Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use (SIMPLIFY): an open-label, single-arm, phase 4, multicentre trial

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Summary

Background Despite revised guidelines that no longer exclude people who inject drugs (PWID) from treatment for hepatitis C virus (HCV) infection, many clinicians are reluctant to treat recent PWID. This study aimed to evaluate the efficacy of sofosbuvir and velpatasvir therapy in people with chronic HCV infection and recent injection drug use.

Methods In this open-label, single-arm phase 4 trial (SIMPLIFY), we recruited participants with recent injection drug use (past 6 months) and chronic HCV genotype 1–6 infection from seven countries (19 sites). Participants received oral sofosbuvir (400 mg) and velpatasvir (100 mg) once daily for 12 weeks. Therapy was given in 1-week electronic blister packs to record the time and date of each dose. The primary endpoint was the proportion of patients with sustained virological response 12 weeks after completion of treatment (SVR12; defined as HCV RNA <12 IU/mL), analysed in all patients who received at least one dose. This study is registered with ClinicalTrials.gov, number NCT02336139, and follow-up is ongoing to evaluate the secondary endpoint of HCV reinfection.

Findings Between March 29, and Oct 31, 2016, we enrolled 103 participants; 29 (28%) of whom were female, nine (9%) had cirrhosis, 36 (35%) had HCV genotype 1, five (5%) had genotype 2, 60 (58%) had genotype 3, and two (2%) had genotype 4. 61 (59%) participants were receiving opioid substitution therapy during the study, 76 (74%) injected in the past month, and 27 (26%) injected at least daily in the past month. 100 (97%) of 103 participants completed treatment; two people were lost to follow-up and one person died from an overdose. There were no virological failures. 97 (94%, 95% CI 88–98) of 103 people achieved SVR12. Three participants with an end-of-treatment response did not have a SVR; two were lost to follow-up and one had reinfection. Drug use before and during treatment did not affect SVR12. Treatment-related adverse events were seen in 48 (47%) patients (one grade 3, no grade 4). Seven (7%) patients had at least one serious adverse event; only one such event (rhabdomyolysis, resolved) was possibly related to the therapy. One case of HCV reinfection was observed.

Interpretation HCV treatment should be offered to PWID, irrespective of ongoing drug use. Recent injection drug use should not be used as a reason to withhold reimbursement of HCV therapy.

Funding Gilead Sciences.

Introduction

Globally, 71 million people are estimated to have chronic hepatitis C virus (HCV) infection.[1] The prevalence of chronic HCV infection is 39% among people who have injected drugs in the past 12 months, 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 people who inject drugs (PWID) who have stopped injecting.[3,4] Increased access to direct-acting antiviral (DAA) therapy among PWID will be critical to the achievement of WHO targets to eliminate HCV as a major public health threat by 2030.

Post-hoc analyses of phase 3 clinical trials have shown that sustained virological response (SVR) after DAA therapy is similar among people receiving and not receiving opioid substitution therapy.[5–9] In a phase 3 trial of people receiving grazoprevir and elbasvir with no previous treatment experience and HCV genotypes 1, 4, or 6 on stable opioid substitution therapy, the intention-to-treat SVR was 91%.[10] However, only 25% of participants reported injection drug use within the previous 6 months.[10] Patients infected with HCV genotype 3 were not eligible for these phase 3 studies. Globally, the prevalence of HCV genotype 3 is higher among PWID than among people who do not (39% *vs* 25%).[11] Data for HCV treatment outcomes across all genotypes among people with recent injection drug use are needed to guide clinical management and support expanded access to treatment.

In the USA and Europe, some jurisdictions have restrictions for the reimbursement of DAA therapy for people with recent illicit drug or alcohol use or those receiving opioid substitution therapy, irrespective of

Lancet Gastroenterol Hepatol 2018; 3: 153–61

Published Online January 5, 2018 http://dx.doi.org/10.1016/S2468-1253(17)30404-1

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Research in context

Evidence before this study

We searched PubMed and Scopus up to Oct 18, 2017, with the search terms "hepatitis C" OR "HCV" AND "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". There were no language or date restrictions. We manually searched the references of identified articles for further relevant papers. Key abstracts at international meetings were also considered. Collectively, data show that adherence and response to direct-acting antiviral (DAA) therapy among people who inject drugs and are receiving opioid substitution therapy in clinical trials are similar to those in populations without a history of injection drug use. However, there are no international studies evaluating hepatitis C virus (HCV) treatment outcomes among people who have injected drugs in the previous 6 months.

