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Real-World Efficacy of Daclatasvir and Sofosbuvir, With and Without Ribavirin, in HIV/HCV Coinfected Patients With Advanced Liver Disease in a French Early Access Cohort

Karine Lacombe, MD, PhD,[1,2] Hélène Fontaine, MD,[3] Catherine Dhiver, MD,[4] Sophie Metivier, MD,[5] Eric Rosenthal, MD, PhD,[6] Teresa Antonini, MD,[7] Marc Antoine Valantin, MD,[8] Patrick Miailhes, MD,[9] Stanislas Harent, MD,[10] Dominique Batisse, MD,[11] Georges-Philippe Pageaux, MD, PhD,[12] Julie Chas, MD,[13] Hugues Aumaitre, MD,[14] Stephanie Dominguez, MD,[15] Thierry Allegre, MD,[16] Alain Lafeuillade, MD,[17] Eric Billaud, MD,[18] Pierre De Truchis, MD,[19] Philippe Perre, MD,[20] Vincent Leroy, MD, PhD,[21] Victor De Ledinghen, MD, PhD,[22] Philippe Sogni, MD, PhD,[23] François Dabis, MD, PhD,[24] Yue Zhao, MD, PhD,[25] Anne Filipovics, MSc,[26] Larysa Fedchuk, MD, PhD,[26] Raoudha Akremi, MD,[26] Yacia Bennai, MD,[26] and Dominique Salmon Ceron, MD, PhD[3,27]

Background: Efficacious, well-tolerated, direct antiviral agents have drastically changed the prognosis of hepatitis C virus (HCV) disease, but real-world data for oral treatments are limited in key populations such as HIV/HCV coinfection with advanced liver disease. Daclatasvir (DCV) efficacy and safety was assessed in the French "Autorisation Temporaire d'Utilisation" (ATU) program, providing DCV ahead of market authorization to patients with advanced HCV disease without other treatment options.

Methods: This was a subanalysis of HIV/HCV coinfected ATU patients treated with DCV plus sofosbuvir (SOF). Recommended duration was 24 weeks; addition of ribavirin (RBV) and/or shorter treatment was at the physician's discretion. The primary efficacy

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From the [1]Department of Infectious and Tropical Diseases, Hôpitaux Universitaires Saint-Antoine, Assistance Publique Hôpitaux de Paris (APHP), Paris, France; [2]Sorbonne Universités, INSERM, UPMC Univ Paris 06, Institut Pierre Louis d'Epidémiologie et de Santé Publique (iPLESP UMRS 1136), Paris, France; [3]Hepatology Unit, Cochin Hospital, APHP, INSERM USM20, Pasteur Institute, Paris, France; [4]Department of Infectious Diseases, CHU de la Conception, Marseilles, France; [5]Department of Hepato-gastroenterology, CHU Purpan, Toulouse, France; [6]Department of Internal Medicine and COREVIH PACA-EST, CHU Archet, Nice, France; [7]Hepatobiliary Centre, CHU Paul-Brousse, Villejuif, France; [8]Department of Infectious and Tropical Diseases, CHU Pitié-Salpêtrière, Paris, France; [9]Department of Infectious and Tropical Diseases, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, Lyon, France; [10]Department of Infectious and Tropical Diseases, Bichat-Claude Bernard Hospital, Paris, France; [11]Department of Clinical Immunology, Georges-Pompidou European Hospital, Paris, France; [12]Department of Hepato-gastroenterology, CHU de Montpellier, Montpellier, France; [13]Department of Infectious and Tropical Diseases, Hôpitaux Universitaires Tenon, APHP, Paris, France; [14]Department of Infectious and Tropical Diseases, CHU Perpignan, Perpignan, France; [15]Department of Clinical Immunology, CHU Henri Mondor, Créteil, France; [16]Department of Hemato-oncology, CH Aix-en-Provence, Aix-en-Provence, France; [17]Department of Infectious Diseases, CHU Toulon, Toulon, France; [18]Department of Infectious and Tropical Diseases, CHU Hôtel Dieu, Nantes, France; [19]Department of Infectious Diseases, Raymond Poincaré Hospital, APHP, Garches, France; [20]Department of Internal Medicine, CHD La Roche-sur-Yon, La Roche-sur-Yon, France; [21]Department of Hepato-gastroenterology, CHU Grenoble Alpes, Grenoble, France; [22]Hepatic Fibrosis Investigation Centre, Haut-Lévêque Hospital, CHU de Bordeaux, Pessac, France; [23]INSERM U1223, Pasteur Institute, Paris-Descartes University and Hepatology Department, Cochin Hospital, Paris, France; [24]INSERM U1219, ISPED University of Bordeaux, Bordeaux, France; [25]Bristol-Myers Squibb Research and Development, Princeton, NJ; [26]Bristol-Myers Squibb Research and Development, Rueil-Malmaison, Paris, France; and [27]Paris Descartes University, Paris, France.

