SUPPLEMENT ARTICLE

Directly Observed Pegylated Interferon Plus Self-Administered Ribavirin for the Treatment of Hepatitis C Virus Infection in People Actively Using Drugs: A Randomized Controlled Trial

Robert J. Hilsden,[1] Gisela Macphail,[2] Jason Grebely,[3,4] Brian Conway,[4,5] and Samuel S. Lee[6]

[1]Departments of Medicine and Community Health Sciences, University of Calgary, and [2]Calgary Urban Project Society Health Center, Alberta, Canada; [3]Kirby Institute, University of New South Wales, Sydney, Australia; [4]Pender Community Health Centre, and [5]Vancouver Infectious Diseases Centre, Vancouver, British Columbia, and [6]University of Calgary Liver Unit, Alberta, Canada

Background. This study investigated the efficacy and safety of directly observed pegylated interferon (peg-IFN) alfa-2a plus self-administered ribavirin (RBV) for the treatment of hepatitis C virus (HCV) among people with active drug use.

Methods. A randomized, open-label, parallel group trial of immediate vs delayed treatment with peg-IFN alfa-2a plus RBV in participants with recent injection drug and/or crack cocaine use (prior 3 months). The primary end point was sustained virologic response (SVR).

Results. Sixty-six participants were randomized (immediate treatment, n = 48; delayed treatment, n = 18). Loss to follow-up was comparable among those randomized to immediate and delayed treatment (23% vs 33%, $P = .389$). In a post hoc intent-to-treat analysis of all randomized individuals, the SVR was 65% (95% confidence interval [CI], 49%–78%; 31/48) in those randomized to immediate treatment as compared to 39% (95% CI, 17%–64%; 7/18) in those randomized to delayed treatment ($P = .060$). Among those who received delayed treatment (12/18), SVR was 58% (7/12). Among 60 participants who received at least 1 dose of study medication, SVR was 63% (95% CI, 50%–75%, n = 38). Recent drug use at baseline (past month) did not impact completion or SVR. Discontinuation due to adverse events occurred in 7%. The HCV reinfection rate was 2.8 per 100 person-years (95% CI, 0.0–14.5 person-years) with 1 reinfection observed among 23 remaining in follow-up post-SVR (median, 1.8 years; range, 0.5–1.8 years).

Conclusions. Among people actively using drugs treated with directly observed peg-IFN alfa-2a plus self-administered RBV, SVR is comparable to that seen in clinical trials of non–drug users, and the rate of HCV reinfection is low.

Clinical Trials Registration. NCT00203606.

Keywords. people who inject drugs; drug users; directly observed therapy; HCV.

The majority of new (>70%) and existing (>50%) cases of hepatitis C virus (HCV) infection in most developed countries (including Canada) occur among people who inject drugs (PWID) [1, 2]. Hereafter, PWID will refer to people with current or "active" injection drug use (which is generally defined as use within the previous 6 months) and to former injectors who are still active non–injection drug users and/or on opioid substitution therapy.

Despite convincing evidence that HCV treatment is safe and effective among PWID [3, 4] and guidelines supporting HCV treatment in this group [5–7], treatment uptake remains low [8–10] even in settings such as Canada and Australia where healthcare and HCV

Correspondence: Samuel S. Lee, MD, University of Calgary Liver Unit, University of Calgary, 3330 Hospital Dr NW, Calgary T2N 4N1, AB, Canada (samlee@ucalgary.ca).

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treatment is publically funded [8, 10]. Barriers to HCV treatment are multifactorial, including those at the level of the patient, system, and practitioner [11]. At the provider level, there is often a lack of consideration for assessment or treatment for HCV among PWID, with providers often citing concerns of adherence, ongoing drug use, relapse to drug use, risk of exacerbation of comorbid psychiatric disease, and reinfection as reasons for not treating HCV among PWIDs [11]. However, there is very little evidence to substantiate these concerns.

Response to HCV treatment is not compromised by a history of injection drug use [3, 4] or active drug use at the time of treatment initiation [12]. In a systematic review and meta-analyses of studies investigating HCV treatment among people actively using drugs, 6 studies were identified (314 drug users) and 56% attained a sustained virologic response (SVR) [12]. However, most studies consisted of small numbers of active PWIDs, were retrospective in design, and were very heterogeneous with respect to definitions used for active drug use. To date, there are no randomized controlled trials that have been performed among PWID.