Added value of this study

Our findings showed that patients with chronic HCV infection and recent injection drug use treated with once-daily sofosbuvir and velpatasvir had high rates of sustained virological response at week 12 after completion of treatment, regardless of ongoing injection drug use. Further, this study used a novel electronic blister pack to monitor 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 after DAA therapy among people who have recently injected drugs.

Implications of all the available evidence

These data show that people receiving opioid substitution therapy and people with recent injecting drug use respond favourably to DAA therapy with sofosbuvir and velpatasvir, irrespective of drug use before or during treatment. Many countries, including the USA, still have restrictions on the reimbursement of DAA therapy for people with recent injection drug use (with varying definitions of what constitutes recent), which has effectively excluded this group of people from accessing treatment. Even in settings where these restrictions for reimbursement do not exist, many practitioners are still reluctant to prescribe DAA therapy for such individuals, given concerns of poor adherence, response to therapy, and risk of reinfection. However, this approach is not consistent with international guidelines that recommend DAA therapy for people who inject drugs and suggest that such individuals should be prioritised because of the potential to reduce transmission. Given that people who inject drugs represent 23% of all new infections globally, HCV treatment should be increased among these people as part of efforts to eliminate HCV. These data provide important evidence to support HCV treatment among people with recent injection drug use and have the potential to change clinical practice and health policy globally.

disease stage.[12,13] The scarcity of data on DAA treatment outcomes in these populations has been used as a rationale for such restrictions.

See Online for appendix

Phase 3 trials[14,15] have shown that combined therapy with sofosbuvir, a nucleotide analogue NS5B polymerase inhibitor, and velpatasvir, an NS5A inhibitor, for 12 weeks results in high rates of SVR, and this therapy is approved for the treatment of HCV genotypes 1–6. We aimed to assess the efficacy and safety of sofosbuvir and velpatasvir for 12 weeks in patients infected with HCV with recent injection drug use.

Methods

Study design and participants

In this international, multicentre, open-label phase 4 trial, we enrolled participants from 19 sites, in Australia (seven sites), Canada (six sites), New Zealand (one site), Norway (one site), Switzerland (two sites), the UK (one site), and the USA (one site). We recruited people from three drug treatment clinics, 12 hospital clinics, a private practice, and three community clinics.[16]

Participants were 18 years or older, had chronic HCV genotypes 1–6 (confirmed ≥6 months), were naive to NS5A-based HCV therapy, and had recently injected drugs (self-reported injection drug use within 6 months of enrolment). Participants with HIV infection or decompensated liver disease, or both, were excluded. Full eligibility criteria are provided in the study protocol (appendix).

All participants gave written informed consent before study procedures started. The study protocol was approved by St Vincent's Hospital, Sydney Human Research Ethics Committee (primary study committee), and local ethics committees at all study sites, and was done according to the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. An independent data and safety monitoring board reviewed the progress of the study.

Procedures

Patients received a fixed-dose combination tablet that contained 400 mg of sofosbuvir and 100 mg of velpatasvir, administered orally once daily for 12 weeks. The trial was originally designed as a phase 2 study before registration of the study drugs (appendix). Participants received all study drugs weekly in an electronic blister pack (Information Mediary Corporation) with an integrated sensor grid that recorded the time and date that each daily dose was punched out of the pack, thus allowing us to track medication adherence. Participants were given the

equivalent of AUS$10 as an incentive to return the blister pack. Once the packs were returned, a specific reader was used to download data on adherence.

We assessed participants at screening, enrolment (baseline), weeks 2, 4, 8, and 12 (end) of therapy, and at weeks 16 (SVR4), 24 (SVR12), and 36 (SVR24) after the beginning of treatment. Participants also visited the study site weekly to receive their medication in the electronic blister pack. We also plan to follow-up participants every 6 months for up to 2 years after the end of treatment (weeks 60, 84, and 108) to evaluate incidence of HCV reinfection and injecting risk behaviour; these follow-up visits were not included in this analysis because the study is ongoing. Study nurses and physicians provided services to reduce risk and harm (eg, access to syringes, other injecting equipment, and opioid substitution therapy) as per standard of care in their country.

Enrolment assessments included HCV RNA load, HCV genotype, standard laboratory and clinical testing, FibroScan transient elastography (where available), and self-reported behavioural questionnaires on tablet computers. Assessments during treatment included physical examinations, measurements of HCV RNA loads (done at local laboratories), and standard laboratory testing. All adverse events were recorded and graded according to the Medical Dictionary for Regulatory Activities.

