Glecaprevir-pibrentasvir for 4 weeks among people with recent HCV infection: The TARGET3D study
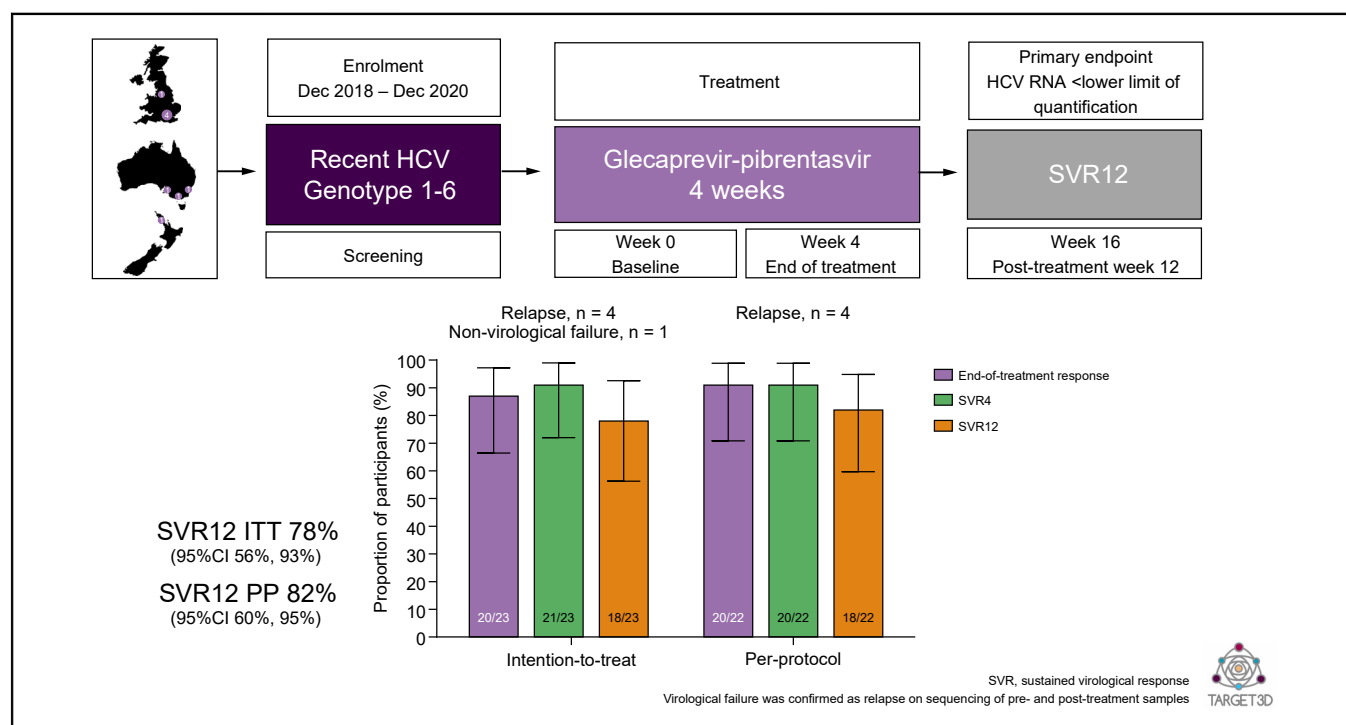
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Graphical abstract

Highlights

- We evaluated the efficacy of 4 weeks' glecaprevir-pibrentasvir in people with recent HCV infection.

- SVR12 was achieved in 78% and 82% of the ITT and PP populations, respectively, and in 100% with baseline HCV RNA ≤6 $\log_{10}$.

- There were four cases of virological failure (relapse).

- The efficacy of 4 weeks' glecaprevir-pibrentasvir was lower than observed with longer treatment durations (≥6 weeks).

Impact and implications

Short duration treatment may aid HCV elimination among key populations. This investigator-initiated single-arm multicentre international pilot trial demonstrated that efficacy of glecaprevir-pibrentasvir for 4 weeks among people with recent HCV infection was sub-optimal (SVR12 78% ITT, 82% PP). Baseline HCV RNA appeared to impact response, with higher efficacy among participants with lower baseline HCV RNA (≤6 $\log_{10}$; SVR12 100% ITT, 12/12). While most achieved SVR, the efficacy of 4 weeks of glecaprevir-pibrentasvir was below that seen with longer treatment durations (≥6 weeks).

Glecaprevir-pibrentasvir for 4 weeks among people with recent HCV infection: The TARGET3D study

