TITLE PAGE

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

Jason Grebely[1], Olav Dalgard[2], Evan Cunningham[1], Behzad Hajarizadeh[1], Graham R Foster[3], Philip Bruggmann[4], Brian Conway[5], Markus Backmund[6], Geert Robaeys[7,8,9], Tracy Swan[10], Janaki Amin[1], Philippa S. Marks[1], Sophie Quiene[1], Tanya L Applegate[1], Martin Weltman[11], David Shaw[12], Adrian Dunlop[13], Margaret Hellard[14], Julie Bruneau[15], Håvard Midgard[2], Stefan Bourgeois[16], Cornelia Staehelin[17], and Gregory J Dore[1] on behalf of the ACTIVATE Study Group

[1]The Kirby Institute, UNSW Australia, Sydney, Australia, [2]Akershus University Hospital, Oslo, Norway, [3]The Liver Unit, Queen Mary University of London, London, United Kingdom,[4]Arud Centres for Addiction Medicine, Zurich, Switzerland, [5]Vancouver Infectious Diseases Center, Vancouver, Canada, [6]Ludwig Maximilians-University Munich, Munich, Germany, [7]Department of Gastroenterology and Hepatology, Ziekenhuis Oost Limburg, Genk, [8]Department of Hepatology, UZ Leuven, Leuven, [9]UHasselt, Hasselt, Belgium, [10]Treatment Action Group, New York, United States, [11]Nepean Hospital, Sydney, [12]Royal Adelaide Hospital, Adelaide, [13]School of Medicine and Public Health, University of Newcastle, Newcastle, [14]Burnet Institute, Melbourne, Australia, [15]Research Center, Centre Hospitalier de l'Universite de Montreal (CRCHUM), Montreal, Canada, [16]Stuivenberg ZNA, Antwerp, Belgium, [17]Department of Infectious Diseases, Bern University Hospital, University of Bern, Bern, Switzerland

Keywords: People who inject drugs, injecting drug use, HCV, therapy, opioid substitution treatment, OST

Corresponding Author:

Jason Grebely, PhD

Associate Professor, Viral Hepatitis Clinical Research Program

The Kirby Institute

UNSW Australia

Phone: +61-2-9385 0957 Fax: +61-2-9385 0876

email: jgrebely@kirby.unsw.edu.au

Word Count: 3,498 words

Running Head: HCV treatment for PWID

Financial Support: Supported in part by a research grant from the Investigator Initiated Studies Program of Merck Sharp &Dohme Corp. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp &Dohme Corp. The Kirby Institute is funded by the Australian Government Department of Health and Ageing. The views expressed in this publication do not necessarily represent the position of the Australian Government. JG is supported by a National Health and Medical Research Council Career Development Fellowship. BH is supported by a National Health and Medical Research Council Early Career Fellowship. MH is supported by a National Health and Medical Research Council Principal Research Fellowship. GD is supported by a National Health and Medical Research Council Practitioner Research Fellowships.

Disclosures: JG is a consultant/advisor and has received research grants from Abbvie, Bristol Myers Squibb, Gilead Sciences and Merck/MSD. OD is a consultant/advisor and has received research grants from Abbvie, Gilead Sciences and Merck/MSD. GRF is a consultant/advisor and has received research grants from Abbvie, Bristol Myers Squibb, Gilead Sciences, Janssen, Roche and Merck/MSD. PB is consultant/advisor and has received research grants from Abbvie, Bristol Myers Squibb, Gilead, Janssen and Merck. BC is consultant/advisor and has received research grants from AbbVie, Gilead and Merck. GR has received research grants from Merck Sharp & Dohme, AbbVie, Janssen Pharmaceuticals, and has acted as a consultant/advisor and for Gilead Sciences, Abbvie, Merck Sharp & Dohme, and Bristol Myers-Squibb. MW is a consultant/advisor for Abbvie, Bristol Myers Squibb, Gilead, Merck, Janssen, Novartis and Roche. MH has received funding from Gilead Sciences, Abbvie and Bristol Myers Squibb for investigator initiated independent research. JB is a consultant/advisor and has received research grants from Gilead Sciences and Merck/MSD. SB is a consultant/advisor and has received research grants from AbbVie, MSD, BMS, Gilead, Janssen. CS has received travel grants through her institution sponsored by Gilead Sciences, Janssen and Merck/MSD. GD is a consultant/advisor and has received research grants from Abbvie, Bristol Myers Squibb, Gilead, Merck, Janssen and Roche.

