Research Article
Viral Hepatitis

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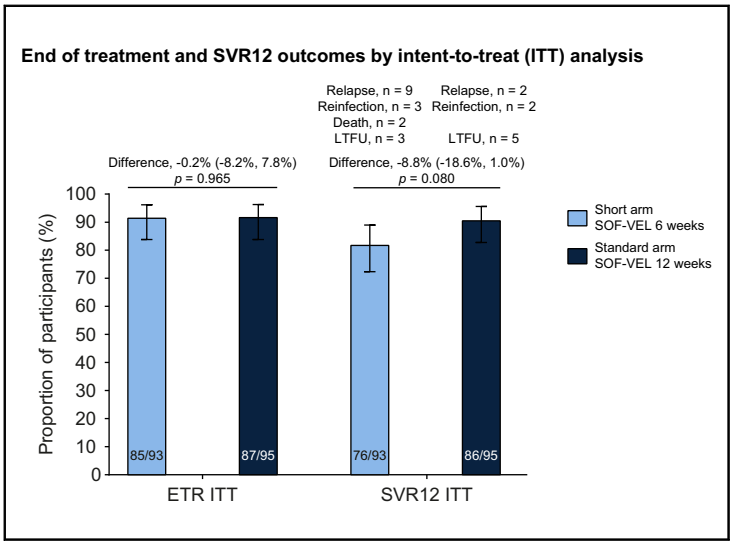
Sofosbuvir/velpatasvir for 12 *vs.* 6 weeks for the treatment of recently acquired hepatitis C infection

Graphical abstract



Highlights

- REACT is a randomised study of short course DAA therapy for recently acquired HCV.
- 188 participants were treated with either 6 or 12 weeks sofosbuvir/velapatasvir.
- The study population was predominantly cis-male and included a high proportion living with HIV.
- The study was stopped early due to the high rate of virological relapse in the short course arm.
- Six weeks of sofosbuvir/velapatasvir cannot be considered non-inferior to 12 weeks.

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Lay summary

In this randomised trial, 188 people with recently acquired hepatitis C infection were randomly assigned to treatment using either a short 6-week course (93 people) or standard 12-week course (95 people) of the hepatitis C treatment sofosbuvir/velpatasvir. There were 9 cases of relapse after treatment with the short course and 2 following the standard course. A shortened course of 6-week therapy for hepatitis C infection appeared to be less effective than a standard 12-week course in people with recently acquired hepatitis C infection.

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Sofosbuvir/velpatasvir for 12 *vs.* 6 weeks for the treatment of recently acquired hepatitis C infection

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Background & Aims: Shortened duration therapy for acute and recent HCV infection has been shown to be highly effective in several small non-randomised studies with direct-acting antiviral regimens; however, large randomised studies are lacking.

Methods: REACT was an NIH-funded multicentre international, open-label, randomised, phase IV non-inferiority trial examining the efficacy of short course (6-week) *vs*. standard course (12-week) therapy with sofosbuvir-velpatasvir for recent HCV infection (estimated duration of infection ≤12 months). Randomisation occurred at week 6. The primary endpoint was sustained virological response 12 weeks after treatment end (SVR12) in the intention-to treat (ITT) population. A total of 250 participants were due to be enrolled, but on advice of the data safety and monitoring board the study was halted early.

Results: The primary analysis population consisted of 188 randomised participants at termination of study enrolment; short arm (n = 93), standard arm (n = 95). Ninety-seven percent were male and 69% HIV positive. ITT SVR12 was 76/93, 81.7% (95% CI 72.4–89.0) in the short arm and 86/95, 90.5% (95% CI 82.7–95.6) in the standard arm. The difference between the arms was -8.8 (95% CI -18.6 to 1.0). In modified ITT analysis, wherein non-virological reasons for failure were excluded (death, reinfection, loss to follow-up), SVR12 was 76/85, 89.4% (95% CI 80.8–95.0) in the short arm and 86/88, 97.7% in the standard arm (95% CI 92.0–99.7; difference -8.3%, p = 0.025).

Conclusions: In this randomised study in recent HCV infection, a 6-week course of sofosbuvir-velpatasvir did not meet the criteria for non-inferiority to standard 12-week therapy.

Lay summary: In this randomised trial, 188 people with recently acquired hepatitis C infection were randomly assigned to treatment using either a short 6-week course (93 people) or standard 12-week course (95 people) of the hepatitis C treatment sofosbuvir/velpatasvir. There were 9 cases of relapse after treatment with the short course and 2 following the standard course. A shortened course of 6-week therapy for hepatitis C infection appeared to be less effective than a standard 12-week course in people with recently acquired hepatitis C infection.

ClinicalTrials.gov Identifier: NCT02625909.

Introduction

Individuals identified in the 'acute' phase of HCV infection have historically responded better to therapy than individuals with chronic HCV infection. Several studies in the interferon based-therapy era confirmed that duration of therapy, if commenced early, could be shortened by as much as half, with equivalent or higher sustained virological response (SVR) or 'cure'.[1–3] This was demonstrated irrespective of whether the infection was considered acute (within the prior 6 months) or recent (within the prior 1 year) at therapy commencement,[4] and was true across at-risk populations including people who inject drugs (PWID)[5] and people with HIV.[6,7]

With the advent of direct-acting antiviral (DAA) therapies, the paradigm of shortened treatment for those with acute or recent HCV infection has been further examined. Although studies with initial regimens (including sofosbuvir and ribavirin) were disappointing,[8,9] several single arm studies with more potent regimens demonstrated encouraging results.[10–12] One of the largest studies, the Dutch Acute HCV in HIV (DAHHS2) study,

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reported an SVR of 99% in 80 individuals with genotype 1 or 4 using a shortened duration of 8 weeks of grazoprevir-elbasvir.[13] Most recently, the first pan-genotypic study in recent HCV infection (TARGET3D) demonstrated an SVR of 96% (per protocol) in 30 individuals using 6 weeks of gleceprevir-pibrentasvir.[14] Although encouraging, these studies are limited by the lack of a control group and small sample sizes, reflecting the difficulties of identifying and recruiting large numbers of individuals in early HCV infection.

Recruiting through a large international network, the Recently Acquired HCV Infection Trial (REACT) aimed to test the hypothesis that 6 weeks (short) of sofosbuvir-velpatasvir is non-inferior to 12 weeks (standard) of sofosbuvir-velpatasvir among people with recent HCV infection.

