Original Investigation

Ombitasvir, Paritaprevir Co-dosed With Ritonavir, Dasabuvir, and Ribavirin for Hepatitis C in Patients Co-infected With HIV-1
A Randomized Trial

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IMPORTANCE Patients co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are at high risk for liver disease progression. However, interferon-based treatments for HCV infection have significant toxicities, limiting treatment uptake.

OBJECTIVE To assess the all-oral 3 direct-acting antiviral (3D) regimen of ombitasvir, paritaprevir (co-dosed with ritonavir [paritaprevir/r]), dasabuvir, and ribavirin in HCV genotype 1–infected adults with HIV-1 co-infection, including patients with cirrhosis.

DESIGN, SETTING, AND PARTICIPANTS TURQUOISE-I is a randomized, open-label study. Part 1a of this pilot study was conducted at 17 sites in the United States and Puerto Rico between September 2013 and August 2014 and included 63 patients with HCV genotype 1 and HIV-1 co-infection who were HCV treatment-naive or had history of prior treatment failure with peginterferon plus ribavirin therapy. The study allowed enrollment of patients, including those with cirrhosis, with a CD4+ count of 200/mm^3 or greater or CD4+ percentage of 14% or more and plasma HIV-1 RNA suppressed while taking a stable atazanavir- or raltegravir-inclusive antiretroviral regimen.

INTERVENTIONS Ombitasvir/paritaprevir/r, dasabuvir, and ribavirin for 12 or 24 weeks of treatment as randomized.

MAIN OUTCOMES AND MEASURES The primary assessment was the proportion of patients with sustained virologic response (HCV RNA <25 IU/mL) at posttreatment week 12 (SVR12).

RESULTS Among patients receiving 12 or 24 weeks of 3D and ribavirin, SVR12 was achieved by 29 of 31 (94%; 95% CI, 79%-98%) and 29 of 32 patients (91%; 95% CI, 76%-97%), respectively. Of the 5 patients who did not achieve SVR, 1 withdrew consent, 2 had confirmed virologic relapse or breakthrough, and 2 patients had clinical history and phylogenetic evidence consistent with HCV reinfection. The most common treatment-emergent adverse events were fatigue (48%), insomnia (19%), nausea (18%), and headache (16%). Adverse events were generally mild, with none reported as serious or leading to discontinuation. No patient had a confirmed HIV-1 breakthrough of 200 copies/mL or greater during treatment.

CONCLUSIONS AND RELEVANCE In this open-label, randomized uncontrolled study, treatment with the all-oral, interferon-free 3D-plus-ribavirin regimen resulted in high SVR rates among patients co-infected with HCV genotype 1 and HIV-1 whether treated for 12 or 24 weeks. Further phase 3 studies of this regimen are warranted in patients with co-infection.

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Hepatitis C virus (HCV) and human immunodeficiency virus 1 (HIV-1) co-infections are common because of similar routes of transmission, including injection drug use, blood transfusion, or sexual contact. Since the advent of effective antiretroviral therapy (ART), liver-related disease has emerged as a leading cause of morbidity and mortality in HCV/HIV-1 co-infected patients.[1,2] Individuals with HCV/HIV-1 co-infection are at 3-fold greater risk for progression to liver cirrhosis or decompensation and at 10-fold greater risk for hepatitis or liver-related mortality than individuals monoinfected with HCV.[3-5]