To evaluate the primary endpoint of SVR12, we measured HCV RNA loads in stored plasma samples using the Abbott RealTime HCV Viral Load assay (lower limit of quantification of 12 IU/mL). Central HCV RNA testing was done on samples collected at baseline, week 12 (end of treatment), week 24 (SVR12), and the most recent timepoint available (up to SVR24). The NS5B region of HCV was sequenced to determine genotypes.

Electronic blister packs were used to measure adherence to sofosbuvir and velpatasvir. We assessed adherence by dividing the number of total doses received during therapy by the total expected number of doses. Because the proportion of patients with adherence was not normally distributed, we calculated median adherence to therapy (eg, midpoint adherence). Among individuals in whom therapy was extended because of several interruptions to treatment, we calculated adherence as the proportion of doses received divided by the total number of weeks of total therapy.

Participants did a self-administered questionnaire on a tablet computer at enrolment, at baseline (start of treatment), every fourth week during treatment, and at 12 weeks after treatment. Participants received the equivalent of AUS$20 for their time. The questionnaires collected information on demographics (age, sex, ethnicity, employment status, education level, and housing status), drug and alcohol use, injecting risk behaviours, drug treatment, and health utility. Stable housing was defined as a rented or privately owned house or flat. To assess alcohol consumption, we used the Alcohol Use Disorders Identification Test–Consumption, which is derived from the first three questions of the full test; scores of 3 or more (women) and 4 or more (men) indicate hazardous consumption or active alcohol use disorders. We used the EuroQol 5D questionnaire 3 level to assess health utility; these data are not presented in this primary analysis because it will be the focus of a secondary analysis.

We used liver stiffness measurements (FibroScan transient elastography) to assess stage of liver fibrosis; the chosen cutoffs for clinical significance were 7·1 kPa for liver fibrosis (F2–F3) and 12·5 kPa for liver cirrhosis (F4).

Outcomes

The primary efficacy endpoint was the proportion of participants with SVR12, which was defined as a HCV RNA load below the limit of quantification 12 weeks after the end of treatment in all participants who received at least one dose of sofosbuvir and velpatasvir. If HCV RNA was not assessed at week 12 post-treatment, the result of the next available HCV RNA assessment was used to calculate SVR. Secondary endpoints were treatment completion, treatment adherence, severe adverse events, treatment discontinuations because of adverse events, changes in drug use during treatment, and HCV reinfection. Sanger sequencing of the NS5A, NS5B, and core–E2 regions was done for all patients with virological recurrence in their samples. Samples were sequenced at baseline and at virological recurrence; we compared sequences using validated genetic distance-based cutoffs to distinguish viral relapse (homologous virus) from reinfection (heterologous virus).[17,18]

