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Research paper

Efficacy of response-guided directly observed pegylated interferon and self-administered ribavirin for people who inject drugs with hepatitis C virus genotype 2/3 infection: The ACTIVATE study

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ABSTRACT

Background: There are few data on treatment for hepatitis C virus (HCV) infection among people with ongoing injecting drug use. This study evaluated the efficacy of response-guided therapy for chronic HCV genotypes 2/3 infection among people with ongoing injecting drug use or receiving opioid substitution therapy (OST). A secondary aim was to identify predictors of HCV treatment response.
Methods: ACTIVATE was a multicentre clinical trial recruited between 2012 and 2014. Participants with genotypes 2/3 were treated with directly observed peg-interferon alfa-2b and self-administered ribavirin for 12 (undetectable HCV RNA at week 4) or 24 weeks (detectable HCV RNA at week 4). Participants were recruited from drug treatment clinics, private practices, hospital clinics and community clinics in Australia, Canada, and five countries in Europe. The primary study outcome was sustained virological response (SVR, undetectable HCV RNA >12 weeks post-treatment).
Results: Among 93 people with ongoing injecting drug use or receiving OST treated for HCV genotype 2/3, 59% had recently (past month) injected drugs, 77% were receiving OST and 56% injected drugs during therapy. Overall SVR was 66% (61/93). SVR was 84% in those with undetectable HCV RNA at week 4

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(12 weeks) compared to 38% in those without (24 weeks). In adjusted analysis, cirrhosis vs. no/mild fibrosis [adjusted OR (aOR) 0.33, 95% CI 0.13, 0.86] predicted reduced SVR, while response at week 4 was associated with increased SVR [aOR 8.11, 95% CI 2.73, 24.10]. Recent injecting drug use at baseline or during therapy was not associated with SVR.
Conclusion: This study demonstrates that people with recent injecting drug use or OST with chronic HCV can achieve responses to interferon-based therapy similar to other populations, despite injecting drugs prior to or during therapy. Cirrhosis was predictive of reduced response to HCV therapy, while response at week 4 (despite shortened therapy) was predictive of improved response.

Introduction

The morbidity and mortality due to hepatitis C virus (HCV) infection among people who inject drugs (PWID) continues to increase (Hajarizadeh, Grebely, & Dore, 2013; Kielland et al., 2014). New highly effective, simple, and tolerable HCV therapies have the potential to enhance treatment uptake. However, strategies for delivering HCV therapy will be required to achieve maximum impact among PWID.

Interferon-based HCV therapy is safe and effective for PWID (Aspinall et al., 2013; Hellard, Sacks-Davis, & Gold, 2009) and international recommendations support HCV treatment for PWID (AASLD/IDSA, 2017; EASL, 2017; Grebely et al., 2015; Robaeys et al., 2013; WHO, 2016). Despite these recommendations, some HCV clinicians remain concerned that adherence, efficacy (including re-infection), and competing morbidity still provide barriers to HCV treatment for PWID (Litwin et al., 2007; Myles, Mugford, Zhao, Krahn, & Wang, 2011).

Successful strategies to optimize adherence to therapy include directly observed therapy (with the morning dose of ribavirin and/or weekly interferon injections observed) and multidisciplinary support programmes (Meyer et al., 2015). The major limitations of studies evaluating interventions to enhance HCV treatment among PWID is that they rely on retrospective data collection, are single-centre, or consist of small numbers. PWID are usually excluded from Phase II/III trials (Grebely, Dore et al., 2016; Grebely, Mauss et al., 2016). There is a need for larger, multicentre, prospective studies evaluating strategies to enhance HCV treatment among PWID with ongoing drug use.

Given that interferon-based HCV therapy is poorly tolerated, and associated with neuropsychiatric side-effects, efforts have been made to identify patients responding to shorter treatment. A rapid virologic response (RVR) after 4 weeks of therapy is predictive of a sustained virological response (SVR) (Jensen et al., 2006). Among patients with genotypes 2/3 and an RVR, SVR may be achieved in 80–95% as compared to 50% of those without RVR (Dalgard et al., 2008; Jensen et al., 2006; Mangia et al., 2005). In patients with genotypes 2/3 and RVR treated for 12–14 weeks, SVR is comparable to 24 weeks of therapy (Dalgard et al., 2004, 2008; Dalgard, Bjøro, Ring-Larsen, & Verbaan, 2010; Mangia et al., 2005).

The primary aim of this study was to evaluate the efficacy of response-guided, directly observed weekly pegylated interferon alfa-2b (PEG-IFN) and self-administered ribavirin treatment for chronic HCV genotypes 2/3 among PWID with ongoing drug use or those receiving opioid substitution therapy (OST). Secondary aims included adherence to HCV therapy, predictors of HCV treatment response, and safety following successful treatment.

Methods

Study participants

From May 11, 2012, to September 30, 2014, participants were enrolled at 17 sites in Australia (n = 5), Belgium (n = 2), Canada (n = 3), Germany (n = 1), Norway (n = 2), Switzerland (n = 3) and the United Kingdom (n = 1). The last participant visit was July 15, 2015. Study recruitment was conducted through a network of drug and alcohol clinics (n = 3), private practices (n = 2), hospital clinics (n = 9), and community clinics (n = 3). Participants attending these clinics who fulfilled the eligibility criteria were offered participation in this study.

Participants had to be >18 years of age, have chronic HCV genotype 2 or 3 infection, be HCV treatment-naïve, and have reported recent injecting drug use (defined as injecting drug use within 12 weeks of enrolment). Due to slower than anticipated recruitment, on June 26, 2013, a study protocol amendment was implemented to also include people currently receiving OST with no recent drug use and people who had injected within 24 weeks prior to enrolment. Participants with HIV infection and decompensated liver disease were excluded. Full eligibility criteria are provided in the study protocol (Supplementary material).

Study design and intervention

ACTIVATE was an international, multicentre open-label study. Participants received directly observed pegylated interferon alfa-2b (PEG-IFN weekly, 1.5 μg/kg/week) and self-administered ribavirin (RBV, 800–1400 mg daily, weight-based).

Participants with an RVR [defined as non-quantifiable HCV RNA (<15 IU/ml detected and <15 IU/ml undetected) or undetectable HCV RNA on qualitative assay at week 4] received 12 weeks of therapy (shortened duration). Participants without an RVR [defined as quantifiable HCV RNA (≥15 IU/ml) or detectable HCV RNA on qualitative assay at week 4] received 24 weeks of therapy (standard duration).