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Correspondence to: Karine Lacombe, MD, PhD, Service de Maladies Infectieuses et Tropicales, Hôpital Saint-Antoine, 184 rue du Fbg Saint-Antoine, 75012 Paris, France (e-mail: karine.lacombe@sat.aphp.fr).

analysis was sustained virologic response at posttreatment week 12 (SVR12; modified intention-to-treat). Safety was assessed by spontaneous adverse event reporting.

Results: The efficacy population (N = 407) was mostly cirrhotic (72%, of whom 18% were decompensated), HCV treatment–experienced (82%), and infected with genotypes 1 (69%), 3 (12%), or 4 (19%). Median CD4 was 555 cells/mm^3; 95% had HIV RNA <50 copies/mL. Most (74%) were treated for 24 weeks; 14% received RBV. SVR12 was 92% overall (95% confidence interval: 88.6% to 94.0%); 90% (86.4% to 93.2%) in patients with cirrhosis; 95% (88.9% to 97.5%) in patients without cirrhosis. SVR12 was consistent across HCV genotypes and antiretroviral regimens. Among 617 patients with safety data, 7 discontinued for an adverse event and 10 died.

Conclusions: DCV+SOF±RBV achieved high SVR12 and was well tolerated in this large real-world cohort of HIV/HCV coinfected patients with advanced liver disease.

Key Words: daclatasvir, sofosbuvir, HIV/HCV coinfection, real-world data, compassionate use, advanced liver disease

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INTRODUCTION

The risk of hepatitis C virus (HCV) infection is estimated to be 6 times higher for HIV-positive individuals than for the HIV-negative population,[1] and although the prevalence of HIV/HCV coinfection varies widely by geography and demography,[1,2] it is consistently high among people who inject drugs (PWID).[1] Thus, HCV coinfection is common among HIV-infected individuals—particularly where injection drug use contributes significantly to HIV epidemiology—with typical HCV prevalence estimates of ~16% observed in HIV-infected cohorts from France[3] and the United States.[2]

HIV infection accelerates HCV-associated liver fibrosis, most notably in those with more advanced immunodeficiency, resulting in high rates of end-stage liver disease and shorter survival after hepatic decompensation events.[4–6] Despite significantly improved life expectancy in HIV infection, liver disease remains a major non-AIDS cause of mortality among coinfected patients.[7] Effective treatment of HCV in HIV/HCV coinfection is therefore a public health priority, particularly for those with more advanced HCV or HIV disease.

Historical uptake of HCV treatment based on pegylated interferon (pegIFN) and ribavirin (RBV) was low among coinfected patients,[8,9] due to poor efficacy and tolerability[10–12] and a high frequency of adherence-limiting comorbidities in this population. The development of pegIFN-free oral regimens of direct-acting antivirals (DAAs) greatly improved the efficacy and tolerability of HCV treatment in coinfection.[13–17] However, data from clinical DAA studies are of limited generalizability to the broader coinfected population. Treatment-limiting pharmacokinetic interactions with DAAs remain a significant issue with some types of combination antiretroviral (ARV) therapy (cART),[18,19] as does the risk of interaction between some DAAs and oral opioids in PWID on drug substitution treatment.[20] Switching cART regimens to avoid DAA–ARV interactions may be possible, but risks loss of HIV control, especially in those with previous ARV experience.[21] The complex medical needs and lifestyles of many HIV/HCV coinfected patients typically result in their exclusion from clinical efficacy studies, which, together with restrictions on permitted ARVs, has resulted in highly stratified recruitment estimated to exclude 60%–94% of the real-world coinfected population.[22]

Daclatasvir (DCV), a pan-genotypic inhibitor of HCV NS5A,[23] and sofosbuvir (SOF),[24] a pan-genotypic inhibitor of NS5B, both have limited ARV drug interactions, usually manageable by straightforward dose adjustments for DCV.[25] In the phase 3 ALLY-2 study, which had the broadest inclusion criteria among recent DAA coinfection studies,[22] DCV+SOF showed high efficacy (97% sustained virologic response) and good tolerability in patients receiving a wide range of cART regimens.[13] Real-world cohorts can enhance clinical study data with findings from much broader patient sets, including those ineligible for clinical studies. Early access programs, which provide promising new drugs ahead of their market authorization to patients with urgent need, are a potentially rich source of such data. More than 7000 patients were referred under early access initiatives for DCV,[26] with the largest being the French "Autorisation Temporaire d'Utilisation" (ATU) program that treated ~4000 HCV-infected patients with advanced liver disease with DCV+SOF, with or without RBV. We present herein an analysis of DCV+SOF±RBV efficacy and safety in HIV/HCV coinfected ATU patients with severe liver disease.