For more than a decade, treatment of HCV with pegylated interferon (pegIFN) plus ribavirin has been recommended for patients co-infected with HIV, though poor sustained virologic response (SVR) rates (17%-36%), well-known treatment-limiting adverse effects, and contraindications have limited broad uptake of HCV treatment in patients with co-infection.[6,7] The addition of newer direct-acting antivirals to pegIFN plus ribavirin has improved SVR rates (63%-89%); however, the requirement for pegIFN restricts both treatment eligibility and acceptance among co-infected patients because of adverse effects.[8-10]
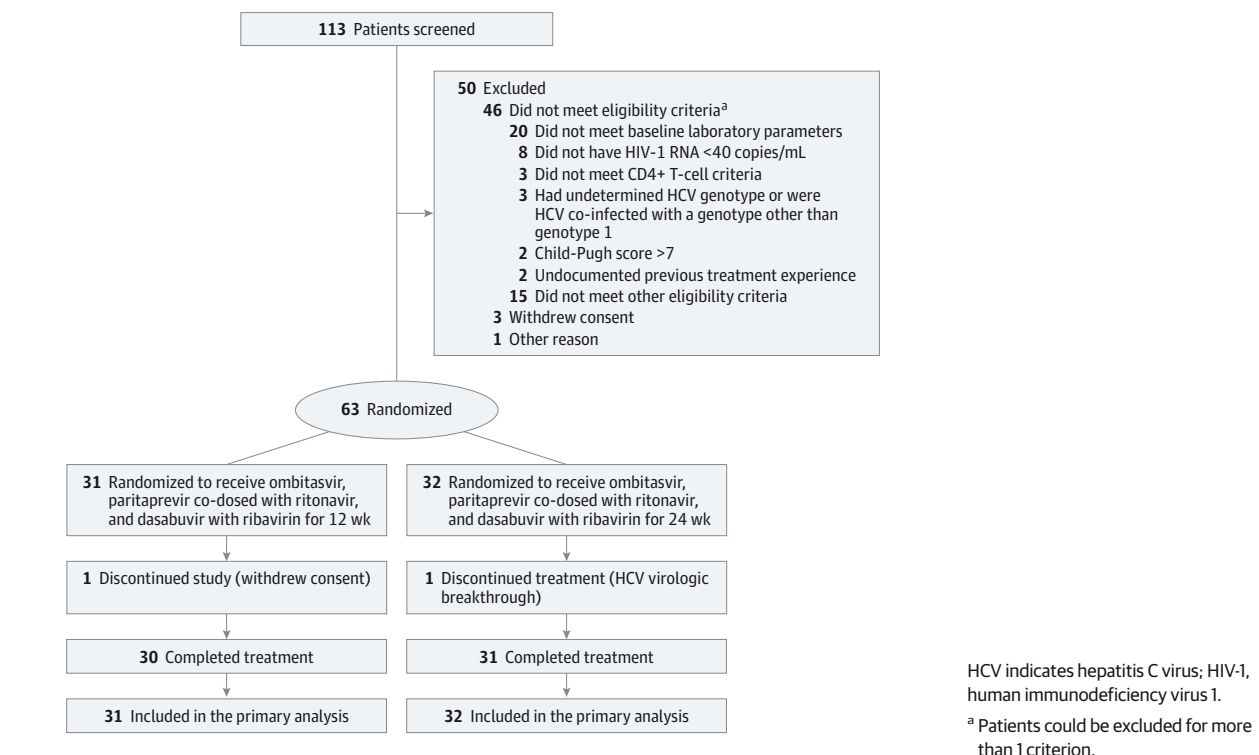
The interferon-free, all-oral regimen of the 3 direct-acting antivirals (3D) ombitasvir, paritaprevir co-dosed with ritonavir, and dasabuvir combined with ribavirin has achieved response rates of 92% to 100% in patients monoinfected with HCV genotype 1, including those with historically difficult-to-cure host and disease characteristics such as prior pegIFN-plus-ribavirin treatment failure, *IL28B* non-CC genotype, and cirrhosis.[11-15] Ombitasvir is a potent HCV NS5A inhibitor, paritaprevir is a potent NS3/4A protease inhibitor, and dasabuvir is a nonnucleoside NS5B polymerase inhibitor. Paritaprevir and ombitasvir are coformulated with the pharmacokinetic enhancer ritonavir (paritaprevir/r) to increase paritaprevir peak, trough, and overall exposures, enabling once-daily dosing. The TURQUOISE-I trial assessed the adverse event profile and virologic outcomes of the 3D regimen with ribavirin for 12 or 24 weeks in patients co-infected with HCV genotype 1 and HIV-1, including those with prior pegIFN-plus-ribavirin treatment experience and with cirrhosis (see the trial protocol in Supplement 1).

Methods

Patients were enrolled at 17 sites in the United States and Puerto Rico between September and December 2013 (Figure). Eligible patients were aged 18 to 70 years with HCV genotype 1 and HIV-1 infection, had plasma HCV RNA greater than 10 000 IU/mL, and were either HCV treatment-naive or previously treated with pegIFN plus ribavirin. Prior treatment experience with any direct-acting antiviral agent was not allowed. Patients were receiving a stable ART regimen inclusive of atazanavir or raltegravir plus 2 nucleos(t)ide analogue reverse transcriptase inhibitors for at least 8 weeks before screening with a plasma HIV-1 RNA of less than 40 copies/mL and CD4+ T-cell count of 200/mm^3 or greater or CD4+ T-cell percentage of 14% or more for at least 24 weeks before and during screening. Patients were

Figure. TURQUOISE-I Part 1a Study Flow Diagram

HCV indicates hepatitis C virus; HIV-1, human immunodeficiency virus 1.

