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VIRAL HEPATITIS

Short-Duration Pan-Genotypic Therapy With Glecaprevir/Pibrentasvir for 6 Weeks Among People With Recent Hepatitis C Viral Infection

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BACKGROUND AND AIMS: Among treatment-naive individuals with chronic hepatitis C viral (HCV) infection and without cirrhosis, glecaprevir/pibrentasvir for 8 weeks is recommended. The aim of this analysis was to evaluate the efficacy of glecaprevir/pibrentasvir for 6 weeks in people with acute and recent HCV infection.

APPROACH AND RESULTS: In this open-label, single-arm, multicenter, international pilot study, adults with recent HCV (duration of infection < 12 months) received glecaprevir/pibrentasvir 300/120 mg daily for 6 weeks. Primary infection was defined by first positive anti-HCV antibody and/or HCV RNA within 6 months of enrollment and either acute clinical hepatitis within the past 12 months (symptomatic seroconversion illness or alanine aminotransferase > 10 × upper limit of normal) or anti-HCV antibody seroconversion within 18 months. Reinfection was defined as new positive HCV RNA within 6 months of enrollment and evidence of prior spontaneous or treatment-induced clearance. The primary endpoint was sustained virologic response at 12 weeks posttreatment (SVR12). Thirty men (median age 43 years, 90% men who have sex with men) received treatment, of whom 77% (n = 23) were human immunodeficiency virus–positive, 47% (n = 14) had ever injected drugs, and 13% (n = 4) had HCV reinfection. The majority had HCV genotype 1 (83%, n = 25), followed by genotype 4 (10%, n = 3) and genotype 3 (7%, n = 2). At baseline, median estimated duration of infection was 29 weeks (range 13, 52) and median HCV RNA was 6.2 $\log_{10}$ IU/mL (range 0.9, 7.7). SVR12 in the intention-to-treat and per-protocol populations was achieved in 90% (27/30) and 96% (27/28), respectively. There was one case of relapse, and there were two cases of nonvirological failure (death, n = 1; loss to follow-up, n = 1). No treatment-related serious adverse events were seen.

CONCLUSIONS: Glecaprevir/pibrentasvir for 6 weeks was highly effective among people with acute and recent HCV infection, supporting further evaluation of shortened-duration pan-genotypic therapy in this setting. (Hepatology 2020;72:7-18).

Interferon-free direct-acting antiviral (DAA) therapy provides the therapeutic tools required for hepatitis C virus (HCV) control and elimination ("treatment-as-prevention").[1] For an HCV

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; DAA, direct-acting antiviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; ITT, intention to treat; LLoQ, lower limit of quantitation; MSM, men who have sex with men; NS5A and NS3, nonstructural proteins 5A and 3; PP, per-protocol; PWID, people who inject drugs; SVR12, sustained virologic response at 12 weeks posttreatment; ULN, upper limit of normal.

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treatment-as-prevention strategy to be effective, there must be broad coverage of HCV testing, expedient linkage of new HCV diagnoses to care and treatment, and targeted interventions in populations with high HCV prevalence and incidence. In 2015, an estimated 1.75 million people were newly infected with HCV, with key at-risk populations including people who inject drugs (PWID) and human immunodeficiency virus (HIV)–positive men who have sex with men (MSM).[2] Optimizing the diagnosis and management of acute HCV infection, particularly in these priority populations, is fundamental to an HCV elimination strategy.

While DAA therapy is established as the standard of care for chronic HCV infection, no DAA regimens are approved for use in acute HCV, despite a growing body of evidence for its effectiveness in this context.[2] Current international guidelines on the management of acute HCV are based on limited data and expert opinion.[3,4] Cost-effectiveness analysis supports immediate treatment of acute HCV compared with deferral until chronic infection, given the cost savings associated with shorter treatment duration and reduced transmission.[5] Pilot studies evaluating shortened-duration DAA therapy have demonstrated very promising results but have been limited by sample size and the genotype-specific regimens used (reviewed in Martinello et al.[2]). To date, the largest trial of DAA therapy among people with acute HCV showed high efficacy with 8 weeks of grazoprevir/elbasvir among people with HCV genotypes 1 and 4 (n = 80, sustained virologic response at 12 weeks posttreatment [SVR12] intention to treat [ITT] 94%).[6]

Glecaprevir/pibrentasvir is a highly effective pangenotypic DAA regimen prescribed for 8 weeks in treatment-naive individuals with chronic HCV and without cirrhosis. The aim of this study was to assess the efficacy and safety of shortened-duration glecaprevir/pibrentasvir for 6 weeks in individuals with recent HCV infection, with an estimated duration of infection less than 12 months.

Participants and Methods

STUDY DESIGN AND PARTICIPANTS

TARGET3D Cohort Two was a prospective, open-label, single-arm, multicenter trial in which adults with recent HCV genotype 1-6 infection received coformulated glecaprevir/pibrentasvir 300/120 mg daily for 6 weeks (administered as three 100/40-mg tablets). Participants were enrolled between October 31, 2017, and August 7, 2018, through a network of

Potential conflict of interest: Dr. Martinello is on the speakers' bureau for AbbVie. Dr. Orkin advises, is on the speakers' bureau for, and received grants from Gilead, ViiV/GlaxoSmithKline, Janssen, and MSD. Dr. Cooke consults for Gilead and is on the speakers' bureau for MSD. Dr. Bhagani is on the speakers' bureau for and received grants from AbbVie and Gilead. Dr. Gane advises, is on the speakers' bureau for, and received grants from AbbVie. He advises and is on the speakers' bureau for Gilead. He advises Janssen. Dr. Petoumenos consults and received grants from ViiV. She received grants from Gilead and Janssen. Dr. Grebely consults, advises, is on the speakers' bureau for, and received grants from AbbVie, Gilead, Merck/MSD, and Cepheid. Dr. Dore advises, is on the speakers' bureau for, and received grants from Gilead, AbbVie, and Merck. Dr. Nelson consults and received grants from MSD, ViiV, Gilead, and AbbVie. He advises and received grants from Bristol-Myers Squibb. He advises Cipla, Hetero, and GlaxoSmithKline. Dr. Matthews received grants from AbbVie and Gilead.