This randomized controlled trial investigated the safety and efficacy of directly observed pegylated interferon (peg-IFN) alfa-2a plus self-administered ribavirin (RBV) for the treatment of HCV infection among people with active drug use. Participants were randomized to receive either immediate or deferred therapy to monitor the occurrence of adverse events among untreated participants.

METHODS

Study Design

In this community-based randomized, open-label trial, participants with recent injection drug and/or crack cocaine use (use in the past 3 months) were randomized to receive either immediate treatment with peg-IFN alfa-2a plus RBV (24 or 48 weeks depending on HCV genotype) or delayed treatment (observational arm). Those randomized to delayed treatment were offered treatment after they completed a period of observation consistent with the treatment duration recommended for the genotype of their HCV infection (24 or 48 weeks depending on viral genotype).The goal was to recruit 100 participants and randomize them in a 7:3 ratio to immediate or delayed treatment. After completion of treatment, participants were followed for up to 96 months.

The study was conducted at 2 inner-city health clinics that serve the homeless and marginalized poor: Calgary Urban Project Society Health Centre in Calgary, Alberta, Canada, and the Pender Community Health Centre in Vancouver, British Columbia, Canada. Measurement of HCV RNA and viral genotyping was performed at each province's provincial virology laboratory. The institutional review boards of the participating centers approved the protocol. All participants provided written informed consent.

Study Participants

Inclusion criteria were age 18–75 years, chronic HCV infection (positive HCV antibody and HCV RNA ≤6 months prior to study entry), HCV genotypes 1, 2, or 3, and active injection drug or crack cocaine use (defined as drug use at least once per month and use within 3 months of the date of randomization). Exclusion criteria were decompensated liver disease, platelet count <60 000/mm^3, serum alanine aminotransferase level >10 times upper limit of normal, serum creatinine level >1.5 times the upper limit of normal, unstable or uncontrolled thyroid disease, clinically significant cryoglobulinemic vasculitis, presence or history of other causes of chronic liver disease, human immunodeficiency virus coinfection, concurrent therapy with immunosuppressive drugs or cytotoxic agents, preexisting or active psychiatric condition (severe untreated depression, major psychoses, suicidal ideation, or suicidal attempts) or other severe medical comorbidities that in the judgment of the responsible physician precluded treatment.

Study Assessments

At baseline, surveys were completed to assess demographics and drug use characteristics. Participants were carefully monitored throughout the study for depression and deterioration in their mental health, including weekly assessments by study nurses, frequent formal assessments using the Beck Depression Inventory (BDI), and dedicated mental health counseling at weeks 1, 4, and 12 of treatment.

Interventions

Treatment consisted of peg-IFN alfa-2a (180 μg subcutaneously once weekly) and RBV. Those with genotype 1 received weight-based RBV (>75 kg–1200 mg daily, <75 kg–1000 mg daily). Those with genotypes 2/3 received 800 mg/day regardless of weight. Patients infected with HCV genotype 1 and genotypes 2/3 were treated for 48 and 24 weeks, respectively. Treatment was terminated in those infected with genotype 1 at week 12 if early virologic response was not achieved (detectable HCV RNA or <2 log reduction in HCV RNA).

Weekly IFN injections were administered at the study sites under direct observation, and a 1-week supply of RBV provided for self-administration. Doses of peg-IFN and/or RBV were adjusted or discontinued based on a predefined schedule for adverse events and laboratory abnormalities. Besides directly observed peg-IFN injections, patients also received the following monitoring and follow-up: (1) weekly visits with the study nurse, (2) monthly assessments by the mental healthcare worker and formal assessment with BDI on each monthly visit, (3) monthly visit with the physician, (4) visit/compliance

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incentives including a $5 food voucher given at each visit. Participants in the delayed treatment arm had monthly visits with a study nurse and mental healthcare worker (including a $5 vouchers).

Study Outcomes

The primary outcome was SVR defined as undetectable HCV RNA 24 weeks after completion of treatment. If HCV RNA testing was not available following the end of treatment, the participant was assumed to have not achieved an SVR. If the 24-week posttreatment test was not completed, but a subsequent test for HCV RNA was negative, the participant was considered to have achieved SVR.

Because the efficacy of combination treatment with peg-IFN and RBV is well established, the primary analysis was to estimate the effectiveness of treatment in the study population and not to formally test differences in the proportion with SVR between the immediate and delayed treatment groups. The purpose of the delayed treatment group was to estimate loss to follow-up and adverse events in an untreated patient population, as it was anticipated that the observed rates could be much higher than those seen in the published trials that excluded those actively using drugs. A secondary objective was to determine reinfection rates in those who achieved an SVR.

