 (high quality). Study duplications were dealt with by selecting the article that provided the most comprehensive account of the study population.

### Data Extraction

Data were extracted by 3 of the authors (EJA, JSD, SC) in duplicate to a standardized spreadsheet, and any differences were resolved by consensus. The following data were extracted:

#### *Primary Study Outcomes*

SVR was defined as the proportion of individuals by intention to treat who had undetectable HCV RNA at least 24 weeks after completion of HCV treatment. Reinfection was defined as an HCV RNA–positive test following SVR.

#### *Secondary Study Outcomes*

Treatment discontinuation was defined as the proportion of individuals by intention to treat who did not complete a full course of treatment (including nonresponse, minor/serious side effects, or loss to follow-up); 80/80/80 adherence was defined as the proportion of individuals by intention to treat who received 80% of the peg-IFN cumulative dose with 80% of the RBV cumulative dose for 80% of the time.

**Table 1. Inclusion Criteria[a]**

| |
|---|
| Population: |
| 1a. Includes individuals who were actively injecting drugs (defined as having injected drugs in the 12 months prior to study entry, or description of the study population as "active" or "current" injection drug users), |
| AND |
| 1b. The proportion of the study population that was actively injecting (if <100%) was reported. |
| Intervention: |
| 2. Includes combination treatment with pegylated interferon and ribavirin for HCV infection. No stipulated period of abstinence from drugs prior to treatment for chronic hepatitis C. |
| Comparison: |
| 3. No comparator group, or the same intervention in former or non-PWID. |
| Outcome: |
| 4. Data on at least 1 of treatment adherence, treatment discontinuation, or SVR (calculated using intention to treat[b]), or reinfection rate following SVR. |
| Study design: |
| 5. All study designs. |

Abbreviations: HCV, hepatitis C virus; PWID, people who inject drugs; SVR, sustained virologic rate.

[a] Due to the small number of studies examining reinfection, the inclusion criteria for this outcome were broadened in criterion 1 to cover "current or former drug users" and in criterion 2, to cover "any treatment for chronic HCV."

[b] To maintain consistency with previous trials of HCV treatment [5, 6], the intention-to-treat population was defined as the number of individuals who received at least 1 dose of pegylated interferon or ribavirin.

#### *Study Characteristics*

The following data were extracted:

For studies examining SVR: study location, design, method of recruitment, patient characteristics (including the proportion who had injected drugs in the previous 12 months), HCV genotype, mode of treatment delivery, and type of treatment. Genotype was categorized as either GT1/GT4 or GT2/GT3 (due to the available data in the primary studies).

For studies examining reinfection: study location, design, recruitment, treatment/risk reduction interventions, patient characteristics (including the proportion of the study cohort who had injected illicit drugs post-SVR), and length of follow-up.

### Data Synthesis

All statistical analyses were undertaken using Stata software, version 11.0 (StataCorp, College Station, Texas).

#### *Deriving Pooled Estimates of SVR, Treatment Discontinuation, and Adherence*

SVR, adherence, and discontinuation and their exact 95% confidence intervals (CIs) were calculated assuming a binomial distribution. Pooled estimates were derived using random- or fixed-effects methods, according to whether significant heterogeneity (defined