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Background & Aims: Short duration treatment may aid HCV elimination among key populations. This study evaluated the efficacy of glecaprevir-pibrentasvir for 4 weeks among people with recent HCV infection.
Methods: In this single-arm multicentre international trial, adults with recent HCV (duration of infection <12 months) received glecaprevir-pibrentasvir 300 mg-120 mg daily for 4 weeks. Primary infection was defined as a first positive anti-HCV antibody and/or HCV RNA measurement within 6 months of enrolment and either acute clinical hepatitis within 12 months (symptomatic illness or alanine aminotransferase >10x the upper limit of normal) or antibody seroconversion within 18 months. Reinfection was defined as new positive HCV RNA within 6 months and prior clearance (spontaneous or treatment). The primary endpoint was sustained virological response at 12 weeks post-treatment (SVR12) in the intention-to-treat (ITT) and per-protocol (PP) populations.
Results: Twenty-three participants (96% men, 70% HIV, 57% ever injected drugs) received treatment, of whom 74% had genotype 1a infection and 35% recent reinfection. At baseline, median duration of infection was 17 weeks (IQR 11–29) and HCV RNA was 5.8 $\log_{10}$IU/ml (IQR 5.2–6.9). SVR12 was achieved by 78% (18/23; 95% CI 56–93%) and 82% (18/22; 95% CI 60–95%) of the ITT and PP populations, respectively, and in 100% (12/12; 95% CI 74–100%) of participants with baseline HCV RNA ≤6 $\log_{10}$. There were four cases of virological failure (relapse); three received retreatment with 12 weeks sofosbuvir-velpatasvir or grazoprevir-elbasvir (SVR, n = 2; loss to follow-up, n = 1). No serious adverse events were reported.
Conclusion: While most achieved SVR, the efficacy of a 4-week regimen of glecaprevir-pibrentasvir was lower than observed with longer treatment durations (≥6 weeks) among people with recent HCV.
Trial Registration: Clinicaltrials.gov Identifier: NCT02634008.
Impact and implications: Short duration treatment may aid HCV elimination among key populations. This investigator-initiated single-arm multicentre international pilot trial demonstrated that efficacy of glecaprevir-pibrentasvir for 4 weeks among people with recent HCV infection was sub-optimal (SVR12 78% ITT, 82% PP). Baseline HCV RNA appeared to impact response, with higher efficacy among participants with lower baseline HCV RNA (≤6 $\log_{10}$; SVR12 100% ITT, 12/12). While most achieved SVR, the efficacy of 4 weeks of glecaprevir-pibrentasvir was below that seen with longer treatment durations (≥6 weeks).

Introduction

Optimising the diagnosis and management of recently acquired HCV infection among key populations, including people who inject drugs (PWID) and gay, bisexual and other men-who-have-sex-with-men (GBMSM), is fundamental to HCV control and elimination strategies.[1,2] The first global hepatitis strategy was adopted by the World Health Organisation in 2016, targeting "elimination of viral hepatitis as a public health threat" by 2030. In 2020, 57 million people were estimated to be living with chronic HCV infection, with 1.5 million new infections per year.[3]

The development of direct-acting antiviral (DAA) therapy, curative oral treatment for HCV infection, has revolutionised clinical management. DAA therapy has been established as the

standard of care for chronic HCV infection, with two pan-genotypic fixed-dose combination regimens recommended as first-line treatment, glecaprevir-pibrentasvir[4] and sofosbuvir-velpatasvir.[5] Several DAA regimens have also been shown to be safe and effective in acute (duration of infection <6 months) and recent (duration of infection <12 months) HCV infection, often for a shorter duration than that used in chronic HCV infection (Table S1, Fig. S1).[1,6–14] However, no DAA regimens are approved for use in this context, despite a growing body of supportive evidence and clinical need. Cost-effectiveness analysis supports immediate treatment of acute HCV infection, given the cost savings associated with reduced transmission and potentially shorter treatment duration.[15]

Glecaprevir-pibrentasvir, an NS3/4a protease inhibitor combined with an NS5A inhibitor, is a highly effective DAA regimen prescribed for 8 weeks for treatment of chronic HCV infection.[4] Our previous pilot study evaluating 6 weeks of glecaprevir-pibrentasvir for people with recent HCV infection demonstrated high efficacy (sustained virological response at 12 weeks post-treatment [SVR12] of 96% in the per-protocol [PP] population).[9] The aim of this study was to evaluate the efficacy and safety of glecaprevir-pibrentasvir for 4 weeks among people with recent HCV infection.

Patients and methods

Study design and participants

TARGET3D Cohort Three was a prospective open-label single-arm multicentre trial in which adults with recent HCV genotype 1-6 infection received co-formulated glecaprevir-pibrentasvir 300 mg-120 mg daily for 4 weeks (administered as three 100 mg-40 mg tablets). Participants were enrolled between December 2018 and December 2020 through a network of tertiary hospital clinics in Australia (n = 3), England (n = 5) and New Zealand (n = 1). The intended sample size for this pilot study was 30 participants. However, enrolment was ceased in December 2020 due to the impact of COVID-19 on research activities.

Adults (aged ≥18 years) with recent HCV infection and HCV RNA ≥10,000 IU/ml at screening were eligible for study inclusion. Individuals with HIV co-infection on antiretroviral therapy for at least 8 weeks prior to the screening visit, with CD4 count >200 cells/mm³ and a plasma HIV RNA below the limit of detection were eligible. The following antiretroviral classes and/or agents were permitted: HIV integrase strand transfer inhibitors, HIV nucleoside reverse transcriptase inhibitors, and HIV non-nucleoside reverse transcriptase inhibitors (rilpivirine only). Individuals with acute or chronic hepatitis B co-infection were excluded.

Additional exclusion criteria included: pregnancy; breast feeding; alternative aetiology of chronic liver disease; decompensated liver disease; hepatocellular carcinoma; systemic anti-neoplastic or immunomodulatory therapy ≤6 months prior to first dose of study drug; any investigational drug ≤6 weeks prior to first dose of study drug; positive anti-HAV IgM Ab or anti-HBc IgM antibody at screening; prior treatment failure with an HCV protease inhibitor; chronic pulmonary disease with functional limitation, severe cardiac disease, organ transplantation (apart from corneal, skin or hair graft), malignancy, severe bacterial or fungal infection, or other severe illness (including psychiatric) which in the opinion of the investigator would compromise the participants safety or ability to comply with the protocol; and the following laboratory values at screening: neutrophil count

<1,500 cells/mm³, platelet count <100,000 cells/mm³, calculated creatinine clearance <50 ml/min, haemoglobin <10 g/dl.