Sample Size

The study aimed to recruit 100 participants with 70 randomized to active treatment. This would have provided a 95% confidence interval (CI) around the estimated SVR rate of ±10%–12%. Recruitment was more difficult than anticipated. Study recruitment was terminated at 66 randomized subjects when it was evident that the desired sample size would not be achieved.

Randomization

Permuted block randomization was stratified by study site. Participants were randomized to either immediate or delayed treatment to achieve a 70:30 ratio based on the desired sample size of 100 total subjects. The randomization scheme was generated using the Stata "ralloc" command (StataCorp, College Station, Texas). Group allocation was performed with sequentially numbered envelopes that were opened at the study site after consent was obtained. Participants and investigators were not blinded to group allocation.

Statistical Methods

All randomized participants were included in the statistical analysis. For the primary effectiveness end point, the proportion of participants in the immediate treatment arm who achieved an SVR was calculated. This analysis was repeated among all participants who received at least 1 dose of study medication. In a post hoc analysis, SVR was compared among those randomized to receive immediate and delayed therapy to assess whether delaying treatment had an impact on SVR. Patient demographic and drug use characteristics and viral genotype were examined as predictors of treatment completion and SVR. Fisher exact test was used to test for statistical significance. For all analyses, statistically significant differences were assessed at $P < .05$; P values are 2-sided. All analyses were performed using the statistical package Stata version 12.0.

RESULTS

Participant Disposition

Participants were recruited from the Calgary Urban Projects Society Health Centre beginning in September 2004 and the Pender Community Health Centre beginning in June 2006. Recruitment was terminated in both sites in December 2007. As shown in Figure 1, 377 participants were screened for inclusion and 66 (18%) were eventually randomized into the study. Among 311 not included, major reasons for exclusion included negative HCV RNA at screening (n = 61), cessation of drugs for >3 months at time of screening (n = 82), significant mental health concerns (n = 28) and alcohol use that would preclude adherence to therapy (n = 35). During the screening process, 72 participants were lost to follow-up.

Participant Characteristics

Of the 316 HCV RNA–positive patients screened for the study, 66 (21%) were randomly assigned to treatment (n = 48) or delayed treatment groups (n = 18; Figure 1). The pretreatment characteristic of participants in the study groups were similar (Table 1). In those receiving immediate and delayed treatment, 83% and 89% had used drugs in the past 30 days at the time of study enrollment, respectively.

Treatment for HCV Infection

Among 48 participants in the immediate treatment group, 77% (n = 37) completed treatment or had treatment stopped early because of no early virologic response. Of the 11 (23%) who did not complete treatment, 3 stopped due to an adverse event, 5 were stopped due to noncompliance, and 3 were lost to follow-up. A dose reduction of the peg-IFN alfa-2a dose was required in 10 (21%) participants and of the RBV dose in 11 (23%) participants. Patient demographics, baseline drug use characteristics, and HCV genotype did not predict treatment completion (Table 2).

Thirty-three percent (n = 6) of participants in the delayed treatment group (n = 18) were lost to follow-up during the observation period, a proportion similar to those that did not complete treatment in the treatment group (23%; $P = .389$). The remaining 12 subjects initiated treatment, and 67% (n = 8) completed treatment.