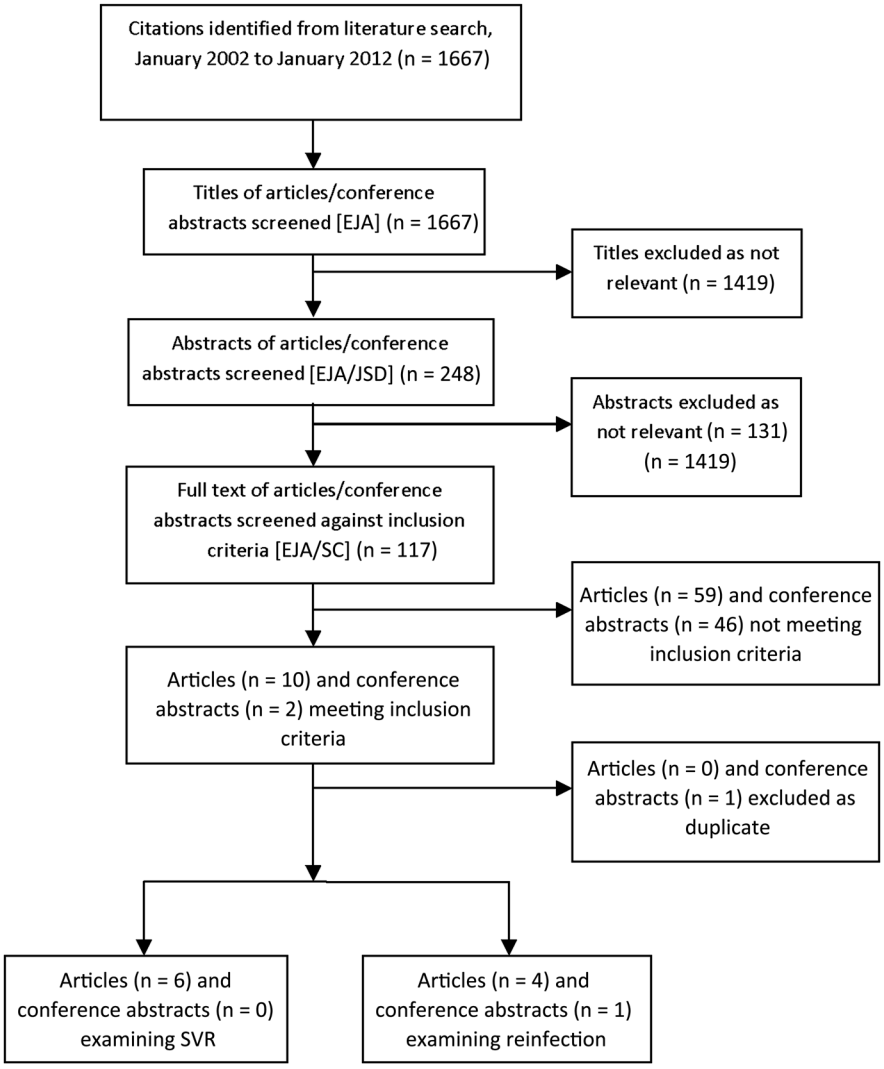


**Figure 1.** Flow diagram of study selection for systematic review of hepatitis C virus treatment outcomes in people who inject drugs. Abbreviation: SVR, sustained virologic response.

as $I^2 > 30\%$) was or was not present, respectively. Sensitivity analysis was used to assess the impact of study quality (restricting to studies with an NOS score ≥6) on the pooled estimate of SVR.

Subgroup meta-analyses (which were determined a priori) were used to obtain pooled estimates of SVR by injecting behavior (all study participants vs participants who reported active injecting) and HCV genotype (GT1/GT4 vs GT2/GT3). Meta-regression was not attempted, due to the small number of primary studies included in the review.

### *Deriving Pooled Estimates of Reinfection*

HCV reinfection rates were calculated as the number of reinfection events per 100 person-years (PY) of follow-up. Exact 95% CIs were calculated assuming a Poisson distribution. Meta-analysis was undertaken using log-transformed incidence rates and corresponding log standard errors in a random-effects model. Subgroup meta-analysis was used to calculate a pooled reinfection rate in individuals who injected drugs post-SVR.

### *Outcome Level Assessments*

The existence of publication bias in the outcomes of SVR or reinfection was assessed using funnel plots. The quality of evidence for each outcome of interest was also assessed by 2 authors (EJA, SC) using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology [12], which rates evidence as high, moderate, low, or very low quality, depending on 4 criteria: study design, study quality, consistency (similarity of estimates of effect across studies), and directness (extent to which the study population, intervention, and outcome measures are similar to those of interest).

