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Shortened therapy of eight weeks with paritaprevir/ritonavir/ombitasvir and dasabuvir is highly effective in people with recent HCV genotype 1 infection

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Summary

Paritaprevir/ritonavir/ombitasvir and dasabuvir with or without ribavirin for 12 weeks are approved for treatment of chronic HCV genotype 1 infection. This study assessed the efficacy of shortened duration paritaprevir/ritonavir/ombitasvir and dasabuvir with or without ribavirin for 8 weeks among people with recent HCV infection. In this open-label single-arm trial conducted in Australia, England and New Zealand, adults with recent HCV (duration of infection <12 months) received paritaprevir/ritonavir/ombitasvir and dasabuvir (with weight-based ribavirin for genotypes 1a and 1, no subtype) for 8 weeks. The primary endpoint was sustained virological response at 12 weeks post-treatment (SVR12) in the intention-to-treat (ITT) population. Thirty people (median age 38 years, male 93%) commenced treatment (with ribavirin, 97%), of whom 77% (n = 23) were HIV-positive, 93% (n = 28) had genotype 1a infection and 53% (n = 16) had ever injected drugs. Median maximum ALT in the preceding 12 months was 433 IU/L (IQR 321, 1012). Acute clinical hepatitis with ALT > 10 x ULN was documented in 83% (n = 25); one participant (3%) had jaundice. At baseline, median estimated duration of infection was 30 weeks (range 11, 51), and median HCV RNA was 5.7 $\log_{10}$ IU/mL (range 2.7, 7.3). SVR12 was achieved in 97% (29/30; early discontinuation at week 2, n = 1; per protocol 100%, 29/29). No relapse or reinfection was observed. In conclusion, paritaprevir/ritonavir/ombitasvir and dasabuvir (with ribavirin) for eight weeks were highly effective among HIV-positive and HIV-negative individuals with recent HCV infection. These data support the use of this shortened duration direct-acting antiviral regimen in this population.

KEYWORDS
acute, direct-acting antiviral, hepatitis C, recent, treatment

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1 | INTRODUCTION

Globally, an estimated 1.75 million new HCV infections occurred in 2015, with at-risk populations including people who inject drugs (PWID) and HIV-positive gay and bisexual men (GBM).[1-3] With interferon-free direct-acting antiviral (DAA) therapy established as the standard of care for chronic HCV infection, the optimal management of acute (within 6 months) and recent (within 12 months) HCV is yet to be defined. Very high efficacy (sustained virological response, SVR) and safety are observed with dual- or triple-class DAA regimens for eight to 12 weeks in chronic HCV infection, particularly among treatment-naïve individuals without cirrhosis.[4-7]

Current recommendations for the treatment of acute HCV infection are based on expert opinion.[8,9] The paradigm of enhanced efficacy with shortened duration interferon-based therapy in recent, as compared with chronic HCV infection, underpins current research questions.[10] Clinical trials evaluating shortened duration DAA regimens in acute and recent HCV infection are underway, with early data providing encouraging results.[11,12] Screening strategies in at-risk populations recommend at least annual HCV testing.[8,9,13,14] If these recommendations are adhered to, HCV primary infection and reinfection should be diagnosed within the first year of acquisition. As individuals diagnosed with recent HCV infection are interested in considering treatment,[15] this initial assessment represents an ideal opportunity for intervention, with benefits at both an individual level and the population level, largely related to averting onward transmission.[16-18] Cost-effectiveness analysis supports immediate treatment of acute HCV with short-duration DAA therapy as compared with treatment deferral until chronic infection, given cost savings associated with shorter treatment duration and reduced transmission.[18]

Paritaprevir/ritonavir/ombitasvir and dasabuvir with or without ribavirin for 12 weeks are approved and recommended as first-line treatment for chronic HCV genotype 1 infection.[8,9] The aim of this study was to assess the efficacy and safety of shortened duration paritaprevir/ritonavir/ombitasvir and dasabuvir with or without ribavirin for 8 weeks in individuals with recent HCV infection (estimated duration of infection <12 months).

2 | METHODS

2.1 | Study design and participants

Treatment of recently AcquiRed GEnoType 1 hepatitis C with the 3D regimen (TARGET3D) was a prospective open-label single-arm multicenter trial in which adults with recent HCV genotype 1 infection received paritaprevir/ritonavir/ombitasvir and dasabuvir for 8 weeks, with weight-based ribavirin (<75 kg: 1000 mg/d; ≥75 kg: 1200 mg/d) for genotype 1a and genotype 1, no subtype. Participants were enrolled between June 2016 and February 2017 through a network of tertiary hospitals in Australia (n = 1), England (n = 4) and New Zealand (n = 1).