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tertiary hospital clinics in Australia (n = 2), England (n = 5), and New Zealand (n = 1).

Adults (age ≥ 18 years) with recent HCV infection and HCV RNA ≥ 10,000 IU/mL at screening were eligible for study inclusion. Individuals with HIV coinfection on antiretroviral therapy for at least 8 weeks prior to the screening visit, with cluster of differentiation 4 (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 (INSTIs; dolutegravir, raltegravir, and elvitegravir/cobicistat), HIV nucleoside reverse transcriptase inhibitors, and HIV non-nucleoside reverse transcriptase inhibitors (rilpivirine only). Individuals with acute or chronic hepatitis B coinfection were excluded.

Additional exclusion criteria included pregnancy; breastfeeding; alternative etiology of chronic liver disease; decompensated liver disease; hepatocellular carcinoma; systemic antineoplastic 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–hepatitis A virus immunoglobulin M antibody or anti–hepatitis B core immunoglobulin M 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 participant's safety or ability to comply with the protocol; and the following laboratory values at screening: neutrophil count < 1,500 cells/mm^3, platelet count < 100,000 cells/mm^3, calculated creatinine clearance < 50 mL/minute, hemoglobin < 10 g/dL.

Recent primary HCV infection was defined as initial detection of anti-HCV antibody and/or HCV RNA within 6 months of enrollment and either (1) documented recent HCV seroconversion (anti-HCV antibody–negative result in the 18 months prior to enrollment), (2) acute clinical hepatitis (jaundice or alanine aminotransferase [ALT] > 10 × upper limit of normal [ULN]) within the previous 12 months with the exclusion of other causes of acute hepatitis, or (3) acute asymptomatic hepatitis (acute rise in ALT >5 × ULN) within the previous 12 months with the exclusion of other causes of acute hepatitis.[7,8] Recent HCV reinfection was defined as new detectable HCV RNA within 6 months of enrollment and evidence of prior spontaneous or treatment-induced clearance (previous positive anti-HCV antibody and undetectable HCV RNA on two or more 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 > 10 × 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 <10 × ULN.

Estimated duration of HCV infection must have been < 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 < 10 × ULN. The estimated date of asymptomatic HCV 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 enrollment, regardless of symptom status.

Sites were instructed to observe participants for 4-12 weeks between screening and baseline, providing an opportunity to assess for spontaneous clearance.[8] 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 (Australia), Northern B Health and Disabilities Ethics Committee (New Zealand), and London-Riverside Research Ethics Committee (England), 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 guidelines. The study was registered with clinicaltrials.gov (NCT02634008).

PROCEDURES

Study visits were undertaken at baseline; treatment weeks 2, 4, and 6 (end of treatment); and posttreatment weeks 4 and 12. 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), with centralized testing performed at St. Vincent's Centre for Applied Medical Research (Sydney, NSW, Australia).

For participants with virological failure, reverse transcription of RNA with random hexamers was performed using the Invitrogen Superscript system (Vilo IV), and the Core-E2, nonstructural protein 5A (NS5A), and NS3 HCV regions were amplified by polymerase chain reaction.[9,10] Sanger sequencing was performed at the Australian Genome Research Facility on the Applied Biosystems 3730xl DNA Analyzer. Sequence curation was performed using RECall.[11] The presence of polymorphisms in NS3 and NS5A at baseline and virological failure were evaluated using Geno2Pheno[HCV].[12]

Behavioral questionnaires were administered at screening, baseline, end of treatment, and posttreatment week 12. The questionnaire included sections on demographics (age, gender, sexual orientation, ethnicity, education, main source of income, and accommodation), opioid substitution treatment (including methadone and buprenorphine), and injecting drug use. At screening, injecting drug use history was collected for lifetime (ever), previous 6 months (current), and previous month (recent). Recent (previous month) associated risk behaviors 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, 4, and 6 (end of treatment).

OUTCOMES

The primary efficacy endpoint was SVR12, defined as plasma HCV RNA below the LLoQ (target not detected or target detected, not quantifiable) at posttreatment week 12. Secondary virological endpoints included end-of-treatment response (defined as HCV RNA below the LLoQ at the end of treatment) and SVR4 (defined as plasma HCV RNA below the LLoQ at posttreatment week 4).

STATISTICAL ANALYSIS

Primary efficacy and safety data were analyzed based on the 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 included participants who completed the prescribed treatment course and had follow-up to posttreatment week 12. The primary analysis was performed after all participants had completed posttreatment 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 or median and interquartile range (IQR), as appropriate. For all efficacy endpoints, means and proportions with two-sided 95% confidence intervals (CIs) were determined. Categorical data were analyzed using the chi-squared or Fisher's exact test. Continuous variables were analyzed using the Mann-Whitney U test. The proportion of individuals engaging in injecting drug use and associated risk behaviors during treatment and follow-up was assessed until posttreatment week 12. 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; StataCorp, College Station, TX).

ROLE OF THE FUNDING SOURCE

The study (including study medications) was funded by an investigator-initiated research grant from AbbVie. The sponsor (The Kirby Institute, University of New South Wales Sydney) collected the data, managed study samples, monitored study conduct, performed the statistical analysis, and drafted the manuscript. Outside of the authorship group,

there was no assistance with manuscript preparation and writing.