Study oversight

All participants provided written informed consent before study procedures. The study protocol was approved by St. Vincent's Hospital, Sydney Human Research Ethics Committee (primary study committee), as well as through local ethics committees at all study sites, and was conducted according to the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice (ICH/GCP) guidelines. The study was registered with clinicaltrials.gov registry (NCT01364090). The sponsor (The Kirby Institute, UNSW Sydney) collected the data, managed study samples, monitored study conduct and performed the statistical analysis. An independent data and safety monitoring board reviewed the progress of the study.

Study assessments

Screening assessments included HCV RNA levels, HCV genotype, standard laboratory and clinical testing and self-reported behavioural questionnaires.

Assessments during treatment included measurement of vital signs, symptom-directed physical examinations, measurements of

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HCV RNA levels (performed at local laboratories), and standard laboratory testing. All adverse events were recorded and graded according to a standard scale (details provided in the study protocol).

HCV RNA levels were also measured on stored serum samples tested centrally with the COBAS TaqMan HCV Test (version 2.0, Roche Molecular Systems, lower limit of quantification of 15 IU/ml). HCV RNA testing was performed on samples collected at baseline, and weeks 4, 12, 24, 36 and 48 (standard duration). HCV genotype/subtype were determined by sequencing of the NS5B region (Murphy et al., 2007).

Directly observed PEG-IFN adherence was recorded by the study nurse. Self-reported RBV adherence was measured monthly during treatment by a patient-administered questionnaire. Adherence was defined as the receipt of at least 80% of scheduled doses for 80% of the scheduled treatment period. For participants in whom therapy was terminated at 12 weeks because of virologic nonresponse, the scheduled treatment period was defined as 12 weeks. On-treatment adherence was calculated by subtracting the number of missed doses from the total duration of treatment (week that treatment was discontinued or completed) and dividing this number by the total therapy duration.

Participants completed a self-administered questionnaire at enrolment (pre-treatment assessment), at baseline (treatment commencement), every fourth week during treatment, and at 12 and 24 weeks of post-treatment follow-up. The questionnaires collected information on demographics (age, gender, ethnicity, employment status, education level, housing status), drug and alcohol use, injecting risk behaviours, drug treatment, quality of life (SF-12) and symptoms of psychological distress (Depression Anxiety Stress Scale, DASS-21). Stable housing was defined as living in a rented or privately owned house or flat.

Social functioning was measured using the short-form Opioid Treatment Index Social Functioning Scale (Darke, Ward, Hall, Heather, & Wodak, 1991; Lawrinson, Copeland, & Indig, 2003; Wiessing et al., 2014). Social functioning scores range from 0 to 18, with higher scores indicating lower social functioning. Alcohol consumption was evaluated by the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C), derived from the first three questions of the full AUDIT (scores $\geq$3 and $\geq$4 indicate hazardous consumption or active alcohol use disorders among women and men, respectively) (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998).

Stage of liver fibrosis was assessed by liver biopsy (METAVIR) (Desmet, Gerber, Hoofnagle, Manns, & Scheuer, 1994), liver stiffness measurement (Transient Elastography [FibroScan®]) or AST-to-Platelet Ratio Index (APRI). For liver stiffness measurements, the chosen cut-offs for significant liver fibrosis and cirrhosis were 7.1 kPa and 12.5 kPa, respectively (Castera, Forns, & Alberti, 2008). APRI was calculated using aspartate aminotransferase (AST) and platelet count: [(AST [U/L]/upper limit of normal)/platelet count (109/L)] $\times$ 100. APRI >1.5 and >2.0 defined significant liver fibrosis and cirrhosis, respectively (Wai et al., 2003).

Study endpoints

The primary efficacy endpoint was the proportion of participants with undetectable HCV RNA at 12 weeks after the end of treatment (SVR12) by intention to treat (ITT). Viral relapse was defined as the detection of HCV RNA following >1 negative results for HCV RNA. If HCV RNA had not been assessed at 24 weeks after the end of treatment, the result of the next available HCV RNA assessment was used to calculate SVR12. For the primary endpoint, HCV RNA levels were measured on stored serum samples tested centrally with the COBAS TaqMan HCV Test (version 2.0, Roche Molecular Systems).

Statistical analysis

The proportion of participants with SVR12 was calculated, including exact two-sided 95% confidence intervals (95% CI). With an anticipated 100 participants and an overall SVR12 of 70%, the two-sided 95% CI for the primary endpoint was expected to be 60%–79%.

Factors hypothesized to be predictive of SVR were determined based on factors previously shown or hypothesized to be associated with HCV treatment response. These predictors included age (stratified by median), sex, education, social functioning score (stratified by median), stable housing, frequency of alcohol consumption at baseline, current OST, recent (past month) injecting drug use at baseline [including injecting use of heroin, methadone (or buprenorphine/suboxone), morphine (or other opiates), methamphetamine, cocaine, and benzodiazepines], frequency of injecting drug use at baseline (never, <weekly, >weekly), benzodiazepine use at baseline (non-injecting), ongoing injecting drug use during therapy, presence of cirrhosis, and >80% adherence to PEG-IFN therapy.

Following unadjusted analyses, multivariable logistic regression was performed to evaluate predictors of SVR among those who reached week 4 of therapy, considering factors significant at the 0.20 level in unadjusted analyses. All models were adjusted for study site. For all analyses, statistically significant differences were assessed at a 0.05 level; P-values were two-sided. All analyses were performed using Stata v12.0 (StataCorp, College Station, Texas).

Results

Participant characteristics

Of 119 participants initially screened, 93 were enrolled and initiated HCV therapy (Fig. 1). The demographic and clinical characteristics of participants included in this study (n = 93) are shown in Table 1. The median age was 41, and 77% were male. At baseline, 77% were receiving OST, 67% had used illicit drugs in the past month and 59% had injected drugs in the past month (Table 1). The genotype distribution included 9% (n = 9) with genotype 2, 89% (n = 83) with genotype 3. There was one participant who was HCV genotype 2b at screening, but upon central lab testing at the completion of the study was shown to be infected with genotype 1a.

Overall treatment completion, adherence and HCV treatment outcomes

As shown in Table 2, among all participants enrolled (n = 93), 76% (71/93, 95% CI: 66%, 85%) completed their intended duration of treatment. Of the 22 not completing treatment (Fig. 1), six people discontinued prior to week 4; reasons for discontinuation included treatment side-effects (n = 3; flu-like symptoms and nausea, n = 2; fatigue and agitation, n = 1), unwillingness to continue therapy (n = 1), lost to follow-up (n = 1), and imprisonment (n = 1). An additional 16 people discontinued treatment during therapy; reasons for discontinuation included on-treatment virological failure (n = 1), side-effects (n = 4; depression, n = 3; aggravated tinnitus, n = 1), medical contraindications to continuing therapy (n = 3, perceived risk of increasing drug use and overdose, n = 2; hospitalisation due to abscess, n = 1), patient unwillingness to continue therapy (n = 4), and lost to follow-up (n = 4).