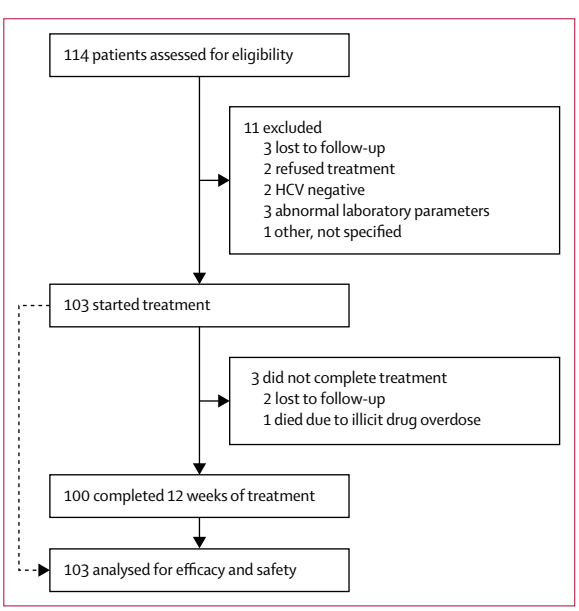

Figure 1: **Study profile**

	Sofosbuvir–velpatasvir for 12 weeks (n=103)
Age (years)	48 (41–53)
Sex	
Male	74 (72%)
Female	29 (28%)
High school or higher education	50 (49%)
Unstable housing*	24 (23%)
Any drug use in the past 6 months	103 (100%)
Any injecting drug use in the past 6 months	103 (100%)
Any non-injecting drug use in the past 30 days	56 (54%)
Any injecting drug use in the past 30 days	76 (74%)
Heroin	57 (55%)
Cocaine	13 (13%)
Methamphetamines	31 (30%)
Other opioids	22 (21%)
Other	7 (7%)
Injecting drug use frequency in the past 30 days	
Never	27 (26%)
Less than daily	49 (48%)
At least daily	27 (26%)
Any alcohol use in the past 30 days	62 (60%)
Hazardous alcohol use in the past 30 days	18 (17%)
History of OST	84 (82%)
Current OST	
Methadone	45 (44%)
Buprenorphine	4 (4%)
Buprenorphine–naloxone	12 (12%)
OST and had injected in past 30 days (baseline)	
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	
1a	35 (34%)
1b	1 (1%)
2	5 (5%)
3	60 (58%)
4	2 (2%)
HCV RNA load, log IU/mL	6·1 (5·3–6·7)
Alanine transaminase, IU/L	61 (39–84)
Stage of liver disease†	
No or mild fibrosis (F0–F1)‡	59 (61%)
Moderate or advanced fibrosis (F2–F3)‡	27 (28%)
Cirrhosis (F4)‡	9 (9%)
Study site distribution	
Canada or USA	40 (39%)
Europe	20 (19%)
Australasia	43 (42%)

Data are n (%), or median (IQR). OST=opioid substitution therapy. *Stable housing was defined as a rented or privately owned house or flat. †Data were unavailable for ten participants. ‡F0–F1 <7·1 kPa, F2–F3 7·1–12·49 kPa, F4 ≥12·5 kPa.

Table 1: **Baseline characteristics**

Statistical analysis

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 how feasible it was to recruit people who had recently injected drugs through the multinational network. Based on the assumption of an overall SVR of 90%, the 95% CI around this estimate was expected to be 82–95%.

For all analyses, we used two-sided p values of 0·05 as the cutoff for statistically significant differences.

We used the Clopper–Pearson method to calculate point estimates and two-sided exact 95% CIs for the proportion of people with SVR for the sofosbuvir and velpatasvir group overall, according to HCV genotype, and for various subgroups. Factors hypothesised to be associated with SVR were chosen based on factors previously shown, or hypothesised, to be associated with treatment responses in people with HCV infection, including age (stratified by median), sex, current opioid substitution therapy, recent (past month) injection drug use at baseline (including heroin, cocaine, methamphetamine, and other opioids), ongoing injection drug use during therapy, frequency of injection drug use, alcohol use, presence of cirrhosis, and adherence to therapy of 90% or greater. We did unadjusted logistic regression analysis to evaluate predictors of SVR. We used Stata (version 12.0) for all analyses.

This study is registered with ClinicalTrials.gov, number NCT02336139.

Role of the funding source

This study (including study drugs) was funded by a research grant from Gilead Sciences. The funder had no role in the analysis and interpretation of the study results. JG, EC, and GD had access to the raw data. The sponsor (The Kirby Institute, UNSW Sydney, Sydney) designed the study, collected data, managed study samples, monitored study conduct, had access to all data, and did the statistical analysis. JG and GD were responsible for the decision to submit for publication.

Results

Of 114 participants screened, 103 were enrolled between March 29, and Oct 31, 2016, and had sofosbuvir and velpatasvir therapy (figure 1; table 1). Most patients had genotypes 1–3; no participants had HCV genotype 5 or 6.

At baseline, most people had injected drugs in the past month, a quarter had injected drugs at least daily in the past month, and more than half were receiving opioid substitution therapy (table 1). The most commonly injected drugs were heroin, methamphetamines, and other opioids. Drug use was fairly stable throughout treatment (figure 2).

Among all participants enrolled, 100 (97%) completed treatment (12 weeks). Of the three people who did not complete treatment (figure 1), two were lost to follow-up

(one following baseline and one at week 8) and one died from a drug overdose at week 3. The overall median follow-up after the end of treatment was 12 weeks (IQR 12–24).

The overall median adherence (ie, the midpoint) was 94% (IQR 88–98). 68 (66%; 95% CI 66–75) of 103 participants were at least 90% adherent to therapy. There was considerable variation in adherence (figure 3). Therapy was extended for 29 participants because of several interruptions to treatment (median 1 day [IQR 1–2; range 1–7]).

99 (96%, 95% CI 90–99) of 103 people had an end-of-treatment response and 97 (94%, 88–98) achieved SVR12. Among the three people who completed treatment but did not achieve an SVR, two were lost to follow-up (including one person who completed treatment but did not have a sample taken at the end of treatment) and one was reinfected with HCV. There were no cases of virological failure or relapse.