Results

PARTICIPANT DISPOSITION AND OVERVIEW OF THE STUDY POPULATION

Between October 31, 2017, and August 7, 2018, 39 individuals were screened and 30 enrolled (Fig. 1). All enrolled participants were male (n = 30, 100%), most of whom identified as MSM (n = 27, 90%). The majority were infected with HCV genotype 1 (n = 25, 83%; 1a, n = 22, 73%; 1b, n = 1, 3%; 1, no subtype, n = 2, 7%), followed by genotype 4 (n = 3, 10%) and genotype 3 (n = 2, 7%) (Table 1). Recent primary HCV infection was documented in 26 (87%) and recent HCV reinfection in 4 (13%); all participants with recent HCV reinfection had previously achieved SVR following treatment (Supporting Table S1). The predominant clinician-determined modes of HCV acquisition were sexual exposure among MSM (n = 22, 73%) and injecting drug use (n = 5, 17%) (Table 1). Median maximum ALT in the preceding

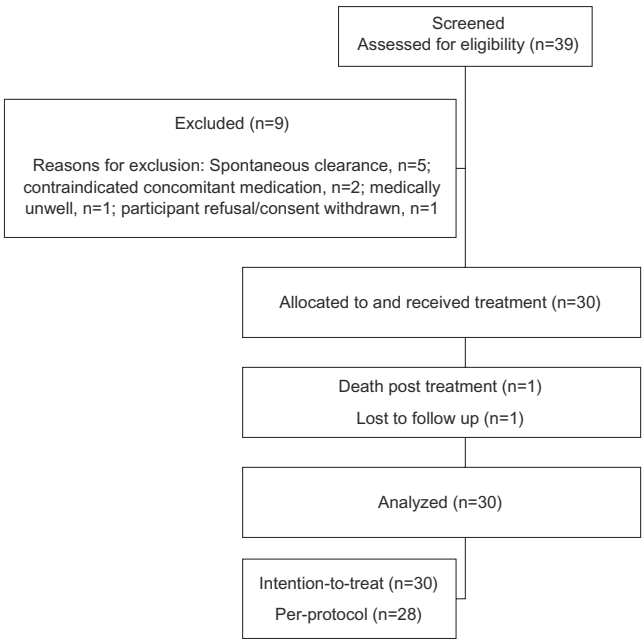

FIG. 1. Participant disposition.

TABLE 1. Baseline Characteristics

	ITT Population (n = 30)
Participant characteristics	
Age (years), median (range)	43 (29-73)
Male, n (%)	30 (100)
Ethnicity, n (%)	
Asian	4 (13)
Latino	3 (10)
Pacific Islander	1 (3)
White	22 (73)
Body mass index (kg/m^2), median (range)	24 (19-29)
HIV infection, n (%)	23 (77)
Characteristics of recent HCV infection	
HCV infection type	
Primary	26 (87)
Reinfection	4 (13)
Mode of HCV acquisition, n (%)	
Injecting drug use	5 (17)
Sexual exposure—MSM*	22 (73)
Sexual exposure—heterosexual	1 (3)
Noninjection drug use	1 (3)
Unknown	1 (3)
HCV genotype/subtype, n (%)	
1a	22 (73)
1b	1 (3)
1, no subtype	2 (7)
3a	2 (7)
4d	4 (10)
Estimated duration of infection (weeks), median (range)	
At screening	23 (8-41)
At baseline	29 (13-52)
Acute HCV,† n (%)	9 (30)
Baseline HCV RNA	
Log_{10} IU/mL, median (range)	6.2 (0.9-7.7)
>1,000,000 IU/mL (>6 log_{10}), n (%)	17 (57)
>10,000,000 IU/mL (>7 log_{10}), n (%)	8 (27)
Presentation of recent HCV, n (%)	
Acute clinical illness—symptomatic and/or ALT >10 × ULN	22 (73)
Jaundice	5 (17)
Asymptomatic seroconversion	8 (27)
ALT (U/L), median (range)	
Peak ALT prior to enrollment	231 (181-3,087)
At screening	218 (20-1,440)
At baseline	203 (30-707)

*Among MSM, 26 identified as gay or bisexual and 1 identified as heterosexual.
†Acute HCV infection (duration of infection <24 weeks) at baseline.

12 months was 381 IU/L (range 26-3,087). Acute clinical hepatitis with ALT > 10 × ULN was documented in 73% (n = 22). Six (20%) participants had a symptomatic seroconversion illness, including 5 (17%) with jaundice. At screening and baseline, median estimated duration of infection was 23 weeks (range 8-41) and 29 weeks (range 13-52), respectively. Median baseline HCV RNA was 6.2 $\log_{10}$ IU/mL (range 1.0-7.7), with baseline HCV RNA > 1,000,000 IU/mL (>6 $\log_{10}$) in 57% (n = 17) and > 10,000,000 IU/mL (>7 $\log_{10}$) in 27% (n = 8). Median baseline ALT was 203 U/L (range 30-707), with a median liver stiffness measurement (FibroScan) of 5.5 kPa (IQR 4.7-7.5).

HIV coinfection was documented in 77% (n = 23); median CD4 count was 571 × 10^6/L (range 341-1,488). All HIV-positive participants were receiving combination antiretroviral therapy (n = 23, 100%), with HIV RNA ≤ 50 copies/mL in 96% (n = 22). At baseline, most (n = 18, 78%) were receiving an INSTI (dolutegravir or raltegravir) plus two nucleoside reverse transcriptase inhibitors (Supporting Table S2). Four (13%) participants required alterations to their antiretroviral regimen given potential drug interactions; all changed from a non-nucleoside reverse transcriptase inhibitor (n = 2) or boosted-protease inhibitor (n = 2) to an INSTI. Of the three HIV-negative MSM enrolled, one was receiving HIV pre-exposure prophylaxis.