METHODS

Patients

ATU program patients coinfected with HIV-1 and HCV were included. Eligible patients for the ATU were adults with chronic HCV infection, no alternative treatment options, and an indication for treatment due to advanced liver disease (physician-assessed F3 or F4 fibrosis and/or severe extrahepatic HCV manifestations), HCV recurrence after liver transplant, and/or an indication for liver or kidney transplant.

Determination of Fibrosis and Cirrhosis

Cirrhosis status was determined through a hierarchical algorithm (Supplemental Digital Content, Table 1, http://links.lww.com/QAI/A979) applied to information provided in the Treatment Access Request (TAR) form. The algorithm considered the patient's fibrosis stage (F0–F4) as reported according to any assessment method, any available transient elastography data, and stage of disease. A reported fibrosis stage of F4 was considered compatible with the definition of cirrhosis; where the stage was <F4 or missing, the patient was also considered cirrhotic if an elastography result ≥14.5 kPa was reported. If elastography data were missing or

inconsistent with the reported fibrosis stage, the stage of disease reported in the physician's assessment of ATU eligibility was used.

Patients with cirrhosis were further categorized on the basis of Child–Pugh class as compensated (Child–Pugh A) or decompensated (Child–Pugh B or C).

Treatment Dose and Duration

Recommended treatment was DCV 60 mg plus SOF 400 mg once daily for 24 weeks. RBV could be added and/or a shorter treatment duration undertaken at physician's discretion. A reduced DCV dose (30 mg daily) was recommended for patients receiving ritonavir-boosted atazanavir or other potent inhibitors of cytochrome P450 3A4 (CYP3A4) or P-glycoprotein, and a dose increase (90 mg) recommended with efavirenz or other moderate inducers of CYP3A4. Potent inducers of CYP3A4 or P-glycoprotein were contraindicated. DCV was not recommended for pregnant women or women of childbearing potential not using effective contraception.

Program Management

The ATU program was not a clinical study, and treatment was undertaken according to standard clinical practice. In accordance with the French regulations, the ATU cohort was approved by the French authorities and TAR forms for individual patients submitted to the program sponsor (Bristol-Myers Squibb) by their attending physicians. On granting of a TAR, the patient's hospital pharmacy could order DCV directly from the sponsor. SOF was not provided.

The provision of outcome data was voluntary. Attending physicians were invited to return completed visit forms to the sponsor at treatment initiation (day 0), treatment weeks 2, 4, 8, 12, 16, 20, and 24 (as appropriate), posttreatment weeks 4, 12 (PT12), and 24, and at treatment discontinuation. Forms reporting pregnancy or adverse events (AEs) were provided by physicians as appropriate. No clarification was requested for the AE data provided.

Data sharing with the databases of the French national prospective cohort of patients with HIV/HCV coinfection (ANRS CO13 HepaVIH) was undertaken for patients enrolled in both this cohort and the ATU to improve the quality and robustness of the results.

Program Assessment

Laboratory assessments were made locally. For each visit form, quantitative HCV-RNA data were provided along with the assay used and its lower limit of quantitation (LLOQ). An outcome of "quantifiable" (>LLOQ) or "unquantifiable" (≤LLOQ) was then assigned. If a qualitative result was reported, HCV-RNA was considered unquantifiable if target RNA was reported as undetected.

Safety was evaluated as frequencies of serious AEs, all AEs, and discontinuations due to AEs. The physician was responsible for AE reporting. Standard pharmacovigilance practice was used, imputing AEs of unreported causality as treatment related.

Analysis Populations and Endpoints

The treated population comprised patients with at least 1 completed visit form and/or AE report, while the primary efficacy population consisted of the subset who had more than 1 day of treatment and detectable HCV-RNA at baseline. The primary efficacy outcome was SVR12, defined as unquantifiable HCV-RNA at PT12. The primary analytic approach was a modified intention-to-treat (mITT) assessment that excluded patients without PT12 virologic data because of loss to follow-up or discontinuation for reasons unspecified or other than predefined treatment failure.