Patients and methods

Study design and randomisation

In this open-label, international, multicentre phase III trial, adults with recent HCV were randomly assigned (1:1) to receive sofosbuvir-velpatasvir 400 mg-100 mg once daily for 6 or 12 weeks. Randomisation was performed at week 5 or 6 on treatment using a permutated block design, with a computer random number generator using fixed block sizes of 4, stratified according to site and HIV status. Block size was known only to the study statistician and clinical trial manager. Participation of patients with HCV/HIV coinfection was capped at 70% of the total study population, additionally, the number of participants with HCV reinfection enrolled to the study was originally capped at 20% of the total study population (although subsequently revised to uncapped). Participants randomised to the short arm completed therapy at the end of 6 weeks, whilst those in the standard arm continued for a further 6 weeks (total of 12 weeks).

Participants

Participants were screened and enrolled at 24 sites: Australia (n = 5), Canada (n = 4), Germany (n = 4), Netherlands (n = 1), New Zealand (n = 1), Switzerland (n = 3), the United Kingdom (n = 4), and the United States (n = 2). Study recruitment was conducted through a network of tertiary viral hepatitis clinics (n = 18), and primary care clinics (n = 6).

Adults (age ≥18 years) with recent HCV infection (genotypes 1-6) and HCV RNA ≥10,000 IU/ml at screening were eligible. Individuals with acute or chronic hepatitis B coinfection were excluded. Full eligibility criteria are provided in the study protocol, available in the supplementary information.

Sites were instructed to observe participants for 4 to 12 weeks between screening and baseline, providing an opportunity to determine whether spontaneous HCV clearance occurred. The timing of treatment initiation was made by the investigator on an individual basis at site level.

Study definitions

Recent primary HCV infection was defined as initial detection of anti-HCV antibody and/or HCV RNA within 6 months of enrolment and either: (i) documented recent HCV seroconversion (anti-HCV antibody negative result in the 18 months prior to enrolment) or (ii) acute clinical hepatitis (jaundice or alanine aminotransferase [ALT] greater than 10x the upper limit of normal [ULN]) within the previous 12 months with the exclusion of other causes of acute hepatitis or (iii) acute asymptomatic hepatitis (acute rise in ALT >5x ULN) within the previous 12 months with the exclusion of other causes of acute hepatitis. Recent HCV reinfection was defined as new detectable HCV RNA within 6 months of enrolment and evidence of prior spontaneous or treatment-induced clearance (previous positive anti-HCV antibody and undetectable HCV RNA on ≥2 occasions).

The presentation of recent HCV infection at the time of diagnosis was classified as either acute clinical or asymptomatic infection. Acute clinical infection included participants with a documented clinical history of symptomatic seroconversion illness (including, but not limited to, the presence of jaundice, nausea/vomiting, abdominal pain, fever and hepatomegaly) and those without clinical symptoms, but with a documented peak ALT greater than 10x the ULN within the 12 months prior to diagnosis. Asymptomatic infection included participants with anti-HCV antibody seroconversion or reinfection, but no acute clinical symptoms or documented peak ALT less than 10x the ULN.

In addition to these definitions of recent primary HCV and recent HCV reinfection, an estimated duration of HCV infection of less than 12 months at screening was required for inclusion. The estimated date of HCV infection in those with acute clinical infection was calculated as 6 weeks before the onset of seroconversion illness or 6 weeks before the first ALT measurement >10x the ULN. The estimated date of HCV infection in those with asymptomatic infection was calculated as the midpoint between the last negative anti-HCV antibody or HCV RNA and the first positive anti-HCV antibody or HCV RNA. For participants who were anti-HCV antibody negative and HCV RNA positive at screening, the estimated date of infection was 6 weeks before enrolment, regardless of symptom status.

Virological definitions

HCV virological suppression was defined as HCV RNA below the lower limit of quantification (LLoQ). An end-of-treatment response (ETR) was defined as HCV RNA below the LLoQ (target not detected or target detected, not quantifiable) at the end of treatment (date of treatment cessation). SVR12 was defined as HCV RNA below the LLoQ ≥12 weeks after the end of treatment. Treatment failure was defined as either virologic failure (HCV RNA above the LLoQ 12 weeks after the end of treatment, with reinfection excluded on sequencing) or non-virologic failure (including reinfection, death, premature treatment discontinuation, loss to follow-up or missing HCV RNA values). Reinfection was defined as HCV RNA above the LLoQ after end of treatment, with detection of an HCV strain that was distinct from the primary infecting strain, confirmed as heterologous virus on sequencing. SVR12 assessment was nominally set at day 84 post treatment, with a lower limit of day 70 post treatment.

Study assessments

In the short duration arm, scheduled study visits were undertaken at baseline, treatment weeks 1, 2, 4 and 6 (end of treatment), and post-treatment weeks 4 and 12. In the standard duration arm, scheduled study visits were undertaken at treatment weeks 1, 2, 4, 6, 8, 10 and 12 (end of treatment), and post-treatment weeks 4 and 12. Randomisation occurred during week 5 on treatment (prior to the week 6 study visit). Study drug was dispensed at all scheduled visits (except week 1) between baseline and end of treatment (14-day supply). Study drug adherence was assessed by pill count and self-reported

adherence questionnaires at each scheduled visit between week 2 and end of treatment.

The presence of HCV RNA in plasma was assessed at all scheduled study visits using Aptima HCV Quant Dx assay, version 2.15.5 (LLoQ 10 IU/ml; Hologic, Inc., Marlborough, MA, USA), with centralised testing performed at St Vincent's Centre for Applied Medical Research (Sydney, NSW, Australia). Sequencing was conducted on HCV RNA extracted from plasma using published methods. Briefly, reverse transcription of HCV RNA was performed with random hexamers using the Invitrogen™ Superscript™ IV VILO™ Master Mix (ThermoFischer Scientific), and the Core-E2, NS5A and NS3 HCV regions were amplified by PCR.[15,16] Sanger sequencing was performed at the Australian Genome Research Facility on the Applied Biosystems™ 3730xl DNA Analyzer. Sequence curation was performed using RECall.[17] The presence of polymorphisms in NS3 and NS5A at baseline (and at virological failure when occurring) was evaluated using Geno2PhenoHCV.[18]

Study endpoints

The primary endpoint was undetectable HCV RNA below the LLoQ at 12 weeks following the completion of sofosbuvir-velpatasvir treatment (SVR12). Secondary endpoints included treatment adherence, and treatment-emergent adverse events.