Sites were instructed to observe participants for 4 to 12 weeks between screening and baseline, providing an opportunity to assess for spontaneous clearance.[2] The exact timing of treatment initiation was made by the investigator on an individual basis at site level.

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.[2,16] 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 6 months apart).

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 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 <10x ULN.

Estimated duration of HCV infection must have been less than 12 months at screening for inclusion in the study. The estimated date of clinical HCV 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 asymptomatic HCV infection was calculated as the midpoint between the date of 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.

Procedures

For assessment of the primary endpoints, study visits were undertaken at baseline, treatment weeks 2 and 4 (end of treatment), and post-treatment weeks 4 and 12. HCV RNA testing was performed at all scheduled study visits with centralised testing performed at St Vincent's Centre for Applied Medical Research (Sydney, NSW, Australia) using the Aptima HCV Quant Dx assay (lower limit of quantitation, 10 IU/ml).

For participants with virological failure, sequencing was undertaken on the first available samples with quantifiable HCV RNA obtained pre- (screening or baseline) and post-treatment. Reverse transcription of RNA with random hexamers was performed using the Invitrogen Superscript™ system (Vilo IV), and the Core-E2, NS5A and NS3 HCV regions were amplified by PCR.[17] Sanger sequencing was performed at the Australian Genome

Research Facility on the Applied Biosystems™ 3730xl DNA Analyzer. Sequence curation was performed using RECall.[18] Where Sanger sequencing was not successful, next-generation sequencing was performed (one participant). For next-generation sequencing, cDNA was amplified in three fragments that spanned the near full-length genome.[19] PCR amplicons were prepared for nanopore with the ONT Rapid Barcoding Kit (SQK-RBK004), according to the manufacturer's protocol and sequenced on a minION flow-cell.[20] The resulting reads were base called using Guppy (4.0.14) and aligned to a relevant HCV genome using the map to reference option in Geneious Prime version 2020.0.5 (https://www.geneious.com). Consensus-level sequences were generated before re-aligning the reads to its own consensus and recalculating the consensus genome for that sample. The presence of polymorphisms in NS3 and NS5A at baseline and virological failure were evaluated using Geno2-Pheno[HCV].[21]

Behavioural questionnaires were administered at screening, baseline, end-of-treatment, and post-treatment week 12. The questionnaire included sections on demographics (age, sex, sexual orientation, ethnicity, education, main source of income and accommodation), opioid agonist therapy (OAT; including methadone and buprenorphine), and injecting drug use. At screening, injecting drug use history was collected for lifetime (ever), previous 6 months, and previous 1 month. Recent (previous month) associated risk behaviours including use of a new sterile needle-syringe for all injections, needle-syringe borrowing and lending, and ancillary injecting equipment sharing were also collected. Study drug adherence was assessed by pill count and self-reported adherence questionnaires at treatment weeks 2 and 4 (end-of-treatment).

Outcomes

The primary efficacy endpoint was SVR12, defined as plasma HCV RNA below the lower limit of quantitation (target not detected [TND] or target detected, not quantifiable [TDnq]) at post-treatment week 12. Secondary virological endpoints included end-of-treatment response (defined as HCV RNA below the lower limit of quantitation at the end of treatment) and SVR4 (defined as plasma HCV RNA below the lower limit of quantitation at post-treatment week 4).

Statistical analysis

Primary efficacy and safety data were analysed in the intention-to-treat (ITT) population, including all participants who received at least one dose of therapy. Loss to follow-up was deemed treatment failure. The PP population included participants who completed the prescribed treatment course (adherence >90%) and had follow-up to post-treatment week 12. The primary analysis was performed after all participants had completed post-treatment week 12 (or discontinued study follow-up).

Categorical parameters were summarised as number and proportion. Continuous variables were summarised as either mean (SD) or median (IQR), as appropriate. For efficacy endpoints, proportions with two-sided 95% CIs were determined. Categorical data was analysed using the Chi-squared or Fisher's exact test. Continuous variables were analysed using the Mann-Whitney U test. 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. The proportion

with treatment-emergent adverse events was calculated, including type, severity, and relationship to study drug.

All statistical tests were two-sided with a significance level of 0.05. Analysis was performed using STATA (version 15.0; Stata-Corp, College Station, TX).

Study oversight

Participants provided written informed consent before study procedures. The study protocol was approved by St Vincent's Hospital, Sydney Human Research Ethics Committee (Australia), Northern B Health and Disabilities Ethics Committee (New Zealand), London-Riverside Research Ethics Committee (England), and local ethics and governance committees at all sites. The study was conducted according to the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice (ICH/GCP). The study was registered with clinicaltrials.gov (NCT02634008).

