Original Investigation

Sofosbuvir and Ribavirin for Hepatitis C in Patients With HIV Coinfection

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IMPORTANCE Treatment of hepatitis C virus (HCV) infection in patients also infected with human immunodeficiency virus (HIV) has been limited due to drug interactions with antiretroviral therapies (ARTs) and the need to use interferon.

OBJECTIVE To determine the rates of HCV eradication (sustained virologic response [SVR]) and adverse events in patients with HCV-HIV coinfection receiving sofosbuvir and ribavirin treatment.

DESIGN, SETTING, AND PARTICIPANTS Open-label, nonrandomized, uncontrolled phase 3 trial conducted at 34 treatment centers in the United States and Puerto Rico (August 2012-November 2013) evaluating treatment with sofosbuvir and ribavirin among patients with HCV genotypes 1, 2, or 3 and concurrent HIV. Patients were required to be receiving ART with HIV RNA values of 50 copies/mL or less and a CD4 T-cell count of more than 200 cells/μL or to have untreated HIV infection with a CD4 T-cell count of more than 500 cells/μL. Of the treatment-naive patients, 114 had HCV genotype 1 and 68 had HCV genotype 2 or 3, and 41 treatment experienced participants who had been treated with peginterferon-ribavirin had HCV genotype 2 or 3, for a total of 223 participants.

INTERVENTIONS Treatment-naive patients with HCV genotype 2 or 3 received 400 mg of sofosbuvir and weight-based ribavirin for 12 weeks and treatment-naive patients with HCV genotype 1 and treatment-experienced patients with HCV genotype 2 or 3 received the same treatment for 24 weeks.

MAIN OUTCOMES AND MEASURES The primary study outcome was the proportion of patients with SVR (serum HCV <25 copies/mL) 12 weeks (SVR_{12}) after cessation of HCV therapy.

RESULTS Among treatment-naive participants, 87 patients (76%) of 114 (95% CI, 67%-84%) with genotype 1, 23 patients (88%) of 26 with genotype 2 (95% CI, 70%-98%), and 28 patients (67%) of 42 with genotype 3 (95% CI, 51%-80%) achieved SVR_{12}. Among treatment-experienced participants, 22 patients (92%) of 24 with genotype 2 (95% CI, 73%-99%) and 16 patients (94%) of 17 (95% CI, 71%-100%) achieved SVR_{12}. The most common adverse events were fatigue, insomnia, headache, and nausea. Seven patients (3%) discontinued HCV treatment due to adverse events. No adverse effect on HIV disease or its treatment was observed.

CONCLUSIONS AND RELEVANCE In this open-label, nonrandomized, uncontrolled study, patients with HIV who were coinfected with HCV genotype 1, 2, or 3 who received the oral, interferon-free combination of sofosbuvir and ribavirin for 12 or 24 weeks had high rates of SVR_{12}. Further studies of this oral regimen in diverse populations of coinfected patients are warranted.

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Up to 7 million persons worldwide are infected with both human immunodeficiency virus (HIV) and hepatitis C virus (HCV).[1] Human immunodeficiency virus and HCV coinfection is associated with high rates of liver fibrosis, cirrhosis, hepatocellular carcinoma, and overall mortality.[2] Coinfected patients who are cured of HCV have improved clinical outcomes and survival.[3]

In treatment-naive patients coinfected with HCV and HIV, treatment for HCV genotypes 1, 2, or 3 infection has required 24 to 48 weeks of peglyated interferon and ribavirin with or without an HCV NS3/4A serine protease inhibitor, telaprevir or boceprevir, resulting in sustained virologic response (SVR) rates of 62% to 74%.[4,5] However, the use of these regimens is limited due to complex dosing of the HCV NS3/4A protease inhibitors, poor tolerability, and drug interactions between HCV and antiretroviral drugs; moreover, up to 70% of patients with HIV/HCV coinfection are not eligible for HCV treatment regimens that include interferon.[6,7] Sofosbuvir is an oral nucleotide analog HCV NS5B polymerase inhibitor recently approved for the treatment of HCV genotypes 1 through 4.[8,9] Sofosbuvir has minimal or no drug interactions with a wide range of antiretroviral drugs.[10] Phase 3 trials of sofosbuvir involving patients with HCV alone have demonstrated high rates of SVR when used in combination with ribavirin for 12 weeks for HCV genotype 2, or 12 to 24 weeks for HCV genotype 3, and in combination with peginterferon and ribavirin for 12 weeks for HCV genotypes 1, 4, 5, and 6.[11-13] The combination of sofosbuvir plus ribavirin for 24 weeks has also shown promise for patients with HCV genotype 1.[14]

We evaluated the rates of SVR and adverse events in patients infected with HIV and HCV genotype 1, 2, or 3 who were treated with the oral regimen of sofosbuvir and ribavirin for 12 or 24 weeks.