Fourteen (47%) participants had ever injected drugs, with 9 (30%) reporting injecting drug use within 6 months of enrollment. (Meth)amphetamine use, ever and current, was predominant, by both injecting (ever, 40%; current, 30%) and noninjecting (ever, 60%; current, 33%) routes of administration. Indeed, (meth)amphetamine was the only drug injected in the 6 months prior to enrollment (Supporting Table S3). Among participants who reported injecting drug use, median age at first injecting was 37 years (range 19-55). Median duration of injecting drug use prior to estimated date of HCV infection was 2.1 years (IQR 1.0-3.6). Only 2 participants (7%) had ever received opioid substitution therapy, with no participants on such therapy at enrollment.

TREATMENT ADHERENCE AND OUTCOMES

Adherence to therapy was high, with all participants completing the 6-week course of therapy. By pill count and self-report, adherence > 95% was 100%, with median on-treatment adherence 100%.

In the ITT population, SVR12 was achieved in 90% (27/30; 95% CI 73%, 98%) (Fig. 2 and Table 2). In the PP population, SVR12 was 96% (27/28; 95% CI 82%, 100%) (for efficacy by genotype, see Supporting Fig. S1). Among participants with HIV coinfection, SVR12 in the ITT and PP populations was 87% (20/23; 95% CI, 66-97%) and 95% (20/21; 95% CI, 76-100%), respectively. Among participants with HCV monoinfection, SVR12 in the ITT and PP populations was 100% (7/7; 95% CI, 59-100%) and 100% (7/7; 95% CI, 59-100%). Among participants with baseline HCV RNA > 6 $\log_{10}$ IU/mL, SVR12

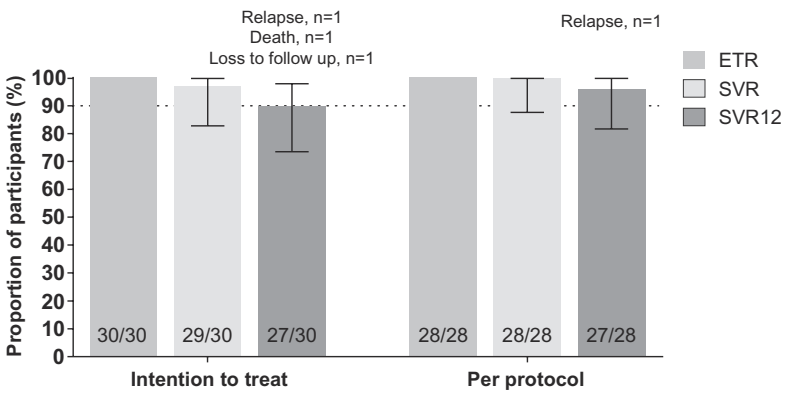

FIG. 2. Primary and secondary efficacy endpoints, by ITT (n = 30) and PP (n = 28) analyses. The dotted line indicates the SVR12 in the ITT population (90%). The PP population excludes two participants—one who was lost to follow-up after end of treatment and another who died after achieving SVR4. Abbreviation: ETR, end-of-treatment response.

in the ITT and PP populations was 88% (15/17; 95% CI, 64-99%) and 94% (15/16; 95% CI, 70-100%), respectively (Fig. 3).

Virological suppression at end of treatment was documented in 100% (30/30; 95% CI, 88-100%) (Fig. 2). At weeks 2, 4, and 6, 70%, 90%, and 100% had HCV RNA below the LLoQ, with 22%, 70%, and 93% having HCV RNA below the lower limit of detection, respectively (Table 2; Supporting Fig. S2). Two participants with detectable HCV RNA (HCV RNA < 10, not quantifiable) at week 6 (end of treatment) achieved SVR12 (HCV RNA target not detected). A rapid biochemical response on treatment was observed (Fig. 4); median ALT values at baseline and week 6 (end of treatment) were 203 U/L (range 30-707) and 22 U/L (range 12-77) ($P < 0.001$) (Supporting Table S4).

Of those participants who did not achieve SVR12 (n = 3), there was one case of virological failure and there were two cases of nonvirological failure. In the cases of nonvirological failure, 1 participant died after posttreatment week 4 (achieved SVR4; HCV RNA target not detected at last study contact) and 1 participant was lost to follow-up after end of treatment (achieved end-of-treatment response; HCV RNA target not detected at last study contact). Virological failure, confirmed as relapse on sequencing, was observed in 1 (3%) participant with acute genotype 1a HCV infection (Fig. 5; Supporting Fig. S3). The participant was a 50-year-old man with HIV infection, who was diagnosed with primary acute HCV in the setting of asymptomatic seroconversion. At screening and baseline, estimated duration of HCV infection was 18 and 24 weeks, respectively, with a narrow seroconversion window as the last negative anti-HCV antibody was only 5 weeks prior to the first positive anti-HCV antibody. Baseline HCV RNA was 7.7 $\log_{10}$ IU/mL. The participant was adherent to treatment, and HCV RNA declined rapidly (week 2, HCV RNA 38 IU/mL [1.6 $\log_{10}$ IU/mL]; week 4, HCV RNA <10 IU/mL [target detected, not quantifiable]; week 6, HCV RNA

TABLE 2. HCV RNA Response During Treatment and Posttreatment—Primary and Secondary Efficacy Endpoints

Response	ITT Population (n = 30)	PP Population (n = 28)
HCV RNA <LLoQ, n (%)		
On treatment		
Week 2	21 (70)	19 (68)
Week 4	27 (90)	25 (89)
Week 6	30 (100)	28 (100)
Posttreatment		
Week 4	29 (97)	29 (100)
Week 12	27 (90)	27 (96)
Virologic failure, n (%)		
Relapse	1 (3)	1 (3)
Nonvirologic failure, n (%)		
Death	1 (3)	—
Loss to follow-up	1 (3)	—
Reinfection, n (%)	0	0