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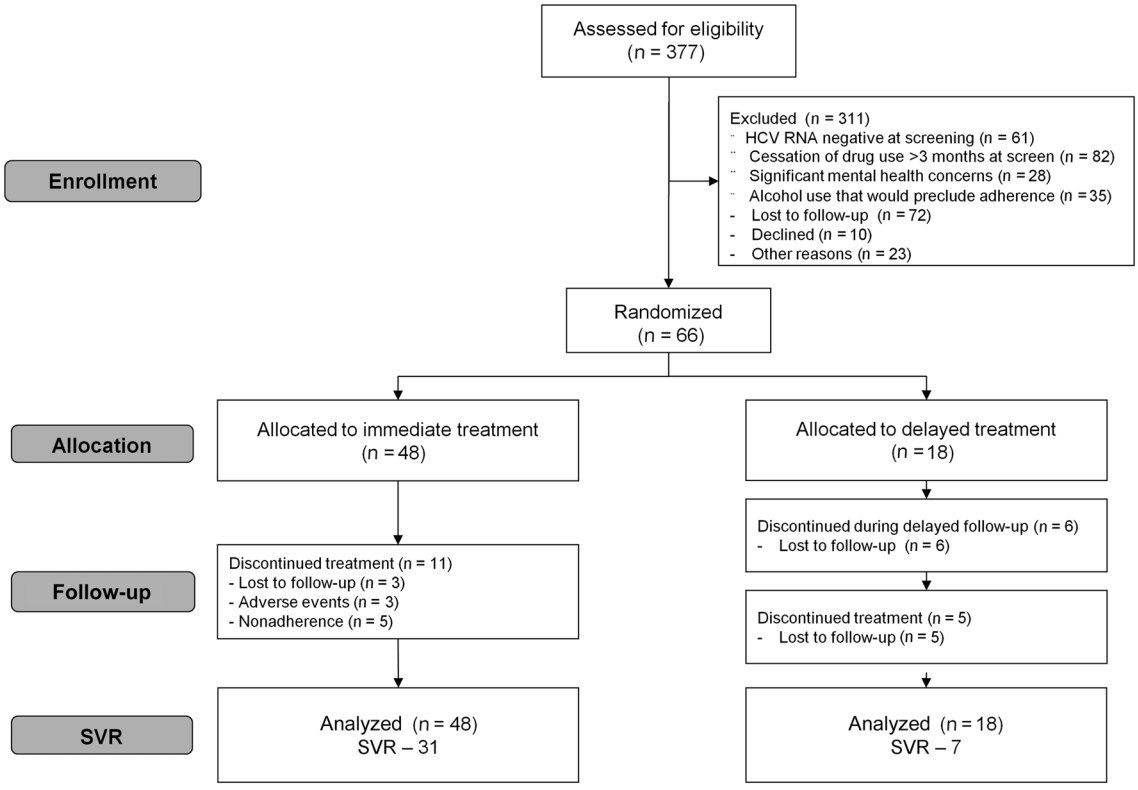

Figure 1. Overview of study population among those randomized to receive immediate (n = 48) or delayed (n = 18) treatment. At least 1 dose of pegylated interferon alfa-2a and ribavirin was administered to 60 participants. Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response.

Sustained Virologic Response

Among participants receiving immediate treatment, the SVR was 65% (95% CI, 49%–78%; 31 of 48, Figure 2). In a post hoc analysis among all randomized individuals, the proportion with SVR was lower in those receiving delayed treatment (39% [95% CI, 17%–64%]; 7 of 18) compared to immediate treatment ($P = .060$). Of the 12 observation group participants who received delayed treatment, 58% (n = 7) had an SVR.

Among all participants who received at least 1 dose of study medication (n = 60), SVR was attained by 63% (95% CI, 50%–

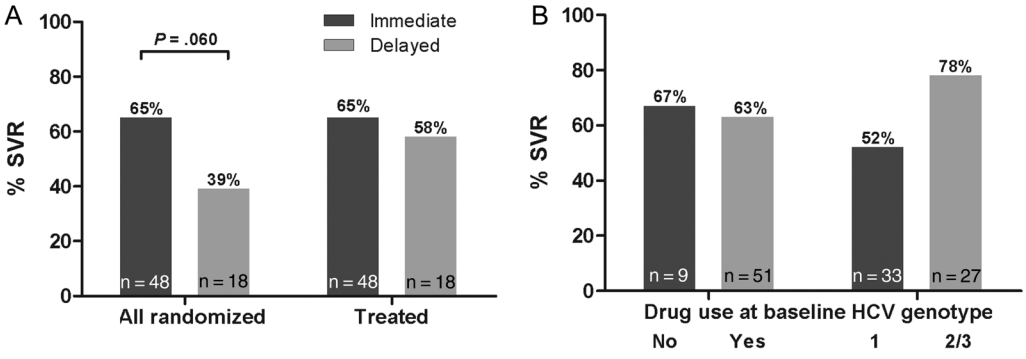

Figure 2. Sustained virologic response rates in those randomized to receive immediate (n = 48) or delayed (n = 18) treatment among all randomized and all participants receiving at least 1 dose of study medication (intent-to-treat; *A*); and stratified by drug use at treatment initation and by hepatitis C virus genotype among all treated participants who received at least 1 dose of study medication (*B*; intent-to-treat, n = 60). Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response.