[a] Patients could be excluded for more than 1 criterion.

allowed to enroll with Child-Pugh A cirrhosis but were excluded if they were co-infected with hepatitis B or HIV-2, if cirrhosis was decompensated, or if they had experienced treatment failure with 2 or more ART regimens. Detailed eligibility criteria and fibrosis scoring methods are in the eTable in Supplement 2.

Race/ethnicity was self-reported by patients from a provided list of options (white, black or African American, Asian, American Indian or Alaska native, native Hawaiian or other Pacific Islander, or multirace) and was assessed because black race has had lower rates of treatment response historically.

Study Design

This multicenter, randomized, open-label study consists of a 2-part phase 2 cohort and a phase 3 cohort. Results through posttreatment week 12 from the pilot portion of the phase 2 cohort (part 1a) are presented (see the interim analysis plan in Supplement 3). Patients were randomized approximately 1:1 to receive coformulated ombitasvir/paritaprevir/r (once daily dose of 25-mg ombitasvir, 150-mg paritaprevir, and 100-mg ritonavir) and dasabuvir (250 mg twice daily) for 12 or 24 weeks (eFigure 1 in Supplement 2). Randomization numbers were generated by computer with a block size of 4 before the start of the study. Patients obtained randomization numbers from an interactive response technology system stratified by their prior pegIFN-plus-ribavirin treatment history (treatment-naive or treatment-experienced) and presence of cirrhosis. In addition, treatment-naive patients were stratified by *IL28B* genotype (CC vs non-CC), and treatment-experienced patients were stratified by type of nonresponse to prior pegIFN-plus-ribavirin treatment (null responder, partial responder, or relapser as defined in the eMethods in Supplement 2). Twice-daily dosing of ribavirin was administered at 1000 mg daily for patients whose body weight was less than 75 kg and 1200 mg daily for patients whose body weight was 75 kg or greater. Because of the coformulation of paritaprevir with ritonavir, those receiving ritonavir-boosted atazanavir stopped the ritonavir component of their ART regimen on initiation of study drugs and restarted after HCV treatment.

All patients provided written informed consent and the study was conducted in accordance with Good Clinical Practice and the ethical principles that have their origin in the Declaration of Helsinki. The study was approved by the institutional review board or independent ethics committees of each participating site.

Study Assessments

Virologic response was defined as an HCV RNA value below the limit of quantitation (<25 IU/mL) using the COBAS TaqMan real-time reverse transcriptase–polymerase chain reaction assay version 2.0 (Roche Diagnostics). The primary efficacy analysis was HCV sustained virologic response at posttreatment week 12 (SVR12) (**Box**). Secondary analyses included rapid virologic response, end-of-treatment response, and sustained virologic response at

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> **Box. Definitions of Hepatitis C Virus (HCV) Virologic Response and Treatment Outcomes**
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> Rapid virologic response: HCV RNA <25 IU/mL at treatment week 4.
>
> End-of-treatment response: HCV RNA <25 IU/mL at treatment week 12 or 24.
>
> Sustained virologic response at posttreatment week 4 (SVR4): HCV RNA <25 IU/mL between end of treatment and posttreatment week 4.
>
> Sustained virologic response at posttreatment week 12 (SVR12): HCV RNA <25 IU/mL between end of treatment and posttreatment week 12.
>
> On-treatment virologic breakthrough: Two consecutive HCV RNA measurements ≥25 IU/mL after HCV RNA <25 IU/mL at any time point during treatment.
>
> Virologic relapse: Two consecutive HCV RNA measurements ≥25 IU/mL after completing treatment in a patient with HCV RNA <25 IU/mL at the end of treatment.

posttreatment week 4 (SVR4), comparisons of SVR12 rates between the 12- and 24-week treatment groups, and percentages of patients with on-treatment HCV virologic failure (ie, breakthrough) and posttreatment relapse. Plasma HIV-1 RNA suppression was assessed using the Abbott RealTime HIV-1 Assay (Abbott Molecular). For patients with HCV on-treatment virologic breakthrough or posttreatment relapse, virologic resistance testing was conducted on plasma samples from baseline and at the time of virologic failure. Detailed HCV and HIV virologic failure criteria and SVR, resistance, and phylogenetic methods are provided in the eMethods in Supplement 2.

