Research Article
Viral Hepatitis

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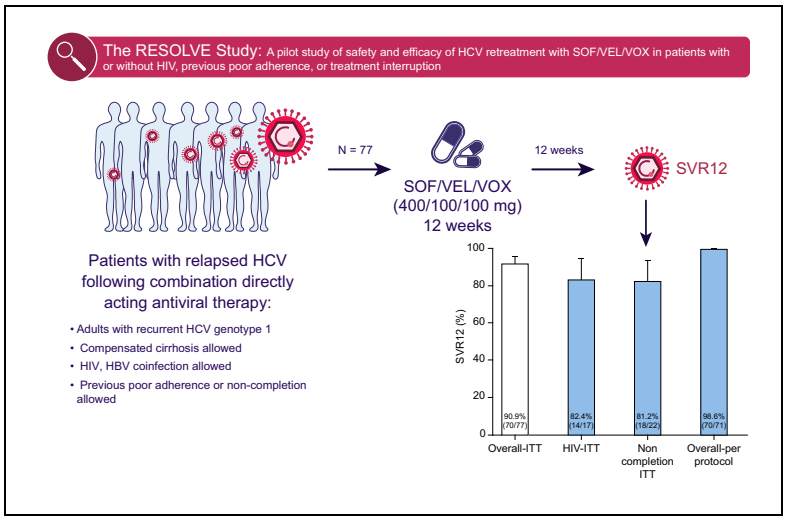
A pilot study of safety and efficacy of HCV retreatment with sofosbuvir/velpatasvir/voxilaprevir in patients with or without HIV (RESOLVE STUDY)

Graphical abstract



Highlights

- This study included 77 patients with relapsed HCV genotype 1, who were treated with 12 weeks of SOF/VEL/VOX.
- >90% of patients achieved sustained virologic response 12 weeks after the end of treatment in an intention-to-treat analysis.
- Treatment responses were similar in patients with HIV, poor adherence or non-completion of therapy.
- SOF/VEL/VOX is a safe, effective, and well-tolerated option for the retreatment of relapsed HCV genotype 1.

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Lay summary

Twelve weeks of the combination of direct-acting antivirals (SOF/VEL/VOX) was safe and effective in patients with relapsed hepatitis C virus infection who had previously received combination therapy with direct-acting antivirals. Treatment response was not diminished by HIV coinfection, or non-completion of previous direct-acting antiviral-based therapy.

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A pilot study of safety and efficacy of HCV retreatment with sofosbuvir/velpatasvir/voxilaprevir in patients with or without HIV (RESOLVE STUDY)

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Background & Aims: Cure rates in response to retreatment with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) are high, but this regimen has not been studied in patients with a history of poor adherence or treatment interruption, nor in patients with HIV/HCV coinfection. Herein, we aimed to assess the safety and efficacy of this combination in patients with genotype 1 HCV infection who had relapsed following combination direct-acting antiviral (DAA) therapy, regardless of HIV infection or previous treatment course.

Methods: The RESOLVE study was a multicenter, open-label, phase IIb study investigating the safety, tolerability and efficacy of SOF/VEL/VOX in 77 patients with virologic rebound following combination DAA therapy. Efficacy was defined as HCV RNA below the lower limit of detection 12 weeks after the end of treatment (SVR12), while safety endpoints included the incidence of grade 3 and 4 adverse events (AEs) following treatment, and the proportion of patients who stopped treatment prematurely due to AEs.

Results: In an intent-to-treat analysis, 70/77 (90.9%, 95% CI 82.1–95.8%) patients achieved SVR12, including 14/17 (82.4%) HIV coinfected participants and 18/22 (81.8%) of those with previous non-completion of DAA therapy. In an analysis of all patients who completed 12 weeks of study medication, 70/71 patients (99%) achieved SVR12. One patient experienced a grade 3 AE, and 4 experienced a grade 4 AE, all unrelated to study participation. Reported AEs were similar in HIV-coinfected patients, and patients receiving dolutegravir-based antiretroviral treatment experienced no clinically significant increases in aminotransferases.

Conclusion: Retreatment with 12 weeks of SOF/VEL/VOX was safe and effective in patients with relapsed HCV following initial combination DAA-based treatment. Treatment response was not affected by HIV coinfection or previous treatment course.

Lay summary: Twelve weeks of the combination of direct-acting antivirals (SOF/VEL/VOX) was safe and effective in patients with relapsed hepatitis C virus infection who had previously received combination therapy with direct-acting antivirals. Treatment response was not diminished by HIV coinfection, or non-completion of previous direct-acting antiviral-based therapy.