Overall, 81% (75/93, 95% CI: 71%, 88%) of participants were >80% adherent to PEG-IFN therapy and 75% (70/93, 95% CI: 65%, 84%) were >80% adherent to RBV therapy (Table 2). The overall on-treatment PEG-IFN and ribavirin adherence (proportion of doses received from the time that treatment was initiated until

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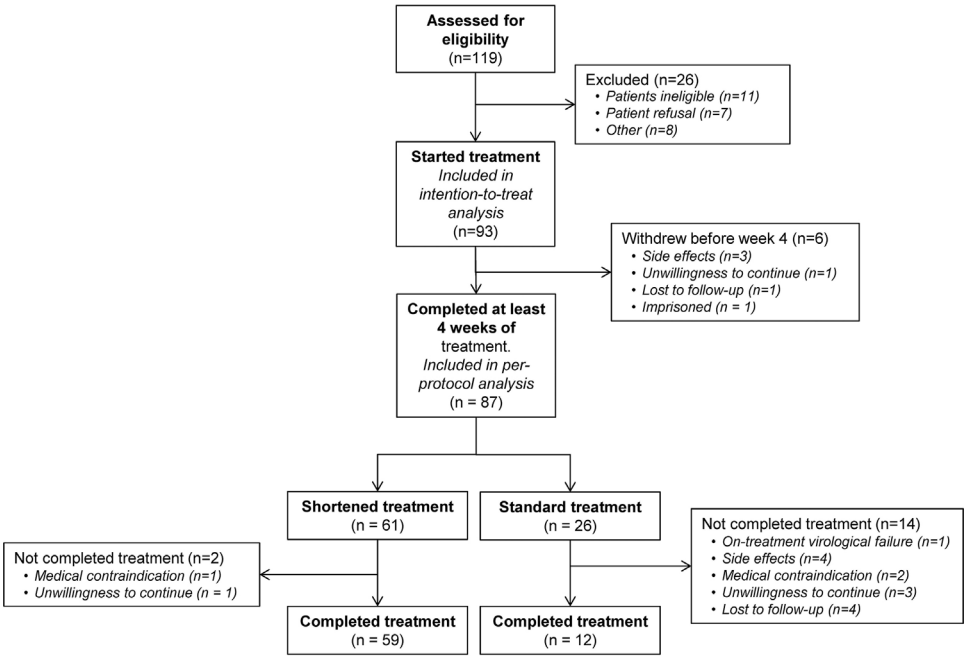

Fig. 1. Participant disposition.

treatment was discontinued or completed) were 98.2% and 94.6%, respectively (Table 2).

In ITT analysis, 75% (70/93, 95% CI: 65%, 84%) had an ETR and 66% [n = 61, 95% CI: 55%, 75%] had an SVR. Among those with post-treatment failure (n = 10, Fig. 2), reasons for failure included viral relapse (n = 5), patient unwillingness to continue therapy (n = 1), lost to follow-up (n = 3) and death (n = 1).

As shown in Fig. 3, among all participants enrolled (n = 93), six participants discontinued therapy before week 4. Among the remaining 87 participants, 70% (n = 61) were undetectable at week 4 (RVR) and received 12 weeks of therapy (shortened duration) and 30% (n = 26) did not have an RVR at week 4 and were allocated to 24 weeks of therapy (standard duration).

HCV treatment completion and adherence

The proportion completing HCV therapy was 97% (59/61) among participants receiving shortened therapy, compared to 46% (12/26) among those receiving standard therapy ($P < 0.001$, Table 2). Among people receiving standard therapy and discontinuing therapy early (n = 14), discontinuations occurred between weeks 4–8 in 38% (n = 5), between weeks 8–12 in 46% (n = 6) and between weeks 12–24 in 23% (n = 3). Compared to participants receiving standard therapy (Table 2), participants receiving shortened therapy had a greater proportion with >80% PEG-IFN adherence (98% vs. 58%, $P < 0.001$) and had higher on-treatment adherence to ribavirin (98% vs. 88%, $P = 0.002$) However, on-treatment adherence to directly observed PEG-IFN therapy was similar between those receiving shortened and standard therapy (99% vs. 99%, $P = 0.131$).

HCV treatment outcomes in those receiving shortened and standard duration treatment

Among participants receiving shortened duration of therapy (RVR, n = 61; Fig. 3), 95% (n = 58) had an ETR and 84% (n = 51) had an SVR, including one individual who was detectable at ETR who achieved an SVR. Among people with post-treatment failure (n = 8, Fig. 3), reasons for failure included viral relapse (n = 3), patient unwillingness to continue follow-up (n = 1), lost to follow-up (n = 3) and death (n = 1). Thus, the proportion with viral relapse after 12 weeks of therapy was 5% (3/58).

Among participants receiving standard duration of therapy (no RVR, n = 26, Fig. 3), 46% (n = 12) had an ETR and 38% (n = 10) had an SVR. This included the one participant with HCV genotype 1a who discontinued therapy at week nine due to patient unwillingness to continue. Among people with post-treatment failure (n = 2, Fig. 3), the only reason for failure was viral relapse (n = 2). The proportion with viral relapse was 17% (2/12).

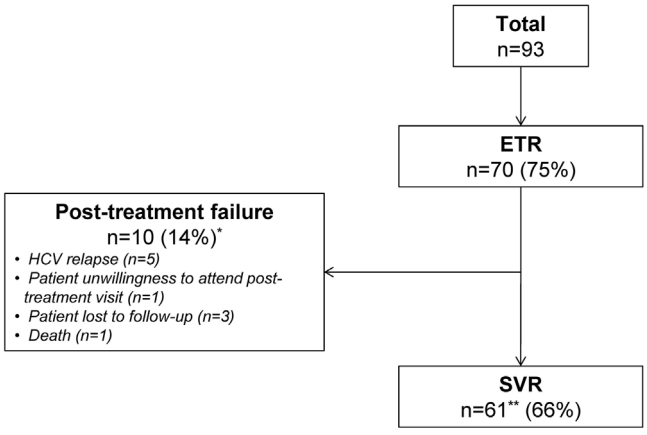

Fig. 2. Overview of response to treatment in ACTIVATE overall.
*Individuals with ETR as the denominator. **One individual had quantifiable at the end of treatment (not achieved ETR) but had unquantifiable HCV RNA at 12 weeks post-treatment (achieved SVR).