## RESULTS

The results of the literature search are shown in Figure 1.

### Studies Reporting on SVR, Adherence, and Discontinuation

Six studies reported on SVR [13–18], of which 4 [14–16, 18] reported on treatment discontinuation and 2 reported on 80/80/80 adherence [13, 16] (Table 2). All 6 were cohort studies: 2 were retrospective [13, 14] and 3 prospective [15–17], and 1 study provided insufficient information to reach a decision [18]. Study size ranged from 21 to 87 study participants. There were 4 higher-quality studies (NOS score ≥6) [13–16].

#### *Study Population*

One study recruited individuals from drug services who were all actively injecting drugs [18]. Three studies recruited individuals attending various drug services, of whom a proportion was actively injecting drugs [13, 15, 16]. The 2 remaining studies were comparative studies: 1 compared individuals who were on OST and/or actively injecting with former PWID not on OST [14], and the other compared individuals who were actively injecting drugs with non-PWID [17]. Comparator groups were not included in the meta-analyses.

The study population represented by the 6 included studies therefore comprised of ever–illicit drug users currently attending services for drug users, and/or individuals actively injecting drugs. This total study population is hereafter referred to as people who use drugs (PWUD). Within the total study population of PWUD, a proportion of individuals was actively injecting drugs, which was defined as self-reported injection drug use in the last 6 months by 2 studies [15, 16], and in the last 12 months by 1 study [14]. The remaining studies did not define active injecting but described their study participants as active injection drug users [17, 18], or current injection drug users [13]. The subgroup of individuals who were actively injecting is hereafter referred to as people who inject drugs (PWID).

#### *Mode of Treatment Delivery*

Three studies provided community-based treatment [13, 15, 18], 2 studies provided hospital-based treatment [16, 17], and 1 study initially provided hospital-based treatment but extended into the community as the service developed [14]. Additional support was reported by 2 studies: 1 provided directly observed peg-IFN, and staff at methadone clinics offered support and monitored side effects [15], and 1 encouraged drug workers to attend HCV appointments and provide general support [14].

#### *Data Synthesis*

The 6 studies included 314 PWUD treated for chronic HCV, of whom approximately 141 (45%) were PWID. There was no evidence of bias based on a funnel plot examining the SVR outcome (Supplementary Appendix 2). Across 6 studies, pooled SVR in PWUD was 56% (95% CI, 50%–61%; Figure 2). A sensitivity analysis restricting to higher-quality studies (NOS score ≥6) produced a pooled SVR of 55% (95% CI, 48%–61%; Table 3).

In subgroups examining SVR by genotype, SVR was 37% (95% CI, 26%–48%) among PWUD with GT1/GT4, and 67% (95% CI, 56%–78%) among PWUD with GT2/GT3. Among PWID, SVR was 61% (95% CI, 51%–72%) for all genotypes.

The pooled estimate of 80/80/80 treatment adherence was 82% (95% CI, 74%–89%) across 2 studies, and the pooled estimate of treatment discontinuation was 22% (95% CI, 16%–27%) across 4 studies.

### Studies Examining HCV Reinfection

Four articles [19–22] and 1 conference abstract [23] reported on reinfection post-SVR (Table 4). All 5 studies were prospective cohorts, with a total study population of 131 (range, 9–42). Three studies recruited drug users who were in receipt of services for drug users at the time they commenced HCV treatment [19, 20, 23]. Two studies recruited current as well as former drug users who were not necessarily in receipt of drug services [21, 22]. One study reported the proportion of PWID (54%) in the study population prior to HCV treatment [19]. The total study population is therefore comprised of current and former PWUD, with an unknown proportion of PWID at treatment commencement. All 5 studies reported the proportion of their study population who injected drugs post-SVR, which ranged from 21% to 50%.