Role of the funding source

Results

Participant disposition and overview of the study population

Between December 2018 and December 2020, 33 individuals were screened and 23 enrolled (Fig. 1). Most participants were
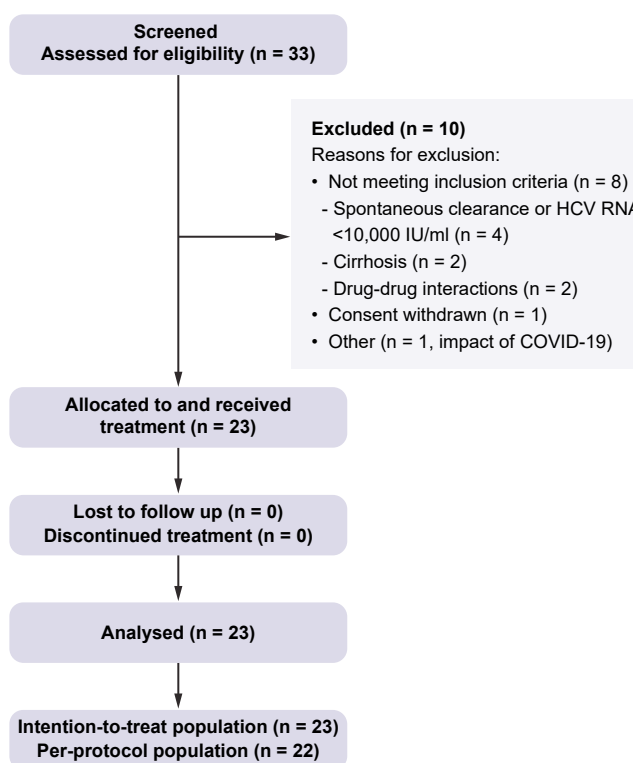

Fig. 1. Participant disposition.

male (n = 22, 96%), identified as GBMSM (n = 21, 91%), and were infected with HCV genotype 1a (n = 17, 74%) (Table 1). Recent primary HCV infection was documented in 15 (65%) and recent HCV reinfection in 8 (35%); all participants with recent HCV reinfection had previously achieved SVR following treatment. The predominant clinician-determined modes of HCV acquisition were sexual exposure among GBMSM (n = 15, 65%) and injecting drug use (n = 7, 30%) (Table 1). Median maximum ALT in the preceding 12 months was 408 U/L (range 26–1,618). Acute biochemical hepatitis with ALT >10x ULN was documented in 61% (n = 14). Three (13%) participants had a symptomatic seroconversion illness (nausea and vomiting, n = 2; abdominal pain, n = 1), but no participant had jaundice. Asymptomatic infection with maximum ALT<10x ULN was seen in 30% (n = 7). At screening and baseline, median estimated duration of infection was 15 weeks (range 5–50) and 17 weeks (range 9–52), respectively, with acute HCV infection (duration of infection <24 weeks) in 17 (74%) at screening and 9 (39%) at baseline. Median baseline HCV RNA was 5.8 $\log_{10}$ IU/ml (range 4.2–7.5), with baseline HCV RNA >1,000,000 IU/ml (>6 $\log_{10}$) in 48% (n = 11) and

>10,000,000 IU/ml (>7 $\log_{10}$) in 22% (n = 5). Median baseline ALT was 181 U/L (IQR 72–308) with a median liver stiffness measurement (Fibroscan®) of 7.0 kPa (IQR 5.1–7.8).

HIV infection was documented in 70% (n = 16), with median CD4 count 648×10^6/L (IQR 574–693) at enrolment. All participants with HIV were receiving combination antiretroviral therapy (n = 16, 100%), with HIV RNA ≤50 copies/ml at screening in 94% (n = 15). At baseline, most (n = 13, 81%) were receiving an HIV integrase strand transfer inhibitor plus two nucleoside reverse transcriptase inhibitors (Table S2). No changes to antiretroviral therapy were required prior to commencement of glecaprevir-pibrentasvir. Of the five GBMSM without HIV at enrolment, three were receiving HIV pre-exposure prophylaxis (tenofovir-emtricitabine).

Thirteen (57%) participants had ever injected drugs, with nine (39%) and six (26%) reporting injecting drug use within 6 months and 1 month of enrolment, respectively. Stimulant injecting and non-injecting use were predominant, with (meth)amphetamine use most reported (injecting: ever 52%, last 6 months 35%; non-injecting: ever 70%, last 6 months 57%) (Table S3). Among participants who reported injecting drug use, median age at first injecting drug use was 28 years (range 15–57). One participant (4%) was receiving OAT at enrolment.
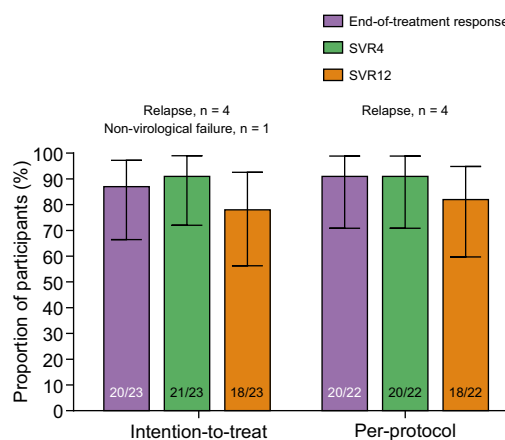
Treatment adherence and efficacy

In the ITT population, SVR12 was achieved in 78% (18/23; 95% CI 56–93%) (Fig. 2, Table 2). In the PP population, SVR12 was achieved in 82% (18/22; 95% CI 60–95%). Among participants with HIV infection, SVR12 was achieved in 75% (12/16; 95% CI 48–93%) and 80% (12/15; 95% CI 52–96%) of the ITT and PP populations, respectively (Fig. S2). Among participants with baseline HCV RNA ≤6 $\log_{10}$ IU/ml, SVR12 was achieved in 100% (12/12; 95% CI 74–100%) of the ITT population (Fig. 3). Among participants with baseline HCV RNA >6 $\log_{10}$ IU/ml, SVR12 was achieved in 55% (6/11; 95% CI 23–83%) and 60% (6/10; 95% CI 26–88%) of the ITT and PP populations, respectively (Fig. 3). Fifteen participants (65%) had baseline HCV RNA <6.5 log10 IU/ml, and all achieved SVR (15/15, 100%). For efficacy by genotype, see Fig. S2.