Adults (age ≥18 years) with recent HCV genotype 1 infection and HCV RNA ≥10 000 IU/mL at screening were eligible for study inclusion. Individuals with HIV co-infection on stable combination antiretroviral therapy (cART) for at least 8 weeks prior to screening visit, with CD4 count >200 cells/mm^3 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 (INSTI; dolutegravir and raltegravir only), HIV protease inhibitors (unboosted atazanavir and darunavir only) and HIV nucleoside reverse transcriptase inhibitors. Individuals with acute or chronic hepatitis B co-infection were excluded. See Supporting information for the complete inclusion and exclusion criteria.

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 alanine aminotransferase (ALT) greater than ten times the upper limit of normal (ULN). The estimated date of asymptomatic HCV infection was calculated as the mid-point 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. See Supporting information for further details.

Study sites were instructed to observe participants for four to 12 weeks between screening and baseline, providing an opportunity to assess for spontaneous clearance.[14] The exact timing of treatment initiation was made by the investigator on an individual basis at site level.

All participants provided written informed consent before study procedures. The study protocol was approved by St Vincent's Hospital, Sydney Human Research Ethics Committee (primary study committee), as well as local ethics committees at all study sites. The study 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 (NCT02634008).

2.2 | Procedures

Study visits were undertaken at baseline, treatment weeks two, four, six and eight (end of treatment) and post-treatment weeks four, 12 and 24. The presence of HCV RNA in plasma was assessed at all scheduled study visits using Aptima HCV Quant Dx assay, version 2.15.5 (lower limit of quantitation [LLoQ] 10 IU/mL; Hologic, Inc., Marlborough, MA, USA). Behavioural questionnaires were administered at screening, baseline, end of treatment and post-treatment weeks 12 and 24. Study drug adherence was assessed by pill count and self-reported adherence questionnaires at treatment weeks two, four, six and eight (end of treatment).

2.3 | Outcomes

The primary efficacy endpoint was SVR12, defined as plasma HCV RNA below the lower limit of quantitation (LLoQ; target not

detected [TND] or target detected, not quantifiable [TDnq]) at post-treatment week 12. Secondary virological endpoints included end-of-treatment response (ETR; defined as HCV RNA below the LLoQ at the end of treatment), SVR4 (defined as plasma HCV RNA below the LLoQ at post-treatment week 4) and SVR24 (defined as plasma HCV RNA below the LLoQ at post-treatment week 24).

2.4 | Statistical analysis

Primary efficacy and safety data were analysed based on 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 per-protocol (PP) population includes participants who completed the prescribed 8-week treatment course 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 summarized as number and proportion. Continuous variables were summarized by either mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. For all efficacy endpoints, means and proportions with two-sided 95% confidence intervals (CI) were determined. Categorical data were analysed using the chi-squared or Fisher's exact test. Continuous variables were analysed using the Mann-Whitney U test. The proportion of individuals engaging in IDU and associated risk behaviours during treatment and follow-up were assessed up until post-treatment week 12. Changes in injecting behaviour between screening, end of treatment and post-treatment week 12 were compared using the McNemar test (exact binomial probability). On-treatment adherence was calculated for each medication individually (paritaprevir/ritonavir/ombitasvir coformulated once daily, dasabuvir twice daily, ribavirin twice daily) 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. All statistical tests were two-sided with a significance level of 0.05. The analysis was performed using Stata (version 15.0; StataCorp, College Station, TX).

3 | RESULTS

3.1 | Participant disposition and overview of the study population

Between 23 June 2016 and 24 February 2017, 35 individuals were screened and 30 enrolled (Figure 1). Participants were predominantly male (n = 28, 93%), most of whom identified as GBM (n = 26, 87%), with genotype 1a infection (n = 28, 93%; genotype 1b, n = 1, 3%; genotype 1, no subtype, n = 1, 3%) (Table 1). Recent primary HCV infection was demonstrated in 26 (87%) and recent HCV reinfection in 4 (13%). Clinician-determined modes of HCV acquisition were sexual exposure in GBM (n = 21, 70%), injecting drug use (IDU; n = 8, 27%) and occupational exposure (n = 1, 3%). Median maximum ALT in the preceding

