**TITLE PAGE**

# Sofosbuvir and velpatasvir for HCV in people with recent injecting drug use: An open-label, multicentre single arm trial

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**Abstract**

**Background:** The aim of this study was to evaluate the efficacy of sofosbuvir and velpatasvir therapy in people with recent injecting drug use. **Methods:** SIMPLIFY is an international open-label, single-arm multicentre study that recruited participants with recent injecting drug use (previous six months) and chronic HCV genotype (G) 1-6 infection between March and October, 2016 in seven countries (19 sites) (ClinicalTrials.gov: NCT02336139). Participants received sofosbuvir/velpatasvir once-daily for 12 weeks administered in a one-week electronic blister pack (records the time and date of each dose) for 12 weeks. The primary study endpoint was sustained virologic response (SVR12, HCV RNA <12 IU/mL at post-treatment week 12) analysed by intent-to-treat analyses. This study is ongoing to evaluate the secondary endpoint of HCV reinfection. **Findings:** Among the 103 participants that commenced therapy, 29 (28%) were female, 9 (9%) had cirrhosis, 36 (35%) had HCV genotype 1, 5 (5%) had genotype 2, 60 (58%) had genotype 3, and 2 (2%) had genotype 4. Overall, 61 (59%) were receiving OST, 76 (74%) injected in the past month, and 27 (26%) injected ≥daily in the past month. Treatment completion was observed in 100 of 103 (97%). There were no virological failures, but three discontinuations (loss to follow-up, n=2; overdose death, n=1). Overall, SVR was 94% (97 of 103, 95% CI, 88%-98%). Three participants with an end of treatment response did not have SVR (loss to follow-up, n=2; reinfection, n=1). Drug use prior to and during treatment did not impact SVR12. Treatment-related adverse events occurred in 47 (46%) patients [1 (1%) grade 3, no grade 4]. Seven (7%) patients had 9 serious adverse events: only one (rhabdomyolysis, resolved) was assessed to be possibly related. There was one death due to illicit drug overdose during treatment, which was assessed to unlikely to be related to treatment. One case of HCV reinfection was observed (38 person-years of follow-up; reinfection rate, 2.7 cases per 100 person-years; 95% CI, 0.1-13.8). **Interpretation:** The clinical implications of these findings

are that HCV treatment should be offered to recent PWID, irrespective of ongoing drug use. Also, recent injecting drug use should not be used as a reason for withholding reimbursement of HCV therapy.

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## RESEARCH IN CONTEXT

*Evidence before this study*

We searched PubMed and Scopus up to October 18, 2017 with the search terms "hepatitis C" or "HCV" in combination with the roots, "direct acting antiviral*", "direct-acting antiviral*", "DAA", "interferon free", "interferon-free", "IFN free", "IFN-free", "inject drug*", "injecting drug*", "drug inject*", "drug use*", "PWID", "opioid substitution*", "OST", "opioid agonist*", "OAT", "methadone therap*", "methadone treat*", or "MMT". No language or date restrictions were specified. The references of identified articles were manually searched for further relevant papers. Key abstracts at international meetings were also considered. Collectively, data demonstrate that adherence and response to DAA therapy among people who inject drugs (PWID) receiving opioid substitution therapy (OST) in clinical trials are comparable to populations without a history of injecting drugs. However, there are no international studies evaluating HCV treatment outcomes among people with recent injecting drug use in the previous six months.

*Added value of this study*

The findings from this study demonstrated that patients with HCV infection and recent injecting drug use treated with once-daily sofosbuvir and velpatasvir administered once-weekly had high rates of SVR12, regardless of ongoing injecting drug use. Further, this study utilizes a novel electronic blister-pack to monitoring adherence to therapy, thereby providing better insight into adherence among people with recent injecting drug use. To our knowledge, this is the first international study to evaluate DAA therapy and the rate of HCV reinfection following DAA therapy among recent PWID.

*Implications of all the available evidence*

These data demonstrate that people with receiving OST and people with recent injecting drug use respond favourably to DAA therapy with sofosbuvir and velpatasvir, irrespective of drug use prior to or during treatment. Many countries, including the United States, still have restrictions against the reimbursement of DAA therapy for people with recent injecting drug use (with varying definitions of what constitutes recent), which has effectively excluded this group from accessing treatment. Even in settings where reimbursement restrictions for recent PWID do not exist, many practitioners are still reluctant to prescribe DAA therapy for people with recent injecting drug use, given concerns of poor adherence, response to therapy, and risk of reinfection. However, this is not consistent with international guidelines recommending DAA therapy for PWID and suggesting that PWID should be prioritized given the potential to reduce transmission. Given that recent PWID represent 23% of all new infections globally, HCV treatment must be increased among PWID as part of efforts to eliminate HCV. These data provide important evidence supporting HCV treatment among recent PWID and has the potential to change clinical practice and health policy globally.