Introduction

Treatment of chronic HCV infection has changed dramatically in the past 5 years. Combinations of direct-acting antivirals (DAAs) can achieve high rates of sustained virologic response (SVR), synonymous with eradication or cure of HCV, of above 95% in clinical trials, regardless of stage of hepatic fibrosis, treatment history, or HCV genotype.[1] Recently, real world efficacy studies have confirmed high cure rates, with SVR rates of 90–95% outside of clinical trials.[2–4] The proportion of patients in these reports who do not achieve SVR is low, at less than 10%, when combining those who have virologic relapse, are lost to follow-up, or discontinue treatment due to adverse events (AEs). Nevertheless, given that there are an estimated 71 million people with chronic HCV worldwide,[5] the number of patients who will require HCV retreatment is substantial and will increase as HCV treatment becomes more accessible.

The fixed-dose combination DAA regimen of sofosbuvir (SOF, a pangenotypic NS5B nucleotide polymerase inhibitor), velpatasvir (VEL, a pangenotypic NS5A inhibitor), and voxilaprevir (VOX, a pangenotypic NS3/4a protease inhibitor) has been shown to be highly effective in the treatment of DAA-experienced patients.[6] The drug was the first Food and Drug Administration (FDA)-approved treatment for chronic HCV in patients who had previously been treated with sofosbuvir or NS5A inhibitors.[7,8] However, there is no data regarding treatment outcomes in patients who discontinued their initial combination DAA-based regimen due to non-completion of therapy, either due to early discontinuation or poor adherence,[6] or in those with concurrent chronic viral infections with HIV and/or hepatitis B virus (HBV) coinfection.[6,8,9]

Keywords: Hepatitis C; HIV; Retreatment after virologic failure, resistance-associated substitutions.
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Indeed, it remains controversial whether HCV treatment is as successful in patients with HIV/HCV coinfection as those with HCV monoinfection. Recent cohort studies have differed regarding whether HIV coinfection predicts poor outcomes, with several studies showing that HIV worsens cure rates for HCV treatment[2,10,11] while others suggest that treatment outcomes are comparable if drug interactions can be managed.[3,4,12] If patients with HIV/HCV coinfection are less likely to respond to combination DAA-based treatments, as some suggest, retreatment regimens will require further study. Data regarding SOF/VEL/VOX safety and efficacy in HIV or HBV coinfected patients is urgently needed, and such data is the objective of the RESOLVE study.

Patients and methods

Study design

RESOLVE is an open-label, phase IIb study investigating the safety, tolerability and efficacy of sofosbuvir, velpatasvir and voxilaprevir (SOF/VEL/VOX) in individuals who had virologic rebound following combination DAA therapy, with or without HIV and/or HBV coinfection. All patients, with and without compensated cirrhosis, received 12 weeks of a fixed-dose combination tablet containing 400 mg of SOF, 100 mg of VEL, and 100 mg of VOX administered once daily with food. Patients were screened and enrolled at 3 sites: the Institute of Human Virology (IHV) at the University of Maryland School of Medicine in Baltimore, MD, and 2 locations (Parkside and Walker Jones) of the Unity Health Care clinics in Washington, D.C. Written informed consent was obtained from all participants at screening. All eligible patients were 18 or older, had documented recurrent HCV genotype 1 (GT1) infection following previous exposure to combination DAA therapy at least 8 weeks prior to enrollment. Those with HBV were controlled on treatment, and those with HIV were stable on a suppressive antiretroviral regimen for at least 4 weeks prior to enrollment. Primary exclusion criteria included hepatic decompensation, poor venous access, other clinically significant illness that could interfere with HCV treatment, and non-HCV chronic liver disease. Patients were also excluded based on abnormal laboratory results, including platelets less than 50,000 cells/ml, estimated glomerular filtration rate <30 ml/min/1.73 m2, albumin <3.0 g/dl, and glycated hemoglobin >10%. All patients had been staged by liver biopsy, vibration-controlled transient elastography, or serologic biomarker testing within 3 years of the screening visit. Patients with cirrhosis had negative screening for hepatocellular carcinoma within 6 months of screening. The full protocol is provided in the supplementary information.

Study oversight

The trial was sponsored by the Institute of Human Virology at the University of Maryland School of Medicine. The study was approved by the Institutional Review Board of the University of Maryland and conducted in compliance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines, and the local regulatory requirements. This clinical trial was registered on Clinicaltrials.gov (NCT02745535).

Assessments

Screening and on-treatment assessments included HCV genotyping, measurement of serum HCV RNA level, and standard laboratory and clinical testing. Serum HCV RNA was measured using the Cobas® AmpliPrep/Cobas® TaqMan® HCV Test version 2.0 (Roche), with a lower limit of detection (LLOD) of 15 IU/ml. The Abbott RealTime HCV genotype II assay was used to determine HCV genotype 1 subtype at screening. Next generation RNA sequencing was performed by LabCorp on those patients with virologic breakthrough or failure following retreatment, to determine whether they had resistance-associated substitutions (RASs). HIV viral load was tested using Cobas® AmpliPrep/Cobas® TaqMan® HIV-1 Test, Version 2.0. AEs were elicited prospectively and at all study visits. AE severity was determined using the Division of AIDS Table For Grading The Severity of Adult and Pediatric Adverse Events (Version 1.0, December 2004; Clarification August 2009), grading on a scale of 1 (mild) to 5 (death). Adherence was assessed by patient reporting and confirmatory pill counts conducted at all on treatment study visits.