Treatment-emergent adverse events were recorded from the first dosing of study drugs until 30 days after the last dose for all patients who received at least 1 dose of study drugs. Adverse event severity and relation to study drugs were assessed by investigators. Vital signs, physical examinations, and clinical laboratory assessments were conducted throughout the study.

Statistical Analyses

An interim analysis from pilot part 1a of the study was planned once all randomized patients in part 1a completed posttreatment week 12 or prematurely discontinued from the study. The intent-to-treat population included all randomized patients who received at least 1 dose of study drugs. For analyses of rapid virologic response, end-of-treatment response, SVR4, and SVR12, 95% confidence intervals were calculated using the Wilson score method for the binomial proportion; comparison of SVR12 rates between treatment groups was performed using Fisher exact test with a 2-sided significance level of .05. Analyses were performed using SAS version 9.3 (SAS Institute).

Results

Sixty-three patients were enrolled and received at least 1 dose of study drugs (**Figure**). The pilot study population

Table 1. Baseline Demographics and Disease Characteristics

	12-Week 3D Plus Ribavirin (n = 31)	24-Week 3D Plus Ribavirin (n = 32)
Male sex, No. (%)	29 (94)	29 (91)
Black race, No. (%)[a]	7 (23)	8 (25)
Age, mean (SD)	50.9 (6.0)	50.9 (8.3)
BMI, mean (SD)[b]	26.4 (3.9)	27.2 (4.3)
Fibrosis stage, No. (%)[c]		
F0-F1	16 (52)	20 (63)
F2	5 (16)	5 (16)
F3	4 (13)	1 (3)
F4	6 (19)	6 (19)
IL28B non-CC genotype, No. (%)	26 (84)	25 (78)
HCV genotype 1a, No. (%)	27 (87)	29 (91)
HCV RNA, mean (SD), $\log_{10}$ IU/mL	6.54 (0.57)	6.60 (0.78)
Prior pegIFN/ribavirin experience, No. (%)[d]		
Naive	20 (65)	22 (69)
Relapse	1 (3)	3 (9)
Partial response	5 (16)	2 (6)
Null response	5 (16)	5 (16)
CD4+ T-cell count, mean (SD), /mm³	633 (236)	625 (296)
CD4+ T-cell percentage, mean (SD)	31.2 (9.2)	29.2 (8.1)
HIV-1 ART regimen, No. (%)		
Atazanavir	16 (52)	12 (38)
Raltegravir	15 (48)	20 (63)

Abbreviations: 3D, 3 direct-acting antiviral regimen of ombitasvir, paritaprevir (co-dosed with ritonavir), and dasabuvir; ART, antiretroviral therapy; BMI, body mass index; HCV, hepatitis C virus; pegIFN, pegylated interferon.

[a] Race was self-reported.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] The fibrosis stage was determined by means of liver biopsy (Metavir, Batts-Ludwig, Knodell, International Association for the Study of the Liver [IASL], Scheuer, Laennec, or Ishak score), FibroScan, or FibroTest. Additional details of scoring are provided in the eTable in Supplement 2. The fibrosis stages range from F0 (no fibrosis) to F4 (cirrhosis).

[d] Prior pegIFN/ribavirin experiences are defined in eligibility criteria of the eMethods in Supplement 2.

comprised 24% black race, 92% men, and 81% IL28B non-CC genotype; 19% had compensated cirrhosis, 89% were infected with HCV genotype 1a, and 16% had a null response to prior pegIFN plus ribavirin. Baseline demographics and disease characteristics were balanced between the treatment groups (Table 1).

Virologic Response During and After Treatment

Plasma HCV RNA suppression was rapid in patients receiving 3D plus ribavirin; 58 of 63 patients (92%) had an HCV RNA below the lower limit of quantitation at treatment week 2, and all patients achieved HCV RNA suppression by treatment week 4. After 12 or 24 weeks of treatment with 3D plus ribavirin, 29 of 31 patients (94%; 95% CI, 79%-98%) and 29 of 32 patients (91%; 95% CI, 76%-97%) achieved SVR12,

respectively (Table 2); the difference between treatment groups was not statistically significant (P > .99). Of the 2 patients in the 12-week treatment group who did not achieve SVR12, 1 experienced HCV relapse at posttreatment week 4; this patient had HCV genotype 1a infection, a history of null virologic response to pegIFN plus ribavirin, and compensated cirrhosis. The other non-SVR patient withdrew consent with an undetectable HCV RNA level at the last study visit (treatment week 10; patient 1, Table 3).