Methods

Patients

We enrolled patients chronically infected with HCV at 34 academic, private practice, and community health centers in the United States and Puerto Rico from August 2012 through March 2013 (Study Protocol available in Supplement 1). Written informed consent was obtained from all patients prior to screening. To be eligible, patients had to be at least 18 years old, coinfected with HCV genotype 1, 2, or 3 and HIV, have a body mass index of 18 or more (calculated as weight in kilograms divided by height in meters squared). We enrolled patients with HCV genotype 1, 2, or 3 who had not received HCV treatment and patients with HCV genotype 2 or 3 who had been previously treated for HCV. Only patients with documentation indicating their cirrhosisis status were enrolled. Persons who inject drugs were not excluded by medical history alone; however, if they were actively using drugs they were excluded if they had a positive urine toxicology result at the screening visit. Patients receiving antiretroviral treatment (ART) were required to have been receiving a stable regimen for at least 8 weeks before screening, have an HIV RNA of less than 50 copies/mL and a CD4 T-lymphocyte count higher than 200 cells/μL. Antiretroviral regimens containing emtricitabine-tenofovir in combination with atazanavir-ritonavir, darunavir-ritonavir, efavirenz, raltegravir, or rilpivirine were included based on drug-interaction studies with sofosbuvir. Patients not receiving ART were required to have a CD4 T-lymphocyte count higher than 500 cells/μL at screening. No more than 20% of the entire study population was permitted to have evidence of cirrhosis at screening as assessed by a liver biopsy within 2 years of screening or by FibroSURE (Laboratory Corporation of America). Race was self-reported. Reasons for screen failure are reported in eTable 1 in Supplement 2.

Study Design

In this multicenter, open-label, nonrandomized, uncontrolled phase 3 trial,[15] all patients received 400 mg of sofosbuvir (Gilead Sciences) administered orally once daily along with ribavirin (Ribasphere, Kadmon) administered orally twice daily, with doses determined according to body weight (1000 mg daily for patients with a body weight <75 kg and 1200 mg daily for patients with a body weight of ≥75 kg). The dose of ribavirin could be decreased or discontinued to help manage hemoglobin reductions according to the product label. The treatment duration was 12 weeks for treatment-naive patients with HCV genotype 2 or 3 and 24 weeks for treatment-naive patients with HCV genotype 1 and for treatment-experienced patients with HCV genotype 2 or 3.

Study Assessments

Serum HCV RNA was measured at screening and at every subsequent visit with the COBAS TaqMan HCV Test, version 2.0 for use with the High Pure System (Roche Molecular Systems) with a lower limit of quantification (LLOQ) of 25 IU/mL. Hepatitis C virus genotyping was determined with Siemens Versant HCV Genotype 2.0 assay. Human immunodeficiency virus RNA was measured at screening and at every subsequent visit using the AmpliPrep/COBAS TaqMan HIV test, version 2.0.

Hepatitis C viral relapse was defined as an HCV RNA level that was higher than the LLOQ at posttreatment weeks 4 or 12 after having an HCV RNA level that was lower than the LLOQ at the end of treatment. *Hepatitis C viral breakthrough* was defined as an HCV RNA level that was the LLOQ or higher during treatment after having previously had an HCV RNA level lower than the LLOQ while taking study drugs, confirmed with 2 consecutive values.