Endpoints

Efficacy was defined as HCV RNA below the LLOD 12 weeks after the end of treatment (SVR12). The primary safety endpoints included incidence of grade 3 and 4 AEs following the treatment regimen and the proportion of patients who stopped treatment prematurely due to AEs.

Statistical analysis

Safety and efficacy data were analyzed with an intention-to-treat population (ITT), including all patients who received at least 1 dose of study medication. Additionally, a per protocol analysis was conducted that included all patients completing the 12-week course of treatment. Baseline demographics were calculated using frequency statistics in Prism (Prism 5.0, GraphPad Software) and comparisons were made using Fisher's exact test.

Role of funding source

Gilead Sciences, Inc. funded the study through an investigator-initiated grant and provided the study drug. They reviewed and offered comments on the protocol and this manuscript, however the corresponding author had full access to all the data in the study, wrote the manuscript, and had final responsibility for the decision to submit for publication.

Results

Patient population

Across all 3 sites, 89 patients were screened and 77 enrolled (54 at the IHV, 14 at Parkside, and 9 at Walker Jones) between May 2016 and January 2018 (Fig. 1). The baseline characteristics of the enrolled patient population are described in Table 1. The participants were primarily Black (n = 66, 86%), non-Hispanic (n = 77, 100%) and male (n = 64, 83%) with GT-1a infection (n = 58, 75%). Seventeen patients (22%) were HIV positive and 3% (n = 2) were coinfected with HBV and HIV. A majority, 51% of participants (n = 39), reported previous intravenous drug use, while 32% of participants (n = 25) reported previous heavy alcohol use. Baseline staging showed 40% (n = 31) had compensated cirrhosis, while 36% (n = 28) had early stage hepatic fibrosis (≤Stage 2). Staging was done in accordance with the American Association for the Study of Liver Diseases (AASLD)/Infectious Disease Society of America (IDSA) guidelines, and was achieved primarily by vibration-controlled transient elastography (40%, n = 31) or FibroSure® (47%, n = 36), but also by

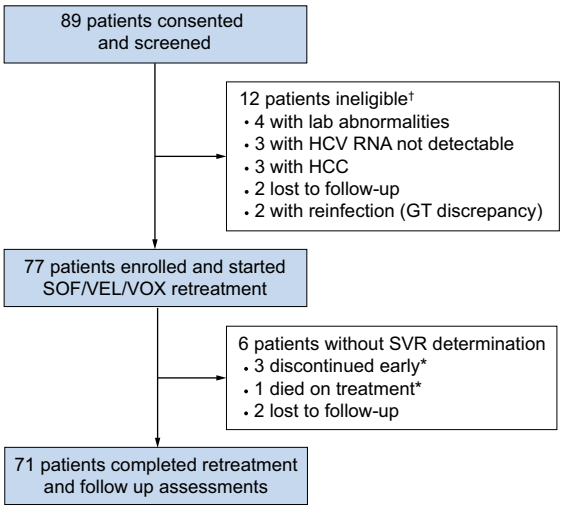

Fig. 1. Study flow diagram of screening, enrollment, and follow-up. Patient flow for screening and enrollment is depicted. GT, genotype; HCC, hepatocellular carcinoma; SOF/VEL/VOX, sofosbuvir, velpatasvir, voxilaprevir; SVR, sustained virologic response.† Total is greater than 12 because 1 patient had laboratory abnormalities and evidence of reinfection with a genotype discrepancy. *Discontinuation or death was deemed unrelated to study drug.

liver biopsy (6%, n = 5) or imaging consistent with cirrhosis (*i.e.* "nodular" appearance to the liver, in which case the diagnosis of advanced fibrosis was confirmed with APRI [asparate aminotransferase to platelet ratio index] and Fibrosis-4 calculations, 6%, n = 5).