Statistical analysis and sample size

The plan was to enrol and randomise 250 participants (1:1 randomisation) in the intention-to-treat (ITT) population. Given a sample size of 250 people, an assumption that the proportion achieving SVR12 would be 90% in the 12-week arm, and a lower confidence bound for an SVR12 difference (6-week arm minus 12-week arm) greater than -12%, the study had approximately 80% power to demonstrate non-inferiority of the 6-week arm compared to the 12-week arm. The non-inferiority margin of 12% was selected in accordance with the principles outlined in guidance on conducting non-inferiority trials,[19,20] with the choice of margin also taking into account the clinical significance of SVR12 in relation to stage of infection. A narrower non-inferiority margin would be justified in the setting of chronic HCV infection, particularly more advanced liver disease. In contrast, given that early intervention is being considered in the context of potential HCV treatment as prevention and elimination strategies, a broader margin was considered pragmatic and appropriate.

A data safety and monitoring board (DSMB) was established prior to trial commencement consisting of a blinded external statistician and 3 clinicians. An initial DSMB review was predetermined for when the first 50 participants in each arm reached the SVR12 visit. At this review, the DSMB requested a further analysis after a total of 60 participants reached SVR4. Following this second review, recruitment was halted in May 2019 given concerns regarding efficacy in the 6-week arm. Participants in screening or on treatment but prior to randomisation continued in the study and received 12 weeks of sofosbuvir and velpatasvir but were not randomised or included in the primary analysis population.

Primary efficacy and safety data were analysed in the ITT population (which included all randomised participants), with loss to follow-up deemed treatment failure. The modified ITT population included participants in the ITT population, but excluded those with non-virological reasons for treatment failure (including death and loss to follow-up) and reinfection. The per protocol population included participants who received >90% of scheduled treatment for >90% of the scheduled treatment period with follow-up virologic data at SVR12 (excluding reinfection and retreatments).

Categorical parameters were summarised as number and proportion. Continuous variables were summarised by either mean SD or median IQR, as appropriate. For all efficacy endpoints, means and proportions with 2-sided 95% CIs were determined. On-treatment adherence was calculated by subtracting the number of missed doses from the total number of doses prescribed for therapy duration and dividing by the total number of doses prescribed for therapy duration. Sofosbuvir-velpatasvir adherence was calculated by pill count and self-reported questionnaire. In calculating adherence, pill count took precedence over self-report if discrepancies were noted. A participant was considered adherent if that individual received ≥95% of scheduled doses for ≥95% of the scheduled treatment period. Analysis was performed using SAS (Version 9.4, SAS Institute Inc, Carey, NC, USA) and STATA (version 15.0; StataCorp, College Station, TX).

Study oversight

All participants provided written informed consent before study procedures. The study protocol was approved by Royal Adelaide Hospital 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 (NCT02625909).

Results

Baseline characteristics

Between March 2017 and July 2019, 277 individuals were assessed for eligibility. Of these, 196 were enrolled and randomised, 97 individuals into the short arm and 99 individuals into the standard arm (Fig. 1). Fifty-five individuals were excluded at screening, 38 (69%) of whom did not meet eligibility criteria, with most not meeting inclusion criteria for HCV RNA >10,000 IU/ml (Table S1). Twenty-six individuals were enrolled, but not randomised at week 6. In the majority (n = 21/26, 80%), the reason for non-randomisation was the participant being before week 6 at time of DSMB recommendation to halt short arm. These participants were immediately extended to 12 weeks. Five individuals were not randomised due to being lost to follow-up between baseline and week 6. Of 196 people randomised, 4 individuals in the short arm were at the week 6 timepoint when the DSMB recommendation was made; treatment was immediately extended to 12 weeks and these patients were excluded from the primary analysis. A further 4 participants correspondingly randomised to the standard arm at the time of the DSMB recommendation were also excluded from the primary analysis population. The final population for primary analysis thus consists of 188 participants, 93 in the short arm and 95 in the standard arm.

The demographic and clinical characteristics of participants were similar between the 2 arms (Table 1). Mean age was 44 years, and the majority of patients were male (98%) and white (84%). Seventy-four percent identified as gay and 69% were HIV positive (100% on antiretroviral therapy, median CD4 605 [IQR