Predictors of SVR in those receiving shortened and standard duration treatment

The proportion with SVR stratified by key characteristics among those who reached week 4 of therapy (n = 87) is shown in Table 3. The SVR was the same among those with (n = 54) and without (n = 33) recent (past month) injecting drug use at baseline (70% vs.

Table 1
Baseline demographic and clinical characteristics stratified by shortened and standard treatment duration arms (n = 93).

Characteristic, n (%)	Overall (n = 93)	Shortened therapy (n = 61)	Standard therapy (n = 26)
Age, median (25%, 75%)	41 (35–49)	41 (34–49)	40 (35–48)
Male sex, n (%)	77 (83)	49 (80)	23 (88)
Mean BMI (SD)	26 (5.4)[c]	27 (5.7)[c]	24 (3.4)
Caucasian ethnicity	84 (90)	56 (92)	22 (85)
High school or higher education	40 (43)	25 (42)	12 (46)
Stable housing	71 (76)	48 (79)	17 (65)
Living alone	41 (44)	27 (44)	13 (50)
Part- or full-time employment	14 (15)[c]	6 (10)[c]	6 (23)
Social functioning score, median (25%, 75%)	17 (13–21)[c]	17 (12–21)	17 (15–22)
History of imprisonment	66 (71)	43 (70)	20 (77)
Drug use in the last 6 months (injecting/non-injecting)	77 (83)	48 (79)	25 (96)
Drug use in the last month (injecting/non-injecting)	62 (67)	41 (67)	19 (73)
Heroin	41 (44)	26 (43)	14 (54)
Cocaine	19 (20)	12 (20)	7 (27)
Amphetamines	16 (17)	8 (13)	7 (27)
Other opiates	13 (14)	10 (16)	3 (12)
Benzodiazapines	18 (19)	12 (20)	6 (23)
Cannabis	35 (38)	21 (34)	12 (46)
History of any injecting drug use	89 (96)	59 (97)	25 (96)
Age of first injecting drug use, median (25%, 75%)	20 (16–26)[c]	20 (17–26)	20 (16–26)
Injecting drug use in the last 6 months	68 (73)	43 (70)	23 (88)
Injecting drug use in the last month	55 (59)	39 (64)	15 (58)
Heroin	33 (35)	23 (37)	10 (38)
Cocaine	10 (11)	7 (11)	3 (12)
Amphetamines	14 (15)	7 (11)	6 (23)
Other opiates	11 (12)	8 (13)	3 (12)
Benzodiazapines	2 (2)	2 (3)	0 (0)
Injecting drug used most often in past month			
Heroin	33 (60)	24 (62)	9 (60)
Cocaine	4 (7)	3 (8)	1 (7)
Amphetamines	13 (24)	7 (18)	5 (33)
Other opiates	4 (7)	4 (10)	0 (0)
Benzodiazapines	0 (0)	0 (0)	0 (0)
Other	1 (2)	1 (3)	0 (0)
Injecting drug use frequency in the last month			
Never	38 (41)	22 (36)	11 (42)
<daily	40 (43)	29 (48)	10 (38)
>daily	15 (16)	10 (16)	5 (19)
Any alcohol use (past month)	36 (40)	29 (48)	5 (19)
Hazardous alcohol use (past month)	15 (17)[b]	11 (19)[a]	3 (12)
Opioid substitution treatment (ever)	82 (88)	56 (92)	21 (81)
OST and recent injecting (past month) at enrolment			
No OST, recent injecting	30 (32)	20 (33)	9 (33)
OST, no recent injecting	23 (25)	15 (25)	5 (19)
OST, recent injecting	40 (43)	26 (43)	12 (44)
OST and recent injecting (past month) at baseline			
No OST, recent injecting	21 (23)	14 (23)	6 (23)
OST, no recent injecting	34 (37)	21 (34)	8 (31)
OST, recent injecting	38 (41)	26 (43)	12 (46)
HCV genotype			
1a	1 (1)	0	1 (4)
2a	2 (2)	1 (2)	0
2b	7 (7)	4 (6)	1 (4)
3a	83 (89)	56 (92)	24 (92)
HCV RNA			
Median HCV RNA (25%, 75%), log IU/ml	6.08 (5.63, 6.70)	5.82 (5.35, 6.56)	6.50 (5.83, 6.79)
≤800,000 IU/ml	42 (45)	34 (56)	8 (31)
>800,000 IU/ml	51 (55)	27 (44)	18 (69)
Median ALT (25%, 75%), IU/l	75 (43, 132)	78 (52, 139)	69 (40, 116)
Stage of liver disease			
No or mild fibrosis (F0–F1)	63 (68)	44 (72)	16 (62)
Moderate or advanced fibrosis (F2–F3)	20 (22)	12 (20)	5 (19)
Cirrhosis (F4)	10 (11)	5 (8)	5 (19)
Study site distribution			
Europe	38 (41)	24 (39)	13 (50)
Australia	40 (43)	27 (44)	9 (35)
Canada	15 (16)	10 (16)	4 (15)

[a] 3 missing values.
[b] 4 missing values.
[c] 1 missing value.

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Table 2
Treatment completion, >80% adherence, on-treatment adherence and dose-modifications to directly observed PEG-IFN and self-administered ribavirin therapy in the ACTIVATE Study (n = 93).

Characteristic, n (%)	Overall (n = 93)	Shortened therapy (n = 61)	Standard therapy (n = 26)
Treatment completion	71 (76)	59 (97)	12 (46)
PEG-IFN >80% adherence	75 (81)	60 (98)	15 (58)
Ribavirin >80% adherence	70 (75)	56 (93)	13 (48)
On-treatment PEG-IFN adherence, mean % (SD)	98.2 (4.5)	98.5 (3.1)	98.7 (3.0)
On-treatment ribavirin adherence, mean % (SD)	94.6 (8.8)	94.8 (8.1)	94.1 (10.8)
PEG-IFN dose-modification	9 (10)	3 (5)	6 (23)
Ribavirin dose-modification	21 (23)	12 (20)	9 (35)