Three patients within the 24-week treatment group did not achieve SVR, including 1 patient with HCV genotype 1a infection, prior null virologic response to pegIFN plus ribavirin, and compensated cirrhosis who experienced on-treatment HCV virologic breakthrough at week 16 of treatment. Two other treatment-naive patients with HCV genotype 1a infection and without cirrhosis had HCV recurrence at posttreatment weeks 8 and 12, respectively.

At the time of virologic failure, 2 prior null responders to pegIFN-plus-ribavirin treatment had resistance-associated variants in all 3 viral targets that were not present at baseline. The patient who relapsed after 12 weeks of treatment had HCV variants D168V in NS3, M28T in NS5A, and S556G in NS5B, and the patient with on-treatment breakthrough in the 24-week group had resistance-associated variants R155K in NS3, Q30R in NS5A, and S556G in NS5B (patients 2 and 3, Table 3).

In contrast, treatment-emergent resistance-associated variants were not observed at any viral target for the 2 treatment-naive patients in the 24-week group who experienced posttreatment HCV recurrence (patients 4 and 5, Table 3). Prompted by these findings, post hoc phylogenetic and sequence analyses were conducted. A lack of phylogenetic sequence clustering was found for HCV NS3/4A, NS5A, and NS5B comparing baseline and posttreatment samples of patients 4 and 5 (eFigure 2 in Supplement 2). Nucleotide sequence identity between the baseline and the posttreatment samples also revealed a low level of genetic relatedness (89.3%-93.8%), similar to the identity observed between distinct isolates within a genotype. These results support HCV reinfection with a genotype 1a isolate unique from the one present at baseline in these 2 patients. Further discussion of these reinfections is available in Supplement 2.

Maintenance of HIV-1 Suppression and Immunologic Response

Three patients (10%) in the 12-week group and 5 (16%) in the 24-week group had at least 1 plasma HIV-1 RNA level of 40 copies/mL or greater during the treatment period. All 8 patients achieved plasma HIV-1 RNA resuppression while maintaining the same HIV-1 ART regimen without interrupting study drugs. No patient had a confirmed HIV-1 RNA level greater than 200 copies/mL while taking study drugs, and no patient required a switch of their HIV-1 ART regimen due to loss of plasma HIV-1 RNA suppression.

Both treatment groups experienced declines in the mean absolute CD4+ T-cell count during treatment, although mean CD4+ T-cell percentage was unchanged (eFigure 3 in Supplement 2). Mean changes in the CD4+ T-cell count were

Table 2. Virologic Response Rates During and After Treatment

	12-Week 3D Plus Ribavirin (n = 31)	24-Week 3D Plus Ribavirin (n = 32)
Response, No. (%) [95% CI][a]		
Rapid virologic response	31 (100) [89-100]	32 (100) [89-100]
End-of-treatment response	30 (97) [84-99]	31 (97) [84-100]
SVR4	29 (94) [79-98]	30 (94) [80-98][b]
SVR12	29 (94) [79-98]	29 (91) [76-97][b,c]
Reasons for not achieving SVR12, No. (%)		
Consent withdrawn	1 (3)	0
Virologic breakthrough during treatment	0	1 (3)
Virologic relapse after treatment	1 (3)	0
HCV reinfection after treatment	0	2 (6)[b,c]

Abbreviations: 3D, 3 direct-acting antiviral regimen of ombitasvir, paritaprevir (co-dosed with ritonavir), and dasabuvir; HCV, hepatitis C virus; SVR4 or SVR12, sustained virologic response at posttreatment week 4 or 12.

[a] 95% CIs calculated using the Wilson score method for the binomial distribution.

[b] Denotes 1 patient with HCV reinfection at posttreatment week 8 (day 56; included in the SVR4 window per the HCV RNA analysis time window).

[c] Denotes 1 patient with HCV reinfection at posttreatment week 12.