The number of participants with SVR did not differ between those with and without recent (past month) injection drug use at baseline (p=0·684), between those with fewer than daily and at least daily injection drug use (p=0·584), between those with and without ongoing injection drug use during HCV therapy (p=0·704), and between those who were at least 90% adherent to therapy and those who were less than 90% adherent to therapy (p=0·371; figure 4). Furthermore, recent (past month) injection drug use at baseline, frequency of recent injection drug use at baseline, opioid substitution therapy at baseline, ongoing injection drug use during therapy, stable housing, liver fibrosis, and frequency of alcohol consumption were not associated with SVR (appendix). There were no factors associated with reduced SVR at week 12 (appendix). Although we intended to do multivariate logistic regression analysis, the high SVR and scarcity of factors found in unadjusted analyses (appendix) precluded the ability to do adjusted analyses.

Of the 103 participants enrolled, 85 (83%) participants had at least one adverse event, of whom 48 (47%) were related to treatment. Seven (7%) participants had at least one serious adverse event (nine events in total); one (resolved rhabdomyolysis) was deemed to be possibly related to treatment (table 2). The most common adverse events (top 3) were fatigue, headache, and nausea (table 2). There were four deaths during the study period (60 person-years of follow-up; mortality incidence of 6·7 cases per 100 person-years [95% CI 1·8–16·2]). During treatment (week 3), one participant from Australia died due to an illicit drug overdose unrelated to treatment (table 2). One person in Australia and two people in Canada died after treatment had finished (two after SVR12 and one after SVR24); all deaths were due to an overdose of illicit drugs.

There was one case of HCV reinfection (38 person-years of follow-up; reinfection rate 2·6 cases per 100 person-years; [95% CI 0·1–13·8]). This person was a 55-year-old man who, at baseline, reported injecting morphine 2–3 times most days in the past month. He was infected with HCV genotype 1a before starting

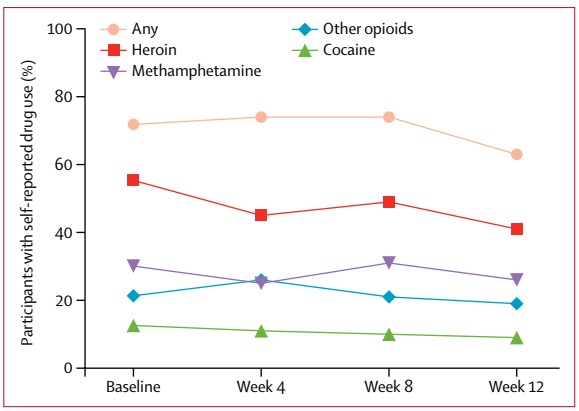

Figure 2: **Self-reported injecting drug use during therapy**
Data for 103 patients at baseline, 100 patients at other timepoints.