Abstract (300 words)

Aims: To estimate the efficacy of response-guided therapy for chronic hepatitis C virus (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.

Design: Multicenter 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).

Setting: Three drug treatment clinics, two private practices, nine hospital clinics and three community clinics in Australia (n=5), Canada (n=3), and Europe (n=9).

Participants: 93 people with ongoing injecting drug use or receiving OST were treated for HCV genotype 2/3 infection (23% female).

Measurements: Primary study outcome was sustained virological response (SVR12, undetectable HCV RNA $\geq$12 weeks post-treatment).

Findings: Among 93 treated, 59% had recently injected drugs (past month), 77% were receiving OST and 56% injected drugs during therapy. SVR was 66% (61/93), with no difference observed by sex (males: 68%, females: 80%, P=0.465). SVR was 84% in those with undetectable HCV RNA at week 4 (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.

Conclusions: People with recent injecting drug use or OST with chronic hepatitis C virus (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 (1, 2). 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 (3, 4) and international recommendations support HCV treatment for PWID (5-9). Despite these recommendations, some HCV clinicians remain concerned that adherence, efficacy (including re-infection), and competing morbidity still provides barriers to HCV treatment for PWID (10, 11).

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 programs (12). 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. There is a need for larger, multicenter, 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) (13). Among patients with genotypes 2/3 and an RVR, SVR may be achieved in 80-95% as compared to 50% of those without RVR (13-15).

In patients with genotypes 2/3 and RVR treated for 12-14 weeks, SVR is comparable to 24 weeks of therapy (14-17).

The primary aim of this study was to evaluate the efficacy of response-guided, directly observed 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 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, available with the full text of this article in the Supplementary Material.

Study design and intervention

ACTIVATE was an international, multicentre open-label study. Participants received directly observed pegylated interferon alfa-2b (PEG-IFN, 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 Australia) 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 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 (18).

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 4^{th} 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 (19). Social functioning scores range from 0-18, 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 ≥ 3 and ≥ 4 indicate hazardous consumption or active alcohol use disorders among women and men, respectively) (20).

Stage of liver fibrosis was assessed by liver biopsy (METAVIR) (21), 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 (22). APRI was calculated using aspartate aminotransferase (AST) and platelet count: [(AST [U/L]/upper limit of normal)/platelet count (10^9/L)] × 100. APRI >1.5 and >2.0 defined significant liver fibrosis and cirrhosis, respectively (23).

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% to 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 (Figure 1). The demographic and clinical characteristics of participants included in this study (n=93) are shown in Table 1. The median age was 41 years, 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 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 (Figure 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 $\geq$80% adherent to PEG-IFN therapy and 75% (70/93, 95% CI: 65%, 84%) were $\geq$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 treatment was discontinued or completed) were 99.6% and 90%, 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, Figure 2A), 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 Figure 2B, 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 95% (58/61) 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=13), 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; Figure 2B), 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, Figure 2B), 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, Figure 2B), 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 therapy. Among people with post-treatment failure (n=2, Figure 2B), the only reason for failure was viral relapse (n=2). The proportion with viral relapse was 17% (2/12).

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. 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 $\geq$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% Confidence Interval (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, 12% (n=11) discontinued treatment prematurely because of an adverse event (Table 4). A total of 24% (n=22) 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 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% (4). 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 interferon-based HCV therapy (13). 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 (13-15), 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 (14-16). 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 (17). 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 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 (24).

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%) (25) or people with ongoing injecting drug use (78%) (4). 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 (26-32). Given the retrospective nature and small sample sizes of previous studies to date, these data from this prospective international clinical trial are important to contribute to international guidelines already recommending HCV treatment among PWID (5-8, 33). 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 (34).