## INTRODUCTION

Globally, an estimated 71 million people have chronic hepatitis C virus (HCV) infection.[1] The prevalence of chronic HCV infection is 39% among people who have recently injected drugs (PWID), representing an estimated 6.1 million people with chronic HCV infection (8% of global infections).[2] There is also a large, but unquantified, burden among PWID who have ceased injecting.[3,4] Enhanced access to DAA therapy among PWID will be critical to achieve the WHO targets to eliminate HCV as a major public health threat by 2030.

Post-hoc analyses of phase 3 clinical trials have demonstrated that sustained virologic response (SVR) following direct-acting antiviral (DAA) therapy is similar in people receiving and not receiving opioid substitution therapy (OST).[5-9] In a phase III trial of people receiving grazoprevir-elbasvir with no previous treatment experience and HCV genotypes 1, 4 or 6 on stable OST, the ITT SVR was 91%.[10] However, only 25% reported injecting drug use within the previous six months.[10] Also, patients infected with HCV genotype 3 (G3) were excluded from these studies. Globally, the prevalence of HCV GT3 is higher among PWID compared to non-PWID (39% vs. 25%).[11] Data on HCV treatment outcomes across all genotypes among recent PWID are needed to guide clinical management and support expanded access to treatment.

In the United States and Europe, there are some jurisdictions with restrictions for the reimbursement of DAA therapy for people with recent illicit drug/alcohol use, or those receiving OST, irrespective of disease stage.[12,13] An argument used for restricting access has been the lack of data on DAA treatment outcomes in these populations.

The combination of sofosbuvir, a nucleotide analogue NS5B polymerase inhibitor, and velpatasvir, a NS5A inhibitor, for 12 weeks result in high rates of SVR and is approved for the treatment of HCV genotypes 1-6.[14,15]

We present the results of an international multicentre, open-label phase IV trial evaluating the efficacy and safety of sofosbuvir-velpatasvir for 12 weeks in patients infected with HCV genotypes 1-4 with recent injecting drug use (last six months).

## METHODS

*Study design and participants*

Participants were enrolled at 19 sites in Australia (n=7), Canada (n=6), New Zealand (n=1), Norway (n=1), Switzerland (n=2), the United Kingdom (n=1), and the United States (n=1) (SIMPLIFY, ClinicalTrials.gov: NCT02336139). Study recruitment was conducted through a network of drug treatment clinics (n=3), hospital clinics (n=12), private practice (n=1), and community clinics (n=3)[16] All patients provided written informed consent.

Participants had to be ≥18 years of age, have chronic HCV genotypes 1-6 (but no patients with genotype 5 or 6 were enrolled), be naïve to NS5A-based HCV therapy, and have recent injecting drug use (self-reported injecting drug use within six months of enrolment). Participants with HIV infection and/or decompensated liver disease were excluded. Full eligibility criteria are provided in the study protocol, available with the full text of this article in the (see appendix p8).

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. An independent data and safety monitoring board reviewed the progress of the study.

*Procedures*

In this international, multicentre open-label phase IV trial, patients with HCV genotypes 1-4 received a fixed-dose combination tablet containing 400 mg of sofosbuvir and 100 mg of velpatasvir, administered orally once daily for 12 weeks. The trial was originally designed as a phase II study prior to registration of the study medications (as stated in the study protocol on appendix p8). Participants received all medication weekly in an electronic blister pack (Information Mediary Corp, Ottawa, Canada) with an integrated sensor grid that recorded the time and date that each daily dose was punched out of the blister pack, indicative of medication adherence. Information on adherence was downloaded using a specific reader following the return of the blister pack (participants received the equivalent of AUS$10 incentive to return the blister pack).

Participants attended study visits at screening, enrollment/baseline (treatment initiation), and weeks 2, 4, 8, and 12 (end of treatment) of therapy. Participants also attended weekly to receive their medication in the electronic blister pack. Participants also attended visits at weeks 16 (SVR4), week 24 (SVR12), and week 36 (SVR24) post-treatment. The study also has visits planned for every 6 months for up to two years following the end of treatment (week 60, week 84, and week 108) to evaluate HCV reinfection incidence and injecting risk behavior, although these study visits were not included in this analysis. Study nurses and physicians provided risk reduction and provision of harm reduction services (e.g. access to needles/syringes, other injecting equipment, and OST) as per standard of care in their country.

Enrollment assessments included HCV RNA, HCV genotype, standard laboratory and clinical testing, Transient Elastography [FibroScan®] (where available), and self-reported behavioural questionnaires on tablet computer. Assessments during treatment included physical examinations, measurements of HCV RNA levels (performed at local laboratories), and

standard laboratory testing. All adverse events were recorded and graded according to MedDRA.

HCV RNA levels for evaluation of the primary endpoint (SVR12) were measured on stored plasma samples tested centrally with the Abbott RealTime HCV Viral Load assay (Abbott Molecular, lower limit of quantification of 12 IU/mL). Central HCV RNA testing was performed on samples collected at baseline, week 12 (end of treatment), week 24 (SVR12), and at most recent available. HCV genotype/subtype was determined by sequencing the NS5B region.