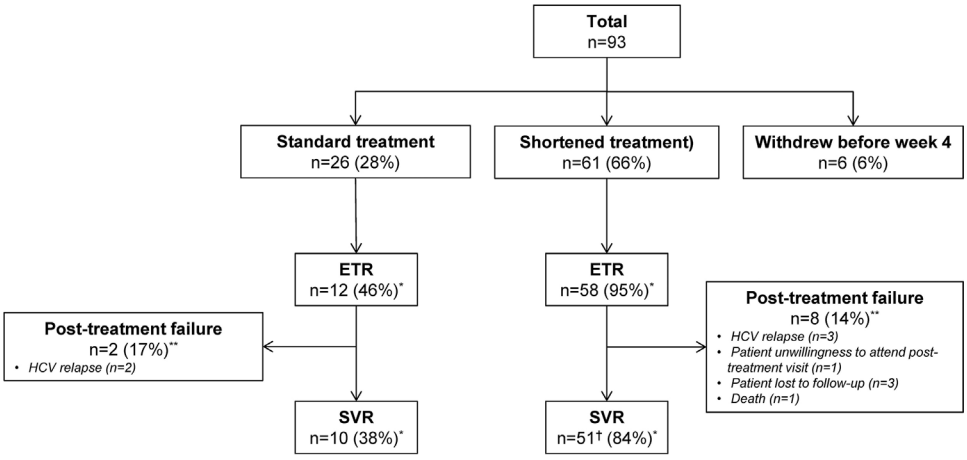

Fig. 3. Overview of response to treatment in ACTIVATE by treatment arm.
*Individuals with in shortened treatment or standard treatment as the denominator. **Individuals with ETR as the denominator. †One individual had quantifiable at the end of treatment (not achieved ETR) but had unquantifiable HCV RNA at 12 weeks post-treatment (achieved SVR).

70%, $P = 0.947$). The SVR was also similar among those with (n = 52) and without (n = 34) ongoing injecting drug use during HCV therapy (69% vs. 73%, $P = 0.668$). The SVR was lower in those with cirrhosis (F4) compared to those with mild (F0–F1) liver disease (60% vs. 72%, $P = 0.007$). The SVR was higher among participants with an RVR receiving 12 weeks of therapy, compared to those without an RVR receiving 24 weeks of therapy (84% vs. 38%, $P < 0.001$). The SVR was also higher among participants who were >80% adherent to PEG-IFN, compared to non-adherent participants (83% vs. 0%, $P < 0.001$). Recent (past month) injecting drug use at baseline, frequency of recent injecting drug use at baseline, OST at baseline and ongoing injecting drug use during therapy were not associated with SVR (Table 3).

In adjusted analyses, cirrhosis at baseline [adjusted odds ratio (AOR) 0.33, 95% CI 0.13, 0.86] was associated with reduced SVR, while RVR at week 4 (AOR 8.11, 95% CI 2.73, 24.10) was associated with increased SVR (Table 3).

Safety

Of the 93 participants enrolled, 11% (n = 10) discontinued treatment prematurely because of an adverse event (Table 4). A total of 12% (n = 11) participants experienced at least one serious adverse event and 98% (n = 91) of participants experienced at least one adverse event (Table 4). The most common adverse events were fatigue (52%), influenza-like illness (39%), headache (38%), nausea (35%), and myalgia (28%). Among the 93 participants who initiated HCV treatment, there was one death during treatment. This participant died of a multiple drug overdose 10 weeks following treatment completion.

Discussion

This international clinical trial evaluated adherence, efficacy, and safety in response-guided, directly observed weekly PEG-IFN and self-administered ribavirin treatment for chronic HCV genotypes 2/3 among PWID with ongoing drug use and those receiving opioid substitution therapy. Overall, SVR was 66%, 84% in those with an RVR (received 12 weeks of therapy) and 38% in those without an RVR (received 24 weeks of therapy). Using response-guided therapy made it possible to shorten therapy in 66% of participants. Stage of liver disease (pre-cirrhosis) and on-treatment RVR were predictors of SVR. In those with an RVR, shortening treatment duration to 12 weeks was also associated with improved adherence to, and safety of PEG-IFN. The response to therapy was similar among people receiving OST and those with injecting drug use prior to or during HCV therapy. Although derived from interferon-containing therapy, these data from the first international clinical trial of HCV therapy among current PWID and those receiving OST have important implications for recommendations for HCV clinical management of these populations.

The overall SVR of 66% is similar to results from a previous systematic review of interferon-based treatment for people with ongoing injecting drug use, where the response among those with HCV genotypes 2/3 was 67% (Aspinall et al., 2013). However, previous studies are limited by retrospective study designs, small sample sizes, and heterogeneous definitions for defining "ongoing" injecting drug use, which may also have affected estimates of SVR.

In this study, individuals with an RVR and shortened interferon-based therapy (12 weeks of therapy) had a markedly higher SVR as compared to those without an RVR (24 weeks), consistent with previous data demonstrating that RVR is predictive of response to

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Table 3
Unadjusted and adjusted analysis of factors associated with SVR12 among those who reached week 4 of therapy in the ACTIVATE Study (n = 87).

	SVR n (%)	No SVR n (%)	Unadjusted OR (95% CI)[a]	P	Adjusted OR (95% CI)[a]	P
Age						
≤41 years	34 (76)	11 (24)	1.00	–		
>41 years	27 (64)	15 (36)	0.58 (0.25, 1.38)	0.219		
Sex						
Female	12 (80)	3 (20)	1.00	–		
Male	49 (68)	23 (32)	0.53 (0.10, 2.88)	0.465		
Education						
<Tertiary	45 (71)	18 (29)	1.00	–		
Tertiary or greater	15 (71)	6 (29)	1.00 (0.42, 2.37)	1.000		
Unknown	1 (33)	2 (67)	0.20 (0.04, 0.90)	0.036		
Social functioning score						
<17	25 (66)	13 (34)	1.00	–		
≥17	36 (73)	13 (27)	1.44 (0.50, 4.14)	0.499		
Stable housing						
No	16 (73)	6 (27)	1.00	–		
Yes	45 (69)	20 (31)	0.84 (0.33, 2.12)	0.718		
Frequency of alcohol consumption						
Weekly or less	52 (70)	22 (30)	1.00	–		
Greater than weekly	8 (73)	3 (27)	1.13 (0.46, 2.79)	0.794		
Unknown	1 (50)	1 (50)	0.42 (0.02, 8.40)	0.573		
OST and recent injecting at enrolment						
No OST, recent injecting	18 (62)	11 (38)	1.00	–		
OST, no recent injecting	14 (70)	6 (30)	1.43 (0.42,4.81)	0.567		
OST, recent injecting	29 (76)	9 (24)	1.97 (0.68, 5.68)	0.210		
Current OST at baseline						
No	16 (64)	9 (36)	1.00	–		
Yes	45 (73)	17 (27)	1.49 (0.50, 4.42)	0.473		
Recent injecting at baseline (last month)						
No	23 (70)	10 (30)	1.00	–		
Yes	38 (70)	16 (30)	1.03 (0.45, 2.36)	0.939		
Frequency of injecting at baseline (last month)						
Never	23 (70)	10 (30)	1.00	–		
Less than weekly	16 (76)	5 (24)	1.39 (0.51, 3.79)	0.518		
Weekly or greater	22 (67)	11 (33)	0.87 (0.37, 2.06)	0.750		
Heroin injecting at baseline (last month)						
No	37 (68)	17 (32)	1.00	–		
Yes	24 (73)	9 (27)	1.22 (0.51, 2.95)	0.650		
Cocaine injecting at baseline (last month)						
No	54 (70)	23 (30)	1.00	–		
Yes	7 (70)	3 (30)	0.99 (0.35, 2.83)	0.991		
Amphetamine injecting at baseline (last month)						
No	53 (72)	21 (28)	1.00	–		
Yes	8 (61)	5 (38)	0.63 (0.25, 1.61)	0.337		
Benzodiazepine use at baseline (last month)						
No	48 (70)	21 (30)	1.00	–		
Yes	13 (72)	5 (28)	1.14 (0.46, 2.80)	0.779		
Liver fibrosis						
F0–F1	43 (72)	17 (28)	1.00	–	1.00	–
F2–F3	14 (82)	3 (18)	1.84 (0.48, 7.04)	0.370	2.28 (0.64, 8.08)	0.203
F4	6 (60)	4 (40)	0.26 (0.10, 0.69)	0.007	0.33 (0.13, 0.86)	0.023
Rapid virological response						
No RVR (24 weeks of therapy)	10 (38)	16 (62)	1.00	–	1.00	–
RVR (12 weeks of therapy)	51 (84)	10 (16)	8.16 (2.93, 22.70)	<0.001	8.11 (2.73, 24.10)	<0.001
PEG-IFN adherence						
<80%	0 (0)	12 (100)	–	–		
>80%	61 (81)	14 (19)	–	<0.001[b]		
Injecting drug use during therapy (last month)						
No	25 (73)	9 (27)	1.00	–		
Yes	36 (69)	16 (31)	0.81 (0.38, 1.74)	0.590[c]		
Unknown	0 (0)	1 (100)	–	–		