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. Therefore, the study population may be more engaged in health services. 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) (35). Given that this population has generally been excluded from large randomized clinical trials, this study provides important data supporting treatment recommendations for PWID (5-9).

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. 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.

References

1. HAJARIZADEH B., GREBELY J., DORE G. J. Epidemiology and natural history of HCV infection, Nat Rev Gastroenterol Hepatol 2013: 10: 553-562.
2. KIELLAND K. B., DELAVERIS G. J., ROGDE S., EIDE T. J., AMUNDSEN E. J., DALGARD O. Liver fibrosis progression at autopsy in injecting drug users infected by hepatitis C: a longitudinal long-term cohort study, J Hepatol 2014: 60: 260-266.
3. HELLARD M., SACKS-DAVIS R., GOLD J. Hepatitis C treatment for injection drug users: a review of the available evidence, Clin Infect Dis 2009: 49: 561-573.
4. ASPINALL E. J., CORSON S., DOYLE J. S., GREBELY J., HUTCHINSON S. J., DORE G. J. et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis, Clin Infect Dis 2013: 57 Suppl 2: S80-89.
5. ROBAEYS G., GREBELY J., MAUSS S., BRUGGMANN P., MOUSSALLI J., DE GOTTARDI A. et al. Recommendations for the management of hepatitis C virus infection among people who inject drugs, Clin Infect Dis 2013: 57 Suppl 2: S129-137.
6. AASLD/IDSA. Recommendations for testing, managing, and treating hepatitis C; 2015.
7. WHO. Guidelines for the screening, care and treatment of persons with hepatitis C infection., Geneva, Switzerland: World Health Organization 2014.
8. EUROPEAN ASSOCIATION FOR STUDY OF L. EASL Clinical Practice Guidelines: management of hepatitis C virus infection, J Hepatol 2014: 60: 392-420.
9. GREBELY J., ROBAEYS G., BRUGGMANN P., AGHEMO A., BACKMUND M., BRUNEAU J. et al. Recommendations for the management of hepatitis C virus infection among people who inject drugs, Int J Drug Policy 2015: 26: 1028-1038.
10. MYLES A., MUGFORD G. J., ZHAO J., KRAHN M., WANG P. P. Physicians' attitudes and practice toward treating injection drug users with hepatitis C: results from a national specialist survey in Canada, Can J Gastroenterol 2011: 25: 135-139.
11. LITWIN A. H., KUNINS H. V., BERG K. M., FEDERMAN A. D., HEAVNER K. K., GOUREVITCH M. N. et al. Hepatitis C management by addiction medicine physicians: results from a national survey, Journal of substance abuse treatment 2007: 33: 99-105.
12. MEYER J. P., MOGHIMI Y., MARCUS R., LIM J. K., LITWIN A. H., ALTICE F. L. Evidence-based interventions to enhance assessment, treatment, and adherence in the chronic Hepatitis C care continuum, Int J Drug Policy 2015: 26: 922-935.
13. JENSEN D. M., MORGAN T. R., MARCELLIN P., POCKROS P. J., REDDY K. R., HADZIYANNIS S. J. et al. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy, Hepatology 2006: 43: 954-960.
14. MANGIA A., SANTORO R., MINERVA N., RICCI G. L., CARRETTA V., PERSICO M. et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3, N Engl J Med 2005: 352: 2609-2617.
15. DALGARD O., BJORO K., RING-LARSEN H., BJORNSSON E., HOLBERG-PETERSEN M., SKOVLUND E. et al. 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 (Baltimore, Md 2008: 47: 35-42.
16. DALGARD O., BJORO K., HELLUM K. B., MYRVANG B., RITLAND S., SKAUG K. et al. Treatment with pegylated interferon and ribavarin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study, Hepatology 2004: 40: 1260-1265.