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Table 1. Characteristics of Participants (N = 66)

Characteristic	Immediate Treatment (n = 48), No. (%)	Delayed Treatment (n = 18), No. (%)
Age, y, median (range)[a]	41 (23–59)	45 (35–54)
Male sex	43 (90%)	17 (94%)
Methadone treatment	10 (21%)	8 (44%)
Drug use, past 30 d	40 (83%)	16 (89%)
Stimulants (cocaine, methamphetamine)	35 (73%)	15 (83%)
Narcotics (heroin, methadone, prescription opioids)	11 (23%)	5 (27%)
Depressants	5 (10%)	3 (17%)
Cannabis	23 (48%)	9 (50%)
Other	1 (2%)	0 (0%)
Alcohol use, past 30 d	12 (25%)	9 (50%)
ALT, U/L, mean (range)	96 (21–371)	92 (16–244)
HCV RNA, log IU/mL, mean (range)	6.7 (2.8–7.4)	6.3 (4.9–6.8)
HCV genotype[a]		
Genotype 1	27 (56%)	10 (56%)
Genotype 2/3	21 (44%)	8 (44%)

All percentages indicate column percentages.

[a] Past 30 days.

Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus.

Table 2. Predictors of Treatment of Completion in the Immediate arm (n = 48)

Predictor	Completed Treatment, No. (%) (n = 37)	*P* Value
Sex		
Male	33 (75%)	. . .
Female	4 (80%)	1.00
Recent drug use at baseline[a]		
Yes	32 (80%)	. . .
No	5 (63%)	.36
Recent alcohol use at baseline[a]		
Yes	11 (92%)	. . .
No	26 (72%)	.25
Methadone treatment at baseline		
Yes	8 (80%)	. . .
No	29 (76%)	1.00
Hepatitis C virus genotype		
Genotype 1	19 (70%)	. . .
Genotypes 2/3	18 (86%)	.30

[a] Past 30 days.

75%; n = 38). Among those with HCV genotype 1 (n = 33) and genotypes 2/3 (n = 27), SVR was 52% (95% CI, 34%–69%; n = 17) and 78% (95% CI, 58%–91%; n = 21; Figure 2), respectively. SVR was similar for those using (n = 51) and not using drugs (n = 9) within 30 days of start of treatment (63% vs 67%; *P* = .60; Figure 2).

Reinfection

Among those with an SVR (n = 31), follow-up data were available in 23 participants. The median post-SVR follow-up time was 1.8 years (range, 0.5–1.8 years). Follow-up was 1.8 years (n = 15), 1.4 years (n = 5), and 0.5 years (n = 3) post-SVR (n = 15). Only 1 participant demonstrated recurrent HCV RNA 1.7 years following treatment, consistent with reinfection (but no HCV genotyping was available) following an HCV RNA–negative test 1.3 years post-SVR. The rate of HCV reinfection over 36 person-years of observation was 2.8 (95% CI, 0.0–14.5) cases per 100 person-years.

Adverse Events

Most adverse events were consistent with those commonly associated with peg-IFN/RBV treatment. Treatment was well tolerated as demonstrated by the small number of patients who discontinued treatment due to adverse events (4 of 60 [7%]).

DISCUSSION

In this randomized controlled trial of directly observed peg-IFN alfa-2a plus self-administered RBV among people with chronic HCV infection and active drug use, nearly 80% completed treatment and two-thirds responded to therapy. Drug use at the time of treatment initiation was not associated with reduced SVR. Unexpectedly, among individuals randomized to receive deferred therapy, one-third were lost to follow-up during the observation phase, suggesting a potential benefit of more timely treatment initiation to maintain engagement in care. Reinfection following successful treatment was low. These data demonstrate that the delivery of directly observed therapy with peg-IFN alfa-2a plus self-administered RBV within multidisciplinary community health centers can be an effective strategy for the treatment of HCV among active PWID.

Overall, 80% completed treatment and 63% had an SVR (genotype 1, 52%; genotypes 2/3, 78%), consistent with results observed from systematic reviews and meta-analyses among those with a history of injecting [3, 4] and active PWID [12]. The SVR in this study also compares favorably to large registration trials [13, 14] and "real-world" experience [15, 16]. Reasons for a high response to therapy are likely multifactorial. PWID often have characteristics associated with favorable HCV treatment response including younger age, HCV genotype 3, and mild liver disease [17]. Peg-IFN was provided as directly observed therapy, shown to be associated with high responses to therapy [18, 19]. Also, the delivery of care within community health center with

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multidisciplinary support has been shown to produce favorable outcomes among PWID [20]. Intensive monitoring and nursing support offered through this study likely provided an opportunity to quickly address issues of noncompliance and side effects. Incentives, such as the food vouchers provided for study visits, may have also contributed to the high proportion remaining in follow-up. These results suggest that when appropriately supported through therapy in a multidisciplinary setting, active PWID can be successfully treated for HCV. The notion that PWID have increased adverse effects of antiviral treatment was not supported by our results. The low rates of discontinuations due to adverse effects and on-treatment dose reductions of peg-IFN and RBV were similar to those of large registration trials [13, 14] and a large accumulated "real-world" experience [21].