Adherence to therapy was high. All participants completed the 4-week course of therapy. By pill count and self-report, 100%

Table 1. Baseline characteristics.

Enrolment characteristics	Total study population (N = 23)
Age (years), median (range)	46 (20, 62)
Sex, n (%)	
Male	22 (96)
Female	1 (4)
BMI (kg/m²), median (range)	23.5 (19.7, 48.9)
Ethnicity, n (%)	
White	17 (74)
Asian	5 (22)
Latino	1 (4)
Higher education or qualification[1], n (%)	15 (65)
Full or part time employment, n (%)	15 (65)
HIV infection, n (%)	16 (70)
Mode of HCV acquisition, n (%)	
Injecting drug use	7 (30)
Sexual exposure – same sex	15 (65)
Sexual exposure – opposite sex	1 (4)
Estimated duration of infection (weeks)	
At screening, median (IQR)	15 (8, 24)
At baseline, median (IQR)	17 (11, 29)
Presentation of recent HCV, n (%)	
Acute clinical illness – symptomatic	3 (13)
Jaundice	0
Nausea/vomiting	2 (9)
Abdominal pain	1 (4)
Acute clinical illness - ALT >10x ULN	14 (61)
Asymptomatic seroconversion (with ALT <10x ULN)	7 (30)
ALT (U/L), median (range)	
Peak ALT prior to enrolment	408 (26, 1618)
At screening	226 (47, 1430)
At baseline	181 (45, 1091)
Log_{10} HCV RNA at baseline, median (IQR)	5.8 (5.2, 6.9)
HCV genotype and subtype, n (%)	
1a	18 (78)[2]
2a	1 (4)
3a	2 (9)
4[3]	2 (9)
Median liver stiffness measurement (Fibroscan®), kPa (IQR)	7.0 (5.1, 7.8)

ALT, alanine aminotransferase; ULN, upper limit of normal.
[1] Completed higher technical qualification, college or university degree.
[2] One participant had mixed infection with genotype 1 and 6.
[3] One participant had genotype 4d and one 4, no subtype.

Fig. 2. Primary and secondary efficacy endpoints in the intention-to-treat (N = 23) and per-protocol (n = 22) populations. The per-protocol population excluded one participant – non-virological failure after achieving SVR4. SVR4/ 12, sustained virological response at 4/12 weeks post treatment.

Table 2. HCV RNA response during and post-treatment – primary and secondary efficacy endpoints.

Response	Intention-to-treat population (N = 23)	Per-protocol population (n = 22)
HCV RNA <LLOQ, n (%)		
On treatment		
Week 2	15 (65)	15 (68)
Week 4 (end of treatment)	20 (87)	20 (91)
Post-treatment, n (%)		
Post-treatment week 4	21 (91)	20 (91)
Post-treatment week 12	18 (78)	18 (82)
Virological failure, n (%)		
Relapse	4 (17)	4 (18)
Non-virological failure, n (%)		n.a.
Death	0	
Loss to follow-up	0	
Other*	1 (4)	

DAA, direct-acting antiviral; LLOQ, lower limit of quantification; TDnq, target detected, not quantifiable; TND, target not detected.
* Other – DAA retreatment prescribed for participant after achieving SVR4 (local testing: HCV RNA TDnq; central testing: HCV RNA TND).

and 96% of participants achieved adherence of >90% and >95%, respectively, with median on-treatment adherence of 100%. Virological suppression at end of treatment was documented in 87% (20/23; 95% CI 66–97%) (Fig. 2). At week two, 65% had HCV RNA below the lower limit of quantitation (Table 2; Fig. S3). Of three participants with quantifiable HCV RNA at week four (end of treatment), two achieved SVR12 and one achieved SVR4 (non-virological failure; see next section for details). A rapid biochemical response on treatment was observed. Median ALT at baseline was 181 U/L (IQR 72–308), declining at week four (end of treatment) to 22 U/L (IQR 18–29) (Fig. 4, Table S4).
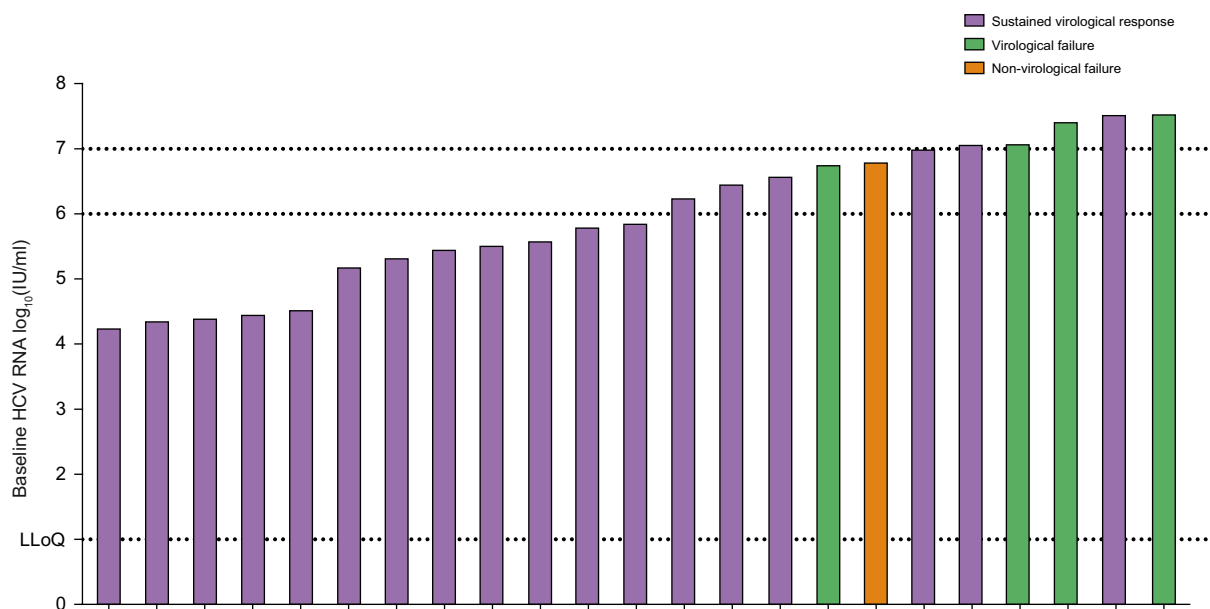
Treatment failure