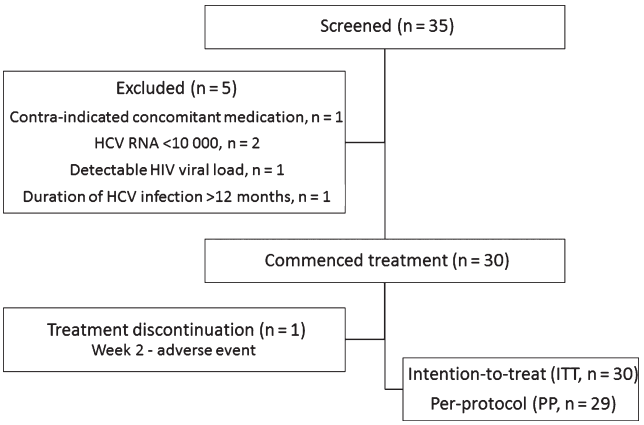

FIGURE 1 Participant disposition

12 months was 433 IU/L (range 19, 3660). Acute clinical hepatitis with ALT > 10 x ULN was documented in 83% (n = 25); one participant (3%) had jaundice. At screening and baseline, median estimated duration of infection was 26 weeks (range 7, 46) and 30 weeks (range 11, 51), respectively. Median baseline HCV RNA was 5.7 $\log_{10}$ IU/mL (range 2.7, 7.3), with baseline HCV RNA >1 000 000 IU/mL (>6 $\log_{10}$) in 43% (n = 13) and >10 000 000 IU/mL (>7 $\log_{10}$) in 17% (n = 5).

HIV co-infection was documented in 77% (n = 23; male 96%, female 4%). Median CD4 count was 640 x 10^6/L. All HIV-positive participants were receiving combination antiretroviral therapy (cART; n = 23, 100%). At screening, most (n = 16, 70%) were receiving an INSTI (dolutegravir or raltegravir) plus two nucleoside reverse transcriptase inhibitors. Seven (30%) required alterations to their antiretroviral regimen in the light of potential drug-drug interactions, including changing from a non-nucleoside reverse transcriptase inhibitor or boosted protease inhibitor to an INSTI (n = 3) and temporary cessation of a pharmacokinetic boosting agent (ritonavir or cobicistat, n = 4) (Table S1). Of the four HIV-negative GBM enrolled, none were receiving HIV pre-exposure prophylaxis.

Sixteen (53%) participants had ever injected drugs, with 12 (40%) reporting IDU within 6 months of enrolment (Table S2). (Meth)amphetamine use was predominant. Of the 16 participants who reported ever using (meth)amphetamine, all had used one or more drugs in this class by both injecting and noninjecting routes of administration. Among participants who reported IDU, median age at first injecting was 29 years (range 17, 52). Median duration of IDU prior to estimated date of HCV infection was 2.1 years (median 0.9, 4.1). Among those reporting IDU within 1 month of enrolment (n = 6), the drugs most often injected were methamphetamine (n = 4, 67%) and heroin (n = 2, 33%), with five (85%) reporting use of sterile needles, syringes and equipment for all recent injections.

3.2 | Efficacy

By ITT analysis, SVR12 was achieved in 97% (29/30; 95% CI 83%, 100%) (Figure 2; Table S3). By PP analysis, SVR12 was 100% (29/29; 95% CI 88%, 100%). Among participants with HIV co-infection, SVR12 was 100% (23/23; 95% CI 85%, 100%). Among participants