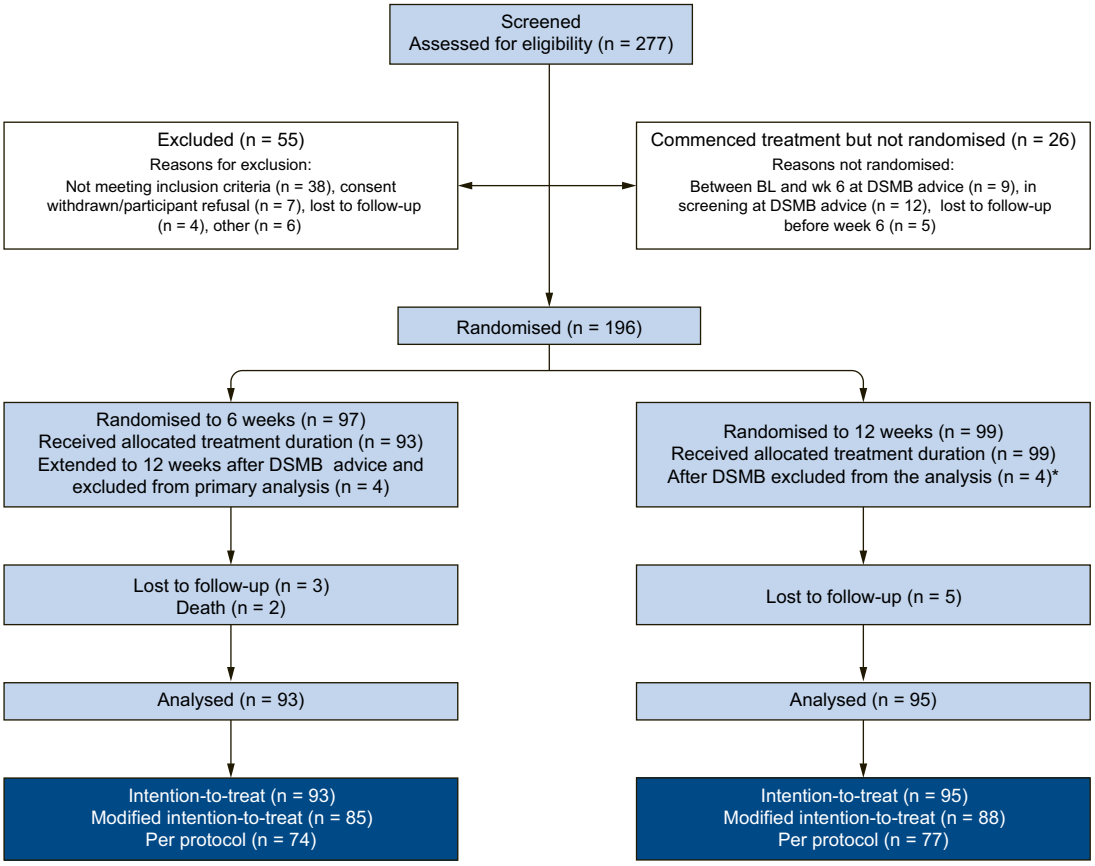

Fig. 1. Participant disposition. *These 4 participants were randomised to 12 weeks within the same timeframe as the 4 participants in short arm who were at randomisation and extended following DSMB advice and therefore excluded from the analyses. BL, baseline; DSMB, data safety and monitoring board.

Table 1. Participant demographic and clinical enrolment characteristics.

	Short duration 6 weeks		Standard duration 12 weeks		Total	
	n = 93	%	n = 95	%	188	%
Sex						
Female	2	2.2	4	4.2	6	3.2
Male	91	97.8	91	95.8	182	96.8
Recent HCV infection						
Primary infection	59	63.4	60	63.2	119	63.3
Reinfection	34	36.6	35	36.8	69	36.7
Race						
Caucasian/White	79	84.9	78	82.1	157	83.5
Asian	4	4.3	4	4.2	8	4.3
Black or African American	0	0.0	2	2.1	2	1.1
Other	9	9.7	8	8.4	17	9.0
Unknown or not reported	1	1.1	3	3.2	4	2.1
Ethnicity						
Hispanic or Latino	3	3.2	8	8.4	11	5.9
Not Hispanic or Latino	89	95.7	87	91.6	176	93.6
Unknown or not reported	1	1.1	0	0.0	1	0.5
HIV positive	65	69.9	65	68.4	130	69.1
Age (mean, SD)	44.2	10.3	43.4	10.2	43.8	10.2
Baseline HCV RNA, $\log_{10}$ IU/ml (median, IQR)	5.6	4.8-6.5	5.4	4.3-6.3	5.6	4.6-6.5
HCV genotype						
1a	58	62.4	57	60.0	115	61.2
1b	4	4.3	2	2.1	6	3.2
1 unknown subtype	1	1.1	0	0	1	0.5
2	0	0.0	4	4	4	2.1

(*continued on next page*)

Table 1. (*continued*)

	Short duration 6 weeks		Standard duration 12 weeks		Total	
	n = 93	%	n = 95	%	188	%
3	15	16.1	17	17.9	32	17.0
4	15	16.1	15	15.8	30	15.9
Mode of HCV exposure[#]						
Injecting drug use	18	19.4	22	22.2	40	21.3
Sexual exposure with person(s) of opposite sex	3	3.2	4	4.2	7	3.7
Sexual exposure with person(s) of same sex	69	74.2	66	69.5	135	71.8
Occupational (needle stick or other exposure)	0	0.0	1	1.1	1	0.5
Use of non-injectable recreational drugs	1	1.1	0	0.0	1	0.5
Other, specify[*]	2	2.2	2	2.1	4	2.1
Max ALT (median, IQR)	364	152-799	360	155-871	362	154-847
Baseline ALT (median, IQR)	114	56-257	128	69-222	126	62-250
Symptomatic presentation	16	17	14	15	30	16
Estimated duration of infection to baseline (weeks, median, IQR)	26.1	17-33.8	25.0	17-35.4	25.8	17-35.2
Injecting drug use characteristics:						
Total respondents	88		89		177	
Injecting drug use						
Never	38	43.2	40	44.9	78	44.1
Ever (total of the groups below)	50	56.8	49	55.1	99	55.9
Not recent (Last injected >6 months ago)[1]	10	20	14	28.5	24	24.2
Recent (Last injected between 1-6 months ago)[1]	14	28	14	28.	28	28.3
Current (Last injected within 30 days)[1]	26	52	21	42.9	47	47.5
In those reporting injecting drug use:						
Age at first use, median (IQR)	34.5	(24-43)	32	(19-40)	33	(21-42)
If injected in the previous 1 month, frequency[2]:						
>3x most days	0	0	0	0	0	0
2-3x most days	3	11.5	2	9.5	5	10.6
Daily	2	7.7	1	4.8	3	6.4
More than weekly, but less than daily	4	15.4	4	19.0	8	17.0
Less than weekly	9	34.6	9	42.9	18	38.3
Missing	2	7.7	2	9.5	4	8.5
Drug injected most in last month[2]						
Heroin	0	0.0	5	23.8	5	10.6
Cocaine	1	3.8	0	0.0	1	2.1
Methamphetamines (ice, base, speed, meth crystal)	12	46.2	10	47.6	22	46.8
Morphine	1	3.8	1	4.8	2	4.3
Other	3	11.5	0	0.0	3	6.4
Fentanyl	1	3.8	0	0.0	1	2.1
Missing	8	30.8	5	23.8	13	27.7
Opioid substitution therapy[3]						
Never	73	83.0	76	85.4	149	84.2
Ever:	12	13.6	8	9.0	20	11.3
Current	3	3.4	5	5.6	8	4.5
Not current	9	10.2	3	3.4	12	6.8

Denominators: [1]ever injected; [2]current (injected in last 30 days); [3]all survey respondents.
ALT, alanine aminotransferase.
[*]Jail, unknown, accidental needle stick, nasal drug use (also reported sexual exposure with other known to be HCV positive and use of non-injectable recreational drugs).
[#]Mode of exposure determined by clinician.

474-798 cells/mm^3]). Sixty-three percent had primary HCV infection whilst just over a third (37%) presented with an HCV reinfection episode. The genotype distribution included 65% (n = 122) genotype 1 (1a n = 115; 1b n = 6; 1, no subtype, n = 1), 2% (n = 4) genotype 2, 17% (n = 32) genotype 3, and 16% (n = 30) genotype 4. Median baseline HCV RNA was 5.6 $\log_{10}$ IU/ml (IQR 4.6–6.5), with baseline HCV RNA >1,000,000 IU/ml (>6 $\log_{10}$) in 38% (n = 72) and >10,000,000 IU/ml (>7$\log_{10}$) in 10% (n = 18). Median duration of HCV infection at baseline was 26 weeks (IQR 17–35).