[a] The models were adjusted for study site, using cluster-robust standard errors.
[b] Fisher exact test, comparing the distribution of SVR between those with <80% PEG-IFN adherence and those with >80%.
[c] n = 86; one participant with unknown injecting status during therapy was not included in the analysis.

interferon-based HCV therapy (Jensen et al., 2006). In previous studies of patients with genotype 2 or 3 and an RVR at week 4 (standard treatment duration), SVR was achieved in 80–95% as compared to 50% of those with no RVR (Dalgard et al., 2008; Jensen et al., 2006; Mangia et al., 2005), consistent with the findings in this study. Data from a pilot trial and two randomized controlled trials have shown comparable SVR in patients with genotype 2/3 infection and RVR, treated for 12–14 weeks compared to 24 weeks of therapy (Dalgard et al., 2004, 2008; Mangia et al., 2005). Further, in a pooled analysis of two Scandinavian treatment trials in patients with RVR and genotype 2 or 3, SVR was obtained in 91% and 95% after 14 or 24 weeks treatment with PEG-IFN alfa-2b/RBV (Dalgard et al., 2010). Although the SVR observed among those with genotypes 2/3 in the ACTIVATE study (84%) was somewhat lower, the proportion with viral relapse in the shortened treatment arms was low (5%), suggesting that shortened therapy did not

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Table 4
Discontinuations and adverse events.

Characteristic, n (%)	Overall (n = 93)	Shortened therapy (n = 61)	Standard therapy (n = 26)
Treatment discontinuation due to an adverse event	10 (11)	1 (2)	6 (23)
Serious adverse event	11 (12)	6 (10)	4 (15)
Any adverse event	91 (98)	60 (98)	26 (100)
Common adverse events			
Fatigue	48 (52)	33 (54)	14 (54)
Influenza like illness	36 (39)	19 (31)	13 (50)
Headache	35 (38)	21 (34)	14 (54)
Nausea	33 (35)	26 (43)	5 (19)
Myalgia	26 (28)	18 (30)	7 (27)
Decreased appetite	25 (27)	19 (31)	6 (23)
Insomnia	19 (20)	15 (25)	4 (15)
Vomiting	18 (19)	11 (18)	5 (19)
Anaemia	17 (18)	12 (20)	5 (19)
Dry skin	17 (18)	12 (20)	5 (19)
Injection site erythema	17 (18)	8 (13)	4 (15)

impact response. Further, it enabled two-thirds of participants to be spared an additional 12 weeks of the potential side-effects of therapy. Cirrhosis at baseline was associated with reduced SVR, consistent with previous studies of interferon-based therapy (Vezali, Aghemo, & Colombo, 2010).

In the ACTIVATE study, shortening therapy from 24 to 12 weeks in people with an RVR was associated with improved treatment completion, adherence and safety. The high proportion with treatment completion (92%) among people receiving 12 weeks of therapy was higher than previous systematic reviews of people receiving 24–48 weeks of interferon-based HCV therapy among people with a history of injecting drug use (83%) (Dimova et al., 2013) or people with ongoing injecting drug use (78%) (Aspinall et al., 2013). The major impact of shortening therapy on treatment completion was a reduction in treatment discontinuations that were observed in those receiving standard duration. Although on-treatment adherence to directly observed pegylated interferon therapy was similar between those 12 and 24 weeks of therapy, adherence to self-administered ribavirin was higher in those receiving only 12 weeks of therapy (98% vs. 88%). The higher proportion of people with treatment completion and self-reported ribavirin adherence likely also contributed to the higher SVR among people with an RVR and 12 weeks of therapy compared to those without an RVR and 24 weeks of therapy.

Ongoing injecting drug use at baseline or during therapy did not impact SVR, consistent with previous data (Bruggmann et al., 2008; Dore et al., 2010; Grebely, Alavi et al., 2016; Grebely et al., 2007; Manolakopoulos et al., 2010; Sasadeusz et al., 2010; Sylvestre, Litwin, Clements, & Gourevitch, 2005). Given the retrospective nature and small sample sizes of previous studies to date, these data from this prospective international clinical trial are important. As such, decisions to initiate HCV therapy should not be made on the basis of ongoing drug use at baseline, given that this is a poor predictor of subsequent response. Further, ongoing drug use during therapy should not be used as a reason for discontinuing therapy. In fact, recent data suggests that HCV treatment response is not associated with increased drug use or used needle and syringe borrowing during follow-up, but is associated with decreased ancillary injecting equipment sharing (Alavi et al., 2015).