17. DALGARD O., BJØRO K., RING-LARSEN H., VERBAAN H. In patients with HCV genotype 2 or 3 infection and RVR 14 weeks treatment is non-inferior to 24 weeks. Pooled analysis of two Scandinavian trials 2009: In Press.
18. MURPHY D. G., WILLEMS B., DESCHENES M., HILZENRAT N., MOUSSEAU R., SABBAH S. 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 2007: 45: 1102-1112.
19. WIESSING L., FERRI M., GRADY B., KANTZANOU M., SPERLE I., CULLEN K. J. et al. 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 2014: 9: e103345.
20. BUSH K., KIVLAHAN D. R., MCDONELL M. B., FIHN S. D., BRADLEY K. A. 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 1998: 158: 1789-1795.
21. DESMET V. J., GERBER M., HOOFNAGLE J. H., MANNS M., SCHEUER P. J. Classification of chronic hepatitis: diagnosis, grading and staging, Hepatology 1994: 19: 1513-1520.
22. CASTERA L., FORNS X., ALBERTI A. Non-invasive evaluation of liver fibrosis using transient elastography, Journal of hepatology 2008: 48: 835-847.
23. WAI C. T., GREENSON J. K., FONTANA R. J., KALBFLEISCH J. D., MARRERO J. A., CONJEEVARAM H. S. et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C, Hepatology 2003: 38: 518-526.
24. VEZALI E., AGHEMO A., COLOMBO M. A review of the treatment of chronic hepatitis C virus infection in cirrhosis, Clinical therapeutics 2010: 32: 2117-2138.
25. DIMOVA R. B., ZEREMSKI M., JACOBSON I. M., HAGAN H., DES JARLAIS D. C., TALAL A. H. Determinants of hepatitis C virus treatment completion and efficacy in drug users assessed by meta-analysis, Clin Infect Dis 2013: 56: 806-816.
26. DORE G. J., HELLARD M., MATTHEWS G. V., GREBELY J., HABER P. S., PETOUMENOS K. et al. Effective treatment of injecting drug users with recently acquired hepatitis C virus infection, Gastroenterology 2010: 138: 123-135 e121-122.
27. GREBELY J., RAFFA J. D., MEAGHER C., DUNCAN F., GENOWAY K. A., KHARA M. et al. Directly observed therapy for the treatment of hepatitis C virus infection in current and former injection drug users, J Gastroenterol Hepatol 2007: 22: 1519-1525.
28. SYLVESTRE D. L., LITWIN A. H., CLEMENTS B. J., GOUREVITCH M. N. The impact of barriers to hepatitis C virus treatment in recovering heroin users maintained on methadone, J Subst Abuse Treat 2005: 29: 159-165.
29. SASADEUSZ J. J., DORE G., KRONBORG I., BARTON D., YOSHIHARA M., WELTMAN M. Clinical Experience with the Treatment of Hepatitis C Infection in Patients on Opioid Pharmacotherapy, Addiction (Abingdon, England) 2010.
30. MANOLAKOPOULOS S., DEUTSCH M. J., ANAGNOSTOU O., KARATAPANIS S., TINIAKOU E., PAPATHEODORIDIS G. V. et al. Substitution treatment or active intravenous drug use should not be contraindications for antiviral treatment in drug users with chronic hepatitis C, Liver Int 2010: 30: 1454-1460.
31. BRUGGMANN P., FALCATO L., DOBER S., HELBLING B., KEISER O., NEGRO F. et al. Active intravenous drug use during chronic hepatitis C therapy does not reduce sustained virological response rates in adherent patients, J Viral Hepat 2008: 15: 747-752.

32. GREBELY J., ALAVI M., MICALLEF M., DUNLOP A. J., BALCOMB A. C., PHUNG N. et al. Treatment for hepatitis C virus infection among people who inject drugs attending opioid substitution treatment and community health clinics: the ETHOS Study, Addiction 2016: 111: 311-319.
33. GREBELY J. E. A. Recommendations for the management of hepatitis C virus infection among people who inject drugs Int J Drug Policy 2015: In Press.
34. ALAVI M., SPELMAN T., MATTHEWS G. V., HABER P. S., DAY C., VAN BEEK I. et al. Injecting risk behaviours following treatment for hepatitis C virus infection among people who inject drugs: The Australian Trial in Acute Hepatitis C, Int J Drug Policy 2015.
35. BARUA S., GREENWALD R., GREBELY J., DORE G. J., SWAN T., TAYLOR L. E. Restrictions for Medicaid Reimbursement of Sofosbuvir for the Treatment of Hepatitis C Virus Infection in the United States, Annals of internal medicine 2015: 163: 215-223.