#### *HCV Treatment and Risk Reduction Interventions*

One study treated patients with peg-IFN or IFN plus RBV [19], 2 studies used IFN with or without RBV [20, 21], and 2 studies did not state which HCV treatment was used [22, 23]. Three studies provided advice or counseling on reducing the risk of reinfection following treatment [19, 20, 22].

#### *Study Follow-up*

Study follow-up visits occurred every 6 months in 1 study [22], and every year in 3 studies [19, 20, 23]. One study [21] did not state the frequency of follow-up. Average follow-up ranged from 2.0 years to 4.7 years.

#### *Confirmation of Reinfection*

Reinfection was defined as a new HCV infection confirmed by sequencing analysis by 1 study [23], and as a positive HCV RNA test during the period of follow-up post-SVR by the remaining 4 studies [19–22]. In all 5 studies, individuals with a positive HCV RNA within 6 months of treatment completion were considered to be cases of relapse (rather than reinfection), and were excluded from the study.

#### *Data Synthesis*

There was no evidence of bias based on a funnel plot examining the outcome of HCV reinfection (Supplementary Appendix 3).

**Table 2. Characteristics and Outcomes of Studies Examining Pegylated Interferon and Ribavirin Treatment for Chronic Hepatitis C Virus Among People Who Use Drugs**

| | Patient Characteristics | | | | | | | Intervention | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| First Author, Year, Location | Study Design and Recruitment | No. | Mean Age | Male | OST | GT1/4 | Definition of Active Injecting (% of Cohort) | Treatment Setting, Type of Treatment, Mode of Delivery | 80/80/80 Adherence (%) | Discontinued (%) | SVR by GT Among PWUD | SVR by GT Among PWID |
| Jafferbhoy 2012, UK [14] | Retrospective cohort. Drug users referred to HCV services. | 87 | 36.8 y | 73% | NA | 36% | Injecting drug use in 12 mo prior to starting treatment (33%) | Hospital- and community-based, nurse-led model. Treatment with peg-IFN alfa-2a/2b + RBV. | NA | 19 (22%) | All: 47%<br>GT1/4: 35%<br>GT2/3: 54% | . . . |
| Lindenburg 2011, Netherlands [15] | Prospective cohort. Drug users visiting drug services and primary care were offered testing and referral to in-house treatment. | 58 | 47.7 y | 77% | 84% | 28% | Injection drug use in 6 mo prior to starting treatment (19%) | Community-based service with visiting specialists. Treatment with peg-IFN alfa-2a/2b (directly observed) + RBV. | NA | 10 (17%) | All: 64%<br>GT1/4: 38%<br>GT2/3: 76% | . . . |
| Sasadeusz 2011, Australia [16] | Prospective cohort. Recruitment of those on OST users who were at tertiary hospitals. | 53 | 37.9 y | 79% | 100% | 42% | Injection drug use in 6 mo prior to starting treatment (36%) | Hospital-based. Treatment with peg-IFN alfa-2a + RBV. | 45 (85%) | 16 (30%) | All: 57%<br>GT1/4: 36%<br>GT2/3: 71% | GT1/4: 43%<br>GT2/3: 75% |
| Papadopoulos 2010, Greece [17] | Prospective cohort. Patients who reported injection drug use attending a tertiary hospital. | 48 | 37.7 y | 87% | NA | 40% | Active injection drug use (100%) | Hospital-based. Treatment with peg-IFN alfa-2a/2b + RBV. | NA | NA | All: 60% | GT1/2/3: 60% |
| Jack 2009, UK [18] | Prospective cohort. Inner-city GPs offering OST. Drug users attending drug services or primary care are referred to HCV nurse. | 21 | NA | NA | NA | 33% | Active injection drug use (100%) | Community-based. Treatment in primary care by nurse under supervision of infectious disease specialist. Treatment with peg-IFN alfa-2a/2b + RBV. | NA | 4 (19%) | All: 62% | GT1/4: 43%<br>GT2/3: 71% |
| Wilkinson 2008, UK [13] | Retrospective cohort. Drug users attending a specialist addiction unit were offered in-house HCV testing and treatment. | 47 | 43.4 y | NA | NA | ~45% | Current injection of heroin or crack (29%) | Community- based. Treatment delivered by hepatologist and nurse at outreach clinics in NSP services or primary care. Treatment with peg-IFN alfa-2a + RBV. | 36 (77%) | NA | All: 53%<br>GT1/4: 45%<br>GT2/3: 56% | . . . |