Adherence to sofosbuvir-velpatasvir was measured using an electronic blister-pack. Adherence was calculated by dividing the number of total doses received during therapy by the total expected number of doses. Given that the portion with adherence was not normally distributed, the median adherence to therapy was calculated (e.g. the mid-point adherence). Among individuals in whom therapy was extended due to intermittent treatment interruption, adherence was calculated as the proportion of doses received divided by the total number of weeks of total therapy.

Participants completed a self-administered questionnaire on tablet computer at enrolment, at baseline (treatment commencement), every 4$^{th}$ week during treatment, and at 12 weeks post-treatment follow-up (participants received the equivalent of AUS$20 reimbursement for their time). The questionnaires collected information on demographics (age, gender, ethnicity, employment status, education level, housing status), drug and alcohol use, injecting risk behaviours, drug treatment, and health utility. Stable housing was defined as living in a rented or privately owned house or flat. 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 (women) and ≥ 4 (men) indicate hazardous consumption or active alcohol use disorders]. Health utility was evaluated using the EQ-5D-3L and is not presented in this primary analysis (it will be the focus of a future secondary analysis).

Stage of liver fibrosis was assessed by liver stiffness measurement (Transient Elastography [FibroScan®]). For liver stiffness measurements, the chosen cut-offs for significant liver fibrosis and cirrhosis were 7.1 kPa and 12.5 kPa, respectively.

*Outcomes*

The primary efficacy endpoint was the proportion of participants with a SVR12, defined as an HCV RNA level below the limit of quantification 12 weeks after the end of treatment in all participants who received at least one dose of sofosbuvir-velpatasvir. If HCV RNA had not been assessed at SVR12, the result of the next available HCV RNA assessment was used to calculate SVR. Secondary endpoints included treatment completion, treatment adherence, severe adverse events, treatment discontinuations because of adverse events, and HCV reinfection. Sanger sequencing of the NS5A, NS5B, and Core-E2 region was performed for all patients with virologic recurrence in samples at baseline and at virologic recurrence, with sequences compared using validated genetic distance-based cut-offs to distinguish viral relapse (homologous virus) from reinfection (heterologous virus).[17,18]

*Statistical analysis*

The primary aim of this study was to evaluate the efficacy of sofosbuvir-velpatasvir for 12 weeks in patients infected with HCV genotypes 1-4 with recent injecting drug use. Secondary

aims included evaluating predictors of HCV treatment response, adherence to HCV therapy, ongoing drug use during treatment, and safety.

A total of 100 participants were planned for enrolment and evaluation as the intention-to-treat population. This study population was chosen to provide a precise measure of treatment response and evaluate the feasibility of recruitment of recent PWID through the multinational network. Assuming an overall SVR of 90%, the 95% confidence intervals (CI) around this estimate was expected to be 82% to 95%.

We used the Clopper-Pearson method to calculate point estimates and two-sided 95% exact confidence intervals for the proportion with SVR for the sofosbuvir-velpatasvir group overall, as well as according to HCV genotype, and various subgroups.

Factors hypothesized to be associated with SVR were determined based on factors previously shown or hypothesized to be associated with HCV treatment response including age (stratified by median), sex, current OST, recent (past month) injecting drug use at baseline (including heroin, cocaine, methamphetamine, and other opioids), ongoing injecting drug use during therapy, frequency of injecting drug use, alcohol use, presence of cirrhosis, and $\geq$90% adherence to therapy. Unadjusted logistic regression was performed to evaluate predictors of SVR.

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). The study was registered with clinicaltrials.gov registry (NCT02336139).

*Role of the Funding source*

The study (including study medications) was funded by a research grant from Gilead Sciences. The sponsor (The Kirby Institute, UNSW Sydney) designed the study, collected the data, managed study samples, monitored study conduct and performed the statistical analysis.

## RESULTS

### *Participant characteristics*

Of 114 participants screened for enrolment, 103 were enrolled between March 29, 2016 and October 31, 2016 and initiated sofosbuvir-velpatasvir therapy (Figure 1). The characteristics of participants included in this study are shown in Table 1. The median age was 48 years (IQR, 41-53), 29 (28%) were female, 9 (9%) had cirrhosis. The genotype distribution included 36 (35%) with genotype 1, 5 (5%) with genotype 2, 60 (58%) with genotype 3, and 2 (2%) with genotype 4. There were no participants with HCV genotype 5 or 6 enrolled.

At baseline, 76 (74%) had injected drugs in the past month, 27 (26%) had injected drugs ≥daily in the past month, and 61 (59%) were receiving OST (Table 1). The most commonly injected drugs were heroin in 57 (55%), methamphetamines in 31 (30%), and other opioids in 22 (21%). Drug use remained stable throughout treatment (Figure 2).

### *Overall HCV treatment completion, adherence and outcomes*

Among all participants enrolled, 100 (97%) completed twelve weeks of treatment. Of the three not completing treatment (Figure 1), two people discontinued due to loss to follow-up (one following baseline, and one at week eight) and one person died from a drug overdose at week three.

