Hepatitis C Treatment for Injection Drug Users: A Review of the Available Evidence

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Globally, ~90% of new hepatitis C infections are attributed to injection drug use, but there is a continuing reluctance to treat injection drug users (IDUs). There is evidence that a sizeable proportion of IDUs who begin hepatitis C treatment achieve a sustained virological response (SVR). In chronic hepatitis C treatment trials, the SVR rate among IDUs appears to be comparable to rates among non-IDUs; in trials prescribing pegylated interferon plus ribavirin, the median rate of SVR among IDUs was 54.3% (range, 18.1%–94.1%), compared with 54%–63% in the large treatment trials. Few trials of acute hepatitis C treatment report on outcomes in IDUs; however, among these trials, the SVR among IDUs was 68.5% ($n = 89$), compared with 81.5% among non-IDUs ($n = 65$). Additional studies are required to determine the optimal circumstances for treatment (e.g., enrollment in drug treatment, the requirement of a period of abstinence from injection drug use, or the establishment of multidisciplinary treatment programs).

Injection drug users (IDUs) account for a disproportionately large burden of hepatitis C infection. Ninety percent of new infections worldwide (~90% in Australia, ~72% in Canada, and ~54% in the United States) are contracted through injection drug use [1–4], and the majority of chronic infections, particularly in developed countries, are attributed to injection drug use [1, 4, 5]. Despite advancements in the management of chronic hepatitis C [6–8] and suggestions that treatment of recently acquired hepatitis C can lead to sustained virological response (SVR) rates of up to 98% [9–11], there continues to be a low rate of treatment uptake among current IDUs.

Studies conducted in IDU populations in developed countries suggest that very few IDUs infected with hepatitis C have received antiviral therapy [12–22]. The Australian annual survey at needle and syringe programs (2001–2007) reported that 90% of persons who know that they are infected with hepatitis C virus have never received treatment, and only 0.9%–2.4% were receiving treatment at the time of the survey [12, 13]. In a cohort of 597 American IDUs, only 26 participants received treatment, and the rate of treatment in this cohort remained relatively stable at <1% per year. [14]

Before 2001, treatment guidelines and recommendations for the management of hepatitis C in many developed countries proscribed treatment of IDUs [23–25]. Although revised guidelines have tended to advocate treating IDUs who fulfill other inclusion criteria [25–32], the low rate of treatment uptake suggests that clinicians remain reluctant to treat patients who inject drugs.

This continuing reluctance to treat IDUs is driven by concerns about the risk of reinfection, high rates of concomitant alcohol abuse, and high rates of concomitant mental health issues, all potentially impacting treatment compliance and effectiveness [33, 34]. Here, we seek to evaluate evidence relating to these concerns by reviewing hepatitis C treatment outcomes, compliance and completion rates among IDUs, and rates of reinfection after treatment.

METHODS

A review was undertaken of published scientific literature about hepatitis C treatment in IDUs. A search was conducted in September 2008 with use of various

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Table 1. Results of Studies of Chronic Hepatitis C Treatment That Allow Comparison of Rates of Sustained Virological Response (SVR) between Injection Drug User (IDU) and Non-IDU Populations