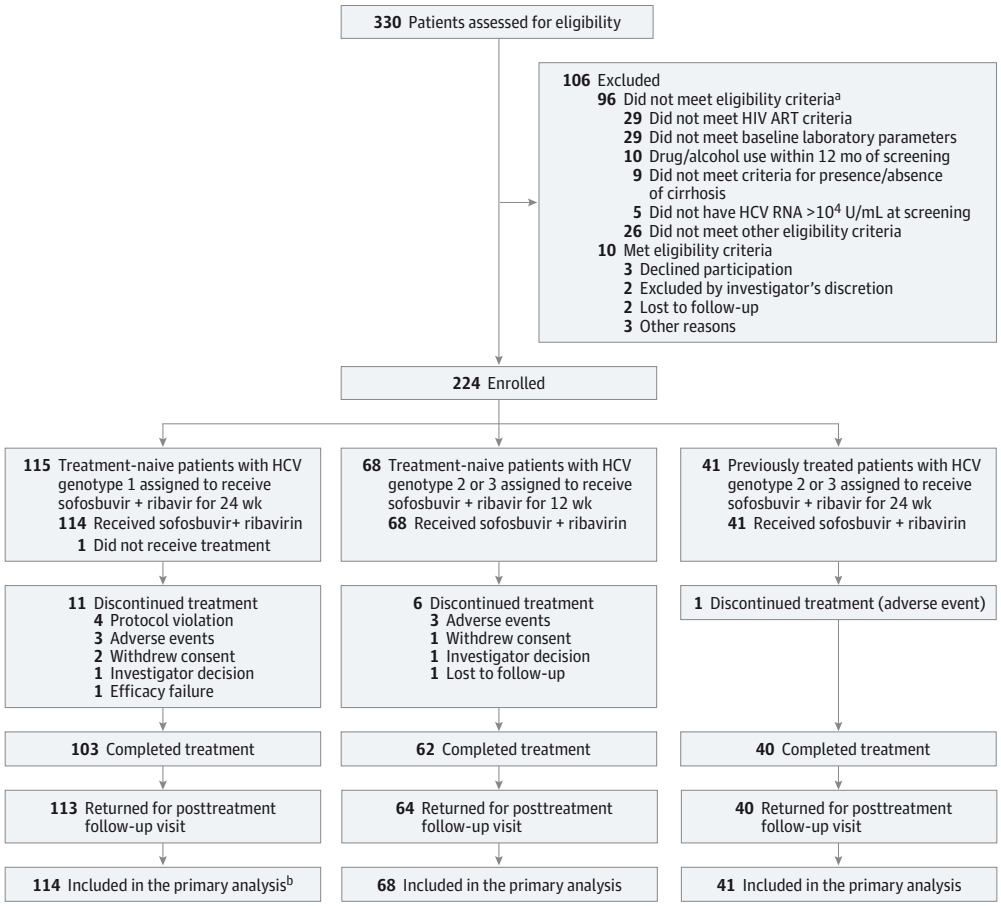
Other assessments conducted during the treatment phase were performed at 1- to 4-week intervals and included physical examination, review of medications, and safety assessments, including evaluations of renal function, hemoglobin levels, and liver function. Posttreatment assessments included safety assessments at the 4-week follow-up visit.

Plasma samples for HCV viral sequencing and possible phenotypic monitoring were collected at baseline (before treatment) and at every visit thereafter. We evaluated HCV *NS5B* gene nucleotide changes that may confer resistance to sofosbuvir at baseline and at the time of virologic relapse or breakthrough.

Statistical Analysis

The primary efficacy end point was SVR_{12}, defined as an HCV RNA value that was less than the LLOQ 12 weeks after discontinuation of study drugs in all patients who were enrolled and who received study drugs.

Figure 1. Flow Diagram of PHOTON-1 Patients



ART indicates antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

[a] Patients could be excluded for more than 1 criterion. See eTable 12 in the Supplement.

[b] Patient who did not receive the study treatment was not included in the efficacy analysis per protocol.

For patients who were treatment naive, we planned to enroll approximately 115 patients with HCV genotype 1 and 55 with genotype 2 or 3. For patients who were previously treated for HCV, we planned to enroll 55 patients with genotype 2 or 3. No inferential statistics or statistical comparisons were planned for efficacy end points.

The point estimates for the SVR_{12} rate along with their 2-sided 95% exact confidence intervals (based on the Clopper-Pearson method) were provided for each treatment group. Exploratory multivariable logistic-regression analyses characterizing the relationship between the SVR_{12} rate and various prespecified demographic and baseline clinical characteristics were performed for each genotype group. A step-wise selection procedure was used to identify factors associated with SVR_{12} rates.

Study Oversight

This study was approved by the institutional review board or independent ethics committees at all participating sites and was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. An independent data and safety monitoring committee reviewed the progress of the study.

Results

Baseline Characteristics

Overall, 330 patients coinfected with HIV and HCV were screened for the study, of whom 224 enrolled in the study and 223 began treatment (**Figure 1** and eTable 1 in Supplement 2). The median number of patients at the 34 sites was 6, with a range of 1 to 17. The demographic and baseline clinical characteristics of the patients are shown in **Table 1**. Cirrhosis was more common in treatment-experienced patients and the median CD4 cell count was 562 to 581 cells/μL. In each treatment group, 90% to 98% of patients were taking ART. Of 11 patients not taking ART, 5 had an HIV RNA level that was less than 50 copies/mL at baseline. Among treatment-naive patients with genotype 1, the majority had subtype 1a and 32% were black.

Response During and After Treatment

Patients treated with sofosbuvir plus ribavirin had a rapid decrease in levels of serum HCV. By treatment week 2, 75% of patients with HCV genotype 1, 91% of treatment-naive patients with HCV genotype 2 or 3, and 98% of treatment-experienced patients with HCV