The overall median adherence (e.g. the mid-point) was 94% (IQR, 88%-98%). Overall, 66% of participants were ≥90% adherent to therapy (68 of 103, 95% CI: 66%, 75%). As shown in Figure 3, there was considerable variation in adherence as measured by electronic blister pack. Overall, 29 participants had therapy extended due to intermittent treatment interruption (median 1 day; 25% 1 day, 75% 2 days; range 1 to 7 days).

In ITT analysis, 96% (99 of 103, 95% CI: 90%, 99%) had an ETR and 94% (97 of 103, 95% CI: 88%, 98%) had an SVR. Among those who completed treatment, but did not achieve an SVR (n=3), reasons for not achieving an SVR included lost to follow-up (n=2, including one person who completed treatment, but did not have a sample taken at ETR) and reinfection (n=1). There were no cases of virological failure or relapse observed.

***Predictors of SVR***

The proportion with SVR stratified by key characteristics is shown in Figure 4 and appendix p1. Unadjusted analyses of factors associated with SVR are shown in appendix p2. SVR was the same among those with (n=76) and without (n=27) recent (past month) injecting drug use at baseline (95% vs. 93%, *P*=0.684). There was no difference in SVR among those with <daily and ≥daily injecting drug use (94% vs. 96%, *P*=0.584). The SVR was also similar among those with (n=83) and without (n=18) ongoing injecting drug use during HCV therapy (96% vs. 94%, *P*=0.704). The SVR was also similar among participants who were ≥90% adherent to therapy, compared to those <90% adherent to therapy (96% vs. 91%, *P*=0.371). 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, stable housing and alcohol consumption were not associated with SVR (see appendix p2). There were no factors associated with reduced SVR (see appendix p2). Although multivariate logistic regression was intended, the high SVR and lack of factors identified in unadjusted analyses precluded the ability for adjusted analyses.

***Safety***

Of the 103 participants enrolled, A total of 78 (76%) of participants experienced at least one adverse event [related to treatment: 47 (46%) grades 1-2; 1 (1%) grade 3; no grade 4) and 7 (7%) participants experienced at least one serious adverse event (none directly related to treatment) (Table 2). The most common adverse events were fatigue in 23 (22%), headache in 19 (18%), nausea in 14 (14%), insomnia in 9 (9%), and arthralgia in 6 (6%). There were four deaths in the study [60 person-years follow-up; mortality incidence; 6.7 cases per 100 person-years (95% CI, 1.8, 16.2]. During treatment (week 2), one death due to an illicit drug overdose unrelated to treatment occurred among a participant from Australia (Table 2). There were three deaths (Australia, n=1, Canada, n=2) following treatment, all due to illicit drug overdose [occurred following SVR12 (n=2) and SVR24]. The overall incidence of mortality for the four people that died was.

***Reinfection***

One case of HCV reinfection was observed (38 person-years follow-up; reinfection rate, 2.6 cases per 100-person-years, 95% CI, 0.1-13.8). The overall median follow-up time following end of treatment was 12 weeks (IQR, 12-24 weeks). This person with reinfection was a 55 year-old male who reported injecting morphine 2-3 times most days in the last month at baseline. He was infected with HCV genotype 1a prior to initiating therapy, was negative at ETR, and had recurrent viraemia with HCV genotype 1a at SVR12. During treatment this participant reported ongoing injecting morphine (frequency of >3 times per day) at the end of treatment, but reported using sterile injecting equipment for all injections. Sequencing and phylogenetic analysis was consistent with reinfection with HCV genotype 1a (nucleotide divergence NS5A, 10.1%; NS5B, 4.6%; Core-E2, 12.0%).

## DISCUSSION

In this international multicenter, open-label phase IV study, the proportion with sustained virologic response following treatment with sofosbuvir-velpatasvir among people with injecting drug use in the last six months was 94%, irrespective of injecting drug use prior to or during therapy. Median adherence to once-daily therapy was 94%. Treatment was well-tolerated, with no impact on injecting risk behaviours. These data provide evidence to inform international guidelines in the management of HCV infection among recent PWID, and support the removal of restrictions for the reimbursement of DAA therapy among people with HCV infection and recent injecting drug use that are in place in many settings.

The overall SVR of 94% among people with injecting drug use in the last six months is consistent with clinical trials among PWID receiving OST.[5-9] However, previous clinical trials either did not include people with recent injecting drug use,[5-7] or included only a subset of people with recent injecting drug use.[8] Among studies including people with recent injecting drug use, including clinical trials[8] and real-world cohorts,[19-21] heterogeneous definitions of recent injecting drug use have been used. Although some of these studies have demonstrated lower SVR in intent-to-treat analyses than observed in phase 3 clinical trials, the majority of non-response was related to loss to follow-up between ETR and SVR12 and not virological failure or relapse. It is also striking that there were no cases of virological failure during treatment in the SIMPLIFY study.