Of those participants who did not achieve SVR12 (n = 5), there were four cases of virological failure and one case of non-

virological failure. In the case of non-virological failure, one participant achieved SVR4 (local HCV RNA TDnq; central HCV RNA TND), but was commenced on sofosbuvir-velpatasvir for 12 weeks between post-treatment week 4 and 12. SVR12 was confirmed following the second course of DAA therapy.

Virological failure, confirmed as relapse on sequencing, was observed in four (17%) participants, with genotype 1a (n = 3) and genotype 4d (n = 1) infection (Table 3). Relapse was diagnosed at 28-, 28-, 91- and 136-days post-treatment, respectively (at study visits for post-treatment week 4 [n = 2] and post-treatment week 12 [n = 2]). Among those with virological relapse, baseline HCV RNA ranged between 6.7 and 7.5 $\log_{10}$ IU/ml. All achieved an end of treatment response, with HCV RNA below the limit of quantification (HCV RNA TDnq, n = 2; HCV RNA TND, n = 2), and all were adherent to >90% of the prescribed 4-week treatment course; one participant reported missing nine tablets overall with on-treatment adherence of 93%. No significant NS3 or NS5a resistance-associated polymorphisms were detected prior to or following treatment. At the discretion of site investigators, three participants with virological failure were prescribed retreatment with sofosbuvir-velpatasvir for 12 weeks (n = 1; commenced 45 days following end of treatment) or grazoprevir-elbasvir for 12 weeks (n = 2; commenced 69- and 192-days following end of treatment); two achieved SVR12 and one was lost to follow up.

Safety

One or more adverse events were reported by eight participants (35%), all of mild or moderate severity (Table 4). Treatment-related adverse events were reported by four participants (17%). The most common adverse event (and the only one that occurred in >5% of the study population) was headache (n = 4, 17%). No serious treatment-emergent adverse events or deaths were reported. During follow up, one participant was diagnosed with both genital herpes simplex virus infection and *Neisseria gonorrhoea* infection (throat and rectum).

Fig. 3. Treatment outcome by baseline HCV RNA. Participants who achieved sustained virologic response are depicted in the purple bars, while those with virological and non-virological failure are depicted in the green and orange bars, respectively.
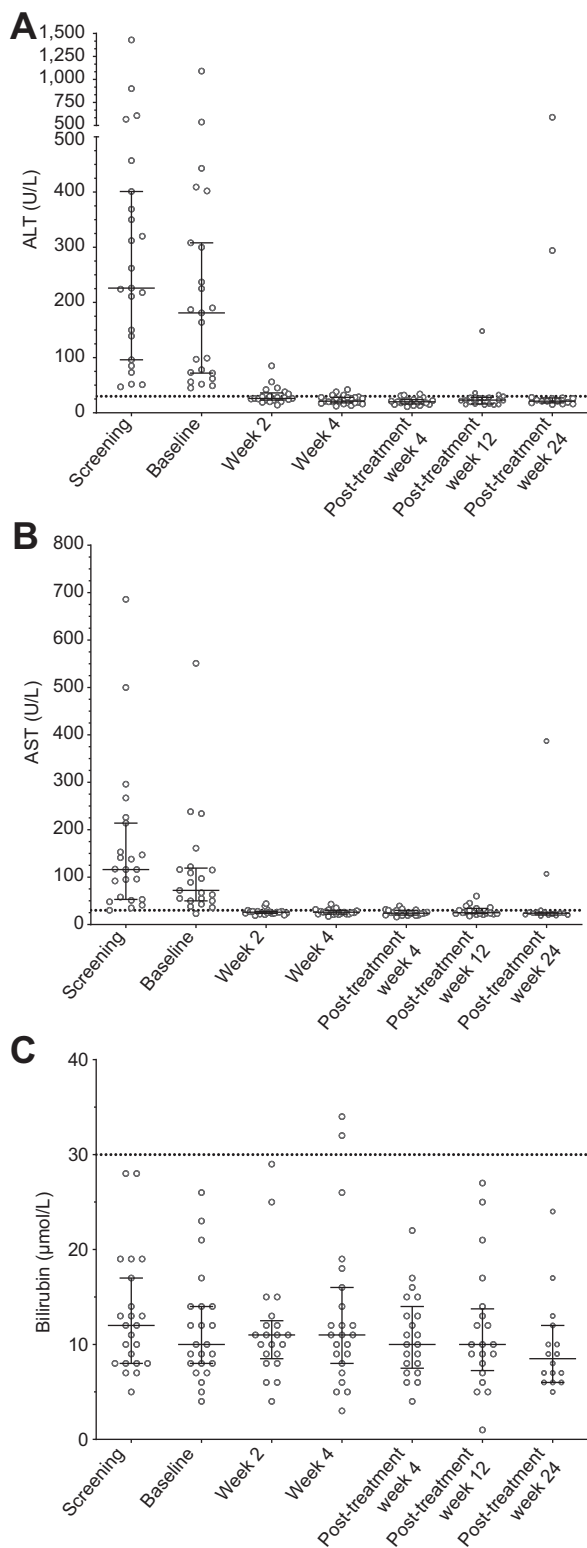
Fig. 4. Change in ALT, AST, and total bilirubin prior to, on and post-treatment. (A) ALT; (B) AST; (C) total bilirubin. Bars depict median and IQR. Dotted line at ULN for each parameter – ALT, ULN 30 U/L; AST, ULN 40 U/L; total bilirubin, ULN 18 umol/L. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Discussion