Table 1. Baseline Demographic Characteristics

Characteristic	Hepatitis C Virus Treatment (HCV)		
	Naive		Experienced
	Genotype 1 (n = 114)	Genotype 2 and 3 (n = 68)	Genotype 2 and 3 (n = 41)
Age, mean (range), y	48 (25-70)	49 (24-71)	54 (34-68)
Body mass index, mean (range)	27.3 (18.5-46.2)	27.4 (19.8-43.5)	27.3 (18.8-39.7)
Men, No. (%)	93 (81.6)	55 (80.9)	37 (90.2)
Race, No. (%)[a]			
White	70 (61.4)	54 (79.4)	32 (78.0)
Black	37 (32.5)	8 (11.8)	7 (17.1)
Other	7 (6.1)	6 (8.8)	2 (4.9)
Ethnicity, No. (%)			
Hispanic or Latino	25 (21.9)	19 (27.9)	10 (24.4)
Not Hispanic or Latino	89 (78.1)	49 (72.1)	31 (75.6)
HCV genotype, No. (%)			
1a	90 (78.9)	NA	NA
1b	24 (21.1)	NA	NA
2	NA	26 (38.2)	24 (58.5)
3	NA	42 (61.8)	17 (41.5)
HCV RNA, Mean (SD), $\log_{10}$ IU/mL	6.6 (0.83)	6.3 (0.60)	6.5 (0.69)
HCV RNA ≥6 $\log_{10}$ IU/mL, No. (%)	92 (80.7)	47 (69.1)	34 (82.9)
IL28B genotype, No. (%)[b]			
CC	30 (26.5)	25 (36.8)	20 (48.8)
CT	57 (50.4)	37 (54.4)	17 (41.5)
TT	26 (23.0)	6 (8.8)	4 (9.8)
Cirrhosis, No. (%)[c]	5 (4.4)	7 (10.3)	10 (24.4)
Interferon ineligible, No. (%)[d]	29 (25.4)	19 (27.9)	NA
Psychiatric illness	25 (86.2)	17 (89.5)	NA
Autoimmune disorder	3 (10.3)	2 (10.5)	NA
Seizure disorder	1 (3.4)	2 (10.5)	NA
Poorly controlled diabetes	1 (3.4)	0	NA
Other reasons	1 (3.4)	1 (5.3)	NA
Baseline ALT >1.5 × ULN	50 (43.9)	45 (66.2)	22 (53.7)
eGFR, mean (SD), mL/min	106.2 (27.7)	110.4 (27.7)	104.9 (29.7)
CD4 T-cell count, median(IQR), cells/μL	583 (455-812)	562 (395-723)	579 (482-744)
Antiretroviral therapy, No. (%)	112 (98.2)	61 (89.7)	39 (95.1)
Tenofovir-disoproxil-fumarate/emtricitabine plus			
Efavirenz	42 (37.5)	20 (32.8)	16 (41.0)
Atazanavir-ritonavir	24 (21.4)	7 (11.5)	8 (20.5)
Darunavir-ritonavir	15 (13.4)	17 (27.9)	2 (5.1)
Raltegravir	21 (18.8)	8 (13.1)	7 (17.9)
Rilpilvirine	7 (6.3)	5 (8.2)	2 (5.1)
Other	3 (2.7)	4 (6.6)	4 (10.3)
Ribavirin dose assignment according to body weight, No. (%)			
1000 mg/d	40 (35)	18 (26)	15 (37)
1200 mg/d	74 (65)	50 (74)	26 (63)

Abbreviations: ALT, Alanine aminotransferase; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NA, not applicable; ULN, upper limit of normal.

[a] Race was self-reported.

[b] IL28B genotype was missing for 1 patient out of the 114 patients with HCV genotype 1.

[c] Of the 22 patients with cirrhosis, 12 were determined by biopsy and 10 by FibroSURE.

[d] Some patients were ineligible to receive interferon for more than 1 reason.

genotype 2 or 3 had HCV RNA levels lower than the LLOQ; by the fourth week of treatment, those proportions increased to 96% in the genotype 1, 99% in genotype 2 or 3, and 100% in treatment-experienced genotype 2 or 3 groups (**Table 2**). Two patients (1 each with genotype 1 and 2) experienced HCV virologic breakthrough; both had undetectable serum levels of sofosbuvir and its metabolite, GS-331007, at the time of HCV breakthrough, suggesting nonadherence to sofosbuvir.

Of the 114 treatment-naive patients with HCV genotype 1, 87 (76%; 95% CI, 67%-84%) achieved SVR_{12} (Table 2). Of the 27 patients who did not, 25 had virologic relapse after stopping study medications, 1 had a treatment breakthrough while