Treatment, study	Study setting and enrollment	Population	No. of participants who initiated treatment	No. (%) of participants who achieved SVR	Statistical difference between groups
IFN					
Van Thiel et al (2003) [35]	Retrospective enrollment through hospital-based clinic; groups matched for age, sex, ethnicity, liver fibrosis score, serum hepatic iron and ferritin levels, and HCV RNA level	Current IDUs (injected drugs within 6 months before initiation of treatment)	120	40 (33.3)	No
		Non-IDUs	120	44 (36.7)	
Single or dual					
Cournot et al (2004) [36][a]	Retrospective enrollment of all HCV-infected patients who attended the gastroenterology unit as an inpatient or outpatient	Current IDUs (ongoing injection of illicit drugs or buprenorphine and not receiving substitution therapy)	19	3 (15.8)	No
		Treatment IDUs (receiving substitution therapy; also, mostly ongoing illicit drug use)	31	11 (35.5)	
		Former IDUs (stopped injecting drugs before treatment and not receiving substitution therapy	49	12 (24.5)	
		Non-IDUs	121	23 (19.0)	
IFN plus RBV					
Dalgard et al (2002) [37][b]	Prospective enrollment to hospital-based multicenter treatment trial	Former IDUs (probable risk factor for acquisition of HCV infection; mandatory 6 months of abstinence before treatment)	69	27 (39.1)	No
		Non-IDUs	47	18 (38.3)	
Schaefer et al (2003) [38]	Prospective enrollment through hospital gastroenterology and psychiatry units	Treatment IDUs (currently receiving substitution therapy; 3-month pretreatment abstinence required)	21	10 (47.6)	No
		Former IDUs (history of addiction; 3-month pretreatment abstinence required)	21	6 (28.6)	
		Non-IDUs	39	14 (35.9)	
Robaeys et al (2006) [39][c]	Retrospective enrollment; analysis of results from multicenter treatment trial [40]	IDUs (history of IDU)	98	34 (34.7)	No
		Non-IDUs	308	90 (29.2)	
Pegylated IFN plus RBV					
Mauss et al (2004) [41]	Prospective enrollment of IDUs in a stable methadone maintenance program; for each IDU, a control patient was matched for sex, age, HCV genotype, and HCV RNA level	Treatment IDUs (receiving stable substitution therapy and abstained from drug use for at least 6 months before treatment initiation)	50	21 (42.0)	No
		Non-IDUs (no IDU or substitution therapy for at least 5 years before initiation of treatment)	50	28 (56.0)	
Schaefer et al (2007) [42]	Prospective enrollment; recruitment source not clear	Treatment IDUs (currently receiving substitution therapy; ongoing users excluded)	18	13 (72.2)	No
		Former IDUs (history of addiction; ongoing users excluded)	13	7 (53.8)	
		Non-IDUs	39	21 (53.8)	
Seal et al (2007) [43][d]	Prospective enrollment through multiple veterans' health care medical centers	Former IDUs (history of IDU; IDU within 6 months before enrollment was usually considered to be an exclusion criterion, although this could be overruled by individual doctors)	447	81 (18.1)	No
		Non-IDUs	345	62 (18.0)	

Table 1. ***(Continued.)***

Treatment, study	Study setting and enrollment	Population	No. of participants who initiated treatment	No. (%) of participants who achieved SVR	Statistical difference between groups
Neri et al (2007) [44]	Prospective enrollment; IDUs enrolled through hospital detoxification department	Treatment IDUs (former heroin users without history of alcoholism or abuse of other drugs; currently receiving substitution therapy)	107	67 (62.6)	Not tested
		Non-IDUs	52	40 (76.9)	
Thomson et al (2008) [45]	Prospective enrollment through multiple clinics	IDUs (IDU probably risk factor for acquisition of hepatitis C)	205	120 (58.5)	No
		Non-IDUs	142	86 (60.6)	

NOTE. The total number of IDUs who initiated treatment was 1268; 452 (35.6%) achieved SVR. HCV, hepatitis C virus; IFN, interferon; RBV, ribavirin.

[a] The report specifies that both single and dual therapy were used but does not give any more details on treatment regimens. Results from this study are in terms of the number of treatment protocols initiated ($n = 220$), not the number of individuals ($n = 177$), because the numbers of individuals in the groups were not reported.

[b] See also Dalgard (2005) [11].

[c] SVR data were available for only 73 IDU and 260 non-IDU participants. Of the participants for whom data were available, 34 (46.6%) of 73 IDUs and 90 (34.6%) of 260 non-IDUs achieved SVR. The lack of data alludes to an explanation of the low response rates in the trial among IDUs, although the reason for lack of data is not reported. The low response rate observed among non-IDUs is explained by the hepatitis C genotypes: 196 of 206 of the non-IDUs for whom response rate data were available had genotype 1, and patients with genotype 1 achieved significantly lower response rates than did patients with other genotypes. After correcting for genotype, IDUs and non-IDUs attained very similar SVR rates (relative risk, 1.09; 95% confidence interval, 0.88–1.35).

[d] Mental health treatment and support services were not offered as part of the treatment protocol, and the trial was conducted through US veteran medical clinics, where the clientele tend to be older than most hepatitis C virus–infected individuals. The authors suggest that these factors may explain the low SVR rates in both the IDU group and the non-IDU group [43].

combinations of the terms "injecting drug," "intravenous drug," "substance abuse–intravenous," "IDU," "hepatitis C," "HCV," "antiviral," "interferon," "peginterferon," "combination therapy," and "treatment." Searches were conducted using PubMed and ISI Web of Science. Reference lists in identified articles were also searched for relevant materials. All English-language literature for which it was possible to determine rates of SVR, treatment completion, and/or compliance for IDUs identified until September 2008 were included in the review. Results from trials that were primarily interested in treating IDUs and those that investigated IDU status as a secondary analysis were combined.