In the SIMPLIFY study, treatment completion was similar to results reported in phase 3 studies of once-daily DAA therapy among people without recent injecting drug use.[5-9] Adherence $\geq$90% was somewhat lower among people with recent injecting drug use in the SIMPLIFY study (66%) compared to phase III clinical trials among people stable on OST or people who

had not used injecting drugs (88-97%).[5-9] However, the methods for evaluation of adherence in clinical trials often relied on the return of medication pill bottles, which likely overestimated the reported adherence in these studies. It is possible that the requirement for once-weekly clinic visits with a medical practitioner and the provision of therapy in a weekly electronic blister pack led to improved adherence in the SIMPLIFY study. Irrespective of this, there was no impact of adherence on SVR in this study, with no cases of virologic failure or viral relapse.

Injecting and non-injecting drug use remained stable prior to and during HCV therapy. This is consistent with previous results observed in the setting of interferon-based therapy[22-24] for people with either recent injecting or receiving OST and elbasvir/grazoprevir therapy for people stable on OST.[8] Importantly, recent injecting drug use prior to or during therapy did not impact SVR.[8]

Only one case of HCV reinfection was observed in this study, resulting in an incidence of 2.7 (95% CI, 0.1-13.8) per 100 person-years. Although the follow-up was short (38 person-years), this rate is consistent with previous studies of people followed after treatment with interferon-based therapies (0.0 to 5.3 per 100 person-years)[22,25-29] and the C-EDGE CO-STAR study of DAA therapy with elbasvir/grazoprevir (2.3 per 100 person-years).[30] Higher rates of reinfection have been observed among people with ongoing[22,26,28] or frequent injecting drug use.[28] Long-term follow-up to three years from treatment initiation is underway for the SIMPLIFY study and further studies of reinfection will be crucial for better understanding the long-term reinfection risk among recent PWID.

Treatment with sofosbuvir-velpatasvir was well-tolerated in this study. There were four deaths during the study period due to illicit drug overdose (6.7 per 100 person-years), clearly

highlighting the drug use co-morbidity mortality risk among this population. It is critical that HCV care is integrated within a framework that also addresses drug-related harms, prevents overdose mortality, addresses social inequalities, and improves drug user health for PWID,

This study has a number of limitations. Participants were recruited from hospital-based HCV clinics, community-based drug treatment clinics, and community health centres with experience in HCV care, and 10% of participants who were assessed for eligibility were not enrolled in the study. Also, HIV-infected people were excluded from this study due the absence of phase 2 and 3 data on sofosbuvir and velpatasvir therapy among people with HIV infection at the time this study was conceived. As such, the study population may not be generalizable to all populations of people with recent injecting drug use and probably reflects a population more engaged in health services. However, among enrolled participants, the population was highly marginalized (74% injected drugs in the last 30 days, and 26% injected drugs $\geq$daily). Although information on drug use risk behaviours were self-reported, and may be prone to response bias and socially desirable responses, self-reported information on drug use has been shown to be reliable and valid.[31] Also, computer-assisted surveys provide greater confidentiality and may elicit more reliable and valid responses than face-to-face interviews.[32] Participants attended the clinic weekly (providing the opportunity to interact with providers) and received their medication in a once-weekly blister pack (including compensation for returning the pack). It is possible that more frequent clinical visits and the incentive for returning the blister pack may have led to improved adherence and treatment completion. However, this study was not designed to evaluate the impact of participant incentives on SVR12. A recent study to evaluate the impact of incentives on SVR12 among people with a history of injecting drug use is underway.[33] In clinical practice, the frequency of clinical follow-up and adherence support requirements should be determined on a case by case basis, taking

into consideration an individual's social circumstances and medical co-morbidities. This study was powered to provide a reasonably precise measure of treatment response and evaluate the feasibility of recruitment of recent PWID through the multinational network. Given the high rate of treatment success (SVR) in the study, we were underpowered to determine factors associated with success/failure. Lastly, for this planned primary analysis, participants were only followed for up to 24 weeks following treatment to evaluate SVR12, hence the conclusions regarding the rate of reinfection should be interpreted with caution. As part of the SIMPLIFY study, further follow-up is ongoing up to two years following treatment to provide a long-term evaluation of HCV reinfection in this study population.

Many countries, including the United States (although this varies by state), still have restrictions against the reimbursement of DAA therapy for people with recent injecting drug use.[12,13] Even in settings where reimbursement restrictions for recent PWID do not exist, many practitioners are reluctant to prescribe DAA therapy for people with recent injecting drug use.[7] In a 2016 study of HCV practitioners (72% were gastroenterology and hepatology specialists), only 15% were willing to treat people currently injecting drugs with all-oral DAA regimens.[34] Reinfection, adherence and medication cost were cited as the most important concerns when determining candidacy.[34] However, this is not consistent with international guidelines from the American Association for the Study of Liver Disease/Infectious Diseases Society of America, the European Study for the Association of the Liver, the International Network for Hepatitis in Substance Users, and the World Health Organization, all of whom recommend DAA therapy for PWID[35-39] and suggest PWID should be prioritized given the potential to reduce transmission.[40]