The likely mode of HCV acquisition was deemed sexual exposure in 142 (76%), injecting drug use (IDU) in 40 (21%), non-injecting drug use in 1 (0.5%), occupational exposure in 1 (0.5%), and other or unknown in 4 (2%). Of the sexual acquisitions, the majority (n = 135/142, 95%) were same sex male-male exposures.

Risk behavioural characteristics

Most participants were in full-time employment (55%) and living in either privately owned (31%) or rental (58%) accommodation. Seventy-nine percent had undergone screening for sexually transmitted infection (STI) within the prior 12 months with 53% reporting a positive STI diagnosis (predominantly syphilis). A history of incarceration was reported in 29 participants (15%). Although IDU was reported as the most likely mode of HCV acquisition in only 40 participants, 99 of 177 (56%) reported ever having injected drugs, and of these 48% injected in last 30 days,

28% in last 1-6 months, and 24% >6 months ago. The most common drug used was methamphetamine (47%). Detailed description of risk behaviour characteristics is given in Table S2.

Treatment efficacy

In the ITT population (n = 188), the ETR was 85/93, 91.4% (95% CI 83.8–96.2) in the short arm and 87/95, 91.6% (95% CI 84.1–96.3) in the standard arm (an absolute difference in proportions of 0.2, p = 0.965). SVR12 in the short arm was 76/93, 81.7% (95% CI 72.4–89.0) and 86/95, 90.5% (95% CI 82.8–95.6) in the standard arm (Fig. 2). The difference between the arms was -8.81 (95% CI -18.6 to 1.0) with the 95% lower confidence bound for the difference falling below the pre-specified level of 12%. The criteria for non-inferiority were therefore not met. Although non-inferiority was not shown, the difference in SVR12 rates between the arms in the ITT analysis was not significant (p = 0.080). A variety of reasons for not achieving SVR12 were observed.

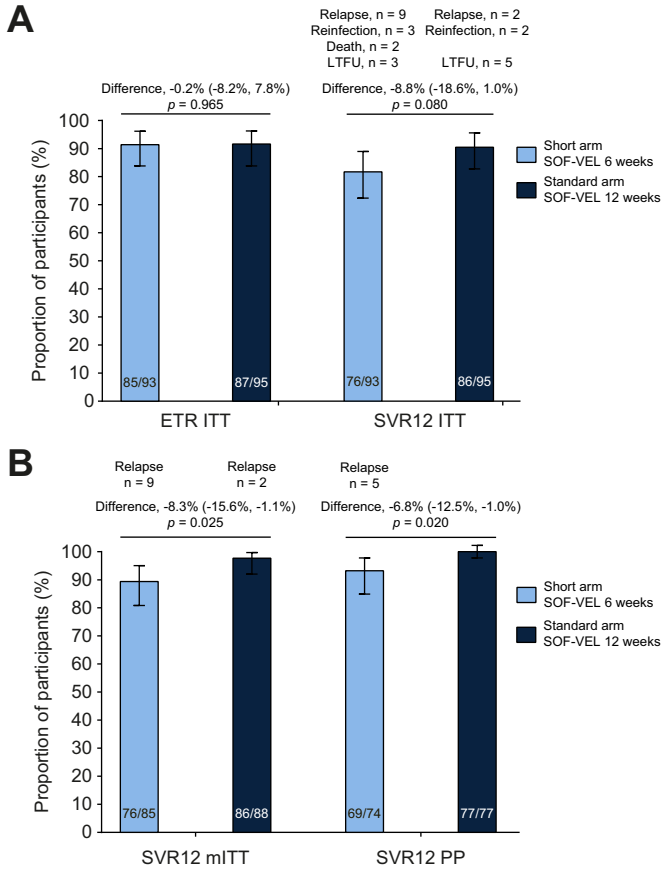

Fig. 2. Virological outcomes at end of treatment and SVR12. (A) ETR and SVR12 outcomes by ITT analysis. Proportion of patients achieving ETR and SVR12 are given in solid bars with 95% CIs for each outcome represented by line bars. The difference in proportions between the 2 arms (represented by horizontal line with 95% CI) at ETR p = 0.965 and SVR12 ITT p = 0.080 (test for equality of proportions). (B) SVR12 outcomes by mITT and PP analyses. Proportion of patients achieving SVR12 by mITT and PP analyses are given in solid bars with 95% CIs for each outcome represented by line bars. The difference in proportions between the 2 arms (represented by horizontal line with 95% CI) at SVR12 (mITT) p = 0.025 and SVR12 (PP) p = 0.020 (test for equality of proportions). ETR, end-of-treatment response; ITT, intention to treat; mITT, modified intention to treat; PP, per protocol; SVR12, sustained virological response 12 weeks after treatment end.

Overall, 2 participants died (both in short arm), 8 were lost to follow-up (3 in short arm, 5 in standard arm), 5 were re-infected (3 in short arm, 2 in standard arm) and 11 had virological relapse (9 in short arm, 2 in standard arm) (Table S3).

By modified ITT analysis in which participants with non-virological failure were excluded (including death, reinfection, lost to follow-up), SVR12 was 76/85, 89.4% (95% CI 80.8–95.0) in the short arm and 86/88 97.7% in the standard arm (95% CI 92.3–99.7; difference -8.3, p = 0.025).

In a further per protocol analysis which included only participants who were >90% adherent and attended an SVR12 visit (excluding participants who were re-infected or retreated), SVR12 was 93.2% (95% CI 84.9–97.8) in the short arm and 100% (95% CI 95.5–100.0) in the standard arm (p = 0.020).

Sixteen participants did not achieve ETR by ITT analysis, with 8 participants in each arm. In the standard arm, all 8 cases were considered ETR failures because of missing data (4 of these achieved subsequent SVR12, 3 still had missing data and 1 patient had virological failure at SVR12). In the short arm, 2 cases were because of missing data and 6 had detectable virus measured at ETR. All but 1 of these 6 patients with detectable virus subsequently achieved SVR12. Thus, only 1 patient with documented detectable virus at ETR subsequently had virological failure.