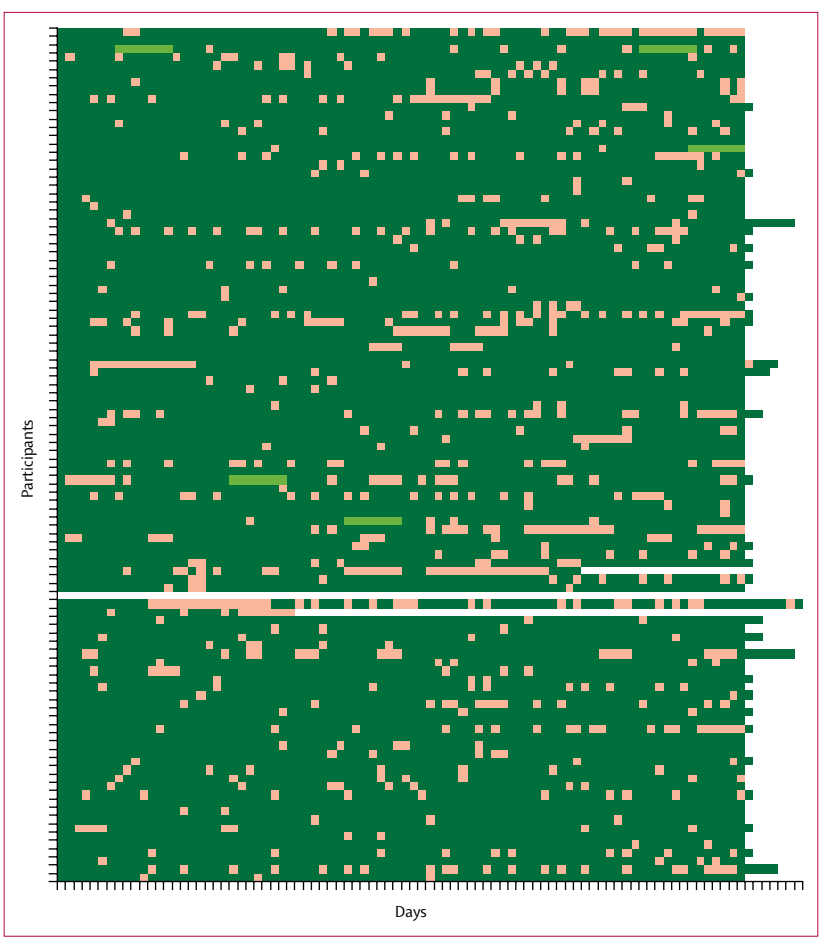

Figure 3: **Daily adherence to therapy with sofosbuvir and velpatasvir therapy in 103 participants, measured by weekly electronic blister packs**
Each row represents an individual patient and each column represents one day of therapy. Green boxes show dose received, pink boxes show no dose received, and white boxes show early discontinuation of treatment. Light green boxes show the pill counts when a blister pack was damaged in a way that prevented electronic scanning but no pills were returned (adherence assumed).

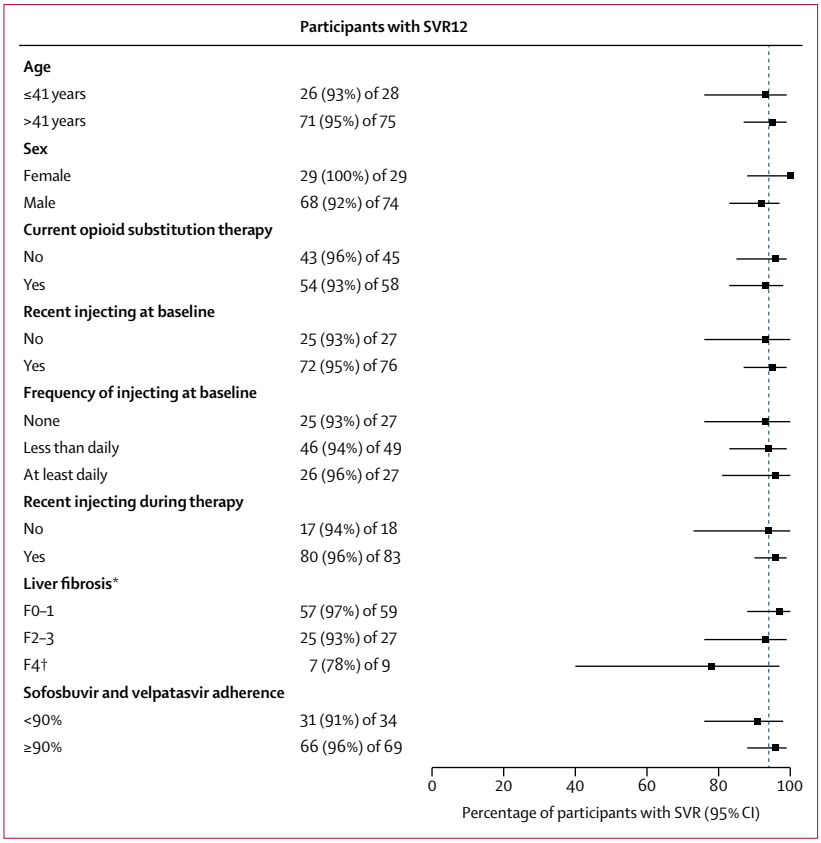

***Figure 4*: Forest plot of SVR12, stratified by key characteristics**
The dotted line shows the overall SVR12 (96%) in the SIMPLIFY study. Recent injection drug use was defined as within 30 days of enrolment. SVR12=sustained virological response at 12 weeks post treatment. *F0–F1 <7·1 kPa, F2–F3 7·1–12·49 kPa, F4 ≥12·5 kPa. †Of the two participants without SVR12, neither had virological failure nor virological relapse.

	Sofosbuvir–velpatasvir for 12 weeks (n=103)
Participants with any adverse event up to 28 days after last dose	
Grades 1–2	78 (76%)
Grade 3	6 (6%)
Grade 4	1 (1%)
Participants with a treatment-related adverse event up to 28 days after last dose	
Grades 1–2	47 (46%)
Grade 3	1 (1%)
Grade 4	0
Serious adverse event	7 (7%)
Treatment-related serious adverse event	1 (1%)
Treatment discontinuation due to adverse event	1 (1%)
Death during treatment	1 (1%)
Common adverse events (top ten)	
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%)
Haematological event	
Haemoglobin level <10 g/dL	0 (0%)
Platelet count 25 000–<50 000 per µL	1 (1%)

Data are n (%).