All participants had been treated with at least 1 combination DAA-based regimen, 89% (n = 69) with LDV/SOF, 5% (n = 4) with daclatasvir (DCV) in combination with either SOF (1%, n = 1) or asunaprevir (ASV, 4%, n = 3), 4% (n = 3) paritaprevir/ritonavir/ombitasvir/dasabuvir (PrOD), 3% (n = 2) grazoprevir/elbasvir (GZR/EBR), 3% (n = 2) simeprevir (SMV) + SOF, and 3% (n = 2) with other regimens (1 patient received SOF/VEL + RBV following initial LDV/SOF failure, and the other relapsed after initial treatment with 4 weeks of LDV/SOF + GS-9451 + GS-9669 and subsequent retreatment with LDV/SOF for 12 weeks as part of a clinical trial[13]). The number of regimens exceeds the number of patients enrolled because 25% (n = 19) had received >1 prior HCV treatment, including 17% (n = 13) with prior IFN-experience (n = 3 in combination with boceprevir), and 14% (n = 11) with >1 DAA-based regimen. More than a quarter, 29% (n = 22) did not complete previous DAA therapy, mainly due to poor adherence (n = 14), treatment interruption (n = 4), lost/stolen medication (n = 2), or AEs (n = 1).

Of those patients with HIV (n = 17), all were on antiretroviral therapy. Eight patients (47%) were on dolutegravir coformulated with abacavir/lamivudine. Other regimens included rilpivirine with emtricitabine/tenofovir disoproxil fumarate (n = 4, 24%), raltegravir with emtricitabine/tenofovir disoproxil fumarate (n = 2, 12%), darunavir boosted with ritonavir (n = 2, 12%) with either tenofovir disoproxil fumarate/emtricitabine (n = 1) or abacavir/lamivudine (n = 1), and atazanavir with abacavir/lamivudine (n = 1, 6%).

Efficacy

Overall, in an intention-to-treat analysis, 90.9% (n = 70) of patients retreated with 12 weeks of SOF/VEL/VOX achieved SVR12, as shown in Fig. 2. In a per protocol analysis of patients (n = 71) who completed 12 weeks of study medication and all study visits, 99% (70/71) achieved SVR12. One patient experienced virologic relapse with the same subgenotype as the original HCV infection, despite having an HCV RNA <LLOD by week 4 on treatment and through the end of therapy (week 12); by post-treatment week 4, HCV RNA was 16,400 copies/ml and by post treatment week 12, HCV RNA was 2,600,000. This patient denies any re-exposure or high-risk behavior and reported 100% adherence to study medications, which was verified by pill counts at on treatment visits. Of the 6 patients who did not complete the treatment course, 3 discontinued early, 1 died, and 2 patients were lost to follow-up. One patient suffered a traumatic subdural hematoma on week 5 of treatment, and the medication was stopped during hospital admission and rehabilitation. Another patient stopped the medication after day 3 of treatment following a hypertensive stroke. A third patient developed colitis on day 5 of treatment and self-discontinued the medication. One patient died on treatment: the patient had a history of compensated cirrhosis at baseline

Table 1. Baseline demographics and clinical characteristics of study participants.

Characteristic	SOF/VEL/VOX (12 weeks)
N	77
Clinic Location, n (%)	
Institute of Human Virology	54 (70)
Parkside	14 (18)
Walker Jones	9 (12)
Age in years, mean ± SD	60 ± 8.0
Gender, n (%)	
Male	64 (83)
Female	13 (17)
Race, n (%)	
Black	66 (86)
White	10 (13)
Other	1 (1)
Ethnicity, n (%)	
Hispanic	0 (0)
Not Hispanic	77 (100)
Genotype, n (%)	
1a	58 (75)
1b	19 (25)
Fibrosis Staging, n (%)	
F0-F2	28 (36)
F3	18 (23)
F4	31 (40)
Coinfections	
HIV, n (%)	17 (22)
HBV/HIV, n (%)	2 (3)
History of IVDU, n (%)	
Yes	39 (51)
No	38 (49)
Previous DAA treatment, n (%)*	
LDV/SOF	69 (89)
PrOD	3 (4)
DCV/ASV	3 (4)
EBR/GZR	2 (3)
SMV + SOF	2 (3)
DCV + SOF	1 (1)
SOF/VEL	1 (1)
Previous interferon treatment, n (%)	13 (17)
Previous non-completion, n (%)	22 (29)
Poor adherence	14 (18)
Interruption	4 (5)
Lost/Stolen medication	2 (3)
Adverse event	1 (1)

BOC, boceprevir; DAA, direct-acting antiviral; EBR, elbasvir; GZR, grazoprevir; IVDU, intravenous drug use; LDV, ledipasvir; PrOD, paritaprevir, ritonavir, ombitasvir, dasabuvir; SOF, sofosbuvir; SMV, simeprevir. *Number of previous DAA regimens exceeds enrollment as some patients had >1 previous combination DAA regimen.