Virological recurrence

Sixteen participants within the study experienced virological recurrence at or before SVR12, 12 in the short arm and 4 in the standard arm. Sequencing from baseline and time of recurrence was performed in all 16. Five participants were identified as having reinfection – 4 on the basis of a genotype switch (1a to 3a, 1a to 4d, 3a to 1a, 4d to 1a) and 1 with the same genotype (1a) at both timepoints but with a genetic distance that indicated heterologous virus at relapse (11.4% in core-E2, 9.4% in NS5A). Eleven (5.8%) participants were classified as relapsing (9 [9.6%] in short arm, 2 [2.0%] in standard arm). All had homologous virus at the time of relapse with a genetic distance in core-E2 of <1.5% compared to baseline. Characteristics of the participants with reinfection and relapse are given in Table 2. Although limited by small numbers, no clear association with baseline characteristics was observed, although those with relapse did have a higher median baseline HCV RNA (6.7 $\log_{10}$ IU/ml, 6.8 $\log_{10}$ IU/ml for just those in the 6-week arm) and longer estimated duration of infection (30 weeks across both arms) than those who did not (5.5 $\log_{10}$ IU/ml and 25 weeks, respectively). The proportion with baseline HCV RNA >7 $\log_{10}$ IU/ml was 8% in the study population overall but 36% in the small group who relapsed. All but 1 of the participants with relapse was >95% adherent to therapy. One participant in the standard arm took only 4 weeks of treatment and subsequently relapsed. Of the 11 participants with virological failure, 8 were detected as virological relapse by SVR4, 1 at SVR12 having not been detected at SVR4, and 2 did not attend an SVR4 visit.

Adherence

Overall adherence within the study was good, although it was higher in the short *vs.* standard arm. Adherence at a level of >80% and >95% was observed in 97% and 95% of participants in the short arm, and 91% and 84% of those in the standard arm (p = 0.13 and 0.031 for >80% and >95% comparisons, respectively) (Table 3).

Table 2. Characteristics of participants with virological failure at SVR12.

Patient	Reason for viral recurrence at SVR12	Sex	Recent infection status at BL	Initial GT	GT at recurrence	Baseline HCV RNA (log IU/ml)	Mode of HCV exposure	HIV positive	Adherent (>95%)	Estimated duration of infection to BL - days	Age (years)
Standard arm											
1	RELAPSE	Male	Reinfection	1b	1b	5.96	IDU	No	No	221	57
2	REINFECTION	Male	Reinfection	1a	3a	5.00	IDU	No	Yes	380	27
3	REINFECTION	Male	Reinfection	1a	4d	6.77	Sexual	Yes	Yes	154	52
4	RELAPSE	Male	Primary	4d	4d	6.92	Sexual	Yes	Yes	134	55
Shortened arm											
1	RELAPSE	Male	Primary	1a	1a	7.43	Sexual	Yes	Yes	178	57
2	RELAPSE	Male	Reinfection	3a	3a	5.58	IDU	No	Yes	228	56
3	RELAPSE	Male	Primary	1a	1a	6.14	Sexual	Yes	Yes	208	32
4	RELAPSE	Male	Reinfection	1a	1a	6.53	Sexual	Yes	Yes	245	46
5	RELAPSE	Male	Reinfection	1a	1a	6.81	Sexual	Yes	Yes	249	47
6	REINFECTION	Male	Reinfection	1a	1a	5.74	Sexual	Yes	Yes	237	51
7	RELAPSE	Male	Primary	1a	1a	7.10	Sexual	Yes	Yes	228	45
8	RELAPSE	Male	Primary	1a	1a	7.22	Sexual	Yes	Yes	175	57
9	RELAPSE	Male	Primary	4d	4d	7.20	Sexual	Yes	Yes	85	43
10	REINFECTION	Male	Reinfection	3a	1a	3.78	Sexual	Yes	Yes	140	45
11	REINFECTION	Male	Primary	4d	1a	5.40	Sexual	Yes	Yes	229	46
12	RELAPSE	Male	Reinfection	1a	1a	6.69	IDU	Yes	Yes	183	53

BL, baseline; GT, genotype; IDU, injecting dug use; SVR12, sustained virological response at 12 weeks after treatment end.

Table 3. On-treatment adherence.

	n adherent	%	95% CI	*p* value diff (Arm 1 *vs.* 2)
80% adherence				0.136
Short arm	90	96.77	90.86–99.33	
Standard arm	86	90.52	82.78–95.58	
90% adherence				0.250
Short arm	89	95.70	89.35–98.82	
Standard arm	86	90.52	82.78–95.58	
95% adherence				0.031
Short arm	88	94.62	87.90–98.23	
Standard arm	80	84.21	75.30–90.81	
100% adherence				0.025
Short arm	78	83.87	74.80–90.68	
Standard arm	66	69.47	59.18–78.53	

Difference in proportion – Fisher's exact *p* value.

Resistance and retreatment

All 11 participants with virological relapse were sequenced for the development of NS3 and NS5A resistance-associated substitutions (RASs). Six participants had no evidence of resistance with wild-type virus at baseline and relapse. Three participants had RASs at baseline that remained unchanged at relapse (M31L, n = 1 (GT4d); Q30H + Y93H (Gt1a), n = 1; 62T, n = 1 (Gt3a)). One participant had Y93H at baseline (GT4d) that had reverted to wild-type at relapse and 1 participant had no RAS at baseline and L31M at relapse (GT1a, short arm). Thus, only 1 of 11 participants with virological relapse potentially had treatment-emergent resistance following short course treatment (L31M). Of the 11 participants with virological relapse, 9 were retreated. Retreatment regimens included sofosbuvir-velpatasvir-voxilaprevir (12 weeks, n = 4), sofosbuvir-velpatasvir (12 weeks, n = 1) and glecaprevir-pibrentasvir (8 weeks, n = 4). All achieved SVR12 apart from 1 whose outcome was unknown due to loss to follow-up.