This study has a number of limitations. Participants were largely recruited from hospital-based HCV clinics, community-based drug and alcohol clinics, and community health centres and 22% of participants who were assessed were not enrolled in the study. Therefore, the study population may not be generalizable to all populations of PWID and may reflect a population more engaged in health services. That being said, the population enrolled was highly marginalized, with 73% of people reported injecting drug use in the last six months and 59% reported injecting drug use in the last month. Also, given the small sample size of this study, it is possible that other factors may have been associated with SVR, but were not identified in this study due to limited power. Lastly, *IFNL3/4* genotype testing was not performed and may have been an additional factor associated with response to HCV therapy.

There still remains reluctance by many providers to treat HCV infection among current PWID (including those receiving OST). In the United States, 88% of US State Medicaid committees have implemented restrictions that exclude those who either have recently used illicit drugs, are injecting drugs, or are receiving OST from receiving HCV direct-acting antiviral (DAA) therapies (irrespective of disease stage) (Barua et al., 2015). Given that this population has generally been excluded from large randomized clinical trials, this study provides important data supporting treatment recommendations for PWID (AASLD/IDSA, 2017; EASL, 2017; Grebely et al., 2015; Robaeys et al., 2013; WHO, 2016).

The development of the ACTIVATE clinical trial network provides an important infrastructure for the evaluation of safer, highly tolerable and more effective interferon-free HCV therapies. The ACTIVATE clinical network is evaluating interferon-free DAA HCV regimens including paritaprevir/ritonavir, ombitasvir, dasabuvir (D3FEAT, NCT02498015) and sofosbuvir/velpatisvir (SIMPLIFY, NCT02336139) among PWID with ongoing drug use and/or those receiving OST.

In conclusion, this study demonstrates that PWID with ongoing drug use and people receiving OST can be successfully treated for chronic HCV infection. Although weekly directly observed therapy may not be the standard of care in many settings, emerging data has demonstrated high adherence and response to self-administered DAA therapy among people receiving OST (Dore et al., 2016; Grebely, Dore et al., 2016; Grebely, Mauss et al., 2016) and people with recent injecting drug use (Read THIS ISSUE 2017, Morris THIS ISSUE 2017, Mason THIS ISSUE 2017). Further research is needed to evaluate DAA HCV therapies among people with ongoing drug use. This will be essential in our efforts to control HCV infection among PWID, reduce HCV-related morbidity and mortality globally and strive for HCV elimination.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugpo.2017.05.020.

References

AASLD/IDSA. *HCV guidance: Recommendations for testing, managing, and treating hepatitis C*. Retrieved March 18, 2017 from https://www.hcvguidelines.org/.

Alavi, M., Spelman, T., Matthews, G. V., Haber, P. S., Day, C., van Beek I, Walsh, N., Yeung, B., Bruneau, J., Petoumenos, K., Dolan, K., Kaldor, J. M., Dore, G. J., Hellard, M., Grebely, J., & on behalf of the ATAHC Study Group (2015). Injecting risk behaviours following treatment for hepatitis C virus infection among people who inject drugs: the Australian Trial in Acute Hepatitis C. *International Journal of Drug Policy*, *26*(10), 976–983.

Aspinall, E. J., Corson, S., Doyle, J. S., Grebely, J., Hutchinson, S. J., Dore, G. J., et al. (2013). Treatment of hepatitis C virus infection among people who are actively injecting drugs: A systematic review and meta-analysis. *Clinical Infectious Diseases*, *57*(Suppl. 2), S80–S89.

Barua, S., Greenwald, R., Grebely, J., Dore, G. J., Swan, T., & Taylor, L. E. (2015). Restrictions for medicaid reimbursement of sofosbuvir for the treatment of hepatitis C virus infection in the United States. *Annals of Internal Medicine*, *163*, 215–223.

Bruggmann, P., Falcato, L., Dober, S., Helbling, B., Keiser, O., Negro, F., et al. (2008). Active intravenous drug use during chronic hepatitis C therapy does not reduce sustained virological response rates in adherent patients. *Journal of Viral Hepatitis*, *15*, 747–752.

Bush, K., Kivlahan, D. R., McDonell, M. B., Fihn, S. D., & Bradley, K. A. (1998). The AUDIT alcohol consumption questions (AUDIT-C): An effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Archives of Internal Medicine*, *158*, 1789–1795.

Castera, L., Forns, X., & Alberti, A. (2008). Non-invasive evaluation of liver fibrosis using transient elastography. *Journal of Hepatology*, *48*, 835–847.

Dalgard, O., Bjoro, K., Hellum, K. B., Myrvang, B., Ritland, S., Skaug, K., et al. (2004). Treatment with pegylated interferon and ribavarin in HCV infection with genotype 2 or 3 for 14 weeks: A pilot study. *Hepatology*, *40*, 1260–1265.

Dalgard, O., Bjoro, K., Ring-Larsen, H., Bjornsson, E., Holberg-Petersen, M., Skovlund, E., et al. (2008). Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. *Hepatology*, *47*, 35–42.

Dalgard, O., Bjøro, K., Ring-Larsen, H., & Verbaan, H. (2010). In patients with HCV genotype 2 or 3 infection and RVR 14 weeks treatment is noninferior to 24 weeks. Pooled analysis of two Scandinavian trials. *European Journal of Gastroenterology & Hepatology*, *22*(5), 552–556.

Darke, S., Ward, J., Hall, W., Heather, N., & Wodak, A. (1991). The opiate treatment index (OTI) researcher's manual. *Technical report number 11*. Sydney: National Drug and Alcohol Research Centre.

Desmet, V. J., Gerber, M., Hoofnagle, J. H., Manns, M., & Scheuer, P. J. (1994). Classification of chronic hepatitis: Diagnosis, grading and staging. *Hepatology*, *19*, 1513–1520.

Dimova, R. B., Zeremski, M., Jacobson, I. M., Hagan, H., Des Jarlais, D. C., & Talal, A. H. (2013). Determinants of hepatitis C virus treatment completion and efficacy in drug users assessed by meta-analysis. *Clinical Infectious Diseases*, *56*, 806–816.

Dore, G. J., Hellard, M., Matthews, G. V., Grebely, J., Haber, P. S., Petoumenos, K., et al. (2010). Effective treatment of injecting drug users with recently acquired hepatitis C virus infection. *Gastroenterology*, *138*, 123–135. e121–e122.

Dore, G. J., Altice, F., Litwin, A. H., Dalgard, O., Gane, E. J., Shibolet, O., Luetkemeyer, A., Nahass, R., Peng, C., Conway, B., Grebely, J., Howe, A. Y. M., Gendrano, I. N., Chen, E., Huang, H., Dutko, F. J., Nguyen, B., Wahl, J., Barr, E., Robertson, M. N., & Platt, H. L. (2016). Elbasvir–Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy — A Randomized Trial. *Annals of Internal Medicine*, *165*(9), 625–634.