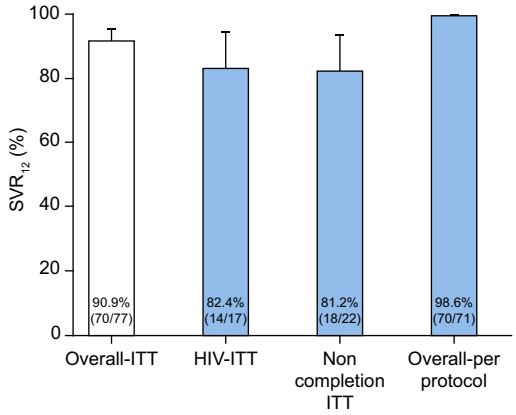

Fig. 2. Rate of sustained virologic response, overall and by subgroup. The rate of sustained virologic response is shown for the overall study group, and for subgroups including those with HIV coinfection, those who had non-completion of their initial combination DAA regimen. Overall SVR12 rate was 90.9% (70/77 patients) by an intention-to-treat analysis, shown in blue. Additional bars depict response rates, also by intention-to-treat, for those with HIV/HCV coinfection, and for those with prior non-completion of treatment. A per protocol analysis of all patients who completed 12 weeks of therapy, regardless of HIV coinfection or previous treatment course, is shown. Error bars show 95% CI for this observed proportion. Differences between groups were not statistically significant by Fisher's exact test. DAA, direct-acting antiviral; SVR12, sustained virologic response at 12 weeks.

with negative ultrasound surveillance for hepatocellular carcinoma (HCC) 6 months prior to enrollment but developed hepatic decompensation at week 9 on treatment, due to thrombosis of the hepatic vein related to a new diagnosis of HCC, and passed away 1 week after diagnosis. These events were all, after review of the medical records, deemed unrelated to the study medication by the primary investigator and independent medical monitor. The final 2 patients were lost to follow-up: 1 at week 4 and another at week 8. Both were subsequently re-engaged in care more than 8 months after discontinuation, with confirmation of virologic relapse and resistance testing.

Of the patients with HIV coinfection (n = 17), 82% (14/17) achieved SVR12, with the remaining 3 patients experiencing virologic relapse (n = 1) and early discontinuation due to unrelated AEs (n = 2, colitis and hypertensive stroke as above). Among patients with HIV coinfection, we observed a median increase in CD4 count of 70 cells/μl (IQR −38 to 129) from pre-retreatment baseline to 12 weeks after the end of treatment, although this was not statistically significant.

For the subset of patients with non-completion of previous treatment with combination DAA therapy, (n = 22), 1 patient (5%) had virologic failure and 3 (14%) discontinued early due to unrelated side effects.

Safety

All participants experienced at least 1 AE. In general, AEs deemed related to study drug were mild. Those reported by ≥5% of participants include fatigue (27%, n = 21), headache (25%, n = 19), diarrhea (21%, n = 16), abdominal pain (9%, n = 7), nausea (9%, n = 7), and constipation (6%, n = 5). There was 1 grade 3, and 4 grade 4 AEs, all unrelated to study participation, including hospitalization for exacerbation of pulmonary hypertension, 2 new carcinoma diagnoses (HCC, squamous cell), hypertensive stroke, and traumatic subdural hematoma. There were 7 grade 3 and 4 laboratory abnormalities listed in Table 3, which were all deemed to be unrelated to study participation by the primary investigator and independent medical monitor.

Regarding safety in HIV-coinfected study participants, AEs were similar to those reported in the cohort as a whole. Of the 8 patients on dolutegravir-based antiretroviral therapy, none experienced clinically significant aspartate aminotransferase or alanine aminotransferase elevations. Monitoring of HIV viral load revealed that no patient experienced an HIV viral "blip" of greater than 100 copies/ml, and we observed no evidence of HBV reactivation or flare in the 2 HIV/HBV/HCV-coinfected patients.

Viral resistance testing

The single patient who experienced virologic failure of genotype 1a after completion of therapy had resistance testing and was found to have a resistance-associated substitution in NS5A, a Y93N, and another in NS3 protease, a Q80K. No NS5B mutations were found.

The patient who discontinued treatment due to the traumatic subdural hematoma after 5 weeks on treatment was found to have experienced virologic relapse on follow-up, and resistance testing was performed, which revealed 2 genotype 1a resistance-associated substitutions in NS5A, M28T and Q30K, and another in NS3 protease, a Q80K. No NS5B mutations were found. The 2 other individuals who discontinued treatment prematurely due to unrelated AEs (after 3 and 5 days of therapy respectively) were subsequently lost to follow-up, and resistance testing could not be performed. Of the remaining 2 patients who were lost to follow-up, both were re-engaged in routine medical care and provided consent and access to their medical records. The patient lost to follow-up at week 4 was reconnected to care 10 months after discontinuing medication, and resistance testing revealed several genotype 1b resistance-associated substitutions in NS5A: R30Q, L31M, Q54H, and Y93H, but no resistance-associated substitutions were noted in NS5B or NS3. The patient lost to follow-up at week 8 of treatment was reconnected to care 8 months after being lost to follow-up, and resistance testing at that time revealed 2 genotype 1b resistance-associated substitutions in NS5A, L31M and Y93H/Y. There were no NS5B or NS3 mutations identified.