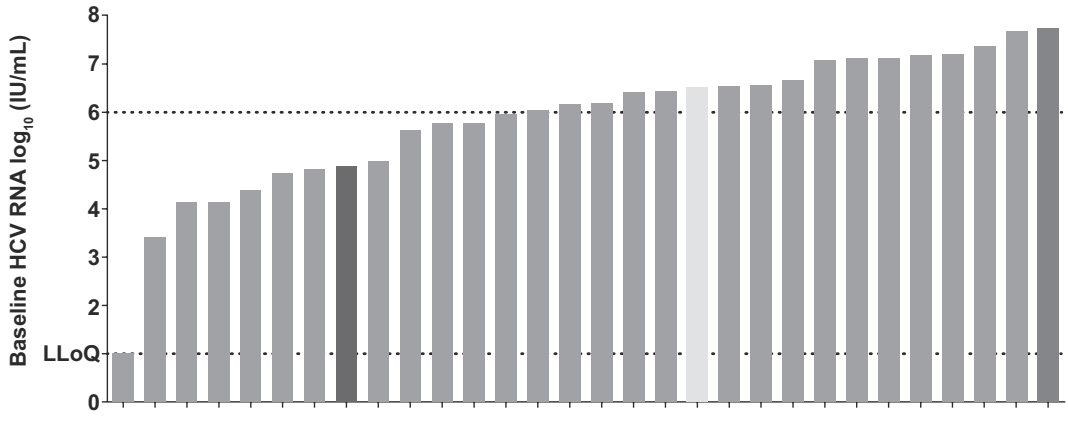

FIG. 3. Treatment outcome by baseline HCV RNA. Median baseline HCV RNA was 6.2 $\log_{10}$ IU/mL (range 0.9-7.7), with baseline HCV RNA > 1,000,000 IU/mL (> 6 $\log_{10}$) in 57% (n = 17). Baseline HCV RNA was 7.7 $\log_{10}$ IU/mL in the one participant with virological failure (relapse). Participants who achieved SVR are depicted in the black bars, and participants who did not achieve SVR due to loss to follow-up, death, or relapse are depicted in the dark gray, striped, and light gray bars, respectively.

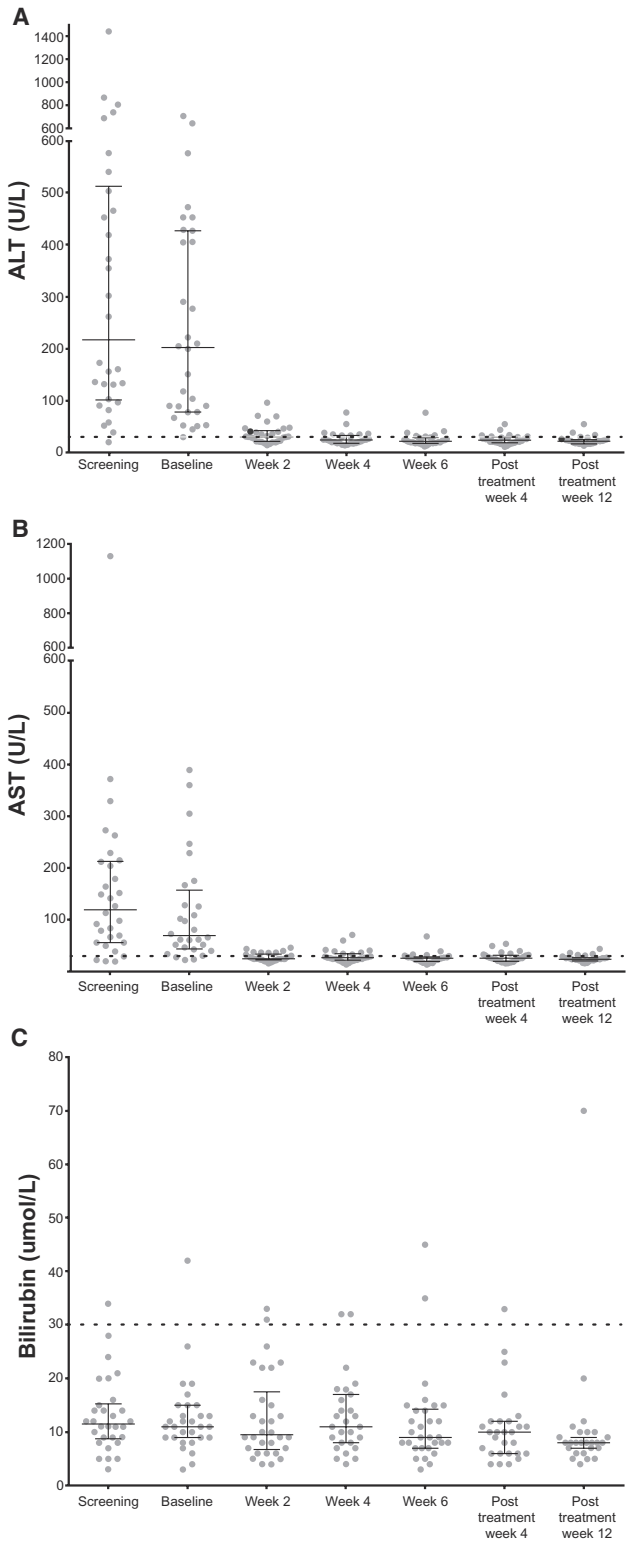

FIG. 4. Change in (A) ALT, (B) aspartate aminotransferase, and (C) total bilirubin prior to treatment, on treatment, and posttreatment. Bars depict median with IQR. Dotted line at ULN for each parameter—ALT, ULN 30 U/L; aspartate aminotransferase, ULN 40 U/L; total bilirubin, ULN 18 μmol/L. Abbreviation: AST, aspartate aminotransferase.

target not detected). Recurrence of HCV viremia was identified at week 12 posttreatment (posttreatment week 4, HCV RNA <10 IU/mL [target detected, not quantifiable]; posttreatment week 12, HCV RNA 7.5 $\log_{10}$ IU/mL). No significant NS3 or NS5A resistance-associated polymorphisms were detected at baseline or posttreatment week 12. The participant received retreatment with sofosbuvir/velpatasvir/voxilaprevir for 12 weeks and achieved SVR12.