Table 3. Patients Not Achieving Sustained Virologic Response at Posttreatment Week 12: Disease and Virologic Characteristics

Patient	Treatment Group, wk	Disease Characteristics HCV Genotype	IL28B Genotype	Fibrosis Stage[c]	Prior pegIFN Plus Ribavirin[d]	Reason for Nonresponse	Time Point Sequenced[a]	HCV Variants[b] NS3/4A	NS5A	NS5B
1	12	1a	TT	F3	Naive	Withdrawn consent	NA	NA	NA	NA
2	12	1a	TT	F4	Null response	Virologic relapse at PTW4	Baseline	None	None	None
							PTW4	D168V	M28T	S556G
3	24	1a	TT	F4	Null response	Virologic breakthrough during treatment wk 16	Baseline	None	None	None
							PTW2	R155K	Q30R	S556G
4[e]	24	1a	CT	F0-F1	Naive	HCV reinfection	Baseline	None	None	None
							PTW8	None	None	None
5[e]	24	1a	CC	F0-F1	Naive	HCV reinfection	Baseline	None	None	None
							PTW12	None	None	None

Abbreviations: HCV, hepatitis C virus; IL28B, interleukin 28B; NA, not assessed; NS3/4A, nonstructural protein 3 and 4A; NS5A, nonstructural protein 5A; NS5B, nonstructural protein 5B; pegIFN, pegylated interferon; PTW, posttreatment week.

[a] The baseline sample and the sample closest in time after virologic failure with an HCV RNA level ≥1000 IU/mL where a product could be amplified were sequenced.

[b] Variants at resistance-associated amino acid positions with >3-fold resistance to ombitasvir, paritaprevir, or dasabuvir.

[c] The fibrosis stage was determined by means of liver biopsy (Metavir, Batts-Ludwig, Knodell, International Association for the Study of the Liver [IASL], Scheuer, Laennec, or Ishak score), FibroScan, or FibroTest. Additional details of scoring are provided in the eTable in Supplement 2. The fibrosis stages range from F0 (no fibrosis) to F4 (cirrhosis).

[d] Prior pegIFN/ribavirin treatment experiences are defined in eligibility criteria of the eMethods in Supplement 2.

[e] Believed to have been reinfected with a different genotype 1a isolate after treatment.

similar to the mean declines observed in the absolute lymphocyte count over time, while the mean total white blood cell count remained stable (eFigures 3 and 4 in Supplement 2). Mean absolute CD4+ T-cell counts returned to baseline by posttreatment week 4.

Safety

Treatment-emergent adverse events occurred in 56 of 63 patients (89%), though the majority were mild or moderate in severity (**Table 4**). No treatment-emergent serious adverse events were reported, and no patient discontinued HCV therapy because of an adverse event. Two treatment-emergent severe ad-

verse events were reported (insomnia and tooth abscess); only the event of insomnia was assessed by the investigator to have been related to study drugs. The most common adverse events were fatigue in 30 patients (48%), insomnia in 12 patients (19%), nausea in 11 patients (17%), and headache in 10 patients (16%) (Table 4). Six patients experienced ocular icterus, all occurring in patients receiving atazanavir-inclusive ART, of whom 1 patient was switched to raltegravir-based ART in response to this event.

Clinically significant chemistry and hematologic abnormalities of grade 3 or 4 were infrequent (Table 4). The most common abnormality was elevated total bilirubin level

Table 4. Treatment-Emergent Adverse Events and Laboratory Abnormalities

	No. (%)	
	12-Week 3D Plus Ribavirin (n = 31)	24-Week 3D Plus Ribavirin (n = 32)
Any AE	28 (90)	28 (88)
Serious AE[a]	0	0
Severe AE[b]	1 (3)	1 (3)
AE leading to discontinuation of study drugs	0	0
AE leading to ribavirin dose modification	5 (16)	6 (19)
Common AEs[c]		
Fatigue	18 (58)	12 (38)
Insomnia	5 (16)	7 (22)
Nausea	5 (16)	6 (19)
Headache	6 (19)	4 (13)
Upper respiratory tract infection	4 (13)	5 (16)
Pruritus	6 (19)	2 (6)
Cough	2 (7)	5 (16)
Ocular icterus	5 (16)	1 (3)
Diarrhea	1 (3)	4 (13)
Hyperbilirubinemia	4 (13)	1 (3)
Laboratory abnormalities of interest		
Alanine aminotransferase >5× ULN	0	0
Aspartate aminotransferase >5× ULN	0	1 (3)
Alkaline phosphatase >5× ULN	0	0
Total bilirubin		
>3-10× ULN	10 (32)	6 (19)
>10× ULN	1 (3)	0
Hemoglobin		
<10-8 g/dL	4 (13)	3 (9)
<8-6.5 g/dL	0	0