Given that recent PWID represent 23% of all new infections globally,[41] HCV treatment must be increased among PWID as part of efforts to eliminate HCV. WHO has set an ambitious goal to eliminate HCV as a major public health threat by 2030. [41] Between 2015 and 2030, the WHO targets include reducing new HCV infections by 80%, and the number of HCV deaths by 65%, and increasing HCV diagnoses from 20% to 90% and the number of eligible persons receiving HCV treatment from 10% to 80%.[41] Modelling studies suggest that scale-up of HCV treatment (4-8 per 100 PWID per year) could lead to substantial reductions in HCV incidence and prevalence.[40,42] Also, treatment of PWID with moderate or mild fibrosis with DAAs is also cost-effective compared with delaying treatment until cirrhosis.[43]

Data from the SIMPLIFY study provides evidence demonstrating high adherence and SVR among people with injecting drug use in the last six months. Further research is needed focusing on strategies to enhance HCV testing, linkage to care, and treatment among marginalized PWID in different settings where they may access care including needle and syringe programmes, homelessness services, supervised consumption rooms, and prisons (particularly real-world data).

## Contributors

JG, GD, PB, PM, JBr, TS, OD, JBy, ML, AD, and SQ contributed to the study design. JG and GD were the study principal investigators. JG, GD, PB, PM, JBr, TS, OD, JBy, ML, AD, SQ, and all other co-authors contributed to the study implementation and study conduct. TLA contributed to the laboratory work. JG, EC, BH, JA, and GD led the study analyses. All authors contributed to the data interpretation. All authors contributed to the writing and review of the report.


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**Declaration of interests**

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## Table 1. Demographic Characteristics of Patients at Baseline

| Characteristic | Sofosbuvir-velpatasvir for 12 weeks |
|---|---|
| Patients, *n* | 103 |
| Age, median (25%, 75%) | 48 (41, 53) |
| Female sex, n (%) | 29 (28) |
| High school or higher education, n (%) | 50 (49) |
| Unstable housing, n (%) | 24 (23) |
| Any drug use in the last six months, n (%) | 103 (100) |
| Any injecting drug use in the last six months, n (%) | 103 (100) |
| Any non-injecting drug use in the last 30 days, n (%) | 56 (54) |
| Any injecting drug use in the last 30 days, n (%) | 76 (74) |
| Heroin | 57 (55) |
| Cocaine | 13 (13) |
| Methamphetamines | 31 (30) |
| Other opioids | 22 (21) |
| Other | 7 (7) |
| Injecting drug use frequency in the last month, n (%) | |
| Never | 27 (26) |
| <daily | 49 (48) |
| ≥daily | 27 (26) |
| Any alcohol use in the last month, n (%) | 62 (60) |
| Hazardous alcohol use in the last month, n (%) | 18 (17) |
| History of OST, n (%) | 84 (82) |
| Current OST, n (%) | |
| Methadone | 45 (44) |
| Buprenorphine | 4 (4) |
| Buprenorphine/naloxone | 12 (12) |
| OST and recent injecting in past 30 days at baseline, n (%) | |
| No OST, no recent injecting | 12 (12) |
| No OST, recent injecting | 33 (32) |
| OST, no recent injecting | 15 (15) |
| OST, recent injecting | 43 (42) |
| HCV genotype, n (%) | |
| 1a | 35 (34) |
| 1b | 1 (1) |
| 2 | 5 (5) |
| 3 | 60 (58) |
| 4 | 2 (2) |
| Median HCV RNA (25%, 75%), log IU/mL | 6.1 (5.3, 6.7) |
| Median ALT (25%, 75%), IU/L | 61 (39, 84) |
| Stage of liver disease, n (%) | |
| No or mild fibrosis (F0-F1) | 59 (61) |
| Moderate or advanced fibrosis (F2-F3) | 27 (28) |
| Cirrhosis (F4) | 9 (9) |

| | |
|---|---|
| Study site distribution, n (%) | |
| Canada/US | 40 (39) |
| Europe | 20 (19) |
| Australasia | 43 (42) |

**Table 2. Discontinuations, Adverse Events, and Hematologic Abnormalities**

| Event | Sofosbuvir-velpatasvir for 12 weeks |
|---|---|
| Patients, *n* | 103 |
| Participants reporting any AE up to 28 days after last dose, n (%) | |
| Grades 1-2, n (%) | 78 (76) |
| Grade 3, n (%) | 6 (6) |
| Grade 4, n (%) | 1 (1) |
| Participants reporting treatment-related AE up to 28 days after last dose, n (%) | |
| Grades 1-2, n (%) | 47 (46) |
| Grade 3, n (%) | 1 (1) |
| Grade 4, n (%) | 0 (0) |
| Serious adverse event, n (%) | 7 (7) |
| Treatment-related serious adverse event, n (%) | 0 (0) |
| Treatment discontinuation due to adverse event, n (%) | 1 (1) |
| Death during treatment, n (%) | 1 (1) |
| Common adverse events, n (%) | |
| Fatigue | 23 (22) |
| Headache | 19 (18) |
| Nausea | 14 (14) |
| Insomnia | 9 (9) |
| Arthralgia | 6 (6) |
| Dizziness | 5 (5) |
| Nasopharyngitis | 5 (5) |
| Back pain | 4 (4) |
| Diarrhoea | 4 (4) |
| Vomiting | 4 (4) |
| Hematologic event, n (%) | |
| Hemoglobin level <10 g/dl | 0 (0) |
| Platelet count 25,000 to <50,000 per $mm^3$ | 1 (1) |