No cases of reinfection have been identified among those participants remaining in follow-up at posttreatment week 24; follow-up will continue for up to 5 years posttreatment.

SAFETY

One or more adverse events were reported by 22 (73%) participants, with the majority being of mild severity (Table 3). Treatment-related adverse events were reported by 8 participants (27%), all of mild or moderate severity. One treatment-emergent serious adverse event was reported. In this case, neutropenia was noted on day 1 of therapy; there were no clinical sequelae, and neutropenia resolved on treatment without intervention. The event was deemed unrelated to the study drug. One participant died following an illicit drug overdose after achieving SVR4, with the event unrelated to study drug or study conduct. Two participants were diagnosed with sexually transmitted infections (lymphogranuloma venereum, n = 1; syphilis, n = 1) during follow-up.

Discussion

Glecaprevir/pibrentasvir for 6 weeks was highly effective, safe, and well tolerated among people with acute and recent HCV infection (SVR12 ITT 90%, SVR12 PP 96%), including among people with HIV coinfection and high baseline HCV RNA (>6 $\log_{10}$ IU/mL). Treatment resulted in rapid HCV RNA suppression and normalization of liver enzymes. No treatment-related serious adverse events were reported.

In line with the high efficacy observed in this study, other studies of shortened duration dual-class and triple-class DAA regimens have demonstrated promising results in recent HCV infection.[2] Among people with acute and recent HCV genotypes 1 and

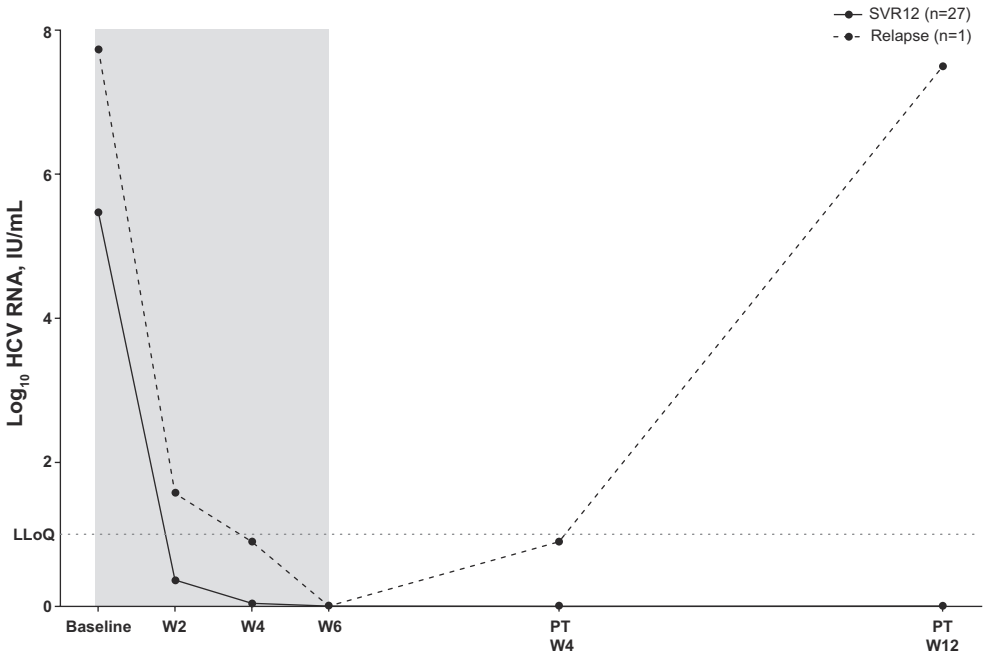

FIG. 5. Viral kinetics in treatment failure. Viral kinetics in the one participant with virological failure (relapse) compared with the geometric mean decline in HCV RNA on treatment in the PP population who achieved SVR12 (n = 27). Abbreviations: PT, posttreatment; W, week.

TABLE 3. Safety and Adverse Events

Adverse Events	ITT Population (n = 30)
Participants reporting any adverse event up to 30 days after last dose, n (%)	18 (60)
Grades 1-2, n (%)	17 (57)
Grade 3, n (%)	1 (3)
Grade 4, n (%)	0
Participants reporting treatment-related adverse event up to 30 days after last dose, n (%)	8 (27)
Grades 1-2, n (%)	8 (27)
Grade 3, n (%)	0
Grade 4, n (%)	0
Serious treatment-emergent adverse event, n (%)	1 (3)
Treatment-related serious adverse event, n (%)	0
Treatment discontinuation due to adverse event, n (%)	0
Death, n (%)	1 (3)
Adverse events: common (≥ 5% of study population), n (%)	
Fatigue	3 (10)
Diarrhea	2 (7)
Nasopharyngitis	2 (7)
Rash	2 (7)
Rhinitis	2 (7)

4 infection, high efficacy was reported with 6 weeks of sofosbuvir/ledipasvir (n = 20, SVR12 ITT 100%; HCV monoinfection only)[13] and 8 weeks of grazoprevir/elbasvir (n = 80, SVR12 ITT 94%, SVR12 PP 99%),[6] paritaprevir/ritonavir/ombitasvir/dasabuvir (n = 30, SVR12 ITT 97%, SVR12 PP 100%),[14] and sofosbuvir/ledipasvir (n = 27, SVR12 ITT 100%).[15] Lower SVR (n = 26, SVR12 ITT 77%, PP 87%) was demonstrated with 6 weeks of sofosbuvir/ledipasvir among HIV-positive MSM.[16] TARGET3D Cohort Two has demonstrated high efficacy with glecaprevir/pibrentasvir for 6 weeks and, importantly, evaluated a short-duration pan-genotypic DAA regimen in this population. While small sample sizes and differences in study design make comparisons between studies problematic, there is a growing body of evidence supporting shortened-duration therapy in acute HCV infection.