RESULTS

Treatment outcomes. Hepatitis C treatment was considered to be successful if a patient was hepatitis C RNA negative 24 weeks after treatment was completed (i.e., SVR). Twenty-two studies were identified that reported on SVR attainment by IDUs with chronic hepatitis C, whether still using, currently abstaining, and/or in drug treatment programs (Tables 1 and 2). An additional 4 studies reported treatment outcomes of IDUs but were excluded because (1) treatment was ongoing for one-third of the participants [58], (2) it was not clear how many patients were assessable for SVR [63], (3) patients who did not adhere to treatment were excluded from the analysis and it was therefore not possible to ascertain how many IDUs had commenced treatment [64], and (4) the study did not report on SVR attainment [65]. Of the 22 studies included, 10 enrolled a group of non-IDUs with which to compare the results for the IDUs (Table 1). The remaining 12 studies recruited IDUs only (Table 2). Study designs varied, as did definitions of IDUs.

In large trials of treatment with pegylated interferon plus ribavirin for chronic hepatitis C, 54%–63% of participants achieved an SVR [6–8]. The median SVR rate among IDUs receiving this regimen was 54.3% (range, 18.1%–94.1%) (Tables 1 and 2). When all chronic hepatitis C trials that included IDUs were combined, regardless of treatment regimen, the median SVR rate among IDUs was 40.6% (range, 15.8%–94.1%) (Tables 1 and 2). In studies in which IDUs were compared with non-IDUs, the SVR among IDUs was often similar to and, at times, higher than that among non-IDUs (Table 1). None of the studies that included non-IDU comparison groups reported a statistically significant difference between the rate of SVR among IDUs and that among non-IDUs.

There is increasing evidence that early treatment of hepatitis C increases the likelihood of attaining an SVR [9, 10]. However, IDUs were greatly underrepresented in many early treatment studies, despite accounting for >90% of new hepatitis C infections globally [3]. Many studies excluded current IDUs entirely [9, 66, 67] and/or reported less than one-quarter of the study sample as having injection drug use as a risk factor for hepatitis C acquisition [9, 10, 67–71].

Table 3 presents the results of studies on acute hepatitis C in which the proportion of IDUs achieving an SVR could be determined. Overall, <200 individuals with acute hepatitis C

Table 2. Results of Studies of Chronic Hepatitis C Treatment in Which the Cohorts Included Only Injection Drug Users (IDUs)

Treatment, study	Study setting and enrollment	Population	No. of IDUs who initiated treatment	No. (%) of IDUs who achieved SVR
IFN and/or IFN plus RBV				
Backmund et al (2001) [46]	Prospective enrollment from detoxification program	Treatment IDUs (fulfilled the *ICD-10* criteria for opiate dependency)	50	18 (36.0)
IFN, IFN plus RBV, or pegylated IFN plus RBV				
Jowett et al (2001) [47]	Retrospective database review in liver unit	IDUs (IDU probable risk factor for acquisition of infection)	50	18 (36.0)
Matthews et al (2005) [48][a]	Unclear; enrolled through 2 hospital-based clinics.	Current IDUs (IDUs referred as current users; undefined)	12	6 (50.0)
Raptopoulou et al (2006) [49]	Unclear; enrolled through hospital-based clinics	Former IDUs (former IDUs not receiving substitution therapy)	163	54 (33.1)
IFN plus RBV				
Huber et al (2005) [50]	Prospective enrollment from opiate maintenance centers	Treatment IDUs (receiving opiate maintenance therapy)	27	13 (48.1)
Sylvestre et al (2005) [51][b]	Prospective recruitment of patients receiving methadone maintenance therapy	Treatment IDUs (receiving methadone maintenance therapy)	76	21 (27.6)
IFN plus RBV or pegylated IFN plus RBV				
Jeffrey et al (2007) [52]	Prospective enrollment from drug rehabilitation center	Treatment IDU (attending drug rehabilitation center)	50	31 (62.0)
Grebely et al (2007) [53]	Prospective enrollment through 2 multidisciplinary health clinics	IDUs (history of IDU, including persons injecting at time of enrollment)	40	22 (55.0)
Pegylated IFN plus RBV				
Sylvestre et al (2005) [54][c]	Unclear; only preliminary results have been published	Treatment IDU (receiving methadone maintenance therapy)	28	12 (42.9)
Belfiori et al (2007) [55]	Prospective enrollment through infectious diseases clinic	Treatment IDUs (received substation therapy for at least 3 months and abstinent during that time)	24	7 (29.2)
Guadagnino et al (2007) [56]	Prospective observational study; enrolled via detoxification programs	Treatment IDUs (persons who have been enrolled in detoxification program for at least 6 months and attended the program regularly during that time)	53	29 (54.7)
Krook et al (2007) [57]	Prospective enrollment via detoxification program	Treatment IDUs (receiving methadone maintenance therapy)	17	16 (94.1)

NOTE. A total of 590 IDUs initiated treatment; 247 (41.9%) achieved sustained virological response (SVR). When the total numbers of IDUs from tables 1 and 2 are combined, 1858 IDUs initiated treatment, and 699 (37.6%; median, 40.6%) achieved SVR. *ICD-10, International Classification of Diseases, Tenth Revision;* IFN, interferon; RBV, ribavirin.