TABLE 1 Patient baseline characteristics

	ITT population (n = 30)
Participant characteristics	
Age (y), median (IQR)	30 (22, 38)
Gender, n (%)	
Male	28 (93)
Female	2 (7)
Race, n (%)	
Asian	6 (20)
Black or African American	2 (7)
White	20 (67)
Mixed	2 (7)
Weight (kg), median (IQR)	72.4 (64.6, 76.4)
BMI (kg/m^2), median (IQR)	22.9 (21.7, 24.9)
Higher education or qualification[a], n (%)	23 (77)
Full- or part-time employment, n (%)	23 (77)
HIV infection, n (%)	23 (77)
CD4 count (10^6/L), median (IQR)	640 (528, 829)
HIV RNA ≤50 copies/mL, n (%)	23 (100)
Combination antiretroviral therapy, n (%)	23 (100)
Characteristics of recent HCV infection	
HCV infection type	
Primary	26 (87)
Reinfection	4 (13)
HCV genotype/subtype, n (%)	
1a	28 (93)
1b	1 (3)
1, unable to subtype	1 (3)
Estimated duration of infection (weeks)	
At screening, median (IQR)	26 (16, 32)
At baseline, median (IQR)	30 (21, 36)
Acute HCV[b], n (%)	13 (43)
Baseline HCV RNA	
Log_{10} IU/mL, median (IQR)	5.7 (5.2, 6.6)
>6 log_{10} IU/mL, n (%)	13 (43)
Mode of HCV acquisition, n (%)	
Injecting drug use	8 (27)
Sexual exposure—gay and bisexual men	21 (70)
Occupational	1 (3)
Presentation of recent HCV, n (%)	
Acute clinical hepatitis	25 (83)
Jaundice	1
ALT > 10 × ULN	25
Asymptomatic infection	5 (17)
ALT (U/L), median (IQR)	
Peak ALT prior to enrolment	433 (321, 1012)
ALT at screening	215 (109, 419)
Median liver stiffness measurement (Fibroscan®), kPa (IQR)	5.8 (4.6, 6.4)
Time from diagnosis of acute HCV to baseline (weeks), median (IQR)	23 (16, 26)

[a]Completed higher technical qualification/college/university degree.
[b]Acute HCV infection (duration of infection <24 wk) at screening.

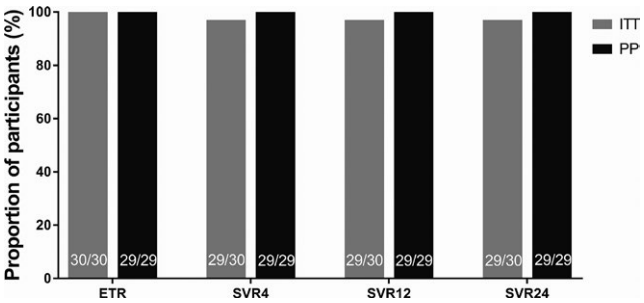

FIGURE 2 Primary and secondary efficacy endpoints, by intention-to-treat (n = 30) and per-protocol (n = 29) analyses. The per-protocol population excludes one participant who discontinued treatment at week 2. ETR, end-of-treatment response;ITT, intention to treat; pp, per protocol; SVR, sustained virological response

with HCV mono-infection, SVR12 was 86% (6/7; 95% CI 42%, 100%; PP 100%, 6/6) (Table S4). High baseline HCV RNA did not impact efficacy, with SVR12 100% (13/13; 95% CI 75%, 100%) among participants with baseline HCV RNA >6 log_{10} IU/mL, including five participants with baseline HCV RNA >7 log_{10} IU/mL (Figure 3).

Treatment failure was observed in one (3%) participant who discontinued after two weeks in the context of hospitalization for an unrelated adverse event. HCV RNA was quantifiable at week four post-treatment (HCV RNA 5.7 log_{10} IU/mL), having been below the LLoQ (TDnq) at discontinuation. At this point, the participant withdrew from the study.

Virological suppression at end of treatment was documented in 100% (30/30; 95% CI 85%, 100%) (Figure 2). In the PP population (n = 29), at weeks two, four, six and eight, 77%, 93%, 100% and 100% had HCV RNA below the LLoQ, with 21%, 66%, 90% and 97% being HCV RNA TND, respectively (Figure S1). One participant had HCV RNA below the LLoQ (TDnq) at week eight (end of treatment) and post-treatment week four, and achieved SVR with HCV RNA TND at post-treatment week 12. Median time to HCV RNA below the LLoQ and HCV RNA TND was 14 days (range 13, 42) and 28 days (range 14, 140), respectively. Baseline HCV RNA and HIV infection did not significantly impact HCV RNA kinetics (Figure S2). A rapid biochemical response on treatment was observed (Figure 4); median ALT at baseline, week two and end of treatment was 152 U/L (IQR 122, 377), 34 U/L (IQR 28, 49) and 21 U/L (IQR 16, 27), respectively (*P* for trend <.001) (Table S5).

