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MAJOR ARTICLE

Sofosbuvir and Velpatasvir for the Treatment of Hepatitis C Virus in Patients Coinfected With Human Immunodeficiency Virus Type 1: An Open-Label, Phase 3 Study

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Background. A safe, simple, effective, and pan-genotypic regimen to treat hepatitis C virus (HCV) infection in patients coinfected with human immunodeficiency virus type 1 (HIV-1) remains a medical need. We assessed the efficacy and safety of the NS5B polymerase inhibitor sofosbuvir and the NS5A inhibitor velpatasvir for HCV in patients coinfected with HIV-1.

Methods. This phase 3, open-label, single-arm study at 17 sites in the United States enrolled patients with HCV of any genotype and HIV-1 coinfection, including those with compensated cirrhosis. All patients received sofosbuvir-velpatasvir once daily for 12 weeks. The primary endpoint was sustained virologic response 12 weeks after treatment (SVR_{12}). Efficacy and safety were assessed in all patients receiving at least 1 dose of treatment.

Results. Of 106 patients, 91 (86%) were men, 48 (45%) were black, and 19 (18%) had cirrhosis. SVR_{12} was achieved by 101 of 106 (95% [95% confidence interval {CI}, 89%–99%]) patients: 74 of 78 (95% [95% CI, 87%–99%]) with genotype 1; all 11 (100% [95% CI, 72%–100%]) with genotype 2; 11 of 12 (92% [95% CI, 62%–100%]) with genotype 3; and all 5 (100% [95% CI, 48%–100%]) with genotype 4. All 19 patients with cirrhosis had SVR_{12}. Two patients relapsed, 2 were lost to follow-up, and 1 withdrew consent. Two discontinued treatment due to adverse events and 2 had serious adverse events. The most common adverse events were fatigue (25%), headache (13%), upper respiratory tract infection (8%), and arthralgia (8%).

Conclusions. Sofosbuvir-velpatasvir for 12 weeks was safe and provided high rates of SVR_{12} in patients coinfected with HCV and HIV-1.

Clinical Trials Registration. NCT02480712.

Keywords. ASTRAL-5; HCV-HIV coinfection; hepatitis C virus; sofosbuvir; velpatasvir.

Approximately 10% of the 40 million patients worldwide who are chronically infected with human immunodeficiency virus type 1 (HIV-1) are coinfected with hepatitis C virus (HCV) [1, 2]. In the absence of effective HCV therapy, patients coinfected with HCV/HIV-1 have a higher rate of liver fibrosis progression and higher risk of cirrhosis and hepatic decompensation [3, 4]. As HIV-related morbidity and mortality has decreased, liver-related complications have become a leading cause of death in coinfected patients [5]. The introduction of direct-acting antiviral agents has provided safe and effective combination treatments for HCV infection in patients coinfected with HIV [6–8]. Current treatment guidelines recommend the same regimens for coinfected patients as for those with HCV monoinfection [9]. However, choosing an appropriate regimen can be complex; clinicians must take into account HCV genotype, prior HCV treatment history, cirrhosis status, and HIV antiretroviral (ARV) regimen in selecting the best drug regimen and duration of treatment. There remains an unmet clinical need for a simple well-tolerated, ribavirin-free, oral regimen with limited potential for interaction with HIV ARV agents that is highly effective against all HCV genotypes.

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Sofosbuvir is a pangenotypic nucleotide NS5B inhibitor that is approved in combination with other antiviral agents for the treatment of HCV of all genotypes. Velpatasvir is an HCV NS5A inhibitor with pangenotypic potency [10]. A fixed-dose combination tablet of sofosbuvir 400 mg and velpatasvir 100 mg (SOF-VEL) is approved in the United States and Europe for the treatment of adults with genotype 1–6 chronic HCV infection [11]. In phase 3 trials involving patients monoinfected with HCV, SOF-VEL once daily for 12 weeks provided high rates of sustained virologic response (SVR) in HCV treatment-naive and previously treated patients infected with HCV of all genotypes [12–14].

The objectives of this open-label phase 3 study were to evaluate the safety and efficacy of SOF-VEL for 12 weeks in a broad range of patients coinfected with HIV-1 and HCV, including those with compensated cirrhosis.