Table 2 shows detailed characteristics of patients who did not achieve SVR.

Discussion

Our results show that retreatment with SOF/VEL/VOX is safe and effective, even in patients with HIV/HCV coinfection and those with prior non-completion of therapy, even when due to poor adherence. We found that overall the response rates were preserved in patients with HIV coinfection or a history of poor adherence. Retreatment was safe and extremely well-tolerated, consistent with previously published studies of SOF/VEL/VOX.[8] No patient discontinued medication due to side effects deemed related to the study medication.

This is the first study of SOF/VEL/VOX in patients with and without HIV coinfection, and similar efficacy was observed in the 2 populations. Patients with HIV on regimens containing dolutegravir have been excluded from previous clinical trials, given the FDA warning regarding elevation in the liver function tests of patients with dolutegravir and viral hepatitis,[14] but this antiretroviral regimen is widely used in patients with HIV and HCV coinfection given the lack of predicted significant drug-

Table 2. Detailed characteristics of participants not achieving SVR with SOF/VEL/VOX.

	Study participant						
	R-PS-04	**R-PS-14**	**R-UM-01**	**R-UM-46**	**R-UM-48**	**R-WJ-05**	**R-WJ-06**
HCV genotype	1a	1a	1a	1b	1b	1a	1a
Baseline HCV RNA copies/ml	542,886	629,000	920,080	1,029,020	1,653,330	1,299,660	3,008,770
Previous regimen(s)	Peg/RBV; LDV/SOF (8 wks, incomplete)	LDV/SOF (8 wks; 16 wks incomplete)	Peg/RBV; SOF/SMV; LDV/SOF (12 wks)	EBR/GZR (12 wks)	Peg/RBV/BOC; LDV/SOF/RBV (12 wks)	Peg/RBV; PrOD (8 wks, incomplete)	LDV/SOF (12 wks; 24 wks)
Fibrosis stage	F4	F2	F4	F3	F4	F4	F4
Baseline RAS	Q80K M28M/T, Q30K	L31M	Q80K	L31M, Y93H	L31M, Q54H, Y93H	M28T	Q80K, Y93N
Clinical outcome	D/c subdural hematoma, Week 5 of treatment	D/c colitis, Day 5 of treatment, LTFU	Died HCC, Week 10 of treatment	LTFU – Week 8 of treatment	LTFU – Week 4 of treatment	D/c hypertensive stroke Day 3 of treatment, LTFU	Relapse Post-treatment Week 4
Post-treatment RAS	Q80K, M28T, Q30K	LTFU	NA	**R30Q/R**, L31M, Y93H/Y	**R30Q**, L31M, Q54H, Y93H	LTFU	Q80K, Y93N

Previous treatment completed unless otherwise noted. BOC, boceprevir; D/c, discontinued early; EBR, elbasvir; GZR, grazoprevir; LDV, ledipasvir; LTFU, lost to follow-up; n. a., not available; Peg, pegylated interferon; PrOD, paritaprevir, ritonavir, ombitasvir, dasabuvir; RAS, resistance-associated substitutions; RBV, ribavirin; SOF, sofosbuvir; SMV, simeprevir. Treatment-emergent RASs are shown in bold.

drug interactions.[15] Approximately half of our HIV+ patients were on dolutegravir-based therapy, and they experienced similar efficacy and side effect rates as both those patients on other antiretroviral regimens and those without HIV coinfection. We did not find any clinically significant liver function test elevations in those patients who received dolutegravir and SOF/VEL/VOX, nor did we observe any HIV viral load blips >100 copies/ml in any HIV coinfected patient during HCV treatment. One patient was taking unboosted atazanavir and experienced no treatment related side effects attributable to this medication; the SOF/VEL/VOX package insert lists atazanavir as a medication with the potential for significant drug interactions, with increased voxilaprevir concentrations.

Patients with previous non-completion of combination DAA-based therapy also did well with SOF/VEL/VOX for retreatment. In a per protocol analysis, 95% (18/19) of patients achieved SVR12, showing that initial non-compliance, treatment interruption, or non-completion of therapy does not appear to diminish future treatment response. Indeed, the majority of those patients (12/14, 86%) with poor adherence to their initial regimen were able to complete treatment and achieve SVR. Thus, initial non-adherence to therapy does not justify withholding retreatment in these patients.