Abbreviations: 3D, 3 direct-acting antiviral regimen of ombitasvir, paritaprevir (co-dosed with ritonavir), and dasabuvir; AE, adverse event; HCV, hepatitis C virus; ULN, upper limit of the normal range.

[a] An AE was classified as serious when it resulted in death, was life-threatening, resulted in hospitalization or prolongation of hospitalization, resulted in persistent or clinically significant disability or incapacity, or was an important medical event necessitating medical or surgical intervention to prevent a serious outcome.

[b] An AE was classified as severe when the event caused considerable interference with the patient's usual activities or may have been incapacitating or life-threatening.

[c] The treatment-emergent AEs listed are events that occurred in more than 10% of patients in either group.

(predominantly indirect). One patient taking atazanavir experienced a single grade 4 elevation in total bilirubin level (13.0 mg/dL) that improved to grade 3 on repeat testing. Among the 17 patients with a grade 3 or 4 total bilirubin elevation, 15 (88%) were receiving atazanavir-inclusive ART. No patients interrupted study drugs because of bilirubin elevations or related adverse events.

No patient experienced a grade 3 hemoglobin decline (<8 g/dL). Grade 2 declines in hemoglobin (<10-8 g/dL) were observed in 4 patients (13%) in the 12-week treatment group and 3 patients (9%) in the 24-week group. Six patients (10%) reduced ribavirin dose because of anemia; all achieved SVR12. No patient required erythropoietin or transfusion. A single patient experienced a grade 3 aspartate aminotransferase elevation after initiating a vigorous physical exercise program and had an adverse event of rhabdomyolysis reported with a total serum creatinine kinase value of 15 990 U/L at a single study visit. Hydration and cessation of the exercise program resolved this event after 6 days.

Discussion

Patients who are co-infected with HCV and HIV-1 are at increased risk for end-stage liver disease, which has become a leading cause of mortality in this population in the era of effective ART. Eradication of HCV has been associated with improved survival and decreased risk of liver-related morbidity[16]; however, because of low response rates and toxicity associated with interferon-based therapies, the effectiveness of HCV treatment has been low in co-infected patients. Therefore, a significant unmet need exists for a highly efficacious, interferon-free treatment. This pilot study population included patients who historically have greater difficulty achieving sustained virologic response based on host, viral, and disease characteristics, including a high proportion of patients with IL28B non-CC genotype and patients with cirrhosis. Nevertheless, the high rates of SVR achieved in this study are consistent with the results from phase 3 studies of this regimen among HCV-monoinfected patients receiving 12 weeks of treatment.[11-15]

In many regions, treatment guidelines recommend that patients co-infected with HCV/HIV be treated with ART; thus, potential drug interactions between antiretroviral drugs and HCV direct-acting antivirals must be carefully considered. Before enrollment of this study, extensive phase 1 drug-drug interaction studies of the complete 3D regimen with tenofovir, emtricitabine, atazanavir, and raltegravir indicated no clinically meaningful alterations in HCV or HIV drug exposures, suggesting that these agents could be combined for patients with co-infection.[17,18] In this study, the majority of patients taking raltegravir- and atazanavir-based ART maintained plasma HIV-1 RNA suppression throughout treatment with 3D plus ribavirin, and no patient had a confirmed HIV-1 RNA level greater than 200 copies/mL during treatment. Although we observed HIV-1 RNA levels between 40 and 200 IU/mL in several patients, these episodes of intermittent HIV-1 viremia resolved without modification of either antiviral drug regimen and occurred at a rate lower than that observed in patients infected with HIV taking ART in ambulatory settings (13%-27%).[19-21] Modest mean declines in absolute CD4+ T-cell counts with preservation of the CD4+ T-cell percentages were observed, consistent with the effect of ribavirin on absolute lymphocyte count observed in this and other clinical trials involving patients with co-infection, including patients with interferon-based and interferon-free HCV treatment regimens.[22,23] Mean absolute CD4+ T-cell counts rebounded above baseline levels after treatment.