***Table 2*: Discontinuations, adverse events, and haematological abnormalities**

therapy, was HCV-negative at the end of treatment, and had recurrent viraemia with HCV genotype 1a at SVR12 (week 24). During treatment, this man continued to inject morphine (more than three times per day); he reported using sterile injection 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 study of people with chronic HCV who had recently injected drugs, the SVR12 after treatment with sofosbuvir and velpatasvir was 94%, irrespective of injection drug use before or during therapy. Median adherence to once-daily therapy was 94%. Treatment was well tolerated and had no effect on injection risk behaviours. These data provide evidence to inform international guidelines on the management of HCV infection in people with recent injection drug use and support the removal of restrictions for the reimbursement of DAA therapy among people with HCV infection and recent injection drug use that are in place in several countries.

The overall SVR of 94% among people with injection drug use in the past 6 months is consistent with findings from clinical trials among PWID receiving opioid substitution therapy.[5–9] However, previous clinical trials either did not include people with recent injection drug use[5–7] or included only a subset of people with recent injection drug use.[8] Among studies that included people with recent injection drug use, including clinical trials[8] and real-world cohorts,[19–21] heterogeneous definitions of recent injection drug use have been used. Although some of these studies have shown lower SVR in intention-to-treat analyses than was observed in phase 3 clinical trials, most non-responses were related to loss to follow-up between the end of treatment and SVR12 and not virological failure or relapse. Notably, there were no cases of virological failure during treatment in our study.

In our study, treatment completion was similar to results reported in phase 3 studies[5–9] of once-daily DAA therapy among people without recent injection drug use. Adherence of 90% or greater was lower among people with recent injection drug use in our study (66%) than it

was among people stable on opioid substitution therapy or people who had not used injection drugs (88–97%) in phase 3 clinical trials.[5–9] However, the methods used for evaluation of adherence in these clinical trials often relied on the return of medication bottles, which probably overestimated the reported adherence. 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 our study. Regardless, adherence did not significantly affect SVR in this study, with no cases of virological failure or viral relapse.

The use of injection and non-injection drugs remained relatively stable before and during HCV therapy. This finding is consistent with previous results for interferon-based therapy[22–24] in people with either recent injection drug use or receipt of opioid substitution therapy. These results are also consistent with data evaluating elbasvir and grazoprevir therapy for people stable on opioid substitution therapy.[8] Notably, recent injection drug use before or during therapy did not affect SVR.[8]

There was only one case of HCV reinfection in our study, resulting in an incidence of 2·6 (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 who were followed up after treatment with interferon-based therapies (0·0–5·3 per 100 person-years)[22,25–29] and is also consistent with the C-EDGE CO-STAR study[30] of DAA therapy with elbasvir and grazoprevir (2·3 per 100 person-years). Increased rates of reinfection have been seen among people with ongoing[22,26,28] or frequent injection drug use.[28] Long-term follow-up up to 3 years from the start of treatment is underway for the SIMPLIFY study and further studies of reinfection will be crucial for better understanding of the long-term reinfection risk among people with recent injection drug use.

Treatment with sofosbuvir and 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), highlighting the high risk of drug-related mortality among PWID. It is crucial that HCV care is integrated within a framework that also addresses drug-related harms, prevents overdose mortality, addresses social inequalities, and improves the health of drug users.

This study has several 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. Furthermore, HIV-positive people were excluded from this study because of 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 might not be generalisable to all populations of people with recent injection drug use and probably reflects a population that is more engaged in health services. However, the population enrolled was highly marginalised; 74% injected drugs in the past 30 days and 26% injected drugs at least daily. Although information on drug use risk behaviours was self-reported, and might be prone to response bias and socially desirable responses, self-reported information on drug use has been shown to be reliable and valid.[31] Furthermore, computer-assisted surveys provide greater confidentiality and might lead to more reliable and valid responses than do face-to-face interviews.[32] Each week, participants attended the clinic (providing the opportunity to interact with providers) and received their supply of medication in a blister pack and their compensation for returning the previous pack. The frequency of these clinical visits and the incentive for returning the blister pack might have led to improved adherence and completion of treatment. However, this study was not designed to evaluate the effect of participant incentives on SVR12. A study to evaluate the effect of incentives on SVR12 among people with a history of injection drug use is ongoing.[33] In clinical practice, the frequency of clinical follow-up and requirements for adherence support should be determined on a case-by-case basis, with consideration of an individual's social circumstances and medical comorbidities. This study was powered to provide a reasonably precise measure of treatment response and evaluate the feasibility of recruitment of people with recent injection drug use through the multinational network. Given the high rate of treatment success (assessed via SVR12), the study was underpowered to determine factors associated with success or failure. Lastly, for this planned primary analysis, participants were only followed up for up to 24 weeks after initiation of treatment to evaluate SVR12; hence the conclusions on the rate of reinfection should be interpreted with caution.