[a] Outcome data were not available for 3 IDUs at time of publication.

[b] Results from this trial are also published elsewhere [54, 59–62].

[c] Treatment was ongoing for 1 IDU at time of publication.

Table 3. Studies of Acute Hepatitis C Treatment in Which the Results for Injection Drug Users (IDUs) Were Available

Treatment, study	Study setting and enrollment	Exclusion of current IDUs	Population	No. of acute HCV cases identified	No. of participants who initiated treatment	No. (%) of participants who achieved SVR	Statistical difference between groups
IFN							
Delwaide et al (2004) [72]	Prospective enrollment by multiple hospital-based hepatologists	NS	IDUs (IDU probable risk factor for infection)	NS	13	7 (53.8)	No
			Non-IDUs		15	14 (93.3)	
IFN, IFN plus RBV, and pegylated IFN plus RBV							
Gerlach et al (2003) [66]	Prospective enrollment from 2 large hepatology referral centers	Yes	IDUs (IDU probable risk factor for infection)	60[a]	7	7 (100)	NS
			Non-IDUs		19	14 (73.7)	
Rocca et al (2003) [73]	Retrospective record review at hospital hepatology unit	NS[b]	IDUs (IDU probable risk factor for infection)	7	5	4 (80.0)	NS
			Non-IDUs	9	8	8 (100)	
Pegylated IFN							
Broers et al (2005) [74]	Prospective enrollment through multiple centers	No[c]	IDUs (active drug use at time of enrollment)	22	11	6 (54.5)	Yes
			Non-IDUs	5	3	2 (66.7)	
McGovern et al (2006) [75]	Prospective enrolment; recruited through correctional and detoxification facilities	No	IDU (IDU probable risk factor for infection)	21	4	2 (50.0)	NA
De Rosa et al (2007) [76][d]	Prospective enrollment at an outpatient clinic for IDUs	NS	IDUs (attending outpatient services for IDUs)	NS	23	17 (73.9)	NA
Calleri et al (2007) [77]	Prospective enrollment through 8 infectious diseases centers	NS	IDUs (IDU definition not specified)	55[e]	26	18 (69.2)	No
			Non-IDUs		20	15 (75.0)	

NOTE. A total of 89 IDUs initiated treatment; 61 (68.5%; median, 69.2%) acheived sustained virological response (SVR). IFN, interferon; NA, not applicable; NS, not specified; RBV, ribavirin.

[a] Breakdown by IDU status was not provided; includes 2 participants excluded from treatment because of ongoing drug use.

[b] Article stated that it was presumed that most participants would be current drug users, but no further information about IDU activity of participants was given.

[c] All IDUs were active drug users at initiation of treatment; 1 stopped using drugs during therapy, and the remaining 10 admitted to occasional use during treatment.

[d] Results from this cohort are also published elsewhere [78]

[e] Breakdown of IDU status was not provided.

Table 4. Chronic Hepatitis C Therapy Completion and Compliance Data from Studies in Which Results for Injection Drug Users (IDUs) Could Be Compared with Results for Non-IDUs