Table 2. Hepatitis C Virologic Response During and After Treatment

Response	Hepatitis C Virus Treatment (HCV)		
	Naive		Experienced
	Genotype 1 (n = 114)	Genotype 2 and 3 (n = 68)	Genotype 2 and 3 (n = 41)
HCV RNA <LLOQ, No./total (%) [95% CI]			
During treatment, wk[a]			
2	85/114 (74.6) [65.6-82.3]	62/68 (91.2) [81.8-96.7]	40/41 (97.6) [87.1-99.9]
4	110/114 (96.5) [91.3-99]	66/67 (98.5) [92-100]	41/41 (100) [91.4-100]
12	111/111 (100) [96.7-100]	61/63 (96.8) [89.0-99.6][b]	40/40 (100) [91.2-100]
24	103/103 (100) [96.5-100]	NA	40/40 (100) [91.2-100]
After treatment, wk			
At wk 4	92/114 (80.7) [72.3-87.5]	53/68 (77.9) [66.2-87.1]	39/41 (95.1) [83.5-99.4]
At wk 12 (SVR_{12})	87/114 (76.3) [67.4-83.8]	51/68 (75.0) [63-84.7][c]	38/41 (92.7) [80.1%-98.5%][d]
Virologic breakthrough during treatment	1/114 (0.9%)	1/68 (1.5%)	0
Relapse in patients with HCV RNA <LLOQ at EOT, No./total (%)			
Completed treatment	19/103 (18.4)	11/61 (18.0)	1/40 (2.5)
Did not complete treatment	6/10 (60.0)	1/6 (16.7)	1/1 (100)

Abbreviations: LLOQ, lower limit of quantification, which is 25 IU/mL; EOT, end of treatment; SVR_{12}, sustained virologic response 12 weeks after cessation of HCV therapy.

[a] HCV RNA lower than LLOQ response during treatment is in patients for whom HCV RNA results are available.

[b] One patient with HCV RNA levels higher than LLOQ had a virologic breakthrough during treatment and the other completed treatment but did not have a week-12 assessment.

[c] The SVR_{12} rate was 88% (95% CI, 70-98) for treatment-naive patients with HCV genotype 2, and 67% (95% CI, 51- 80) for treatment-naive patients with HCV genotype 3 infection.

[d] The SVR_{12} rate was 92% (95% CI, 73-99) for treatment-experienced patients with HCV genotype 2, and 94% (95% CI, 71-100) for treatment-experienced patients with HCV genotype 3.

taking medication as described above, and 1 patient withdrew consent before treatment week 20 and was therefore not assessable for testing. The SVR_{12} rates for treatment-naive patients with HCV genotype 1 by subgroups, including sex, age, HCV subtype, presence of cirrhosis, and type of coadministered antiretrovirals, are shown in **Figure 2** and eTable 2 in Supplement 2. Notably, SVR_{12} rates were 82% (95% CI, 73%-89%) among the 103 patients with HCV genotype 1 who completed study treatment and 27% (95% CI, 6%-61%) among the 11 patients who discontinued study treatment early. Among patients with HCV genotype 1, exploratory multivariable analysis indicated that nonblack race (OR, 2.87; 95% CI, 1.01-8.20; P = .049), HCV genotype 1a (OR, 3.42; 95% CI, 1.15-10.16; P = .03), and completing 24 weeks of study treatment (OR, 17.54; 95% CI, 3.77-83.33; P < .001) were associated with achieving SVR_{12} (eTable 3 in Supplement 2).

Of the 26 treatment-naive patients with HCV genotype 2 receiving 12 weeks of treatment, 23 (88%; 95% CI, 70%-98%) achieved SVR_{12}. Of the 3 patients who did not, 1 patient had virologic breakthrough during the treatment phase for nonadherence and 2 patients could not be assessed because one patient withdrew consent and another was lost to follow-up. Of the 42 treatment-naive patients with HCV genotype 3 receiving 12 weeks of treatment, 28 (67%; 95% CI, 51%-80%) achieved SVR_{12}. Among the 14 patients who did not, 12 experienced virologic relapse and 2 could not be assessed because one patient was lost to follow-up and another died after completing treatment. For subgroup rates for patients with HCV genotype 2, see eTable 4 in Supplement 2, and for patients with HCV genotype 3, see eTable 5 in Supplement 2.