Evaluation of factors that impact the effectiveness of short-duration therapy in acute HCV is difficult given low rates of treatment failure seen across studies. Baseline HCV RNA may impact efficacy with short-duration (≤ 6 weeks) DAA therapy, with higher baseline HCV RNA associated with posttreatment

relapse in studies of both acute[16,17] and chronic[18,19] HCV infection. In this study, one case of posttreatment relapse was seen in a participant with genotype 1a HCV infection, well-controlled HIV infection, and very high baseline HCV RNA (7.7 $\log_{10}$). In the aforementioned study among HIV-positive MSM who received sofosbuvir/ledipasvir for 6 weeks, three cases of relapse also occurred in participants with high baseline HCV RNA (>6.9 $\log_{10}$ IU/mL).[16]

To robustly evaluate the efficacy of short-duration (≤6 weeks) DAA therapy, optimal DAA regimen choice is essential, with mathematical modeling showing that induction of a rapid second-phase viral decline should permit shorter treatment durations[20]; this rapid second-phase viral decline occurs following administration of HCV NS3/4A protease inhibitors and NS5A inhibitors but not nucleoside analogues.[20-22] As such, use of glecaprevir/pibrentasvir, a potent pan-genotypic DAA regimen containing an HCV NS3/4A protease inhibitor and an NS5A inhibitor, is ideal.

Limitations of this study include the generalizability of the study population and the limited number of non–genotype 1 infections in the enrolled population. The study population was entirely male and predominantly HIV-positive MSM, with the majority acquiring HCV through sexual exposure as opposed to injecting drug use. This population is likely to be more engaged with health care and is not necessarily representative of other populations at risk of HCV acquisition. Further, among the participants who did report injecting drug use, the median age at commencement of injecting was relatively old at 37 years. This combined with a short median duration of injecting (2.1 years) prior to HCV diagnosis and predominant methamphetamine use suggests that this MSM-PWID population may be substantially different from other populations of PWID. This is particularly important given increasing HCV incidence among other PWID populations in low- to middle-income countries and the United States. While annual HCV incidence appeared to have peaked in most countries prior to 2005 (with the exception of Russia[23-25]), the opioid epidemic and an increase in injecting drug use are associated with a recent rise in HCV incidence in the United States, particularly among young, white, nonurban populations.[26,27] Interventions will need to be tailored to the population at risk.

The study aimed to recruit participants with HCV genotypes 1-6. However, given the location of the study sites, most participants had HCV genotype 1, similar to other DAA studies in acute and recent HCV to date. Larger studies of short-duration pan-genotypic DAA therapy in well-characterized populations with varied HCV genotypes (particularly genotype 3) will be very valuable in determining the utility of DAA therapy in recent HCV infection. Further evidence will soon be available with other registered studies examining the efficacy of shortened-duration sofosbuvir/velpatasvir (sofosbuvir/velpatasvir for 8 weeks, single arm, NCT03818308; sofosbuvir/velpatasvir, randomized controlled trial, 6 versus 12 weeks, NCT02625909). Following Cohort Two, TARGET3D Cohort Three is currently examining the efficacy and safety of glecaprevir/pibrentasvir for 4 weeks in recent HCV infection; the results from TARGET3D Cohorts Two and Three will inform the design of a phase 3 randomized trial. These studies will further enhance our understanding of the utility of shortened-duration DAA therapy in recent HCV infection.

In order to achieve HCV elimination targets,[28] increased diagnosis and treatment of recent HCV infection will be required.[29] Striving for microelimination in high-incidence populations is an important step toward reaching HCV elimination targets. High and increasing HCV incidence rates among populations of PWID and HIV-positive MSM highlight the need to determine the optimal duration of therapy and choice of DAA regimen in recent infection, including for treatment of reinfection. Access to HCV care and treatment for people at high risk of onward transmission, including those with recent HCV infection, should be a priority.[1] HCV treatment-as-prevention efforts should be enhanced by the immediate commencement of DAA therapy in people with recent HCV. A targeted "test and treat" (and retreat) strategy, with short-duration DAA therapy among at-risk populations, may be one of the most cost-effective public health strategies in attempts to eliminate HCV.[30]