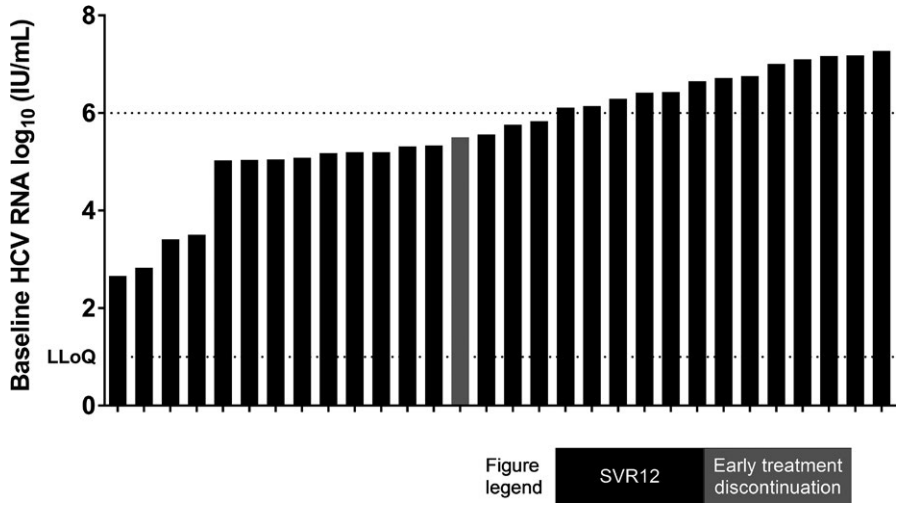

FIGURE 3 Treatment outcome by baseline HCV RNA. Median baseline HCV RNA was 5.7 $\log_{10}$ IU/mL (range 2.7-7.3), with baseline HCV RNA >1 000 000 IU/ml (>6 $\log_{10}$) in 43% (n = 13). Shortened duration paritaprevir/ritonavir/ombitasvir and dasabuvir (with ribavirin) for 8 weeks was highly effective (SVR12 ITT 97%, PP 100%), among people with high baseline HCV RNA (>6 $\log_{10}$ IU/mL; SVR12 ITT 100%). Sustained virological response (SVR)

Among the 29 participants who completed treatment and remained in follow-up, no virological failure, post-treatment relapse or reinfection was observed up to post-treatment week 24 (SVR24 ITT 97% [29/30, 95% CI 83%, 100%]; SVR24 PP 100% [29/29, 95% CI 88%, 100%]).

3.3 | Treatment adherence

Adherence to therapy was high among the 29 (97%) participants (per-protocol population) who completed the scheduled 8-week treatment course (28 of whom received ribavirin). By pill count, paritaprevir/ritonavir/ombitasvir adherence >90% and 100% were 97% (n = 28) and 83% (n = 24), respectively, with mean on-treatment adherence 98% (SD 6%). By pill count, dasabuvir adherence >90% and 100% were 93% (n = 27) and 79% (n = 23), respectively, with mean on-treatment adherence 98% (SD 4%). By pill count, ribavirin adherence >90% and 100% were 89% (n = 25) and 86% (n = 24), respectively, with mean on-treatment adherence 98% (SD 6%).

Two participants did not demonstrate >90% paritaprevir/ritonavir/ombitasvir or dasabuvir adherence by pill count. The first participant had 70% paritaprevir/ritonavir/ombitasvir, 85% dasabuvir and 100% ribavirin adherence (with 100% adherence to week 4), and the second had 91% paritaprevir/ritonavir/ombitasvir, 82% dasabuvir and 77% ribavirin adherence. Both achieved SVR12.

By self-report, paritaprevir/ritonavir/ombitasvir and dasabuvir adherence >90% and 100% were 93% (n = 27) and 76% (n = 22), respectively, with mean on-treatment adherence 99% (SD 5%).

3.4 | Safety

One or more adverse events were reported by 29 (97%) participants, with the majority being of mild severity (Table 2). Treatment-related adverse events were reported by 20 participants (67%), all of mild or moderate severity. Three serious adverse events (SAEs) were reported in three participants, none related to the study drugs. The three SAEs were (i) hospitalization for management of migraine, (ii) hospitalization for management of renal haematoma and (iii) hospitalization for investigation of syncope and hypertension. The last case related to the participant who discontinued treatment prematurely (week 2). Study drugs were ceased on hospital admission by the treating team and the participant subsequently withdrew from the study. All SAEs resolved without sequelae.

No significant haematological toxicity was noted (Table 2; Table S5). Median decline in haemoglobin between baseline and end of treatment was 10 g/L (IQR 3, 23). No ribavirin dose modification was required. In those with HIV infection, median decline in CD4 count at end of treatment was 80 x 10^6/L (IQR 48, 201) with no loss of HIV virological control.