MATERIALS AND METHODS

Patients

We enrolled patients at 17 sites in the United States between 17 July 2015 and 9 October 2015. Patients were at least 18 years of age and were chronically infected with HIV-1 and HCV of any genotype. Eligible patients were required to be on a protocol-approved ARV regimen for at least 8 weeks before screening and to have evidence of HIV-1 RNA suppression (<50 copies/mL) with a $CD4^+$ T-cell count of >100 cells/μL. Protocol-approved ARV regimens were cobicistat-boosted elvitegravir/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF), FTC/TDF/rilpivirine, or FTC/TDF or abacavir/lamivudine plus 1 of the following: ritonavir-boosted atazanavir, ritonavir-boosted darunavir, ritonavir-boosted lopinavir, raltegravir, or rilpivirine. Alternative combinations were allowed on a case-by-case basis. A minimum creatinine clearance of 60 mL/minute, as calculated by the Cockcroft-Gault equation, was required for enrollment. Approximately 30% of patients were permitted to have received previous HCV treatment (excluding prior NS5A or NS5B inhibitors), and up to 30% of patients could have compensated cirrhosis as defined by (1) liver biopsy, (2) transient elastography of >12.5 kPa, or (3) a FibroTest score >0.75 and an aspartate aminotransferase–to–platelet ratio index (APRI) >2. Full inclusion and exclusion criteria are provided in Supplementary Table 1.

Study Design

In this open-label phase 3 study, all patients received a fixed-dose combination tablet containing 400 mg of SOF and 100 mg of VEL once daily for 12 weeks with or without food. All patients were scheduled for follow-up out to 24 weeks after the end of treatment (Supplementary Table 2).

Study Assessments

Serum HCV RNA was measured using the COBAS Ampliprep/COBAS TaqMan HCV Quantitative Test, version 2.0. HCV genotype and subtype was determined using the Siemens VERSANT HCV Genotype INNO-LiPA 2.0 Assay. Plasma HIV-1 RNA was measured using the AmpliPrep/COBAS TaqMan HIV-1 Test, version 2.0. For HCV viral sequence analysis, plasma samples were collected at baseline/day 1 and each subsequent visit as well as at any unscheduled visit. All adverse events were recorded and graded according to a standardized scale. Blood samples were collected from all patients at each on-treatment visit and archived for pharmacokinetic analysis of SOF, its metabolite GS-331007, VEL, and tenofovir. A full schedule of procedures and assessments by study visit is provided in Supplementary Table 2.

Deep sequencing of HCV NS5A and NS5B—the target regions of VEL and SOF, respectively—was performed for all patients at baseline, and again for all patients who experienced virologic failure. The full-length HCV NS5A and NS5B coding regions were amplified and deep sequenced with the Illumina MiSeq deep sequencing platform (Illumina, San Diego, California) by DDL Diagnostic Laboratory (Rijswijk, the Netherlands). To detect emergent resistance-associated substitutions (RASs), the sequences from baseline samples were compared with those taken at the time of virologic failure. NS5A inhibitor class RASs were defined as specific amino acid changes that conferred >2.5-fold reduced susceptibility to any NS5A inhibitor in vitro and/or any treatment-emergent variant observed in ≥2 patients that occurred at positions 24, 26, 28, 30, 31, 32, 38, 58, 92, and 93, which have previously been associated with resistance. NS5B nucleotide inhibitor RASs included S96T, N142T, L159F, E237G, S282T, any S282 variant other than T, C/M289L/I, L320F/I/V, and V321A/I. NS5A and NS5B RASs present in >15% of sequence reads are considered relevant and were reported [15].

Endpoints and Statistical Analysis

The primary efficacy endpoint was the proportion of patients with sustained virologic response, defined as HCV RNA below the limit of quantification (<15 IU/mL) at 12 weeks after the end of treatment (SVR_{12}) among all patients who received at least 1 dose of study treatment. Secondary endpoints included the proportion of patients with HCV RNA <15 IU/mL during treatment and the proportion of patients with virologic failure. The primary safety endpoint was the proportion of patients discontinuing study treatment due to 1 or more adverse events. HIV virologic failure was defined as confirmed HIV RNA ≥50 copies/mL at the 4-week follow-up visit, or discontinuation from study prior to the 4-week follow-up visit for any adverse event related to ARVs or HIV disease, or any change in ARV therapy during the study period due to HIV RNA ≥50 copies/mL. HIV virologic rebound was defined as at least 2 HIV RNA ≥400 copies/mL at 2 consecutive postbaseline visits at least 2 weeks apart.