EASL (2017). EASL recommendations on treatment of hepatitis C 2016. *Journal of Hepatology*, *66*, 153–194.

Grebely, J., Alavi, M., Micallef, M., Dunlop, A. J., Balcomb, A. C., Phung, N., et al. (2016). Treatment for hepatitis C virus infection among people who inject drugs attending opioid substitution treatment and community health clinics: The ETHOS study. *Addiction*, *111*, 311–319.

Grebely, J., Dore, G. J., Zeuzem, S., Aspinall, R. J., Fox, R., Han, L., McNally, J., Osinusi, A., Brainard, D. M., Subramanian, G. M., Natha, M., Foster, G. R., Mangia, A., Sulkowski, M., & Feld, J. J. (2016). Efficacy and safety of sofosbuvir/velpatasvir in patients with chronic hepatitis C virus infection receiving opioid substitution therapy: Analysis of Phase 3 ASTRAL trials. *Clinical Infectious Diseases*, *63*(11), 1479–1481.

Grebely, J., Mauss, S., Brown, A., Bronowicki, J., Puoti, M., Wyles, D., Natha, M., Zhu, Y., Yang, J., Kreter, B., Brainard, D. M., Yun, C., Carr, V., & Dore, G. J. (2016). Efficacy and safety of ledipasvir/sofosbuvir with and without ribavirin in patients with chronic HCV genotype 1 infection receiving opioid substitution therapy: Analysis of Phase 3 ION trials. *Clinical Infectious Diseases*, *63*(11), 1405–1411.

Grebely, J., Raffa, J. D., Meagher, C., Duncan, F., Genoway, K. A., Khara, M., et al. (2007). Directly observed therapy for the treatment of hepatitis C virus infection in current and former injection drug users. *Journal of Gastroenterology and Hepatology*, *22*, 1519–1525.

Grebely, J., Robaeys, G., Bruggmann, P., Aghemo, A., Backmund, M., Bruneau, J., et al. (2015). Recommendations for the management of hepatitis C virus infection among people who inject drugs. *International Journal on Drug Policy*, *26*, 1028–1038.

Hajarizadeh, B., Grebely, J., & Dore, G. J. (2013). Epidemiology and natural history of HCV infection. *Nature Reviews Gastroenterology & Hepatology*, *10*, 553–562.

Hellard, M., Sacks-Davis, R., & Gold, J. (2009). Hepatitis C treatment for injection drug users: A review of the available evidence. *Clinical Infectious Diseases*, *49*, 561–573.

Jensen, D. M., Morgan, T. R., Marcellin, P., Pockros, P. J., Reddy, K. R., Hadziyannis, S. J., et al. (2006). Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *Hepatology*, *43*, 954–960.

Kielland, K. B., Delaveris, G. J., Rogde, S., Eide, T. J., Amundsen, E. J., & Dalgard, O. (2014). Liver fibrosis progression at autopsy in injecting drug users infected by hepatitis C: A longitudinal long-term cohort study. *Journal of Hepatology*, *60*, 260–266.

Lawrinson, P., Copeland, J., & Indig, D. (2003). The brief treatment outcome measure: Opioid maintenance pharmacotherapy (BTOM) manual. *NDARC technical report no. 156*. Sydney: University of New South Wales.

Litwin, A. H., Kunins, H. V., Berg, K. M., Federman, A. D., Heavner, K. K., Gourevitch, M. N., et al. (2007). Hepatitis C management by addiction medicine physicians: Results from a national survey. *Journal of Substance Abuse Treatment*, *33*, 99–105.

Mangia, A., Santoro, R., Minerva, N., Ricci, G. L., Carretta, V., Persico, M., et al. (2005). Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *New England Journal of Medicine*, *352*, 2609–2617.

Manolakopoulos, S., Deutsch, M. J., Anagnostou, O., Karatapanis, S., Tiniakou, E., Papatheodoridis, G. V., et al. (2010). Substitution treatment or active intravenous drug use should not be contraindications for antiviral treatment in drug users with chronic hepatitis C. *Liver International*, *30*, 1454–1460.

Meyer, J. P., Moghimi, Y., Marcus, R., Lim, J. K., Litwin, A. H., & Altice, F. L. (2015). Evidence-based interventions to enhance assessment, treatment, and adherence in the chronic hepatitis C care continuum. *International Journal on Drug Policy*, *26*, 922–935.

Murphy, D. G., Willems, B., Deschenes, M., Hilzenrat, N., Mousseau, R., & Sabbah, S. (2007). Use of sequence analysis of the NS5B region for routine genotyping of hepatitis C virus with reference to C/E1 and 5′ untranslated region sequences. *Journal of Clinical Microbiology*, *45*, 1102–1112.

Myles, A., Mugford, G. J., Zhao, J., Krahn, M., & Wang, P. P. (2011). Physicians' attitudes and practice toward treating injection drug users with hepatitis C: Results from a national specialist survey in Canada. *Canadian Journal of Gastroenterology*, *25*, 135–139.

Robaeys, G., Grebely, J., Mauss, S., Bruggmann, P., Moussalli, J., De Gottardi, A., et al. (2013). Recommendations for the management of hepatitis C virus infection among people who inject drugs. *Clinical Infectious Diseases*, *57*(Suppl. 2), S129–S137.

Sasadeusz, J. J., Dore, G., Kronborg, I., Barton, D., Yoshihara, M., & Weltman, M. (2010). Clinical experience with the treatment of hepatitis C infection in patients on opioid pharmacotherapy. *Addiction*, *106*(5), 977–984.

Sylvestre, D. L., Litwin, A. H., Clements, B. J., & Gourevitch, M. N. (2005). The impact of barriers to hepatitis C virus treatment in recovering heroin users maintained on methadone. *Journal of Substance Abuse Treatment*, *29*, 159–165.

Vezali, E., Aghemo, A., & Colombo, M. (2010). A review of the treatment of chronic hepatitis C virus infection in cirrhosis. *Clinical Therapeutics*, *32*, 2117–2138.

Wai, C. T., Greenson, J. K., Fontana, R. J., Kalbfleisch, J. D., Marrero, J. A., Conjeevaram, H. S., et al. (2003). A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*, *38*, 518–526.

WHO (2016). *Guidelines for the screening care and treatment of persons with chronic hepatitis C infection*. World Health Organization.

Wiessing, L., Ferri, M., Grady, B., Kantzanou, M., Sperle, I., Cullen, K. J., et al. (2014). Hepatitis C virus infection epidemiology among people who inject drugs in Europe: A systematic review of data for scaling up treatment and prevention. *PLoS One*, *9*, e103345.

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