3.5 | Longitudinal behavioural assessment

Injecting drug use risk behaviour (in the past 30 days) was assessed during study follow-up. The proportion reporting recent IDU was 20% (n = 6) at enrolment, 20% (n = 6) at baseline, 17% (n = 5) at end of treatment, 10% (n = 3) at post-treatment week 12 and 10% (n = 3) at post-treatment week 24. There was no significant change in injecting drug use between enrolment or baseline and end of treatment (P = .636) or post-treatment week 12 or 24 (P = .111). Among participants reporting recent IDU, the proportion reporting needle and syringe sharing was 17% (n = 1) at enrolment, 40% (n = 2) at baseline, 33% (n = 1) at post-treatment week 12 and 33% (n = 1) at post-treatment week 24. No one reported needle and syringe sharing between baseline and end of treatment.

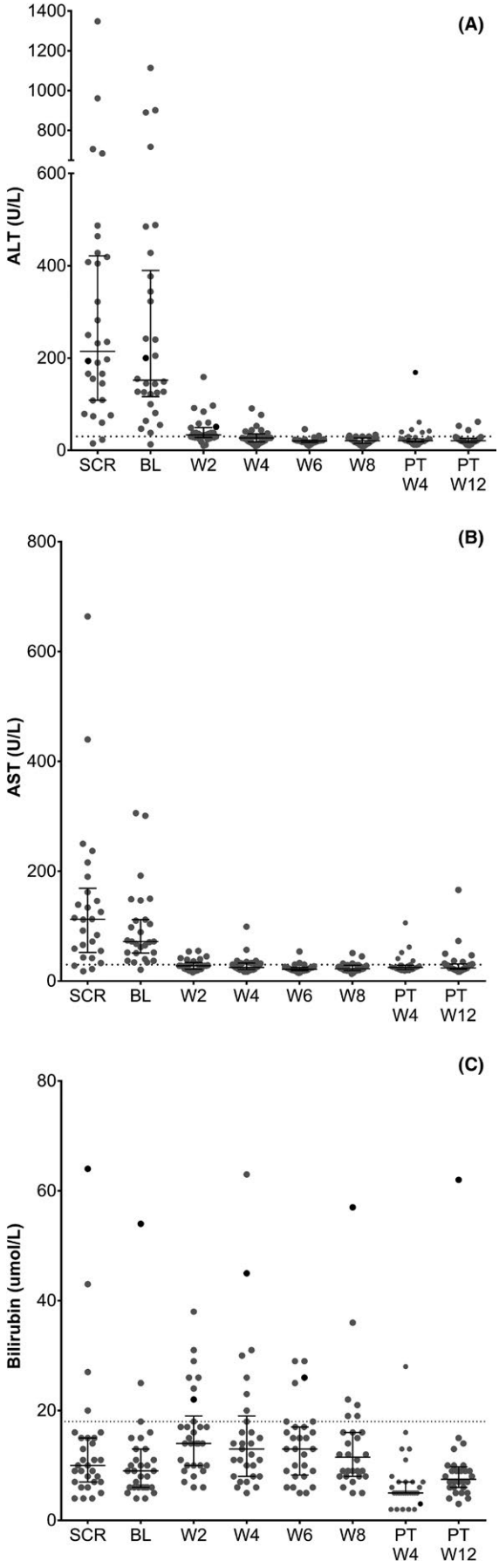

FIGURE 4 Change in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin prior to, on and post-treatment. Panel A: ALT. Panel B: AST. Panel C: Total bilirubin. Bars depict median with interquartile range. Dotted line at upper limit of normal (ULN) for each parameter—ALT and AST, ULN 30 U/L; total bilirubin ULN 18 μmol/L. In Panel A, black circle indicates the participant who discontinued treatment at week 2. In Panel C, black circle indicates a HIV-positive participant receiving ritonavir-boosted atazanavir. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; EOT, end of treatment; PT W12, post-treatment week 12; SCR, screening; ULN, upper limit of normal

4 | DISCUSSION

Shortened duration paritaprevir/ritonavir/ombitasvir and dasabuvir (with ribavirin) for 8 weeks was highly effective, safe and well tolerated among people with acute and recent HCV genotype 1 infection (SVR12 ITT 97%, PP 100%), including people with HIV co-infection (SVR12 ITT 100%) and high baseline HCV RNA (>6 $\log_{10}$ IU/mL; SVR12 ITT 100%). Treatment resulted in rapid HCV RNA suppression and normalization of liver enzymes. No virological failure or post-treatment relapse was seen following shortened duration therapy.