Statistical hypothesis testing and formal sample size calculations were not performed. With approximately 100 patients

enrolled into the study, we calculated that a 2-sided 95% confidence interval of the SVR_{12} rate will extend at most 5.9% in both directions from the observed SVR_{12} rate, assuming the expected SVR_{12} rate is 90%. Point estimates and 2-sided 95% exact confidence intervals (CIs) (Clopper-Pearson method) of the SVR_{12} rates for each treatment group were calculated by HCV genotype (1a, 1b, 2, 3, 4) and selected subgroups.

Study Oversight

The design of this study was in compliance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the institutional review board at each participating site.

RESULTS

Of the 149 patients screened, 107 were enrolled and 106 received at least 1 dose of study treatment (Figure 1 and Supplementary Table 3). Patient baseline demographics are presented in (Table 1). Ninety-one of the 106 patients (86%) were male, 45% were black, 29% were HCV treatment-experienced, and 18% had compensated cirrhosis. Overall, 62% of patients had genotype 1a, 11% had genotype 1b, 10% had genotype 2, 11% had genotype 3, and 5% had genotype 4.

Patients were receiving a broad range of ARV regimens: protease inhibitor based (47%), integrase inhibitor based (34%), nonnucleotide reverse transcriptase inhibitor based (12%), and other regimens (7%). Fifty-three percent of patients were receiving TDF as part of a ritonavir- or cobicistat-boosted regimen and 33% with TDF in a nonboosted regimen. Mean $CD4^+$ cell count at baseline was 598 cells/μL (range, 183–1513 cells/μL). Mean estimated glomerular filtration rate (by the Cockcroft-Gault equation) was 98.4 mL/minute (range, 57.4–198.4 mL/minute).

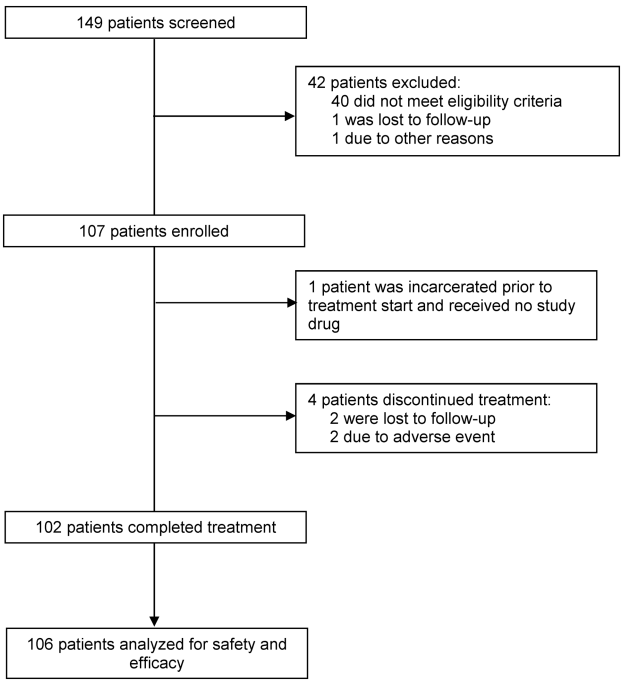

Figure 1. Patient disposition.

Table 1. Demographic Characteristics of Study Patients

Characteristic	SOF - VEL for 12 wk (n = 106)
Age, y, mean (range)	54 (25–72)
Male sex	91 (86)
Race	
White	54 (51)
Black	48 (45)
Asian	3 (3)
Other	1 (1)
BMI, kg/m^2, mean (range)	27.2 (18.6–43.4)
Baseline HCV RNA, log_{10} IU/mL, mean (range)	6.3 (5.0–7.4)
ALT, U/L, mean (range)	70 (15–326)
HCV genotype	
1a	66 (62)
1b	12 (11)
2	11 (10)
3	12 (11)
4	5 (5)
Cirrhosis	19 (18)
IL28B genotype	
CC	24 (23)
CT	52 (49)
TT	30 (28)
HCV treatment history	
Experienced	31 (29)
Naive	75 (71)
$CD4^+$ count, cells/μL, mean (range)	598 (183–1513)
Antiviral regimen	
Pharmacologically boosted protease inhibitor based	50 (47)
Nonnucleoside reverse transcriptase inhibitor based	13 (12)
Integrase inhibitor based	36 (34)
Other	7 (7)
Antiviral regimen by TDF use	
Pharmacologically boosted TDF-containing regimen[a]	56 (53)
Nonboosted TDF-containing regimen	35 (33)
Regimen not containing TDF	15 (14)
eGFR by Cockroft-Gault, mL/min, mean (SD)	98.4 (25.9)

Data are presented as No. (%) unless otherwise specified.