Abbreviations: GP, general practice; GT, genotype; HCV, hepatitis C virus; NA, not available; NSP, Needle and Syringe Programme; OST, opioid substitution therapy; peg-IFN, pegylated interferon; PWID, people who inject drugs; PWUD, people who use drugs; RBV, ribavirin; SVR, sustained virologic response.

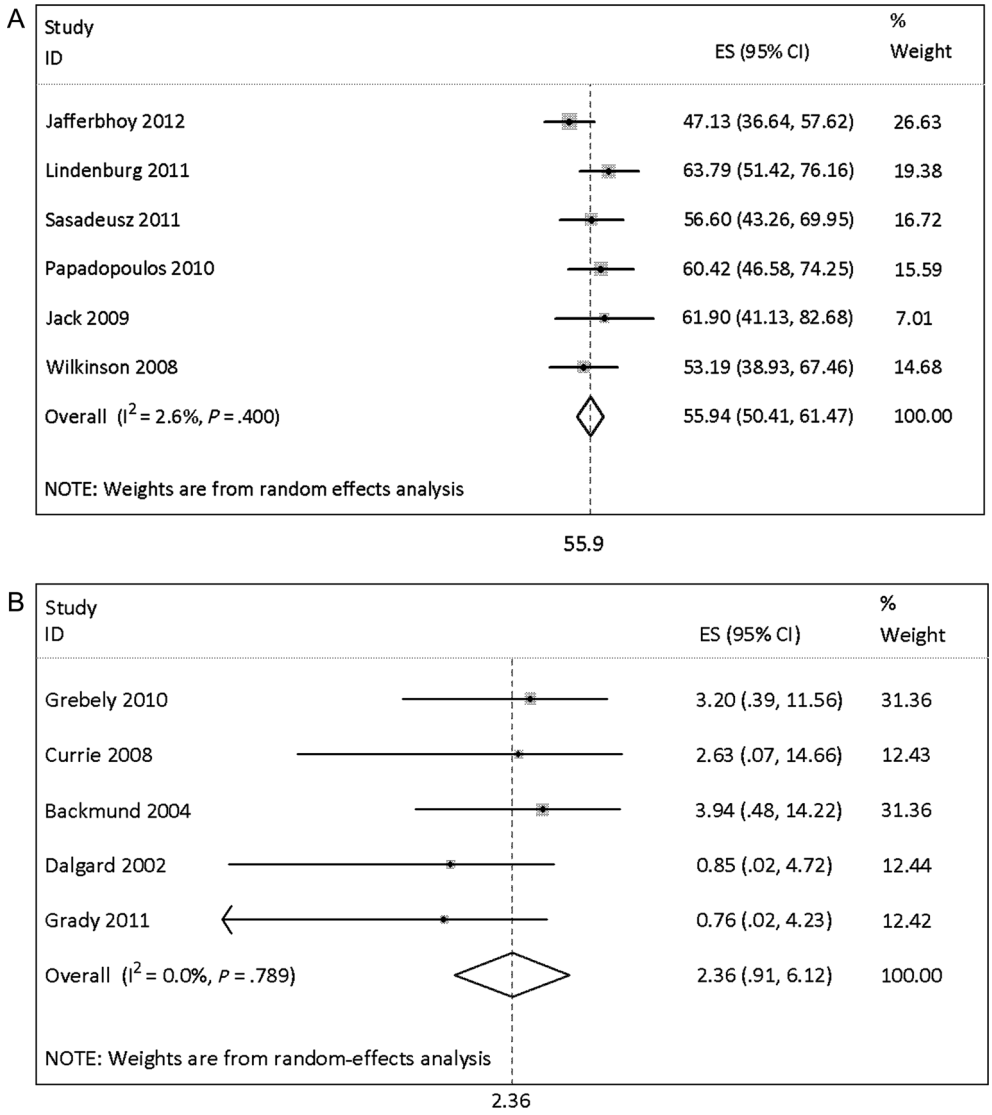


**Figure 2.** *A*, Forrest plot of studies examining treatment sustained virologic response among people who use drugs (PWUD) with chronic hepatitis C virus. *B*, Forrest plot of studies examining reinfection among ever-PWUD treated for chronic HCV. Abbreviations: CI, confidence interval; ES, effect size.

The pooled estimate of reinfection was 2.4 (95% CI, .9–6.1) per 100 PY. Among individuals who reported injection drug use post-SVR, the risk of HCV reinfection was 6.4 (95% CI, 2.5–16.7) per 100 PY.

### GRADE Assessment

The quality of evidence for the SVR and treatment discontinuation outcomes was assessed as low (evidence derived from observational studies). The quality of evidence for the adherence outcome was assessed as very low (observational studies, sparse data). The quality of evidence for the reinfection outcome was also assessed as very low (observational studies, and concern about directness due to study population including former PWID). (Supplementary Appendix 4).

## DISCUSSION

We found that among a population of PWUD, nearly half of whom reported actively injecting, pooled SVRs were 37% in GT1/4, and 67% in GT2/3 after peg-IFN/RBV treatment for chronic HCV. Further, our results demonstrate high adherence, low