Study	Population	No. of participants who initiated treatment	No. (%) of participants who completed treatment	No. (%) of participants who did not comply with treatment protocol	Definition of noncompliance
Kraus et al (2001) [81]	Former IDUs (IDU probable risk factor for infection)	41	NR	12 (29.3)	Failure to present for initiation of therapy, missing >1 scheduled visit without stating a reason, or relapse of IDU or alcohol abuse and termination of IFN therapy without consulting the physician
	Non-IDUs	33	NR	5 (15.2)[a]	
Neri et al (2002) [65]	Treatment IDUs (former heroin users without history of alcoholism or abuse of other drugs; currently receiving substitution therapy)	47	30 (63.8)	NR	NA
	Non-IDUs	30	30 (100)	NR	
Schaefer et al (2003) [38]	Treatment IDUs (currently receiving substitution therapy; 3-month pretreatment abstinence required)	21	18 (85.7)	3 (14.3)	Not defined
	Former IDUs (history of addiction; 3-month pretreatment abstinence required)	21	12 (57.1)[b]	3 (14.3)	
	Non-IDUs	39	33 (84.6)	3 (7.7)	
Van Thiel et al (2003) [35]	Current IDUs (injected drugs within 6 months before initiation of treatment)	120	102 (85.0)[a]	NR	Noncompliance with therapy (namely, IFN)
	Non-IDUs	120	112 (93.3)	NR	
Cournot et al (2004) [36][c]	Current IDUs (injecting illicit drugs or buprenorphine and not receiving substitution therapy)	19	NR	NR[b]	NA
	Treatment IDUs (receiving substitution therapy; also, most ongoing illicit drug use)	31	NR	NR	
	Former IDUs (stopped IDU before treatment and not receiving substitution therapy)	49	NR	NR	
	Non-IDUs	121	NR	NR	
Mauss et al (2004) [41]	Treatment IDUs (receiving stable substitution therapy and abstained from drug use for at least 6 months)	50	25 (50.0)	15 (30.0)	Not defined
	Non-IDUs (no IDU or substitution therapy for at least 5 years)	50	38 (76.0)	6 (12.0)	
Robaeys et al (2006) [39]	IDUs (history of IDU)	98	NR	8 (8.2)[a]	Failure to present for HCV PCR testing at the end of treatment
	Non-IDUs	308	NR	21 (6.8)	
Schaefer et al (2007) [42]	Treatment IDUs (currently receiving substitution therapy; ongoing users excluded)	18	13 (72.2)[a]	2 (11.1)	Not defined[d]
	Former IDUs (history of addiction; ongoing users excluded)	13	11 (84.6)	0 (0)	
	Non-IDUs	17	16 (94.1)	0 (0)	
Seal et al (2007) [43]	Former IDUs (history of IDU; IDU within 6 months before enrollment was usually considered to be an exclusion criterion, although this could be overruled by individual doctors)	447	310 (69.4)[a]	5 (1.1)	Not defined
	Non-IDUs	347	243 (70.0)	4 (1.2)	

Table 4. ***(Continued.)***

Study	Population	No. of participants who initiated treatment	No. (%) of participants who completed treatment	No. (%) of participants who did not comply with treatment protocol	Definition of noncompliance
Neri et al (2007) [44]	Treatment IDUs (former heroin user without history of alcoholism or abuse of other drugs; currently receiving substitution therapy)	107	77 (71.9)	NR	NA
	Non-IDUs	52	48 (92.3)	NR	

NOTE. Of a total of 844 IDUs who initiated treatment (in studies in which completion rates were reported), 598 (70.9%) completed therapy, compared with 520 (79.4%) of 655 non-IDUs. Of 709 IDUs who initiated treatment (in studies in which compliance rates were reported), 48 (6.8%) were noncompliant, compared with 39 (4.9%) of 794 non-IDUs. HCV, hepatitis C virus; IFN, interferon; NA, not available; NR, not reported; PCR, polymerase chain reaction.

[a] No statistically significant difference between groups.

[b] Significantly different from the other groups ($P < .05$).

[c] This study reported numbers of treatment protocols rather than participants. Treatment protocols lost to follow-up and treatment protocols interrupted because of adverse effect were reported. However, they were not included in this analysis, because the numbers were inconsistent with the reported percentages

[d] Not explicitly defined but differentiated from patients who dropped out due to either psychiatric or somatic side effects. The study also notes that patients who were recruited but did not turn up for pre-treatment counselling were not included in the study. The number of potential patients in this group was not noted.

were treated in these 8 studies [66, 72–78]. One hundred fifty-four individuals initiated treatment for hepatitis C, and 114 achieved an SVR (68.5% of IDUs enrolled; 81.5% of non-IDUs enrolled). Within individual studies, the proportion of IDUs achieving an SVR ranged from 50.0% to 100% (median, 69.2%).

In the only study that clearly targeted current IDUs for recruitment [74], hepatitis C treatment was considered for 22 individuals, and achievement of an SVR was not significantly related to IDU status. However when only those individuals who began therapy ($n = 14$) were included, the odds of achieving an SVR were significantly lower among IDUs than among non-IDUs. Because the numbers in this study (and, indeed, in all of the studies of acute hepatitis C that included IDUs) were low, it is unclear whether IDUs can achieve rates of SVR of $\geqslant$80%, as reported in the major clinical trials [9, 10]. Ongoing studies that include larger numbers of IDUs (such as the Australian Trial in Acute Hepatitis C) should provide more information about the proportion of IDUs who can be expected to achieve an SVR when treated during the early stage of infection and the impact of injection drug use during treatment.