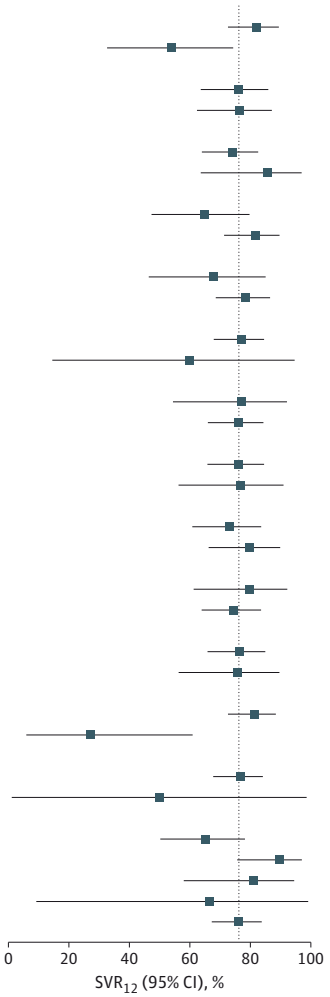
Of the 24 treatment-experienced patients with HCV genotype 2 receiving 24 weeks of treatment, 22 (92%; 95% CI, 73%-99%) had achieved SVR_{12}. One patient from this group withdrew consent and could not be assessed and another had virologic relapse. Notably, the latter patient only received 8 weeks of study treatment and was found to have discordant NS5B sequencing from screening HCV genotyping (genotype 1 by sequencing and genotype 2 by the screening INNO-LiPA), which may represent a chimeric virus. Two other patients with discordant NS5B sequencing and INNO-LiPA analysis in this group completed 24 weeks of treatment and achieved SVR_{12}. Of the 17 treatment-experienced patients with HCV genotype 3, 16 (94%; 95% CI, 71%-100%) achieved SVR_{12}, with 1 patient having viral relapse at the 12-week SVR assessment. Among both treatment-naive and treatment-experienced patients with HCV genotype 2, an exploratory multivariable analysis demonstrated only study drug completion to be associated with SVR (OR, 200; 95% CI, 4->1000; P = .002: eTable 6 in Supplement 2). Among both treatment-naive and treatment-experienced patients with HCV genotype 3, no baseline factors were associated with SVR_{12} by exploratory multivariable analysis, although treatment-experienced patients assigned to the 24-week treatment group had numerically higher SVR_{12} rates (OR, 8; 95% CI, 0.96-66.6; P = .06: eTable 7 in Supplement 2).

Viral Resistance Testing

Baseline population sequencing was performed in 219 patients. No S282T mutation was detected in any patient at baseline. The L159F mutation was detected in 2 patients with one patient achieving SVR_{12} and the other experiencing viral re-

Figure 2. Rates of 12-Week Sustained Virologic Response by Subgroup in Treatment-Naive Patients With Hepatitis C Virus Genotype 1 Receiving 24 Weeks of Sofosbuvir and Ribavirin

	No. of Patients With SVR	Total No. of Patients
Genotype		
1a	74	90
1b	13	24
Age, y		
<50	48	63
≥50	39	51
Sex		
Men	69	93
Women	18	21
Race		
Black	24	37
Nonblack	63	77
Ethnicity		
Hispanic/Latino	17	25
Non-Hispanic/Latino	70	89
Cirrhosis		
No	84	109
Yes	3	5
HCV RNA level, $\log_{10}$ IU/mL		
<6	17	22
≥6	70	92
Body mass index		
<30	67	88
≥30	20	26
Baseline ALT		
≤1.5 × ULN	47	64
>1.5 × ULN	40	50
IL28B		
CC	24	30
Non-CC	62	83
Interferon classification		
Eligible	65	85
Ineligible	22	29
Study drug completion status		
Completed	84	103
Prematurely discontinued	3	11
ARV at enrollment		
Yes	86	112
No	1	2
ARV Class		
NNRTI	32	49
PI	35	39
Integrase inhibitor	17	21
Other	2	3
Overall	87	114



The position of the solid squares indicates the rate of virologic response 12 weeks after the end of treatment for each subgroup; the horizontal lines indicate 95% confidence intervals. The vertical line represents the overall rate of sustained virologic response (SVR) for all patients with genotype 1. Body mass index is calculated as weight in kilograms divided by height in meters squared. ARV indicates antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SVR_{12}, sustained virological response for 12 weeks; and ULN, upper limit of normal.

lapse. No baseline V321A mutations were identified. An NS5B deep sequencing (1% detection threshold) was performed for 30 patients at baseline and at the time of virologic breakthrough (n = 2) or relapse (n = 28).

In the 2 patients with HCV virologic breakthrough, deep sequencing did not demonstrate S282T, L159F, or V321A NS5B mutations. Deep sequencing for the 28 patients with viral relapse (1% detection threshold) demonstrated no evidence of the S282T or V321A mutations. The L159F mutation emerged in 4 patients (2 genotype 3a patients at 1.1% and 1.2%; 1 genotype 1a patient at >99%; and 1 genotype 1b patient at >99%), but did not confer phenotypic shift to sofosbuvir resistance in vitro.

Safety

Of the 223 patients who received at least 1 dose of the study drug, 7 (3%) discontinued treatment due to an adverse event (**Table 3** and eTable 8 in Supplement 2). Serious adverse events were experienced by 14 patients (6%) (eTable 9 in Supplement 2). The incidence of serious adverse events and adverse events leading to discontinuation was similar in the 12- and 24-week groups. One death occurred: a patient with HCV genotype 3 committed suicide 9 days after completing 12 weeks of treatment per protocol.