discontinuation of therapy, and a low rate of reinfection among PWUDs. Whereas previous reviews of treatment in PWID have focused on treatment outcomes among individuals maintained on OST, or who reported a defined period of abstinence from drugs [7, 8], we have limited our review to studies where all or a known proportion of the study participants reported actively injecting drugs. However, a limitation of our review is that we restricted to studies of peg-IFN/RBV

**Table 3. Meta-analysis of Studies Examining Sustained Virologic Response Among People Who Use Drugs**

| Inclusion Criteria | Subgroup | No. of Studies | Pooled Estimate of SVR (95% CI)[a] | Heterogeneity ($I^2$) | Heterogeneity *P* Value |
|---|---|---|---|---|---|
| All studies | | 6 | 55.9% (50.4–61.3) | 3% | .40 |
| Sensitivity analysis | Higher-quality studies (≥6 by NOS) | 4 | 54.5% (48.3–60.6) | 29% | .24 |
| Meta-analysis subgroups | | | | | |
| | All studies (PWUD) | | | | |
| | Genotype 1/4 | 4 | 36.9% (25.6–48.2) | 0% | .99 |
| | Genotype 2/3 | 4 | 67.1% (55.9–78.3) | 46% | .14 |
| | PWID | | | | |
| | All genotypes | 3 | 61.4% (51.2–71.5) | 0% | .98 |
| | Genotype 1/4 | 2 | 42.9% (17.5–68.2) | 0% | 1.00 |
| | Genotype 2/3 | 2 | 73.1% (55.2–91.0) | 0% | .84 |

Abbreviations: CI, confidence interval; NOS, Newcastle-Ottawa Scale; PWID, people who inject drugs; PWUD, people who use drugs; SVR, sustained virologic response.

[a] Random-effects method used if $I^2 \geq 30\%$.

treatment, and therefore our results have less direct relevance to the use of newer treatments such as protease inhibitors.