Glecaprevir-pibrentasvir for four weeks was safe and well-tolerated among people with acute and recent HCV infection. Treatment resulted in rapid HCV RNA suppression and normalisation of liver enzymes. Few treatment-related adverse events were reported, with no serious adverse events. However, lower efficacy was seen following glecaprevir-pibrentasvir for four weeks as compared with glecaprevir-pibrentasvir and other contemporary DAA regimens, including sofosbuvir-velpatasvir and grazoprevir-elbasvir, for longer durations (≥six weeks). Efficacy appeared to be associated with baseline HCV RNA; all participants with baseline HCV RNA <6.5 $\log_{10}$ IU/ml achieved SVR (15/15, 100%). Conversely, most participants with baseline HCV RNA >7$\log_{10}$ IU/ml (3/5, 60%) experienced virological failure.

Clinical trials have demonstrated that several pan-genotypic and genotype-specific DAA regimens are safe and effective among people with acute and recent HCV infection. To date, sofosbuvir-velpatasvir has been most comprehensively evaluated in this population. In a phase three international open-label randomised non-inferiority trial, sofosbuvir-velpatasvir for six weeks was not non-inferior to 12 weeks, with lower efficacy in the six-week arm (SVR12 ITT 82%; 76/93; 95%CI 72%, 89%) than the 12-week arm (SVR12 ITT 91%; 86/95; 95%CI 83%, 96%).[6] In the PP analysis (adherence >90%, attended follow-up at post-treatment week 12), SVR12 was 93% in the six-week arm (95%CI 84, 95) and 100% in the 12-week arm (95%CI 96, 100). In small single arm pilot trials, high efficacy was also seen with sofosbuvir-velpatasvir for eight weeks (n = 20; SVR12 PP 100%)[8] and glecaprevir-pibrentasvir for six weeks (n = 30; SVR12 PP 96%).[9] Using genotype-specific regimens, high efficacy (>95%) was reported with eight weeks of grazoprevir-elbasvir (SVR12 PP 96%-99%),[7,10] paritaprevir-ritonavir-ombitasvir and dasabuvir (SVR12 PP 100%),[11] and sofosbuvir-ledipasvir (SVR12 PP 100%).[12] Six weeks of sofosbuvir-ledipasvir demonstrated similarly high efficacy among people without HIV infection (SVR12 PP 100%), but lower efficacy among GBMSM with HIV (SVR12 PP 87%).[13,14] In comparison with previous studies, the efficacy of glecaprevir-pibrentasvir for four weeks in this trial was sub-optimal (SVR12 PP 82%). Further evaluation of glecaprevir-pibrentasvir among people with acute HCV infection is ongoing, with other trials assessing the efficacy of treatment for four (NCT04042740) and eight weeks (NCT04903626).

Baseline HCV RNA appears to impact efficacy with short (≤6 weeks) duration therapy, with higher levels associated with post-treatment relapse in acute[6,9,14,22] and chronic[23,24] HCV infection. Among GBMSM with HIV who received sofosbuvir-ledipasvir for six weeks, three cases of virological relapse occurred in participants with high baseline HCV RNA (>6.9 $\log_{10}$ IU/ml).[14] Among people who received sofosbuvir-velpatasvir for six weeks, median baseline HCV RNA was >1$\log_{10}$ higher among people with relapse (6.9 $\log_{10}$ IU/ml) as compared with the overall study population (5.5 $\log_{10}$ IU/ml).[6] Among people who received glecaprevir-pibrentasvir for six weeks, one case of virological relapse was observed in a participant with very high baseline HCV RNA (7.7 $\log_{10}$ IU/ml).[9] In this study, participants with relapse had baseline HCV RNA ranging between 6.7 and 7.5 $\log_{10}$ IU/ml, while all participants with baseline HCV RNA <6.5 $\log_{10}$ IU/ml achieved SVR. Baseline HCV RNA appeared to have less impact on efficacy among people with acute and recent HCV who received DAA therapy for eight weeks, regardless of

Table 3. Characteristics of participants with virological failure.