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)†	27 (5.7)†	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)†	6 (10)†	6 (23)
Social functioning score, median (25%, 75%)	17 (13-21)†	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)†	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)‡	11 (19)¥	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)

[¥]3 missing values, [‡]4 missing values, [†]1 missing value

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)	58 (95)	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)	99.6 (1.7)	99.7 (1.4)	99.1 (2.3)
On-treatment ribavirin adherence, mean % (SD)	90.0 (25.9)	98.4 (5.4)	87.5 (24.0)
PEG-IFN dose-modification	9 (10)	3 (5)	6 (23)
Ribavirin dose-modification	21 (23)	12 (20)	9 (35)

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)*	*P*	Adjusted OR (95% CI)*	*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**		
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†		
Unknown	0 (0)	1 (100)	-	-		

* The models were adjusted for study site, using cluster-robust standard errors

** Fisher exact test, comparing the distribution of SVR between those with <80% PEG-IFN adherence and those with ≥80%

† n=86; One participant with unknown injecting status during therapy was not included in the analysis

Table 4. Discontinuations and Adverse Events.

Characteristic, n (%)	Overall (n=93)	Shortened therapy (n=60)	Standard therapy (n=27)
Treatment discontinuation due to an adverse event	10 (11)	1 (2)	6 (23)
Serious adverse event	22 (24)	10 (16)	6 (23)
Any adverse event	91 (98)	60 (100)	26 (98)
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)

Figure 1. Participant disposition.