Our pooled SVRs are slightly lower than those quoted by the major clinical trials of peg-IFN/RBV treatment (46%–52% in GT1 and 76%–80% in GT2/GT3) [5, 6], but are similar to the results of 2 "real-life" studies undertaken outside of clinical trials (39%–46% in GT1 and 70%–84% in GT2/GT3) [24, 25]. This suggests that SVRs may indeed be slightly lower among PWUD but that the difference in real-life settings is likely to be small. Our findings therefore support current guidelines [9] that decisions about treatment should be made independently of an individual's injection drug use status.

Although we graded the quality of evidence for the SVR outcome as low, this was mainly due to the observational design of the studies, and randomized trials would not be possible for ethical reasons. Two studies in our review used nonrandomized comparator groups comprising never or former PWID, but these groups were too small to be used in a meta-analysis. However, our subgroup meta-analysis comparing PWUD and PWID found a similar pooled SVR in both groups, suggesting that among a population of patients accessing services for drug use, those who report active injecting have the same chance of SVR as those who do not report injecting, all other factors being equal. Unfortunately, we were unable to investigate other factors that may have affected treatment outcomes, due to the small number of studies and a lack of comparable data across studies. However, it has previously been suggested that lower social functioning, current opiate pharmacotherapy [26], and a history of untreated depression [27] are associated with a lower chance of SVR. An assessment of a patient's social circumstances and the availability of support (in addition to injecting behavior) should therefore be an important aspect of any decision about starting HCV treatment.

Although most of the studies in our review were specifically designed to increase the uptake of HCV treatment in PWID, the individuals who commenced treatment are likely to be a highly selected population. In one study, <50% of patients with chronic HCV were judged to be eligible for treatment [15], and in another, only 20% of individuals with chronic HCV actually attended for assessment [13]. The results of our review therefore relate to a specific population of PWID who are eligible and motivated enough to attend for treatment.

Our pooled estimate of treatment adherence was relatively high (82%), and treatment discontinuation was relatively low (22%) in PWUD, although these estimates were derived from a very small number of studies. Our estimate of treatment discontinuation is similar to the 15%–25% quoted by studies treating non-PWID outside of clinical trial settings [24, 25]. However, our estimate of treatment adherence is somewhat higher than previous reports [28], although this may in part be explained by the varying definitions of adherence across studies, with some calculating on-treatment adherence (ie, taking into consideration the number of missed doses while on therapy), and others calculating cumulative adherence (ie, including individuals who have discontinued therapy early) [29]. A greater standardization of definitions used to calculate adherence is needed to allow more meaningful comparisons between studies in the future [29].

The pooled risk of HCV reinfection was low (2.4 per 100 PY), suggesting only a small impact of reinfection on the longer-term effectiveness of treatment in PWUD. However, the total number of PY of observation across the 5 studies was very low, creating considerable uncertainty around this estimate. There was also

**Table 4. Characteristics and Outcomes of Studies Examining Hepatitis C Virus Reinfection After Sustained Virologic Response in Ever-People Who Use Drugs**