The 3D-plus-ribavirin regimen was well tolerated with no reported serious adverse events and no discontinuations

due to adverse events, and the majority of events observed were categorized as mild or moderate. Indirect hyperbilirubinemia was consistent with the known inhibition of the bilirubin organic anion transporting polypeptide 1B by HCV protease inhibitors,[24,25] ribavirin-related hemolytic anemia,[26] and the well-known inhibitory effect of atazanavir on uridine diphospho-glucuronosyltransferase 1A1.[27] Patients receiving atazanavir-inclusive ART experienced the majority of bilirubin-related adverse events and grade 3 or 4 laboratory abnormalities, though these events had no effect on treatment responses or premature discontinuations.

Data on the use of interferon-free regimens to treat patients co-infected with HCV/HIV-1 are limited and have primarily assessed treatment-naive patients. In the PHOTON-1 study of 114 patients who were HCV treatment-naive and co-infected with HCV genotype 1 and HIV-1, 5 of whom had cirrhosis, taking the HCV NS5B nucleotide polymerase inhibitor sofosbuvir with ribavirin for 24 weeks achieved an SVR12 rate of 76%.[23] The response rates of this regimen were attenuated among patients with HCV genotype 1b compared with 1a infection (54% vs 82%) and patients with cirrhosis (60%). In the similarly designed PHOTON-2 study, taking sofosbuvir with ribavirin for 24 weeks achieved an SVR12 of 85% for 112 patients who were HCV treatment-naive and co-infected, though lower response rates of 65% were again observed in patients with cirrhosis.[28] In the C-Worthy study, 59 patients with HIV/HCV genotype 1 co-infection were treated with grazoprevir plus elbasvir with or without ribavirin and achieved SVR rates of 97% and 87%, respectively.[29] Notably, C-Worthy did not enroll co-infected patients with cirrhosis or those who had a history of treatment failure with pegIFN plus ribavirin and only included patients receiving raltegravir-inclusive ART.

Another important finding in this study was the observance of HCV reinfection in 2 patients who appeared to have achieved HCV eradication after 24 weeks of treatment. Phylogenetic and sequence analysis in these patients provided strong evidence for HCV reinfection with a different genotype 1a isolate than was present prior to treatment. Both reported unprotected anal intercourse with a sexual partner after treatment. Furthermore, 1 patient was aware that this frequent sexual partner was HCV-infected. The reinfection rate

observed parallels previous reports of high rates of HCV reinfection after successful treatment in other studies of individuals with HIV infection and high-risk behaviors, particularly among persons who inject drugs and men who have sex with men.[30] These observations underscore the need for ongoing education and harm-reduction interventions for patients initiating HCV therapy, as well as the need for an effective HCV vaccine.

Our findings have several limitations. In part 1a of this study, only patients receiving either atazanavir or raltegravir-inclusive regimens were assessed. Patients taking stable darunavir-containing HIV-1 ART regimens are being evaluated in the ongoing part 1b of the study. The efficacy and safety of the 3D-plus-ribavirin regimen for patients co-infected with HCV/HIV-1 need to be further investigated in larger studies; however, response rates reported here are similar to those in studies of HCV-monoinfected patients, which suggest that difficult-to-cure patients, such as prior pegIFN null responders with cirrhosis and HCV genotype 1a, may benefit from longer treatment duration.[13,23,31] All co-infected patients in part 1a of this study were treated with 3D plus ribavirin; however, randomized clinical trials conducted with patients with HCV monoinfection found that the addition of ribavirin to the 3D regimen was not associated with increased SVR in patients with genotype 1b infection where 100% of 301 patients infected with genotype 1b achieved SVR after 12 weeks of treatment with 3D alone.[14,15,32] Additional studies are planned to assess the role, if any, of ribavirin in the treatment of patients with genotype 1b HCV/HIV-1 co-infection. Other limitations of this study are the exclusion of patients with CD4+ T-cell counts less than 200/mm^3 and patients not receiving HIV ART.

Conclusions

In this open-label, randomized uncontrolled study, treatment with the all-oral, IFN-free 3D-plus-ribavirin regimen resulted in high SVR rates among patients co-infected with HCV genotype 1 and HIV-1 whether treated for 12 or 24 weeks. Further phase 3 studies of this regimen are warranted in co-infected patients.

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