Abbreviations: ALT, alanine aminotransferase, BMI, body mass index; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; SD, standard deviation; SOF, sofosbuvir; TDF, tenofovir disoproxil fumarate; VEL, velpatasvir.

[a]Includes ritonavir and/or cobicistat-containing regimens.

Efficacy

Of the 106 patients enrolled and treated, 101 (95% [95% CI, 89%–99%) achieved SVR_{12} (Table 2). By genotype, SVR_{12} was achieved by 63 of 66 (95% [95% CI, 87%–99%]) patients with genotype 1a; by 11 of 12 (92% [95% CI, 62%–100%]) patients

Table 2. Efficacy Analysis

Characteristic	SOF - VEL for 12 wk (n = 106)
HCV RNA below the LLOQ during treatment, no./No. (%)	
Week 2	70/103 (68)
Week 4	95/103 (92)
Week 6	102/103 (99)
HCV RNA below the LLOQ after treatment, No. (%)	
Week 4	101 (95)
Week 12	
Overall, No. (%, 95% CI)	101 (95, 89–99)
By genotype, no./No. (%, 95% CI)	
Genotype 1a	63/66 (95, 87–99)
Genotype 1b	11/12 (92, 62–100)
Genotype 2	11/11 (100, 72–100)
Genotype 3	11/12 (92, 62–100)
Genotype 4	5/5 (100, 48–100)
By HCV treatment history, no./No. (%)	
Treatment naive	71/75 (95)
Treatment experienced	30/31 (97)
By cirrhosis status, no./No. (%)	
Yes	19/19 (100)
No	82/87 (94)
Virologic failure, No. (%)	
Breakthrough	0
Relapse	2 (2)
Lost to follow-up, No. (%)	2 (2)
Withdrew consent, No. (%)	1 (1)

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; LLOQ, lower limit of quantitation; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir.

with genotype 1b; by 11 of 11 (100% [95% CI, 72%–100%]) patients with genotype 2; by 11 of 12 (92% [95% CI, 62%–100%]) patients with genotype 3; and by all 5 (100% [95% CI, 48%–100%]) with genotype 4.

SVR_{12} was achieved by all 19 (100%) patients with cirrhosis, by 45 (94%) of the 48 black patients enrolled, and by 29 of the 31 (94%) who had received previous treatment for HCV. SVR_{12} rates by treatment experience and cirrhosis status are provided in Supplementary Table 4.

Resistance was assessed in all 103 patients who had a virologic outcome. Overall, 13 patients (13%) had NS5A RASs at baseline using a 15% sensitivity threshold, including substitutions at positions 28, 30, 31, and 93. All patients with baseline NS5A RASs achieved SVR_{12}, including the 3 patients with VEL-specific RASs Y93H (GT1a and GT3a) and Q30H/R+L31M (GT1a) (see Supplementary Tables 5–7 for further details on the resistance analysis).

Of the 5 patients who did not achieve SVR, 2 were lost to follow-up, 1 withdrew consent, and 2 experienced posttreatment HCV relapse after completing 12 weeks of treatment. The 2 patients with virologic failure (2% of the study population) were both black women with genotype 1a HCV infection and no evidence of cirrhosis (Supplementary Table 7). One was a prior nonresponder to pegylated interferon plus ribavirin on ritonavir-boosted lopinavir plus FTC/TDF. The other was treatment-naive on ritonavir-boosted darunavir plus abacavir/lamivudine. Both patients achieved HCV RNA suppression on treatment (by 2 and 6 weeks) and HCV relapse was detected at posttreatment week 4. No evidence of RASs at baseline or time of relapse (1% and 15% thresholds) was found. On-treatment pill count and blood levels of the study drugs suggested adherence, and HCV reinfection was excluded by sequence analysis.

Pharmacokinetics

Pharmacokinetic parameters of SOF, GS-331007, VEL, and tenofovir were determined using established population pharmacokinetic models. Tenofovir exposure was assessed following results showing increased tenofovir exposure when coadministered with SOF-VEL in phase 1 studies in healthy patients [16, 17].