With little evidence to guide practice, current international recommendations for the management of acute HCV infection are conservative and based on expert opinion.[8,9] The 2016 AASLD/IDSA guidelines support "the same [DAA] regimens for acute HCV as recommended for chronic HCV infection" (level of evidence: class IIa, level C),[8] while the 2016 EASL guidelines recommend sofosbuvir plus an NS5A inhibitor (ledipasvir, velpatasvir or daclatasvir) for 8 weeks, with a longer duration of 12 weeks for those with HIV and/or baseline HCV RNA >1 000 000 IU/mL (>6 $\log_{10}$ IU/mL; level of evidence: class IIb, level C).[9] As with the excellent results observed in this study, pilot studies of shortened duration dual- and triple-class DAA regimens for four, six and 8 weeks have demonstrated promising results in acute and recent HCV infection. In cohorts of acute HCV genotype 1 mono-infection, high SVR was demonstrated with four[11] (n = 14, SVR12 ITT 100%) and six[12] weeks (n = 20, SVR12 ITT 100%) of sofosbuvir/ledipasvir and 8 weeks of sofosbuvir plus simeprevir[11] (n = 15, SVR12 ITT 87%; PP 100%). Among HIV-positive GBM with acute HCV genotypes 1a and 4, lower SVR (n = 26, SVR12 ITT 77%; PP 87%) was demonstrated with 6 weeks of sofosbuvir/ledipasvir[19]; the three cases of relapse occurred in participants with high baseline HCV RNA (>6.9 $\log_{10}$ IU/mL). Very recently, excellent efficacy was reported with 8 weeks of sofosbuvir/ledipasvir (n = 27, SVR12 ITT 100%) among HIV-positive GBM[20]; in this cohort, median baseline HCV RNA was 6.2 $\log_{10}$ IU/mL (IQR 4.5, 6.6). Combined, these studies offer exciting potential, suggesting that, as with interferon-based therapy, DAA treatment duration may be reduced in recent as compared with chronic HCV infection.

Key differences in study design (including eligible study population, duration of infection, baseline HCV RNA) limit comparison between studies. While the EASL guidelines suggest stratification

TABLE 2 Safety and adverse events

Adverse events	ITT population (N = 30)
Clinical adverse events	
Participants reporting any AE up to 28 days after last dose, n (%)	29 (97)
Grades 1-2, n (%)	28
Grade 3, n (%)	1
Grade 4, n (%)	0
Participants reporting treatment-related AE up to 28 days after last dose, n (%)	20 (67)
Grades 1-2, n (%)	20
Grade 3, n (%)	0
Grade 4, n (%)	0
Serious adverse event, n (%)	3 (10)
Treatment-related serious adverse event, n (%)	0
Treatment discontinuation due to adverse event, n (%)	1 (3)
Treatment discontinuation due to treatment-related adverse event, n (%)	0
Death, n (%)	0
Adverse events	
Common (≥10% of study population), n (%)	
Fatigue	9 (30)
Diarrhoea	8 (27)
Headache	7 (23)
Insomnia	6 (20)
Influenza-like illness	4 (13)
Mood swings	4 (13)
Nasopharyngitis	4 (13)
Dizziness	3 (10)
Dry skin	3 (10)
Haematological parameters	
Baseline haemoglobin, g/L (median, IQR)	147 (141, 156)
Decline in haemoglobin at end of treatment, g/L (median, IQR)	10 (3, 23)
Haemoglobin [a], n (%)	
Grade 2	0
Grade 3	0
Grade 4	0
Platelet count, cell/mm^3 [n (%)]	
50 000-99 999	0
25 000-49 999	0
<25 000	0
Biochemical parameters	
Baseline alanine aminotransferase, U/L (median, IQR)	152 (122, 377)
Decline in alanine aminotransferase at end of treatment, U/L (median, IQR)	115 (76, 320)
Baseline total bilirubin, mmol/L (median, IQR)	9 (6, 13)
Total bilirubin, n (%)	
>2.5-3.0 mg/dL (43-51 mmol/L)	0
>3.0 mg/dL (>51 mmol/L)	2 (7) [b]

[a]At any time during treatment and up to 28 days post.
[b]One participant was on atazanavir, with elevated bilirubin from screening.