Most adverse events were grade 1 or 2 in severity with the most common adverse events in all treatment groups being fatigue, insomnia, nausea, and headache. The most common laboratory abnormalities included anemia and elevations in indirect bilirubin. Thirty-four patients (15%) had decreases in hemoglobin to lower than 10 mg/dL with 3 patients experiencing decreases in hemoglobin to less than 8.5 mg/dL. Forty-three patients (19% of total participants) required dose reduction of ribavirin; the use of erythropoietin was prohibited in this study (Table 3). Overall, 32 patients (14%) experienced elevations of total bilirubin to higher than 3.0 mg/dL (to convert bilirubin from mg/dL to µmol/L, multiply by 17.104). Consistent with ribavirin-associated hemolysis, the maximum increase was observed during the first 2 weeks of treat-

Table 3. Discontinuations, Adverse Events, and Hematologic Abnormalities

Parameter	No (%) of Patients With Hepatitis C Virus (HCV)		
	Treatment Naive		Treatment Experienced
	Genotype 1 (n = 114)	Genotype 2 and 3 (n = 68)	Genotype 2 and 3 (n = 41)
Duration of treatment, mean (SD), wk	23.0 (4.04)	11.7 (1.52)	23.8 (2.44)
Discontinuation due to adverse events	3 (2.6)	3 (4.4)	1 (2.4)
Death	0	1 (1.5)	0
Serious adverse events[a]	8 (7.0)	5 (7.4)	1 (2.4)
Common adverse events[b]			
Fatigue	41 (36.0)	24 (35.3)	19 (46.3)
Insomnia	15 (13.2)	14 (20.6)	8 (19.5)
Nausea	18 (15.8)	12 (17.6)	6 (14.6)
Headache	16 (14.0)	9 (13.2)	5 (12.2)
Irritability	14 (12.3)	7 (10.3)	2 (4.9)
Cough	14 (12.3)	4 (5.9)	4 (9.8)
Upper respiratory tract infection	13 (11.4)	8 (11.8)	5 (12.2)
Diarrhea	12 (10.5)	6 (8.8)	5 (12.2)
Dizziness	7 (6.1)	1 (1.5)	5 (12.2)
Anemia	13 (11.4)	6 (8.8)	3 (7.3)
Laboratory events			
Decreased hemoglobin concentration, g/dL			
<10	21 (18.4)	8 (11.8)	3 (7.3)
<8.5	2 (1.8)	1 (1.5)	0
Total bilirubin			
>3 to ≤6 mg/dL	13 (11.4)	3 (4.4)	4 (9.8)
Taking atazanavir	12 (92.3)	3 (100)	4 (100)
Not taking atazanavir	1 (7.7)	0	0
>6 mg/dL	9 (7.9)	1 (1.5)	2 (4.9)
Taking atazanavir	8 (88.9)	1 (100)	2 (100)
Not taking atazanavir	1 (11.1)	0	0

[a] None of the serious adverse events was deemed related to study drugs.

[b] Adverse events occurring in at least 10% of patients in any group.

ment with sofosbuvir plus ribavirin and no patient had a grade 3 or 4 increase in direct bilirubin levels. Thirty (94%) of 32 of these patients were taking ritonavir-boosted atazanavir as part of the baseline ART regimen (Table 3). Four patients changed ART regimens from atazanavir to darunavir due to increased indirect bilirubin during the study with all patients having normalization of total bilirubin levels following the change in ART (eTable 10 in Supplement 2). All patients with elevations in total bilirubin had a return to baseline levels by the posttreatment week 12 evaluation.

There were no clinically significant changes in HIV RNA levels in those patients not receiving ART at baseline (eTable 11 in Supplement 2). Of patients taking ART with suppressed HIV viremia upon entering the study, 2 experienced HIV viral breakthrough. One of these patients had increases in HIV RNA levels due to documented nonadherence to ART and the other resuppressed the HIV RNA without changes to the ART regimen.

Consistent with the known lymphopenic effect of ribavirin, there was a decrease in absolute lymphocyte counts and absolute CD4 T-cell counts during study treatment.[16] The CD4 T-cell percentage did not change throughout study treatment (eTable 12 in Supplement 2). Absolute CD4 T-cell counts returned to baseline by posttreatment week 12 assessments (eTable 12 in Supplement 2).

Discussion

In this open-label, nonrandomized, uncontrolled study, patients with HIV who were coinfected with HCV genotype 1, 2, or 3 who received the oral, interferon-free combination of sofosbuvir and ribavirin for 12 or 24 weeks had high rates of SVR_{12}.

For patients coinfected with HCV genotype 1, the SVR rate of 76% following 24 weeks of sofosbuvir plus ribavirin was similar to results observed in coinfected patients in smaller, phase 2 studies of 48 weeks of treatment with an HCV protease inhibitor plus peginterferon and ribavirin[4,5] and to results observed in a smaller study of 24 weeks of sofosbuvir plus ribavirin in HCV monoinfected patients.[14] In our coinfected patient population, patients with HCV genotype 1 and characteristics that have historically been considered difficult to cure had high rates of SVR_{12} following receipt of the 24-week treatment regimen of sofosbuvir and ribavirin. By exploratory multivariable analysis, the strongest factor associated with SVR_{12} was completion of the treatment regimen. Patients infected with HCV genotype 1a had a higher rate of SVR_{12} than did those infected with HCV genotype 1b. This finding may be explained by the small number of patients with genotype 1b infection or by confounding factors such as black race, which were more common in persons infected with genotype 1b than in those