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

Given that PWID represent 23% of all new infections globally,[41] HCV treatment for these individuals should be increased 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, WHO targets include reductions in new HCV infections by 80% and the number of HCV deaths by 65%, and increases in HCV diagnoses from 20% to 90% and the number of eligible people receiving HCV treatment from 10% to 80%.[41] Modelling studies suggest that scaling up HCV treatment (annually, four to eight people treated per 100 PWID) could lead to substantial reductions in HCV incidence and prevalence.[40,42] Additionally, treatment with DAAs for PWID and have moderate or mild fibrosis is also cost-effective compared with delaying treatment until cirrhosis.[43]

Data from this phase 4 SIMPLIFY study show high adherence and SVR among people who have injected drugs in the past 6 months. Further research (particularly real-world data) is needed, focusing on strategies to improve HCV testing, linkage to care, and treatment among marginalised PWID, particularly in different settings where they might access care, including needle and syringe programmes, homelessness services, supervised consumption rooms, and prisons.

Contributors

JG, GJD, PB, PM, JBr, TS, OD, JBy, ML, AD, and SQ designed the study. JG and GD were the principal investigators. TLA was responsible for the laboratory work. JG, , BH, JA, and GJD led the study analyses. All authors contributed to the implementation, conduct, data interpretation, and writing and review of this work.

Declaration of interests

JG reports grants and personal fees from AbbVie, Cepheid, Gilead Sciences, and Merck. OD reports grants from Gilead Sciences during this study and grants from Gilead Sciences, Merck, and AbbVie. PB reports grants and personal fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Merck Sharp & Dohme. MH reports grants from Gilead Sciences, Bristol-Myers Squibb, and AbbVie. JBr reports consultant fees from Gilead Sciences and Merck. AHL reports grants and personal fees from Gilead Sciences and Merck. GVM reports grants and personal fees from Gilead Sciences and grants from AbbVie. JP reports personal fees from Janssen and Genetech. CC reports grants and personal fees from Gilead Sciences. JJF reports grants and personal fees from AbbVie, Merck, Gilead Sciences, and Janssen, personal fees from Contravir, and grants from Abbott. CF reports grants and non-financial support from Kirby Institute during this study and grants from Gilead Sciences, ViiV HealthCare, and Merck. GJD reports grants, personal fees, and non-financial support from AbbVie, Merck, Bristol-Myers Squibb, and Roche; grants and personal fees from Janssen; personal fees and non-financial support from Gilead Sciences; and personal fees from GlaxoSmithKline and Abbott Diagnostics. PR reports fees for educational talks from Gilead Sciences, Merck Sharp & Dohme, and AbbVie, and is on the advisory board for Merck Sharp & Dohme. BC reports grants, personal fees, and non-financial support from Gilead Sciences, Merck, and AbbVie. EG reports personal fees from being a Clinical Advisor for Gilead Sciences, Merck, Janssen, and AbbVie, and personal fees from Gilead Sciences Speaker Bureau and AbbVie Speaker Bureau. JFD reports grants and personal fees from Gilead, Merck Sharp & Dohme, Janssen, and AbbVie. All other authors declare no competing interests.

Acknowledgments

We thank the study participants, researchers, and staff for their contribution to the research. We also thank Diana Brainard, John McHutchison, and others at Gilead Sciences for their support.

This work was supported by funding from Gilead Sciences. The Kirby Institute, which sponsored this study, 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. GJD is supported by a National Health and Medical Research Council Practitioner Research Fellowship. BH is supported by a National Health and Medical Research Council Early Career Fellowship. EBC holds a UNSW Sydney Tuition Fee Scholarship and is also supported through a PhD Scholarship from the CanHepC Trainee Program. JG, GVM, and GJD have received funding from the US National Institute on Drug Abuse, US National Institutes of Health for an unrelated project (1R01DA040506-01).

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