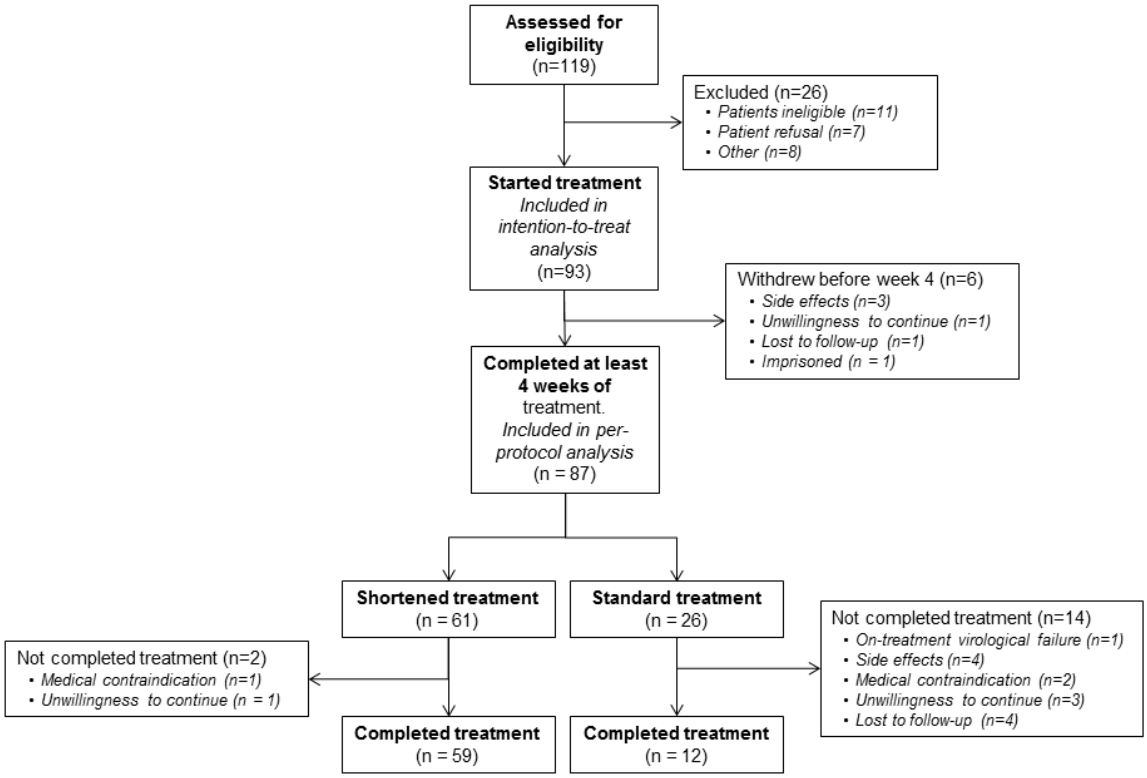
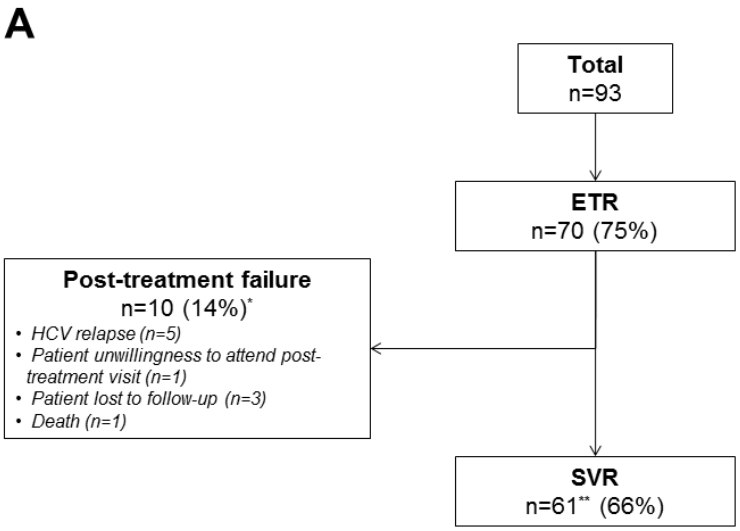
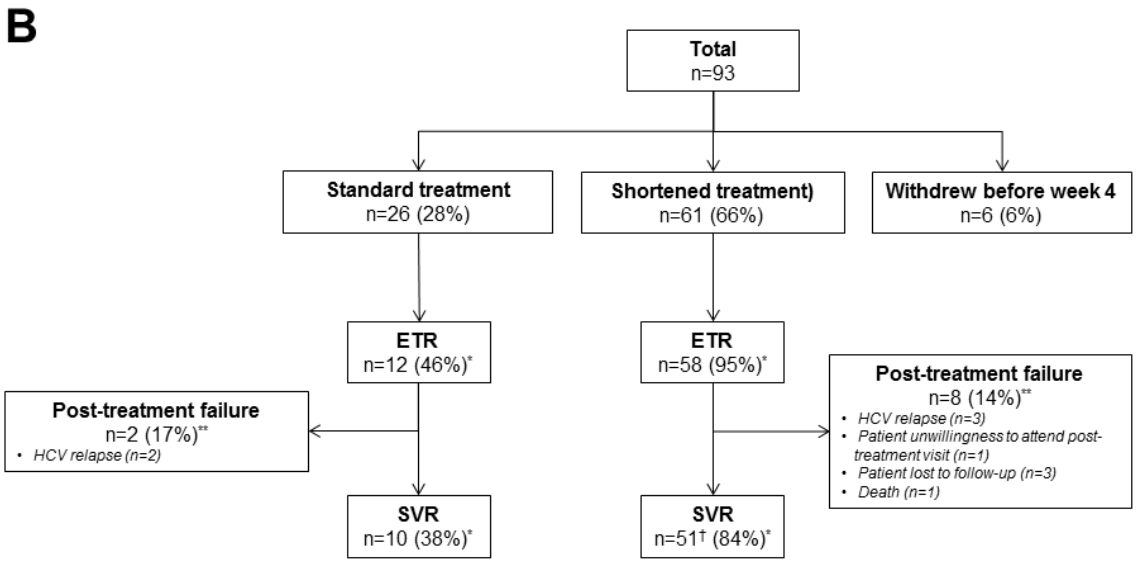


Figure 2. Overview of response to treatment in ACTIVATE A) overall and B) by treatment arm.



** 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).*



** 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).