Safety

In the randomised population of 188 participants, 2 deaths occurred, both in the short arm and following the SVR4 timepoint (at which point both participants had undetectable HCV RNA). The cause of death was illicit drug use plus ischaemic heart disease in one and unknown in the other; neither were considered treatment-related given they occurred at least 1 month following treatment cessation. Overall, 55% of participants experienced at least 1 adverse event (AEs), but only 23% experienced a treatment-related AE (22 in short arm; 21 in standard arm). Ninety-eight per cent of treatment-related AEs were Grade 1-2 with only 1 Grade 3 treatment-related AE and no Grade 4 events. The only AE occurring in >10% of the study population was fatigue, reported in 11.2% of people. Serious AEs were reported in 6 participants – 1 in the short arm and 5 in the standard arm (Table S4); only 1 was considered a possible treatment-related serious AE. This participant experienced an episode of rhabdomyolysis (rash and raised creatinine kinase) 1 week after commencing medication and was briefly hospitalised. Although the serious AE was considered possibly treatment-related and the participant was advised to stop taking treatment, medication was continued, and the episode spontaneously resolved with full completion of therapy. Therefore, no participant discontinued treatment due to AEs. Six participants discontinued treatment for non-safety reasons, 5 were lost to follow-up during the treatment period (all in the second half of therapy in the standard arm), 2 of whom subsequently returned for subsequent visits; 1 decided not to continue treatment and was subsequently lost to follow-up by SVR12 (also in standard arm).

Discussion

In this randomised study of shortened treatment duration for individuals with recent HCV, sofosbuvir-velpatasvir for 6 weeks failed to meet the pre-specified criteria for non-inferiority and the study was terminated early following the second DSMB review. The suboptimal efficacy in the short arm was driven largely by a higher post-treatment relapse, observed in 10% (n = 9) of participants compared with 2% (n = 2) of participants in the standard arm. The REACT study thus found that a 6-week course

of sofosbuvir-velpatasvir did not reach non-inferiority against the standard 12-week course in the setting of recently acquired HCV infection and cannot be considered as effective as the 12-week course.

Although virological relapse was higher in the short compared to the standard arm, there were only 11 participants in total with this endpoint, thus limiting power to detect associations. Those with relapse were slightly older, had higher baseline HCV RNA and marginally longer duration of HCV. Although none of these factors could be definitively associated with failure it is notable that the median baseline HCV RNA was 1.3log higher in the 6-week relapsers than in patients who achieved SVR12, and the median duration of infection was 5 weeks longer. This may suggest that patients without these negative prognostic factors may indeed do well with shortened therapy. Failure did not appear linked to the presence of RASs at baseline. Seven of the 11 participants with relapse had wild-type at baseline and only 1 gained a RAS (L31M) at the failure timepoint. This participant was successfully retreated with sofosbuvir-velpatasvir-voxilaprevir for 12 weeks. Retreatment was left at the discretion of the site investigator and it is noteworthy that almost all participants were retreated and achieved SVR12. These findings are encouraging for salvage from short course therapy and confirm previous findings from studies in chronic HCV infection.[21]

Short course therapy (4-6 weeks) for both acute and chronic HCV infection has been explored using a number of DAA regimens with varying success.[9,12,14,22,23] Results have generally been suboptimal in established chronic HCV infection, 1 exploratory study reported SVR rates in the region of 20–40% with 3- and 4-agent DAA regimens.[23] In a small study (n = 16) of young PWID with early liver disease (age <50 years, liver stiffness measurement <8.0 kPa) in Denmark using 4 weeks of sofosbuvir-ledipasvir plus ribavirin, SVR12 was higher at 93% by per protocol analysis with just 1 case of relapse (SVR12 ITT 75%).[24] A subsequent study by the same group and in the same target population demonstrated similar results using a combination of glecaprevir-pibrentasvir plus ribavirin with an ITT SVR of 75%.[25] A lower ITT SVR of 59% was observed in 17 patients treated with 4 weeks glecaprevir-pibrentasvir alone. Results with short course DAA therapy in the setting of acute and recent HCV infection have been more encouraging, although again somewhat varied. Two studies from Germany, 1 in HIV-negative and 1 in HIV-positive participants, evaluated sofosbuvir-ledipasvir for 6 weeks for acute HCV infection with genotype 1 or 4 and reported an ITT SVR of 100% and 77%, respectively.[10,11] A further larger study in genotype 1 and 4 using 8 weeks of grazoprevir-elbasvir, the DAHHS2 study, confirmed extremely high SVR with only 1 virological failure in 80 HIV-positive participants.[13] TARGET3D, the only study to date using a pan-genotypic regimen, reported only 1 virological failure in a smaller group of 30 individuals treated with 6 weeks of glecaprevir-pibrentasvir.[14] None of these studies was randomised and a variety of different definitions were used to characterise the often-heterogeneous study populations. In contrast, REACT is a randomised study evaluating the pan-genotypic regimen of sofosbuvir-velpatasvir; although the results appear conclusive, the study was not powered to look at differences within sub-populations and results cannot be extrapolated to all regimens and settings.

In the context of treatment of recent HCV infection among high-risk populations, there is clearly subsequent risk for HCV reinfection. Reinfections were observed in 5 (2.6%) participants at or prior to SVR12, with 4 identified by genotype switch and 1 with the same genotype confirmed through sequencing and genetic diversity evaluation. The study population had high levels of sexual and injecting risk. Although IDU was identified as the most likely route of HCV in only 21%, a history of injecting drugs was reported by 56%, 75% of whom had injected in the prior 6 months. Methamphetamine was overwhelmingly the commonest drug injected. In relation to sexual risk, over half (53%) of participants reported an STI in the prior 12 months and just under half (48%) of the HIV-negative population were receiving pre-exposure prophylaxis (PrEP). New HCV acquisitions among gay and bisexual men using PrEP appear to be increasing in several European countries,[26–28] and HCV testing should be considered as part of a routine sexual health check among those taking PrEP. Post-SVR12, HCV RNA testing was performed 3-monthly for up to 24 months in the REACT population and will provide important further insights regarding populations at risk for reinfection.

Within the REACT cohort, no safety issues were identified and adherence to therapy and protocol were high. Reported AEs were mild, and no participant had to discontinue therapy due to side effects. Adherence was high and not a factor in most treatment failures. Ninety-three per cent of participants took more than 80% of doses and 90% took more than 95% of doses. Interestingly, adherence was higher in the short arm, suggesting that short duration therapy may have advantages in terms of treatment completion. Lost to follow-up rates were also low – only 8 (4%) participants were lost before SVR12. This may in part reflect that in some REACT sites, treatment for recent HCV could only be accessed through clinical trial protocols providing additional motivation for protocol adherence, and in many sites participants were already enrolled in regular HIV care and/or opioid substitution programmes. It is also true that some participants (n = 5) were lost on-treatment prior to randomisation and are not included in this analysis.