As DAAs continue to be more widely used, the relevance of RASs remains uncertain, particularly in the context of previous treatment experience. A recent analysis of registrational studies of SOF/VEL/VOX found no impact of pre-existing RASs nor did they find patterns of treatment-emergent RASs on SOF/VEL/VOX treatment.[16] Of the patients who did not achieve SVR, those who presented for follow-up testing were noted to all have NS5A RASs: 75% (3/4) had Y93 substitutions (although this pre-existed retreatment in all 3 patients). Half (2/4) of those who did not achieve SVR12 had NS3 protease inhibitor Q80K NS3/4 substitutions (which have not been associated with reduced susceptibility to VOX[17]), but overall, of the 11 patients with previous protease inhibitor experience (including simeprevir, grazoprevir, boceprevir, asunaprevir, and GS-9451), 8/11 (73%, 95% CI 43–91%) achieved SVR12.

An unanticipated finding of this study was that 3 patients screened for retreatment after initial evidence of treatment failure were actually found to have undetectable HCV RNA when testing was repeated 12 weeks after the completion of initial combination DAA therapy. Our study shows that when virus is detected following DAA treatment, this should be verified before retreatment is initiated.

The strengths of this study include the inclusion of patients who had not previously been studied with this regimen, specifically patients with HIV coinfection, thus providing evidence supporting the safety and efficacy of SOF/VEL/VOX in patients receiving dolutegravir antiretroviral therapy. We also were able to include a majority of non-white patients, traditionally underrepresented in clinical trials and disproportionately affected by hepatitis C. Historically, treatment and SVR rates in this population have been lower in both clinical practice and research settings. This study further demonstrates the efficacy of retreatment in a sample reflective of the real-world population, and underscores the need to consider disparities in HCV treatment in marginalized and hard to treat populations, especially for those who are DAA-experienced. Finally, we studied the breadth of patients with previous DAA-experience, including patients with prior non-completion of therapy due to poor adherence or treatment interruption, who have not previously been studied.

Our study has a few limitations, including its open-label and non-randomized design. Additionally, we were unable to exclude occult reinfection (that is, reinfection with the same subgenotype within the 3 months following initial combination DAA therapy), but in a real-world setting, this would be indistinguishable from virologic failure. Another limitation is our relatively small sample size, and it is important to note that our study was not powered to compare outcomes between patients with and without HIV coinfection. However, the strong evidence for efficacy of retreatment with SOF/VEL/VOX in this study supports its excellent efficacy in a challenging patient population.

In summary, our data supports the use of SOF/VEL/VOX in the retreatment of patients who have not previously achieved SVR12 in response to combination DAA treatments. This is the first study of this retreatment regimen in HIV/HCV coinfection, particularly in combination with dolutegravir-based antiretroviral therapy, and it shows that the regimen is a safe and effective option for these patients. Additionally, in patients with previous poor adherence, treatment interruption, or non-completion of therapy, this regimen was also safe, effective, and well-tolerated.

Table 3. Adverse events, discontinuation of treatment, and hematologic abnormalities.

Event	Number of patients (%)	Notation
Any adverse event	77 (100)	
Treatment discontinuation due to adverse event	4 (5.2)	HCC (unrelated) Hypertensive stroke (unrelated) Colitis (unrelated) Traumatic subdural hematoma (unrelated)
Serious adverse event	5 (6.5)	Pulmonary hypertension exacerbation (unrelated) HCC (unrelated) SCC (unrelated) Hypertensive stroke (unrelated) Traumatic subdural hematoma (unrelated)
Death	1 (1.3)	Patient with HCC/hepatic decompensation
Adverse event in ≥5% of patients		
Fatigue	21 (27.3)	
Headache	19 (24.7)	
Diarrhea	16 (20.8)	
Abdominal pain	7 (9.0)	
Nausea	7 (9.0)	
Constipation	5 (6.4)	
Grade 3/4 laboratory abnormalities		
Aspartate aminotransferase >5x ULN	1 (1.3)	Patient with HCC/hepatic decompensation
Creatinine >2x baseline	2 (2.6)	Transient, resolved at repeat lab draw
Glucose level >250 mg/dl	2 (2.6)	Both patients with pre-existing diabetes mellitus
INR >2x ULN	2 (2.6)	Transient, resolved at repeat lab draw

HCC, hepatocellular carcinoma; INR, international normalized ratio; SCC, squamous cell carcinoma; ULN, upper limit of normal.

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Conflict of interest

Dr. Wilson and Dr. Kottilil report an investigator-initiated grant and drug support during the conduct of the study. Dr. Husson reports grants and non-financial support from Merck, Sharpe, and Dome, outside the submitted work. Dr. Tang, Ms. Price and Dr. Kattakuzhy report grants from Gilead Sciences, Inc. outside the submitted work. Dr. Chua reports grants and personal fees from Gilead Sciences Inc., outside the submitted work. Dr. Rosenthal reports grants and non-financial support from Gilead Sciences, during the conduct of the study; grants and non-financial support from Gilead Sciences, and grants and non-financial support from Merck outside the submitted work. Dr. Kottilil reports grants and other from Gilead Sciences, grants and other from Merck, and grants from Arbutus during the conduct of the study. Ms. Covert, Ms. Hoffmann, Dr. Emmanuel, Ms. Comstock, Dr. Mathur, and Dr. Masur have nothing to disclose.