Sex Age	HIV IDU	Recent HCV status[1] Genotype	Baseline HCV RNA, $\log_{10}$ IU/ml	Virological failure Time to diagnosis[2]	Adherence	RAS[3]	Retreatment Prescribed DAA regimen Outcome
Male 37	Yes Yes	Reinfection 1a	7.4	Relapse 91 days	97%	No	No
Male 55	No Yes	Primary 1a	7.1	Relapse 28 days	100%	No	Yes Sofosbuvir-velpatasvir 12 wk SVR
Male 49	Yes Yes	Reinfection 1a	7.5	Relapse 136 days	100%	No	Yes Grazoprevir-elbasvir 12 wk SVR
Male 28	Yes No	Primary 4d	6.7	Relapse 28 days	93%	No	Yes Grazoprevir-elbasvir 12 wk Lost to follow-up (wk 4)

DAA, direct-acting antiviral; IDU, injecting drug use; RAS, resistance associated substitution.
[1] At enrolment.
[2] Time to diagnosis: Days between end of treatment and diagnosis of virologic failure.
[3] No significant NS3 or NS5a resistance-associated polymorphisms detected pre- or post-treatment.

regimen.[7,8,10–12] Therapeutic strategies involving shorter durations are still being evaluated and may be particularly useful among key populations and in specific settings.

Predicting who is likely to respond to short duration DAA therapy would have implications for models of care in "difficult-to-reach" populations, including people in prison (particularly those on remand) and people who are hospitalised for serious injecting-related infection, mental health, and drug-related comorbidities. Simplified models are required for broad treatment uptake; adding complexity would be counter to elimination efforts. However, with increasing use and availability of point-of-care HCV RNA testing, quantitative HCV RNA results are available at diagnosis. A "test and treat" strategy with treatment duration based on point-of-care HCV RNA could be evaluated, improving cost and adherence. Determining the necessary effective treatment duration may also assist in development of long-acting injectable DAA therapy (potentially co-formulated with long-acting OAT). A targeted "test and treat" (and retreat) strategy, with point-of-care HCV RNA testing and shortened duration DAA therapy among at risk populations, may be one cost-effective public health strategy to eliminate HCV.[25,26]

While virological failure following DAA therapy for acute and recent HCV infection is uncommon with currently available regimens, retreatment can be successfully prescribed if required. For people who fail first-line DAA therapy for chronic HCV infection,

sofosbuvir-velpatasvir-voxilaprevir for 12 weeks is commonly used as salvage therapy,[27] with other retreatment regimens including glecaprevir-pibrentasvir for 16 weeks[28] and sofosbuvir plus glecaprevir-pibrentasvir for 12 or 16 weeks.[29] Among people with virological failure following treatment for acute and recent HCV infection, various retreatment regimens have been used, including sofosbuvir-velpatasvir-voxilaprevir for 12 weeks, sofosbuvir-velpatasvir for 12 weeks, glecaprevir-pibrentasvir for eight weeks, and grazoprevir-elbasvir for 12 weeks,[6,9] with many receiving retreatment with what would be considered first-line therapy for chronic HCV (as seen among participants who received retreatment in this trial). Additionally, emergence of clinically significant resistance-associated substitutions has occurred rarely among this population, with no role for resistance-associated substitution testing to guide individualised retreatment regimens. No significant NS3 or NS5a resistance-associated polymorphisms were detected prior to or following glecaprevir-pibrentasvir for four or six weeks,[9] and only one participant (genotype 1a infection) had a treatment-emergent resistance-associated substitution (baseline: wild-type; relapse: L31M) following sofosbuvir-velpatasvir for six weeks.[6] There have been no documented cases of virological failure among people retreated with either a standard or salvage regimen after DAA treatment failure for acute and recent HCV infection.

Limitations of this study include sample size, generalisability of the study population, and limited number of non-genotype 1 infections in the enrolled population. The study population was largely composed of white gay and bisexual men with HIV infection, a group who are likely to be more engaged with healthcare and are not necessarily representative of other populations at risk of HCV acquisition, including PWID with opioid use disorder. This is particularly important given increasing HCV incidence among populations of PWID in low-middle income countries and the United States. Few women or people from culturally and linguistically diverse groups, and limited numbers of people with non-genotype 1 infection have been recruited in studies evaluating DAA therapy for treatment of acute and recent HCV infection.

Enhanced diagnosis and treatment of people with recent HCV infection is necessary to achieve HCV elimination, with targeted interventions required among populations with high incidence. High HCV incidence among key populations, including PWID, people in prison and GBMSM with HIV, highlights the need for further strategic development, with optimal therapeutics

Table 4. Safety and adverse events.

Adverse events	ITT (N = 23)
Participants reporting any AE up to 30 days after last dose, n (%)	8 (35)
Grades 1-2, n (%)	8 (35)
Grade 3, n (%)	0
Grade 4, n (%)	0
Participants reporting treatment-related AE up to 30 days after last dose, n (%)	4 (17)
Grades 1-2, n (%)	4 (17)
Grade 3, n (%)	0
Grade 4, n (%)	0
Serious treatment-emergent adverse event, n (%)	0
Treatment-related serious adverse event, n (%)	0
Treatment discontinuation due to adverse event, n (%)	0
Death, n (%)	0
Common AEs (≥5% of study population), n (%)	
Headache	4 (17)

AE, adverse event.

administered alongside harm reduction and infection prevention. HCV treatment-as-prevention efforts will be enhanced by the immediate commencement of DAA therapy in people with recent HCV. Favourable efficacy and safety of contemporary DAA regimens among people with acute and recent HCV infection, combined with the current standard of care for people with chronic HCV infection supports treatment of all people with HCV infection, regardless of duration.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100867.

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