of treatment duration in acute HCV by HIV serostatus and baseline HCV RNA,[9] there is no definitive evidence to suggest that treatment duration should be extended to 12 weeks in these subpopulations. In this study, neither baseline HCV RNA nor HIV infection impacted upon the efficacy of 8 weeks of paritaprevir/ritonavir/ombitasvir and dasabuvir. Similarly, 8 weeks of sofosbuvir/ledipasvir was highly effective in HIV-positive GBM with acute HCV, regardless of baseline HCV RNA.[20] In pilot studies to date of short (≤6 weeks)-duration DAA therapy, baseline HCV RNA did appear to impact efficacy, with higher baseline HCV RNA associated with post-treatment relapse in studies of both acute[19,21] and chronic[22,23] HCV infection. To robustly evaluate the efficacy of short-duration (≤6 weeks) DAA therapy in recent HCV infection, optimal DAA regimen choice will be paramount. As modelling suggests that induction of a rapid second-phase viral decline could permit shorter treatment duration,[24] the evaluation of a potent dual- or triple-class second-generation DAA regimen, which includes an HCV NS3/4A protease inhibitor and NS5A inhibitor, would be ideal. The potential role of ribavirin in shortened duration DAA regimens remains uncertain.

Limitations of this study include sample size, relative specificity of the population and the use of a genotype-specific DAA regimen. As the study population was composed predominantly of GBM enrolled through tertiary clinics, a group engaged with health care, it may not be representative of PWID populations more broadly. TARGET3D, as with the other DAA studies in acute and recent HCV to date, was restricted to participants with HCV genotype 1 infection. Studies of short-duration pan-genotypic DAA therapy in well-characterized populations will be extremely valuable in determining the utility of DAA therapy in recent HCV infection and may permit a markedly simplified management strategy suitable for broad clinical implementation. TARGET3D, Parts Two and Three (NCT02634008), is examining the efficacy and safety of glecaprevir/pibrentasvir for 6 and 4 weeks, respectively, in recent HCV infection; Part Two is open to recruitment. DAHHS-2 (NCT02600325) is evaluating the efficacy of grazoprevir/elbasvir for 8 weeks in people with acute HCV genotypes 1 and 4 and HIV co-infection. REACT (NCT02625909), an international randomized control trial, is examining the efficacy and safety of short (6 weeks) versus standard duration (12 weeks) sofosbuvir/

velpatasvir for recent HCV infection (n = 250). These studies will further enhance our understanding of the utility of short-duration DAA therapy in recent HCV infection.

With high HCV incidence in populations of PWID and HIV-positive GBM, determining the optimal timing of treatment initiation, duration of therapy and DAA regimen choice in recent infection are important, including treatment of reinfection. To achieve HCV elimination targets,[25] increased diagnosis and treatment of recent HCV infection will be required.[16] If short-duration therapy with a pan-genotypic DAA regimen is shown to be highly effective in individuals in the first year following infection acquisition, this will have significant implications for screening and treatment strategies in high-risk populations. Access to HCV care and treatment for people at high risk of onward transmission, including those with recent HCV infection, should be a priority.[26]

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CONFLICT OF INTERESTS

MM has received speaker payments from AbbVie.

SB has participated in advisory boards and is on the speaker's bureau for AbbVie and Gilead.

EG has participated in the advisory boards and also in speakers' bureau for Gilead Sciences Inc, Janssen and AbbVie.

CO has received honoraria for advisory boards, lecture fees and travel scholarships from MSD, Janssen, Gilead, ViiV and AbbVie, and has received research grant funding from all the above.

GC is a consultant/advisor for and has received grant funding from Gilead and MSD.

GJD is an advisory board member and has received honoraria from Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb and AbbVie, has received research grant funding from Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb, Vertex, Boehringer Ingelheim and AbbVie, and travel sponsorship from Roche, Merck, Janssen, Gilead, and Bristol-Myers Squibb.

KP has received unrestricted grant funding grants from Boehringer Ingelheim Pty Ltd, Bristol-Myers Squibb Australia Pty Ltd, Gilead Sciences Pty Limited, Janssen-Cilag Pty Ltd, Merck Sharp & Dohme (Australia) Pty Ltd, ViiV Healthcare.

ET, TLA, PM, NP, AS declares no conflict of interests.

JG is a consultant/advisor and has received research grants from AbbVie, Bristol-Myers Squibb, Cepheid, Gilead Sciences Inc and Merck.

MN has received advisory board payments, speaker payments and research funding from AbbVie, Bristol-Myers Squibb, Gilead and MSD.

GVM has received research funding, advisory board payments and speaker payments from Gilead and AbbVie, and research funding and speaker payments from Janssen.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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