infected with genotype 1a. Overall, the observed HCV responses in patients with HIV-HCV coinfection were consistent with those previously reported in patients with HCV monoinfection. Furthermore, because sofosbuvir and its metabolites do not have significant interactions with the cytochrome P450 system, sofosbuvir plus ribavirin could be coadministered with a wide range of antiretroviral drugs including those that induce (eg, efavirenz) or inhibit (eg, ritonavir) or are metabolized by (eg, darunavir; atazanavir) these enzymes. Importantly, more than one-quarter of patients coinfected with HIV and HCV treated with sofosbuvir plus ribavirin were not eligible for interferon-containing HCV treatment regimens due to contraindications to its use. Among treatment-naive and previously treated patients with HCV genotype 2, high rates of SVR_{12} were observed with both the 12- and 24-week regimens. Among patients with HCV genotype 3, there was a substantially higher rate of SVR_{12} in treatment-experienced patients treated for 24 weeks with sofosbuvir and ribavirin (94%) than in those treated for 12 weeks (67%). This observation is consistent with the results of the VALENCE[13] study, which demonstrated higher rates of SVR_{12} in HCV genotype 3 monoinfected patients treated for 24 weeks than for those treated for 12 or 16 weeks in other studies. These data suggest that the sofosbuvir and ribavirin treatment durations for HIV-infected patients with HCV genotype 2 or 3 infection should mirror those established for HCV monoinfected patients, namely, 12 and 24 weeks for HCV genotypes 2 and 3, respectively.

No S282T mutations were detected in patients with viral relapse or breakthrough, confirming the high barrier to resistance demonstrated in other studies of sofosbuvir.[11,12] In vitro analyses identified no other mutations that conferred phenotypic resistance to sofosbuvir.

Rates of premature discontinuation of study drug were low in both 12- and 24-week regimens (3%-4%), rates lower than those observed in the phase 2 studies of HCV protease inhibitors (8%-20%), but were somewhat higher than those observed in phase 3 studies of sofosbuvir and ribavirin in HCV monoinfected patients.[4,5,11,12] The most common adverse events were mild to moderate in severity and included fatigue, insomnia, nausea, and headache. No serious adverse events related to the study drugs were observed. Laboratory abnormalities were consistent with known effects of ribavirin therapy, including decreases in hemoglobin and absolute CD4 T-cell counts. Among patients taking ritonavir-boosted atazanavir, increases in indirect bilirubin were observed, typically early in the course of therapy. This finding is consistent with the ribavirin-induced hemolysis in the setting of UGT1A1 inhibition by atazanavir, which has been previously reported.[5,17,18] Although this increase was not associated with elevations in serum liver enzyme levels or other markers of liver injury, 4 patients elected to switch to another boosted HIV protease inhibitor with normalization of total bilirubin. For all patients with elevations in indirect bilirubin, levels returned to baseline after ribavirin treatment was completed.

No other untoward effects of sofosbuvir and ribavirin on HIV disease or its treatment with antiretrovirals were detected. Among patients not taking antiretroviral therapy at entry, no HIV-specific antiviral effect of sofosbuvir was observed, consistent with in vitro data.[8] Among those taking antiretroviral therapy, 2 patients experienced HIV virologic rebound, but both were documented to be poorly adherent to ART.

This study has several limitations. First, patients with cirrhosis (10%) and women (17%) were underrepresented. In addition, relatively few patients with advanced HIV disease (AIDS or low CD4 cell count) were enrolled; as such, the safety, tolerability, and efficacy of sofosbuvir plus ribavirin among such patients is not known and additional studies are warranted. Furthermore, the absence of a control group limits the ability to derive definitive conclusions regarding the safety and efficacy of this regimen. Lastly, sofosbuvir was not studied in combination with other anti-HCV therapies such as peginterferon alfa or other HCV direct-acting antivirals. The combination of sofosbuvir, ribavirin, and peginterferon has been studied in 23 HIV-HCV coinfected patients receiving concurrent antiretroviral therapy, of whom, 21 achieved SVR_{12}.[19] In addition, studies of sofosbuvir in combination with ledipasivir, an inhibitor of HCV NS5A, are under way in patients coinfected with HIV and HCV (ClinicalTrials.gov identifier: NCT02073656).

Conclusions

In this open-label, nonrandomized, uncontrolled study, HIV-infected patients with HCV genotypes 1, 2, or 3 coinfection who received an oral combination of sofosbuvir plus ribavirin for 12 or 24 weeks had high rates of sustained HCV virologic response 12 weeks after cessation of therapy. Further studies of this regimen in more diverse populations of coinfected patients are needed.

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