Treatment completion and compliance. The likelihood of attaining an SVR improves if a patient receives a high percentage of doses of the prescribed therapy and receives close to the maximum dosage [79, 80]. Of the 22 studies reporting treatment outcomes for chronic hepatitis C, 21 also reported completion and/or compliance data. In addition, 3 studies that reported completion or compliance data but not SVR rates among IDUs were identified (Tables 4 and 5)

In the studies that allowed any comparison of IDU status and treatment completion, 70.9% of IDUs (median, 71.9%) completed treatment, compared with 79.4% of non-IDUs (median, 92.3%) (Table 4). In the studies involving only IDUs, 62.6% (median, 65.0%; range, 46.6%–100%) completed treatment (Table 5). Overall, the median completion rate among IDUs was 70.7%. Many studies did not formally assess whether treatment completion among IDUs was lower than that among non-IDUs. Of the 5 studies that reported this data (with 48, 81, 177, 240, and 794 participants) [35, 36, 38, 42, 43], only 1 found a statistically significant difference between groups. In univariate analysis, this study ($n = 81$) found that former IDUs were less likely to complete treatment than were IDUs in methadone maintenance programs and non-IDUs. No multivariate analysis was performed.

Compliance data for IDUs is limited. Only 6 studies provided compliance data comparing IDUs with non-IDUs (Table 4); in these studies, the overall rate of noncompliance among IDUs was 6.8% (median, 12.7%), compared with 4.9% (median, 7.3%) among non-IDUs. However, variation in the definition of treatment compliance makes it difficult to assess whether compliance among IDUs was truly lower than that among non-IDUs. Of the 3 studies (with 74, 220, and 406 participants) that formally compared compliance data for IDUs with that for non-IDUs [36, 39, 81], only 1 ($n = 220$) found a statistically significant difference between the groups. In univariate analysis, this study found that IDUs whose drug use was ongoing at their initial evaluation were more likely to be lost to follow-up during the treatment period than were IDUs who had ceased injection drug use, IDUs receiving drug treatment, and participants with no history of injection drug use. Compliance was not assessed using multivariate analysis [36]. When the results from all studies that reported rates of noncompliance among

Table 5. Chronic Hepatitis C Therapy Completion and Compliance Data from Studies in Which Only Injection Drug Users (IDUs) Were Eligible for Recruitment

Study	Population	No. of IDUs who initiated treatment	No. (%) of IDUs who completed treatment	No. (%) of IDUs who were noncompliant	Compliance definition
Backmund et al (2001) [46]	Treatment IDU (fulfilled the *ICD-10* criteria for opiate dependency)	50	27 (54.0)	5 (10.0)	Not clear
Jowett et al (2001) [47]	IDUs (IDU probable risk factor for acquisition of infection)	50	26 (52.0)	NR	…
Huber et al (2005) [50]	Treatment IDUs (receiving opiate maintenance therapy)	27	17 (63.0)	NR	Not clear; 20 of 27 were reported to have violated protocol
Matthews et al (2005) [48]	Current IDUs (IDUs referred as current users; undefined)	12	7 (58.3)	4 (33.3)	Completed >80% of treatment course
Sylvestre et al (2005) [54][a]	Treatment IDUs (receiving methadone maintenance therapy)	28	24 (85.7)	NR	…
Raptopoulou et al (2006) [49]	Former IDUs (former IDUs not receiving substitution therapy)	163	76 (46.6)	NR	…
Sylvestre et al (2007) [61][b]	Treatment IDUs (receiving methadone maintenance therapy)	71	54 (76.1)	23 (32.4)	Monthly self report and timing to return for more drugs: compliant if took >80% of each drug and at least 80% of recommended course
Belfiori et al (2007) [55]	Treatment IDUs (received substitution therapy for at least 3 months and abstinent during this time)	24	18 (75.0)	NR	…
Guadagnino et al (2007) [56]	Treatment IDUs (have been enrolled in detoxification program for at least 6 months and attended the program regularly during that time)	53	34 (64.2)	NR	Unclear; accessed by monthly report
Grebely et al (2007) [53]	IDUs (history of IDU, including persons injecting at time of enrollment)	40	26 (65.0)	6 (15.0)	Unclear; documented by nurses[c]
Hallinan et al (2007) [63]	Treatment IDUs (enrolled in community-based drug treatment program)	14	10 (71.4)	NR	…
Jeffrey et al (2007) [52]	Treatment IDUs (attending drug rehabilitation center)	50	39 (78.0)	7 (14.0)	Monitoring drugs collected from pharmacy
Krook et al (2007) [57]	Treatment IDUs (receiving methadone maintenance therapy)	17	17 (100)	0 (0)	All patients completed treatment[d]

NOTE. Of a total of 599 IDUs who initiated treatment (in studies in which completion rates were reported), 375 (62.6%) completed therapy (973 [67.4%; median, 70.4%] of 1443 in tables 4 and 5 combined). Of a total of 240 IDUs who initiated treatment (in studies in which compliance rates were reported), 45 (18.8%) were noncompliant (93 [9.8%; median, 14.2%] of 949 in tables 4 and 5 combined). *ICD-10, International Classification of Diseases, Tenth Revision;* NR, not reported.