Active drug use at HCV treatment initiation in this study was not associated with lower completion or SVR. This is consistent with other data suggesting that active drug use prior to HCV treatment is not associated with lower completion [22], or SVR [12, 19, 23–27]. These prospective data provide further support for international guidelines stating that active drug use should not be used as a criteria for excluding people from treatment [5–7], particularly when provided within multidisciplinary HCV care programs.

Among participants interested in initiating treatment and randomized to delayed treatment, one-third were lost to follow-up during the observation period and did not return. The delayed treatment arm in this study was originally intended as an observational arm to assess loss to follow-up and adverse events. However, in a post hoc analysis, intent-to-treat SVR among all randomized participants was lower among those with delayed as compared to immediate therapy (39% vs 65%). Among those who eventually received treatment, the SVR (58%) was comparable to that in the group that received immediate treatment (63%). This suggests that significant delays in starting treatment should be avoided once initial engagement in care has been achieved, proving the adage to "strike while the iron is hot," especially in this patient population.

Those who initiated treatment in this study represented a highly selected group. Of the 316 HCV RNA–positive participants assessed for treatment, only 21% met the entry criteria, consistent with treatment uptake in other community-based studies among PWID [20, 28, 29]. Exclusion occurred mainly due to issues related to cessation of drug use prior to study enrollment (>3 months since last use) and mental health or alcohol use. Irrespective of this limitation of generalizability, there is clearly a subset of active PWID who respond favorably to therapy with appropriate monitoring and support. Last, although this study focused specifically on active drug users, continued HCV assessment and treatment among those who stop using drugs may also represent a complementary window of opportunity for HCV treatment.

HCV reinfection rates were low in this study, at 2.8% per year, consistent with previous studies ranging from 1%–5% per year among PWID [30]. Larger and longer-term studies are needed to provide more precise estimates of HCV reinfection rates following successful treatment among active PWID and to understand factors associated with reinfection.

There were several limitations to this study. The initial enrollment target of 100 participants was not reached, due to very significant delays in recruiting eligible and willing participants. However, it is believed that a sample size was achieved that allowed meaningful conclusions to be drawn regarding overall treatment safety and efficacy in this important population. Also, the original study was not designed to evaluate the impact of delayed treatment on SVR, but rather to estimate loss to follow-up and adverse events in an untreated control population of PWID. As such, the finding that immediate treatment was associated with better outcomes compared to delayed therapy should be interpreted with caution, because it is based on a very small number of patients and the study was not specifically designed to answer this question. Last, this study did not include any protease inhibitor–based therapy.

Despite the fact that the majority of HCV infection in the developed world occurs among PWID and the burden of HCV-related disease is supplanting drug-related harms as the major contributor to morbidity and mortality [31], very few have received HCV treatment [8–10]. A recent Canadian survey of treating physicians found that 80% would not consider active PWID for HCV treatment [32]. The reasons suggested for this lack of enthusiasm or low uptake of treatment in PWID include (1) poor compliance/adherence, (2) poor efficacy, (3) increased side effects of treatment, and (4) high reinfection rates. Our study strongly suggests that these suppositions do not apply or are incorrect and these reasons should not be used to withhold therapy among active PWID.

This is the first randomized controlled trial to investigate HCV treatment among active PWID, providing important clinical information guiding practitioners in the appropriate management of HCV among PWID. This trial demonstrates that HCV treatment with directly observed weekly peg-IFN plus self-administered RBV is safe and effective among active PWID, with drug use at treatment initiation not impairing response to therapy. More immediate engagement in HCV treatment may lead to an increased proportion treated and responding to therapy. Finally, HCV reinfection in this study was low. As we move forward, the availability of safer, more tolerable, and more effective IFN-free direct-acting antivirals for HCV will substantially enhance the proportion of PWID assessed and treated for HCV infection. Further randomized controlled trials investigating strategies to enhance treatment of HCV infection among PWID will be urgently required if we are to address the burden of HCV in the developed world.

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Notes

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