The exposure of SOF, GS-331007, and VEL were generally similar following administration of SOF-VEL with a variety of ARVs, including unboosted and boosted regimens (Supplementary Table 8). Exposures of SOF, GS-331007, and VEL were similar to those observed in HCV-monoinfected patients in SOF-VEL phase 2 and 3 studies. Tenofovir exposure was similar when TDF was administered as part of boosted or unboosted regimens with SOF-VEL (Supplementary Table 9). These exposures were also within the range of exposure observed in HIV-monoinfected patients using boosted ARV regimens in the absence of SOF-VEL [18].

Safety

Overall, 75 patients (71%) experienced at least 1 adverse event, most of which were mild to moderate in severity (Table 3). The most common adverse events were fatigue (25%), headache (13%), upper respiratory tract infection (8%), arthralgia (8%), and diarrhea (8%). Two patients (2%) experienced serious adverse events. A 50-year-old white man had a serious event of acute radial nerve palsy on day 18 of treatment, but continued treatment and achieved SVR_{12}. The other patient, a 61-year-old black man with cirrhosis, had 3 serious adverse events: (1) infection of the toe on day 27 of treatment, followed by (2) sepsis and urinary tract infection on day 46 of treatment and (3) persistent elevations in alanine and aspartate aminotransferase levels (attributed to sepsis and antibiotics). This individual discontinued study treatment on day 48 and achieved SVR_{12}. The only other patient who discontinued study treatment due to adverse events was a noncirrhotic 53-year-old white man with genotype 3a HCV who withdrew consent after experiencing a single episode of vomiting on day 4 of treatment. In both cases of treatment discontinuation, the adverse events were judged as unlikely to be related to study medications by the investigator. $CD4^+$

Table 3. Safety Analysis

Characteristic	SOF - VEL for 12 wk (n = 106)
Patients experiencing any adverse event	75 (71)
Patients experiencing serious adverse event	2 (2)
Patients discontinuing treatment drug due to adverse event	2 (2)
Deaths	0
Adverse event occurring in >5 patients overall, any grade	
Fatigue	26 (25)
Headache	14 (13)
Upper respiratory tract infection	9 (8)
Arthralgia	8 (8)
Diarrhea	8 (8)
Insomnia	7 (7)
Nausea	7 (7)
Laboratory abnormalities	
Neutrophils, 500–749 cells/μL	2 (2)
International normalized ratio of prothrombin time, >2.0 × ULN	1 (1)
AST, >10.00 × ULN	1 (1)
Creatine kinase, <10.0 × ULN	2 (2)
Creatinine, >3.00 mg/dL	1 (1)
Lipase, >3.0 × ULN	1 (1)
Hypophosphatemia, <1.0 mg/dL	1 (1)
Hyperglycemia, >250 mg/dL	2 (2)
Hyperbilirubinemia, >2.5 × ULN	8 (8)
Hyperuricemia, <1.0 mg/dL	1 (1)
Hematuria, >75 RBC/HPF	2 (8)
Urine blood, 3	1 (1)
Glycosuria, 4+ by dipstick	2 (2)

Data are presented as No. (%).

Abbreviations: AST, aspartate aminotransferase; HPF, high-power field; RBC, red blood cells; SOF, sofosbuvir; ULN, upper limit of normal; VEL, velpatasvir.

cell counts remained stable and no patient experienced HIV virologic rebound.

Seven patients (7%) had grade 3 and 1 patient (1%) grade 4 elevations of total bilirubin (unconjugated hyperbilirubinemia); all were receiving ritonavir-boosted atazanavir, and all had graded total bilirubin elevations at baseline/day 1 and during treatment. The only other grade 3 chemistry laboratory abnormalities reported for >1 patient were increased creatine kinase associated with exercise (2 patients), and increased serum glucose associated with a history of diabetes mellitus (2 patients).