[a] Treatment was ongoing for 1 IDU at the time of analysis.

[b] Results from the same study were also reported elsewhere [51, 54, 59, 60, 62].

[c] Six IDUs had to discontinue treatment because of nonadherence associated with ongoing illicit drug use.

[d] Some potential participants were not included in the study because they failed to present for treatment after being deemed eligible.

IDUs were combined, the overall rate of noncompliance was 9.8% (median, 14.2%; range, 0.0%–33.3%) (Tables 4 and 5).

The impact of prior drug use on treatment. Six studies on chronic hepatitis C provided quantitative information on the participants' histories of injection drug use (duration of use and/or number of lifetime injections). None investigated whether variations in history of injection drug use affected treatment outcomes [37, 51, 53, 55–57]. Four studies reported the duration of pretreatment abstinence [49, 51, 53, 57]. Of these, 2 evaluated the impact of pretreatment abstinence for≥6 months on SVR attainment, and neither found that it had a significant impact.

The impact of concurrent injection drug use on treatment. Five studies on chronic hepatitis C assessed participants' injecting behavior during the treatment period, and 3 reported on SVR attainment among participants who injected at least once during the treatment period. SVR rates were slightly lower among these participants (14.8%–52.6%, compared with 34.8%–57.0% among IDUs in these trials who abstained from injection drug use during treatment). It is important to note, however, that numbers were small (in total, 71 nonabstinent IDUs and 95 abstinent IDUs), and no statistically significant differences were reported [46, 51–53, 57].

In addition, 3 studies reported on how often these nonabstinent IDUs injected drugs during the treatment period, and 2 of these studies reported on SVR attainment, by frequency of injection. The SVR rates among participants who injected drugs regularly (at least every second day; 0% and 22.2%) were lower than the SVR rates among other IDUs in the same studies (30.9% and 65.2%), but very few participants injected drugs regularly (8 of 76 and 9 of 40) [51, 53]. Neither study reported a statistically significant difference in SVR rates between the groups, although subsequent analysis of one of these studies reported that participants who injected daily or every second day throughout treatment were less likely to comply with the treatment regimen [61]. This result was not adjusted to account for other factors influencing treatment compliance.

Concurrent enrollment in drug treatment and multidisciplinary treatment programs. Thirteen studies included groups of IDUs who were enrolled in drug treatment programs before initiation of hepatitis C treatment. In total, there were 257 IDUs in these groups, and the median SVR rate was 47.6% (range, 27.6%–94.1%) (Tables 1 and 2). Eight studies reported that chronic hepatitis C treatment was administered in multidisciplinary programs that were specifically designed for IDUs and provided care for hepatitis C, addiction, and mental health [36, 51–57]. Three hundred eighty-seven IDUs participated in these studies, and the median SVR rate was 48.8% (range, 26.3%–94.1%).

Many of these studies did not outline which services were offered as part of their hepatitis C treatment programs, nor did they specify how many of their participants were enrolled in drug treatment programs. These factors made it difficult to compare outcomes of IDUs in these studies with outcomes of IDUs in other studies.

Risk of reinfection. There is a concern that, even after successful hepatitis C treatment, current IDUs will develop new infections through ongoing unsafe injecting practices [34, 82]. Thus, the benefits of treatment may be outweighed by the combined risk of adverse effects of treatment and reinfection.

Although rates of reinfection as high as 31–47 cases per 100 person-years have been observed in cohorts of IDUs after spontaneous clearance of infection [83, 84], reported rates of reinfection after antiviral treatment have been much lower (0.8 cases per 100 person-years in a study in which 27 former IDUs were followed up for 13–82 months after treatment [median, 65 months] [11, 37] and 0–2 cases per 100 person-years in another study in which 18 former IDUs were followed up for a total of 50.8 person-years after treatment [85]). In the former trial, 9 of the 27 former IDUs who participated experienced relapse of injection drug use after treatment. The rate of reinfection among those who experienced relapse of drug use was 2.5 cases per 100 person-years [11, 37].

DISCUSSION

Reviewing the literature in this field was challenging; many large trials demonstrating the efficacy of hepatitis C therapy excluded IDUs unless they had a substantial period of abstinence from injection drug use [6–9, 67, 86]. As a consequence, treatment outcomes in IDUs could be assessed only by examining results from smaller trials and medical record reviews in settings where IDUs were not excluded from treatment. There was considerable variation in SVR rates among IDUs in different trials, ranging from 15.8% to 94.1% for chronic hepatitis C and from 50.0% to 100.0% for acute hepatitis C. This variation may be attributable to variations in the study designs (e.g., recruitment criteria) and variations in the treatment of participants (e.g., treatment regimen or psycho-social support). Nonetheless, when combined, the results from these trials provide the broadest and most rigorous account to date of hepatitis C treatment outcomes in IDUs.