| Study Characteristics (Conference Abstract) | | | | Patient Characteristics and Study Outcomes | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| First Author, Year of Publication | Location and Study Design | Recruitment and Exclusion Criteria | Treatment and Risk Reduction Interventions | SVR[b] | Age at Recruitment, y | % Male | PWID Post-SVR | Lost to Follow-up | Reinfection (Confirmed)[b] | Length of Follow-up (Follow-up in PWID Post-SVR) | Reinfection [Reinfection if PWID Post-SVR][a] |
| Grebely, 2010 [19] | Vancouver, Canada Prospective cohort | Illicit drug users attending 2 community clinics offering addiction services. HCV treatment from visiting ID specialists. 54% injected drugs in the 6 mo prior to HCV therapy. | RBV + peg-IFN alfa-2a/2b or IFN alfa-2b. Counseling on risk of reinfection | 35 | Mean, 44 | 86% | 16 (46%) | 11% | 2 (0) | 62.5 PY (37.7 PY) | 3.2 (.4–11.6) [5.3 (.6–19.2)] |
| Currie, 2008 [22] | San Francisco, USA Prospective cohort | Injection drug users who were part of a larger longitudinal study that recruited by advertising at hospital entrances, ID departments, liver and methadone clinics. | Antiviral treatment. HCV and drug counseling | 9 | Mean, 46 | 89% | 2 (22%) | NA | 1 (0) | 38.0 PY (3.5 PY) | 2.6 (.1–14.7) [28.6 (.7–159.2)] |
| Backmund, 2004 [20] | Munich, Germany Prospective cohort | Opiate-dependent injection drug users receiving inpatient drug detoxification treatment were recruited to a study of HCV treatment. | IFN alfa-2a ± RBV. Counseling on risk of reinfection | 18 | Median, 32 | 61% | 9 (50%) | NA | 2 (1) | 50.8 PY (23.8 PY) | 3.9 (.48–14.2) [8.4 (1.0–30.4)] |
| Dalgard, 2002 [21] | Oslo, Norway Prospective multicenter cohort | Individuals infected by injection drug use were recruited to a trial of HCV treatment. Patients had to state that they had been abstinent for 6 mo prior to HCV treatment. | IFN alfa ± RBV | 27 | Median, 30 | 67% | 9 (33%) | NA | 1 (1) | 118.0 PY (40.0 PY) | 0.9 (0–4.7) [2.5 (0–13.9)] |
| Grady, 2011 [23][a] | The Netherlands Prospective cohort | Illicit drug users who received HCV treatment through the Amsterdam cohort study of drug users. | HCV treatment delivered in multidisciplinary setting | 42 | NA | NA | 9 (21%) | NA | 1 (1) | 131.6 PY (32.3 PY) | 0.8 (0–4.2) [3.1 (.1–17.3)] |

Abbreviations: HCV, hepatitis C virus; ID, infectious disease; IFN, interferon; NA, not available; PY, person-years; PWID, people who inject drugs; RBV, ribavirin; SVR, sustained virologic response.

[a] Reinfection rate per 100 PY (95% confidence interval).

[b] No. of individuals in cohort who achieved SVR after treatment for HCV.

[c] No. confirmed by genotyping or sequencing analysis.

uncertainty around the extent of loss to follow-up, which was only quoted by one of the studies in the review [19]. Further, the inclusion of former PWUD in the study population (for whom the risk of relapse to injection drug use may be lower) and the incorporation of harm reduction programs into some of the studies may have reduced the observed risk of HCV reinfection.

In assessing reinfection risk, consideration should also be given to how cases of HCV reinfection are distinguished from cases of HCV relapse. All of the reinfection studies in our review excluded individuals who received a positive HCV test within 6 months of their end of treatment date, even though some of these individuals may have experienced early reinfection with HCV, rather than early relapse. Conversely, participants who became HCV positive following SVR were assigned as cases of reinfection rather than late relapse, with only 1 study confirming reinfection using HCV sequencing [21]. Although late relapse is rare in patients treated with peg-IFN and RBV, it is considerably more common (4.7% after 5 years in one study [30]) in patients treated with interferon monotherapy, which was used in at least 2 of the studies included in our review [20, 21]. HCV sequencing (or at least genotyping) should ideally be performed in individuals with recurrence of virus, to distinguish between HCV reinfection and relapse. Our pooled estimate of reinfection risk should therefore be interpreted with caution.

We have demonstrated that acceptable treatment outcomes can be achieved in patients who report actively injecting drugs and who are eligible and committed to starting HCV treatment. Because of the small number of studies available, we were not able to investigate other factors, such as the mode of treatment delivery and the availability of treatment support, that are likely to affect treatment outcomes. There was considerable uncertainty around the risk of HCV reinfection following treatment. Further studies on the risk of reinfection are needed to assess the longer-term effectiveness of HCV treatment in PWID.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

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