Overall, few patients experienced renal laboratory abnormalities. Figure 2 shows creatinine clearance across study visits. Three patients, all receiving TDF-containing regimens, had a change from baseline of ≥0.4 mg/dL in serum creatinine while on treatment (Supplementary Table 10). One patient, a 54-year-old white man on ritonavir-boosted atazanavir plus FTC/TDF with a history of chronic kidney disease (unclear etiology) and hypertension, developed worsening renal function at week 4 of treatment, with serum creatinine of 3.29 mg/dL (1.43 mg/dL at baseline), creatinine clearance of 26.5 mL/minute (61.4 mL/minute at baseline), 3+ proteinuria, and normoglycemic glycosuria. This event was predated by a bout of gastroenteritis with dehydration. At subsequent visits, serum creatinine ranged from 1.97 to 2.66 mg/dL. The patient completed study treatment without modification of his ARV regimen and achieved SVR_{12}. Two other patients experienced increases of ≥0.4 mg/dL in serum creatinine from baseline, but these increases were transient and asymptomatic. One was a 41-year-old white man on raltegravir plus FTC/TDF who had a transient increase in serum creatinine to 1.44 mg/dL (from 0.98 mg/dL at baseline) at week 10 while on trimethoprim-sulfamethoxazole for a ruptured ear drum and sinus infection. The other patient was a 57-year-old black man with a history of intravenous drug use on ritonavir-boosted atazanavir plus FTC/TDF who had an unconfirmed, transient increase in serum creatinine to 1.32 mg/dL (0.91 mg/dL at baseline) at week 2, which was back to 1.01 mg/dL by the week 4 visit. Neither patient required changes to their ARV regimens. Two patients (2%) were identified as having a change from baseline in creatinine clearance to <50 mL/minute while on treatment, including the 54-year-old patient described above. The second was a 69-year-old black man on elvitegravir/cobicistat/FTC/TDF plus darunavir who had a creatinine clearance of 49 mL/minute (64.2 mL/minute at baseline) accompanied by an increase in serum creatinine to 1.59 mg/dL (1.21 mg/dL at baseline) at week 2. This occurred in the setting of daily ingestion of protein powder and ibuprofen for knee pain.

Among all patients receiving TDF, serum creatinine remained stable from baseline through the end of treatment and at the posttreatment week 12 follow-up visit (Figure 2). By posttreatment week 12, creatinine values were close to baseline with an overall median change from baseline of +0.02 mg/dL (interquartile range, 0.08–0.10 mg/dL).

DISCUSSION

In this open-label, phase 3 study, 12 weeks of treatment with SOF-VEL resulted in high rates of SVR_{12} in patients coinfected with HIV-1 and genotype 1–4 HCV. The study included patients with characteristics historically associated with lower response to interferon-based therapies: cirrhosis, prior treatment experience, HIV coinfection, and black race. None of these factors appeared to be associated with virologic failure, which occurred in only 2 patients. The 100% SVR_{12} rate in patients with cirrhosis, and 97% SVR_{12} rate in those with prior treatment failure, are consistent with the findings of the larger ASTRAL 1–3 studies, which also demonstrated high SVR_{12} rates in HCV-monoinfected individuals that included historically difficult-to-treat populations. Moreover, this high success rate was seen without the addition of ribavirin or the extension of therapy beyond 12 weeks [13–15]. In the ION-4 study of ledipasvir-SOF in patients with HCV/HIV-1 coinfection, black race was unexpectedly found to be significantly associated with virologic relapse. Although in the current study the 2 patients with virologic relapse were black women, neither patient was on

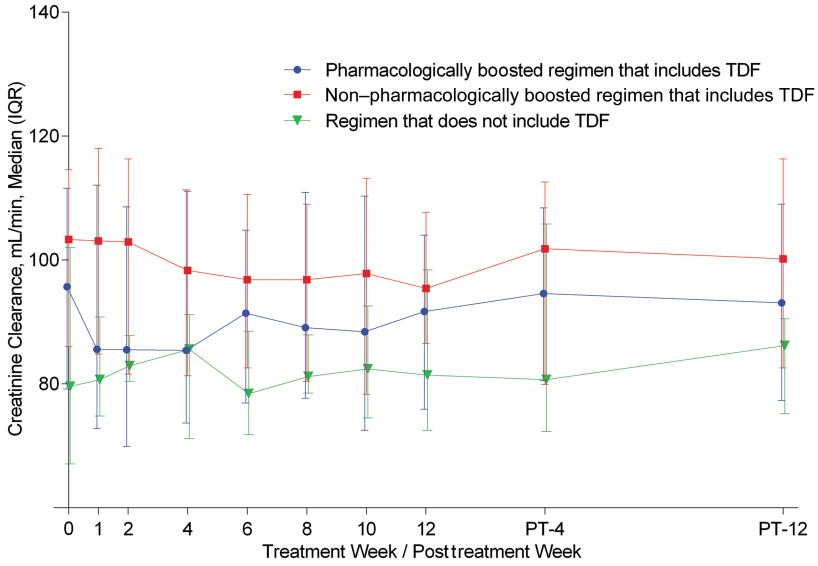

Figure 2. Median creatinine clearance by antiretroviral regimen type and treatment visit. Abbreviations: IQR, interquartile range; PT, posttreatment; TDF, tenofovir disoproxil fumarate.