Although this was a relatively large randomised trial, it does have a number of limitations impacting on our ability to make broad generalisations. Firstly, despite attempts to include sites likely to see a variety of individuals with HCV acquisition, including the addition of extra sites during the study period, the study population was overwhelmingly male, limiting its generalisability to females. Similarly, most participants were HIV positive and not infected through IDU. This group may be different in engagement to HIV-negative people who inject drugs, particularly in terms of patterns of drug use. Relatively few (17%) were injecting opioids although this is now the greatest source of new HCV infections across the United States.[29] Future studies should address this expanding epidemic and the role of short course therapy in this population. Third, the study population included a heterogeneous group of patients with recently acquired infection, including acute patients and those with symptomatic and asymptomatic infection. Although the small number of overall failures limited the ability to draw conclusions within sub-populations there was only 1 relapse patient in each arm with duration of infection less than 6 months at treatment commencement, while most participants had a duration of infection >6 months (median 26 weeks). Finally, sofosbuvir-velpastasvir was the only regimen evaluated in this study.

Engagement of individuals early in HCV infection is crucial for HCV elimination efforts. Despite higher relapse in the short arm,

REACT confirms that treatment initiated early in infection is safe, feasible and highly effective. Even with a relapse rate of 10% in the short arm, generation of resistance was limited and almost all participants were able to be quickly and successfully retreated. Nevertheless, acknowledging the caveats on generalisability above, REACT clearly demonstrates that, at least in this predominantly HIV-positive population, 6 weeks of sofosbuvir/velpatasvir is suboptimal and patients should be treated with at least an 8-week course[30] REACT provides important data on HCV therapeutic intervention outcomes for recent infection among a high-risk population, with implications for individual care and HCV elimination strategies.

Abbreviations

AE, adverse event; ALT, alanine aminotransferase; DAA, direct-acting antiviral; DSMB, data safety and monitoring board; ETR, end-of-treatment response; ITT, intention-to treat; LLoQ, lower limit of quantification; PrEP, population were receiving pre-exposure prophylaxis; PWID, people who inject drugs; RASs, resistance-associated substitutions; STI, sexually transmitted infection; SVR, sustained virological response; SVR12, sustained virological response 12 weeks after treatment end; ULN, upper limit of normal.

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Conflict of interest

GVM: grants from Gilead Sciences and AbbVie Inc, outside the submitted work; SB: grants from Gilead Sciences, outside the submitted work; personal fees for Advisory Boards and lectures/presentations from Gilead Sciences, outside the submitted work; MvDW: grants and personal fees from AbbVie, grants and personal fees from Gilead, grants and personal fees from Johnson & Johnson, grants and personal fees from MSD, grants and personal fees from ViiV, outside the submitted work; JR: personal fees from Gilead Sciences, Janssen, Merck, Theratechnologies and ViiV, outside the submitted work; JF: grants and personal fees from Gilead Sciences, grants and personal fees from AbbVie, personal fees from GSK, personal fees from Roche, grants from Janssen, grants from Eiger, grants and personal fees from Enanta, personal fees from Arubutus, outside the submitted work; AR: Advisory boards: MSD, Gilead Sciences, Travel grants: Gilead Sciences, Pfizer, AbbVie; Research support: Investigator initiated trial grant from Gilead Sciences. All remuneration went to his home institution and not to Dr. Rauch personally; CT: Gilead Advisory board (Remdesivir) 2020; MSD Advisory board (HCV) 2018; educational grants from Gilead and AbbVie (Annual Preceptorship on HCV in PWID), outside the submitted work; JB: grants from NIH, during the conduct of the study; personal fees from AbbVie, grants and personal fees from Gilead, outside the submitted work; AK: grants from PCORI, grants from NIH/NIAID, grants from NIH/NIA, grants from UpToDate, Inc., personal fees from Biomarin, Inc., personal fees for lectures/presentations: CME companies, Clinical Care Options companies, Mentor Planning and Practice Point, personal fees from DKBMed for communications, personal fees for academic work from Geisinger Health Systems and St. Luke's/Roosevelt, personal fees from Ken Krayesek Law Offices, personal fees from Duke University, outside the submitted work; MH: grants from Gilead Sciences, grants from AbbVie, outside the submitted work; EG: personal fees from Gilead Scientific Advisory Board, personal fees from AbbVie Scientific Advisory Board, personal fees from Janssen Scientific Advisory Board, outside the submitted work; MN: grants, personal fees and non-financial support from AbbVie, grants, personal fees and non-financial support from MSD, grants, personal fees and non-financial support from BMS, grants, personal fees and non-financial support from Gilead Sciences, payment or honoraria: Gilead, AbbVie, BMS and MSD, travel support: Gilead, AbbVie, BMS and MSD, personal fees from MBS DMSB or equivalent, outside the submitted work; PI: grants and personal fees from Gilead Sciences, personal fees from AbbVie, personal fees from ViiV, outside the submitted work; JG: grants and personal fees from AbbVie, grants and personal fees from Gilead Sciences, grants and personal fees from Merck, grants and personal fees from Cepheid, grants from Hologic, grants from Indivior, payment or honoraria: AbbVie, Gilead Sciences and Cepheid, travel support: AbbVie, Gilead Sciences and Cepheid, receipt of testing equipment and cartridges from Cepheid, receipt of testing reagents from Hologic, outside the submitted work; KP: grants from Gilead sciences Australia and ViiV Healthcare Australia, outside the submitted work; GD: grants, personal fees and non-financial support from Gilead Sciences, AbbVie and Merck, grants from Bristol-Myers Squibb, outside the submitted work; DS, MM, TA and PM: nothing to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

GVM and GJD designed and proposed the study, with study design contributions from SB, MVdV, JR, JF, AR, JB, AK, MH, EG, TA, JG, KP. GVM, GD, SB, MVdV, JR, JF, AR, CT, JB, AK, MH, EG, MR, PI were involved in participant recruitment and data collection. GVM, GD, SB, MVdV, JR, JF, AR, JB, AK, MH, EG, TA, JG, MM, PM, KP provided study governance through the Protocol Steering Committee. KP conducted the data analyses, with oversight from MM and GVM. GVM, MM and GJD drafted the manuscript, with input from all authors. All authors have seen and approved the final version of the manuscript.

Data availability statement

Due to the sensitive nature of some of the data, including that related to injecting drug use, data included in this manuscript has not been placed in an open access database. However, data is available to be shared on request to the protocol steering committee.

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Supplementary data

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