**Figure 1. Study flow chart.**

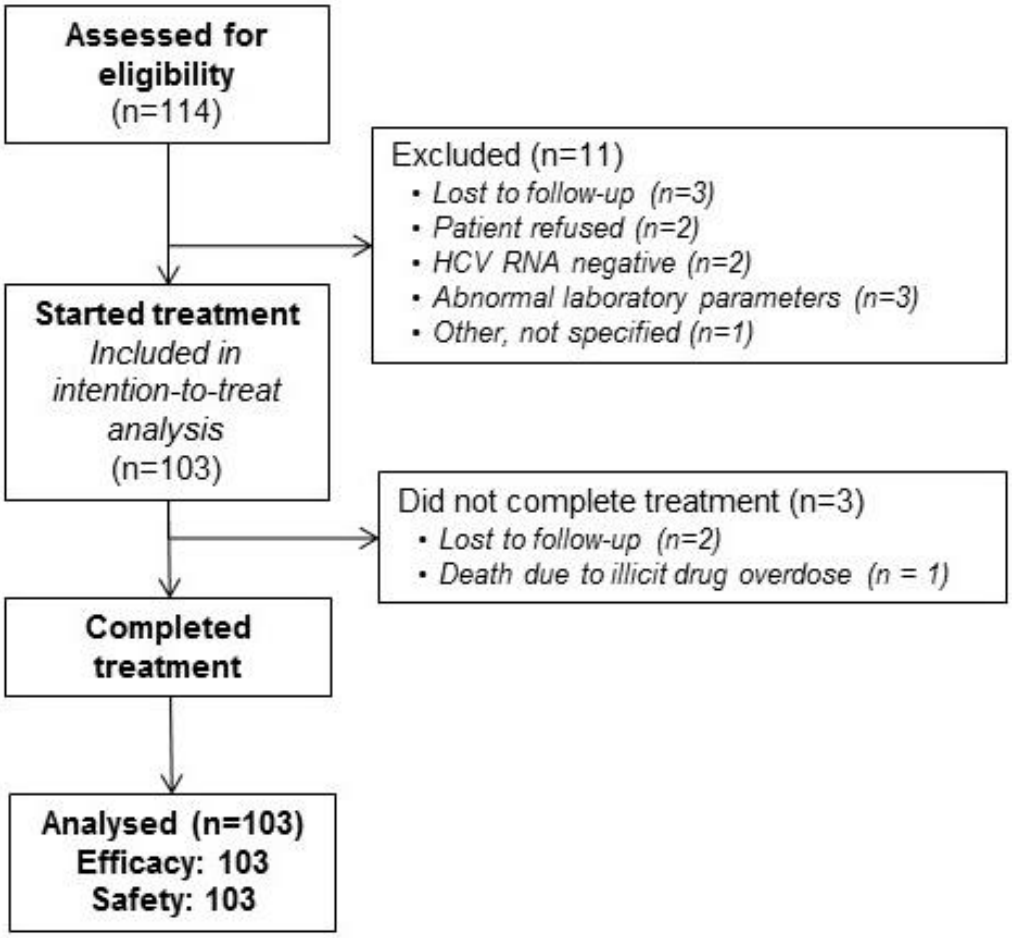

**Figure 2. Self-reported injecting drug use during therapy**

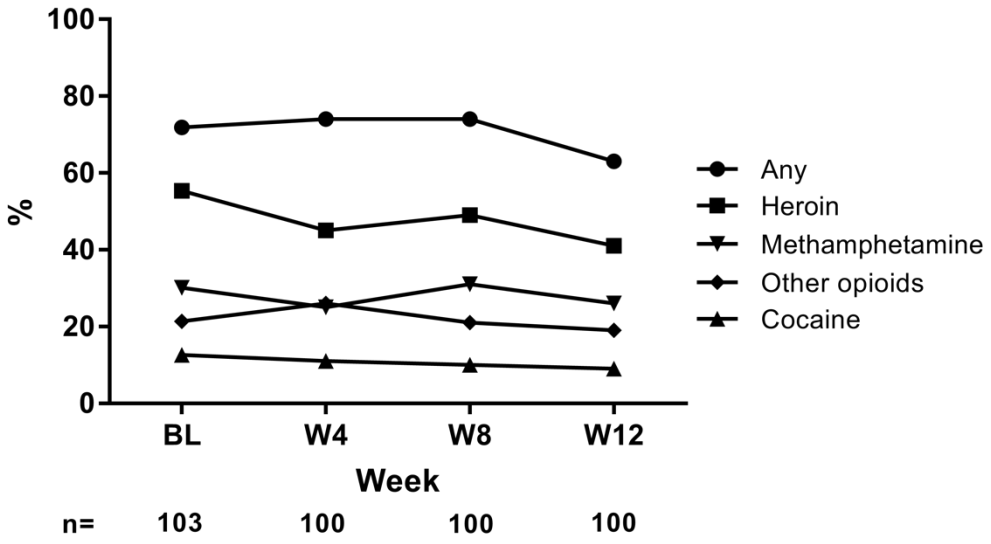

**Figure 3. Daily adherence to sofosbuvir-velpatasvir therapy as measured by weekly electronic blister packs (n=103).** Each row represents an individual patient and each column represents one day of therapy. Green boxes represent dose received, yellow