Although we acknowledge the limitations of this review, the available evidence suggests that IDUs can be successfully treated for hepatitis C. In the reported studies, the median SVR rates among IDUs (40.6% for chronic hepatitis C and 69.2% for acute hepatitis C) suggest that a substantial proportion of treated IDUs achieved an SVR. In a clinical setting, where the decision to initiate treatment is based on the possible risks and benefits for each patient, this suggests that injection drug use should not preclude treatment.

Moreover, the relatively small variation in treatment outcomes in IDU and non-IDU groups within trials that included

a non-IDU comparison group, compared with the great variation in SVR rates between studies, suggests that IDU status may be less important to treatment outcomes than other factors. Although 2 studies found that particular groups of IDUs [36, 38] were less likely to complete or comply with treatment than were other participants in univariate analysis, neither assessed completion or compliance rates with use of multivariate analysis.

Only 5 studies prospectively assessed drug use by participants during treatment, and only 3 studies, all with small sample sizes, analyzed the effect of drug use during treatment on treatment efficacy. None found a statistically significant difference in rates of SVR between participants who used drugs during treatment and those who did not, indicating that the available evidence does not clearly show that using illicit drugs during treatment diminishes chances of treatment success. Although it is plausible that the effect of drug use on treatment depends on the regularity of use, only 2 trials distinguished different levels of drug use. In these trials, very few participants reported regular use, and thus, the trials were not sufficiently powered to detect a significant difference in treatment outcomes. Moreover, these 2 trials were also the only trials to investigate whether a long duration of pretreatment abstinence had an effect on treatment outcomes, and neither detected an effect. In the absence of evidence to the contrary, ongoing drug use should not be an automatic exclusion criteria for hepatitis C treatment; instead, patients should be treated on a case-by-case basis [26, 29–32, 87].

Despite national hepatitis C treatment guidelines in many developed countries that no longer automatically exclude current drug users from treatment, there remain vast gaps in our understanding of the optimal management of hepatitis C in IDUs. Most studies conducted included very small numbers of participants, and very little research has been undertaken that has (1) primarily aimed to analyze factors associated with hepatitis C treatment outcomes in IDUs; (2) had sufficient numbers of IDUs to compare multiple outcome variables; (3) not had study exclusion criteria that restricted IDU access, such that some IDUs might choose not to identify their status so that they could access hepatitis C treatment; and/or (3) assessed the impact of differences in injecting behavior before or during treatment on treatment outcomes.

Clinical research and trials are needed to better understand how to select patients who can be treated successfully for hepatitis C and to determine the optimal timing of that treatment. The minimum duration of drug abstinence, if indeed drug abstinence is necessary, needs to be assessed. If complete abstinence from drug use is not necessary, there is a need to determine the level of drug use that makes it highly unlikely that a patient will be compliant and complete treatment successfully, thereby diminishing the likelihood of their obtaining an SVR. It is equally important to determine the role of treatment for drug dependency in improving hepatitis C treatment compliance; that is, is treatment for drug dependence necessary for all drug users, and if not, is there a subset of IDUs who would benefit from such treatment?

The structure of clinics providing hepatitis C treatment and easy access to multidisciplinary teams or at least to treatment for addiction is likely to play an important role in the successful treatment of IDUs with hepatitis C [52, 56, 88, 89]. However, to date, there has been very little research that clearly identifies which factors or interventions have an impact on treatment compliance or treatment outcomes.

Although this analysis is limited by the small numbers of patients included in each trial and the variation in trial recruitment and treatment regimens, the results suggest that IDUs can be successfully treated for both chronic and acute hepatitis. Although there are many potential obstacles blocking current IDUs from hepatitis C treatment, it is important to view them as only potential obstacles. When assessing the benefits and risks of hepatitis C treatment, clinicians need to be mindful that their assessment is evidence based (when evidence is available) and that suitable efforts need to be made to remove or overcome the barriers preventing an individual from receiving treatment.

Ultimately, anyone infected with hepatitis C, including drug users, whether former or current, should be given sufficient information and the opportunity to make an informed decision about receiving treatment for their infection. There is simply no evidence to support the contention that IDUs should be prohibited from receiving hepatitis C treatment solely on the basis of their past or current drug use status. Efforts should be made to ensure that treatment is available, accessible, and appropriate for IDUs, who are by far the largest subpopulation infected with hepatitis C virus. Of importance, additional studies are required to determine the optimal circumstances, such as enrollment in drug treatment or multidisciplinary treatment programs or requirement of a period of abstinence from injection drug use, to facilitate successful treatment outcomes.

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