efavirenz (excluded in the trial), and an adverse interaction with ARVs was not assessed to be a likely contributor to viral relapse. Furthermore, the overall SVR rate was 94% in both black and white patients (45/48 and 51/54, respectively). While the rate of virologic failure was 4% (2 patients) in black patients and 0% in white patients, the study was not powered to detect a difference among racial groups. Taken together, the SVR_{12} rates observed in this population of patients with HIV/HCV coinfection are consistent with those observed in the ASTRAL 1–3 phase 3 registrational trials [13–15].

The presence of RASs at baseline, particularly those associated with resistance to NS5A inhibitors, has emerged as a factor in decreased response to NS5A inhibitor–containing direct-acting antiviral therapies in certain populations [19–21]. One of the potential advantages of this VEL-containing regimen is that it appears to have improved efficacy in patients with baseline NS5A RASs without the addition of ribavirin or extension of treatment duration. Consistent with the experience in the larger ASTRAL 1–3 studies, no virologic failures were seen in our small sample size of patients (n = 13) with NS5A class RASs at baseline.

The safety profile of SOF-VEL for 12 weeks was also consistent with that observed for HCV-monoinfected adults treated with SOF-VEL. A major consideration in treating HCV in patients coinfected with HIV-1 is the potential for interactions with ARV drugs. Similar to ledipasvir-SOF, SOF-VEL has been shown to increase plasma tenofovir exposure when coadministered with TDF in phase 1 studies [17, 22]. The current study enrolled patients receiving a wide variety of ARV regimens, including a relatively large number (n = 56) of patients on ritonavir- or cobicistat-boosted regimens. We found that treatment with SOF-VEL for 12 weeks was safe and well tolerated when used with a pharmacologically boosted agent and TDF. Interestingly in this study, tenofovir exposure was within the range of exposure observed in HIV-monoinfected patients using boosted ARV regimens in the absence of SOF-VEL. In addition, there were no discontinuations due to renal adverse events, and no trends suggestive of renal toxicity were identified with intensive renal laboratory monitoring.

Three patients experienced increases in creatinine of >0.4 mg/dL during the study, including 2 patients on pharmacologically boosted ARV regimens that included TDF. All 3 patients had comorbid conditions (hypertension), epidemiologic factors (black race), or concomitant medications associated with an increased risk of renal dysfunction. This suggests that coadministration of SOF-VEL with TDF in the setting of a pharmacologically boosted ARV regimen may be safe in select populations with GFR >60 mL/minute but other risks for renal dysfunction. Although 1 patient had persistent changes in renal function, no renal safety signal attributable to SOF-VEL was identified regardless of ARV regimen. These data support the current prescribing information for SOF-VEL, which allows for the coadministration of this regimen with most ARVs except those with moderate cytochrome P450 (CYP) induction potential such as efavirenz or etravirine [11].

One of the major limitations of the present study is that despite its promising results, the numbers of patients in some difficult-to-treat subgroups (ie, patients with cirrhosis, and NS5A RASs at baseline) are insufficient to definitively confirm the efficacy and safety of SOF-VEL in these coinfected patients. However, when considered in the context of the companion ASTRAL 1–3 studies, and other trials suggesting that HIV-1

coinfection itself does not adversely impact response, the present study should reassure clinicians that coinfected patients can be effectively treated with the same regimen as monoinfected patients. Generalizability of these results to the coinfected population at large is limited by the small number of patients we enrolled with cirrhosis as well as HCV genotypes 1b, 2, 3, and 4, as well as the fact that no patients with HCV genotype 5 or 6 were enrolled.

In conclusion, SOF-VEL for 12 weeks provides a simple, safe, and highly effective treatment for patients coinfected with HCV and HIV-1. Its effectiveness in a broad range of patients across a wide range of ARV regimens suggests that it could be used by the majority of patients with HIV/HCV coinfection including those with prior treatment experience, compensated cirrhosis, and non–genotype 1 HCV infection.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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