boxes represent no dose received, and white box represent early treatment discontinuation. Light green boxes represent the pill counts when a blister pack was damaged in which no pills were returned. There were no cases of virological failure or viral relapse.

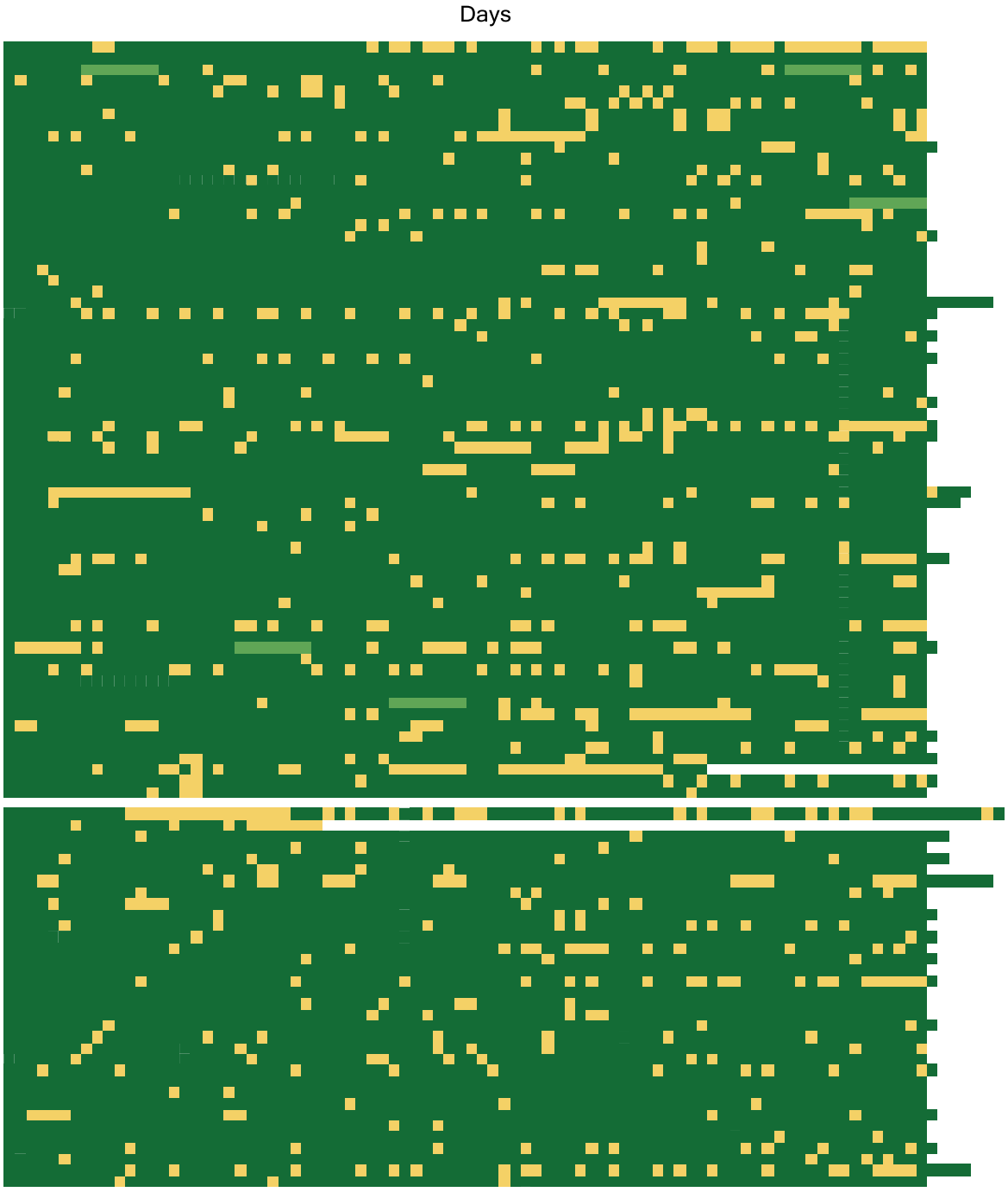

**Figure 4. SVR12, stratified by key characteristics.** The dotted line represents the overall SVR12 in the SIMPLIFY study (96%).