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REFERENCES

1) Hajarizadeh B, Grebely J, Martinello M, Matthews GV, Lloyd AR, Dore GJ. Hepatitis C treatment as prevention: evidence, feasibility, and challenges. Lancet Gastroenterol Hepatol 2016;1:317-327.
2) Martinello M, Hajarizadeh B, Grebely J, Dore GJ, Matthews GV. Management of acute HCV infection in the era of direct-acting antiviral therapy. Nat Rev Gastroenterol Hepatol 2018;15:412-424.
3) Pawlotsky J-M, Negro F, Aghemo A, Berenguer M, Dalgard O, Dusheiko G, et al. EASL recommendations on treatment of hepatitis C 2018. J Hepatol 2018;69:461-511.
4) AASLD-IDSA HCV Guidance Panel. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. Clin Infect Dis 2018;67:1477-1492.
5) Bethea ED, Chen Q, Hur C, Chung RT, Chhatwal J. Should we treat acute hepatitis C? A decision and cost-effectiveness analysis. Hepatology 2018;67:837-846.
6) Boerekamps A, De Weggheleire A, van den Berk GE, Lauw FN, Claassen MAA, Posthouwer D, et al. Treatment of acute hepatitis C genotypes 1 and 4 with 8 weeks of grazoprevir plus elbasvir (DAHHS2): an open-label, multicentre, single-arm, phase 3b trial. Lancet Gastroenterol Hepatol 2019;4:269-277.
7) Hajarizadeh B, Grebely J, Dore GJ. Case definitions for acute hepatitis C virus infection: a systematic review. J Hepatol 2012; 57:1349-1360.
8) European Aids Treatment Network Acute Hepatitis C Infection Consensus Panel. Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference. AIDS 2011;25:399-409.
9) Lamoury FM, Jacka B, Bartlett S, Bull RA, Wong A, Amin J, et al. The influence of hepatitis C virus genetic region on phylogenetic clustering analysis. PLoS One 2015;10:e0131437.
10) Lindstrom I, Kjellin M, Palanisamy N, Bondeson K, Wesslen L, Lannergard A, et al. Prevalence of polymorphisms with significant resistance to NS5A inhibitors in treatment-naive patients with hepatitis C virus genotypes 1a and 3a in Sweden. Infect Dis (Lond) 2015;47:555-562.
11) Woods CK, Brumme CJ, Liu TF, Chui CKS, Chu AL, Wynhoven B, et al. Automating HIV drug resistance genotyping with RECall, a freely accessible sequence analysis tool. J Clin Microbiol 2012;50:1936-1942.
12) Kalaghatgi P, Sikorski AM, Knops E, Rupp D, Sierra S, Heger E, et al. Geno2pheno[HCV]—a web-based interpretation system to support hepatitis C treatment decisions in the era of direct-acting antiviral agents. PLoS One 2016;11:e0155869.
13) Deterding K, Spinner CD, Schott E, Welzel TM, Gerken G, Klinker H, et al. Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. Lancet Infect Dis 2017;17:215-222.
14) Martinello M, Bhagani S, Gane E, Orkin C, Cooke G, Dore GJ, et al. Shortened therapy of eight weeks with paritaprevir/ritonavir/ombitasvir and dasabuvir is highly effective in people with recent HCV genotype 1 infection. J Viral Hepat 2018;25: 1180-1188.
15) Naggie S, Fierer DS, Hughes M, Kim AY, Luetkemeyer A, Vu V, et al. 100% SVR with 8 weeks of ledipasvir/sofosbuvir in HIV-infected men with acute HCV infection: results from the SWIFT-C Trial [Abstract]. Hepatology 2017;66:113A.
16) Rockstroh JK, Bhagani S, Hyland RH, Yun C, Dvory-Sobol H, Zheng W, et al. Ledipasvir–sofosbuvir for 6 weeks to treat acute hepatitis C virus genotype 1 or 4 infection in patients with HIV coinfection: an open-label, single-arm trial. Lancet Gastroenterol Hepatol 2017;2:347-353.
17) Martinello M, Gane E, Hellard M, Sasadeusz J, Shaw D, Petoumenos K, et al. Sofosbuvir and ribavirin for 6 weeks is not effective among people with recent hepatitis C virus infection: the DARE-C II study. Hepatology 2016;64:1911-1921.
18) Lawitz E, Poordad F, Gutierrez JA, Wells JT, Landaverde CE, Evans B, et al. Short-duration treatment with elbasvir/grazoprevir and sofosbuvir for hepatitis C: a randomized trial. Hepatology 2017;65:439-450.
19) Dahari H, Canini L, Graw F, Uprichard SL, Araujo ES, Penaranda G, et al. HCV kinetic and modeling analyses indicate similar time to cure among sofosbuvir combination regimens with daclatasvir, simeprevir or ledipasvir. J Hepatol 2016;64:1232-1239.
20) Perelson AS, Guedj J. Modelling hepatitis C therapy—predicting effects of treatment. Nat Rev Gastroenterol Hepatol 2015;12:437-445.
21) Guedj J, Dahari H, Rong L, Sansone ND, Nettles RE, Cotler SJ, et al. Modeling shows that the NS5A inhibitor daclatasvir has two modes of action and yields a shorter estimate of the hepatitis C virus half-life. Proc Natl Acad Sci USA 2013;110:3991-3996.
22) Guedj J, Perelson AS. Second-phase hepatitis C virus RNA decline during telaprevir-based therapy increases with drug effectiveness: implications for treatment duration. Hepatology 2011;53:1801-1808.
23) Hatzakis A, Chulanov V, Gadano AC, Bergin C, Ben-Ari Z, Mossong J, et al. The present and future disease burden of hepatitis C virus (HCV) infections with today's treatment paradigm—volume 2. J Viral Hepat 2015;22:26-45.
24) Razavi H, Waked I, Sarrazin C, Myers RP, Idilman R, Calinas F, et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. J Viral Hepat 2014;21:34-59.
25) Sibley A, Han KH, Abourached A, Lesmana LA, Makara M, Jafri W, et al. The present and future disease burden of hepatitis C virus

infections with today's treatment paradigm—volume 3. J Viral Hepat 2015;22:21-41.
26) Zibbell JE, Asher AK, Patel RC, Kupronis B, Iqbal K, Ward JW, et al. Increases in acute hepatitis C virus infection related to a growing opioid epidemic and associated injection drug use, United States, 2004 to 2014. Am J Public Health 2018;108:175-181.
27) Liang TJ, Ward JW. Hepatitis C in injection-drug users—a hidden danger of the opioid epidemic. N Engl J Med 2018;378:1169-1171.
28) World Health Organization. Global Health Sector Strategy on Viral Hepatitis, 2016–2021. Geneva: Switzerland; 2016.
29) Martin NK, Thornton A, Hickman M, Sabin C, Nelson M, Cooke GS, et al. Can hepatitis C virus (HCV) direct-acting antiviral treatment as prevention reverse the HCV epidemic among men who have sex with men in the United Kingdom? Epidemiological and modeling insights. Clin Infect Dis 2016;62:1072-1080.
30) Cousien A, Tran VC, Deuffic-Burban S, Jauffret-Roustide M, Mabileau G, Dhersin JS, et al. Effectiveness and cost-effectiveness of interventions targeting harm reduction and chronic hepatitis C cascade of care in people who inject drugs; the case of France. J Viral Hepat 2018;25:1197-1207.

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