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

Authors' contributions

EW, JHo, BE, HM and SKo contributed to the conception and design of the study. EW, ECov, JHo, ECom, LT, JHu, JC, AP, PM, ER, and SKa contributed to acquisition of the data, EW, ECov, JHo, ECom and BE contributed to the analysis of the data. EW, ECov, JHo, ECom, BE, and SKo contributed to interpretation of the data, EW, ECov, and JHo contributed to the drafting of the article, All authors contributed to critical revision and had final approval of the version of the manuscript to be published.

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Supplementary data

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References

[1] Naggie S, Muir AJ. Oral combination therapies for hepatitis C virus infection: successes, challenges, and unmet needs. Annu Rev Med 2017;68:345–358.
[2] Arias A, Aguilera A, Soriano V, Benítez-Gutiérrez L, Lledó G, Navarro D, et al. Rate and predictors of treatment failure to all-oral HCV regimens outside clinical trials. Antivir Ther 2017;22(4):307–312.
[3] Tang L, Parker A, Flores Y, Dellario M, Dickson C, Amoroso A, et al. Treatment of hepatitis C with 8 weeks of ledipasvir/sofosbuvir: highly effective in a predominantly black male patient population. J Viral Hepat 2018;25(2):205–208.
[4] Tapper EB, Bacon BR, Curry MP, Dieterich DT, Flamm SL, Guest LE, et al. Real-world effectiveness for 12 weeks of ledipasvir-sofosbuvir for genotype 1 hepatitis C: the Trio Health study. J Viral Hepat 2017;24 (1):22–27.
[5] Polaris Observatory HCVC. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2(3):161–176.
[6] Bourliere M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. N Engl J Med 2017;376(22):2134–2146.
[7] FDA. FDA approves Vosevi for Hepatitis C. www.fda.gov; 2017.
[8] Mathur P, Kottilil S, Wilson E. Sofosbuvir/velpatasvir/voxilaprevir: a highly effective option for retreatment of hepatitis C in difficult-to-treat patients. Antivir Ther 2018.
[9] AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. Unique Populations – Patients with HIV/HCV Coinfection. May 24, 2018 2018. https://www.hcvguidelines.org/unique-populations/hiv-hcv.
[10] Boesecke C, Ingiliz P, Berger F, Lutz T, Schewe K, Schulze Zur Wiesch J, et al. Liver cirrhosis as a risk factor for direct-acting antiviral therapy

failure in real-life hepatitis C virus/human immunodeficiency virus coinfection. Open Forum Infect Dis 2017;4(3):ofx158.
[11] Gayam V, Hossain MR, Khalid M, Chakaraborty S, Mukhtar O, Dahal S, et al. Real-world clinical efficacy and tolerability of direct-acting antivirals in hepatitis C monoinfection compared to hepatitis C/HIV coinfection in a community care setting. Gut Liver 2018.
[12] Milazzo L, Lai A, Calvi E, Ronzi P, Micheli V, Binda F, et al. Direct-acting antivirals in hepatitis C virus (HCV)-infected and HCV/HIV-coinfected patients: real-life safety and efficacy. HIV Med 2017;18(4):284–291.
[13] Wilson EM, Kattakuzhy S, Sidharthan S, Sims Z, Tang L, McLaughlin M, et al. Successful retreatment of chronic HCV genotype-1 infection with ledipasvir and sofosbuvir after initial short course therapy with direct-acting antiviral regimens. Clin Infect Dis 2016;62(3):280–288.
[14] Tivicay (dolutegravir) [package insert]. Gilead Sciences, Inc, Foster City, CA. 2013.
[15] Soriano V, Labarga P, Fernandez-Montero JV, Mendoza C, Benítez-Gutiérrez L, Peña JM, et al. Drug interactions in HIV-infected patients treated for hepatitis C. Expert Opin Drug Metab Toxicol 2017;13(8):807–816.
[16] Sarrazin C, Cooper CL, Manns MP, Reddy KR, Kowdley KV, Roberts SK, et al. No impact of resistance-associated substitutions on the efficacy of sofosbuvir, velpatasvir, and voxilaprevir for 12weeks in HCV DAA-experienced patients. J Hepatol 2018;69(6):1221–1230.
[17] Pham LV, Jensen SB, Fahnoe U, Pedersen MS, Tang Q, Ghanem L, et al. HCV genotype 1–6 NS3 residue 80 substitutions impact protease inhibitor activity and promote viral escape. J Hepatol 2019;70(3):388–397.