Treatment failure was defined as absence of SVR12 for virologic or specific nonvirologic reasons. Virologic failure comprised virologic breakthrough (quantifiable HCV-RNA on-treatment from week 2 after an unquantifiable measure), or relapse [unquantifiable HCV-RNA at end of treatment (EOT) but quantifiable at PT12], or undefined virologic failure—quantifiable HCV-RNA at all on-treatment/follow-up visits or at all on-treatment visits for patients with no posttreatment data. Nonvirologic treatment failure comprised missing HCV-RNA at PT12 due to treatment discontinuation for AEs or death on or after treatment.

An observed-values sensitivity analysis was also performed, which excluded nonvirologic treatment failures.

Statistical Analysis

Intermittent missing data were imputed as the worse of the flanking outcomes, except for missing PT12 data, which were back-imputed from the next available measurement.

Treatment duration was derived from documented start and end dates or inferred from the pharmacovigilance database or the day 0/last on-treatment visit dates if missing. Treatment duration was analyzed as 12 or 24 weeks based on treatment length between the derived start and end dates: those treated for ≤14 weeks were analyzed as 12 weeks, and >14 weeks as 24 weeks. Sensitivity subgroup analyses were undertaken for actual durations: <10, 10 to <14, 14 to <20, and ≥20 weeks. Comparisons between baseline characteristics were made using 2-tailed t tests or Wilcoxon rank sum tests for continuous variables, and χ^2 or Fisher's exact tests for categorical variables.

RESULTS

Patients

Between ATU cohort initiation in March 2014 and closure in October 2014, 669 HIV/HCV coinfected patients treated with DCV were enrolled by 265 physicians. From these, 617 records were available for safety assessments and 407 for mITT efficacy (Supplemental Digital Content, Fig. 1, http://links.lww.com/QAI/A979).

TABLE 1. Baseline Characteristics

Parameter, n (%) Unless Otherwise Indicated	All Treated* (N = 407)	DCV+SOF 12 wk (n = 87)	DCV+SOF+RBV 12 wk (n = 16)	DCV+SOF 24 wk (n = 260)	DCV+SOF+RBV 24 wk (n = 42)
Age, median (range), yrs	52.1 (34–74)	52.5 (38–73)	51.5 (46–58)	52.1 (34–70)	51.4 (42–74)
Male	288 (72)	58 (70)	9 (56)	188 (73)	32 (80)
HCV-RNA, median (IQR) $\log_{10}$ IU/mL	6.1 (5.5–6.5)	6.0 (5.5–6.4)	6.0 (5.5–6.7)	6.1 (5.6–6.5)	6.1 (5.6–6.7)
HCV-RNA ≥6 $\log_{10}$	223 (55)	45 (52)	7 (44)	146 (56)	24 (57)
HCV GT†					
1 overall‡	278 (69)	58 (68)	10 (63)	179 (69)	30 (73)
1a	213 (53)	44 (52)	7 (44)	136 (53)	25 (61)
1b	58 (14)	12 (14)	3 (19)	38 (15)	5 (12)
3	47 (12)	5 (6)	4 (25)	35 (14)	3 (7)
4	75 (19)	22 (26)	2 (13)	42 (16)	8 (20)
HCV recurrence after liver transplant	13 (3)	1 (1)	0	7 (3)	5 (12)
Advanced fibrosis (F3)§	77 (19)	30 (36)	1 (6)	42 (16)	4 (10)
Cirrhosis	290 (72)	46 (54)	14 (88)	195 (75)	33 (83)
Child–Pugh class‖					
A	203 (82)	29 (74)	11 (100)	141 (83)	22 (85)
B	40 (16)	8 (21)	0	27 (16)	3 (12)
C	5 (2)	2 (5)	0	2 (1)	1 (4)
MELD category¶					
<10	63 (53)	8 (38)	8 (80)	35 (53)	12 (57)
10 to <15	28 (24)	7 (33)	1 (10)	14 (21)	6 (27)
≥15	27 (23)	6 (29)	1 (10)	17 (26)	3 (14)
Hepatocellular carcinoma	12 (3)	2 (2)	0	9 (3)	1 (2)
Extrahepatic manifestations	45 (11)	15 (18)	2 (13)	25 (10)	3 (8)
DCV dose, mg					
30	122 (30)	28 (32)	6 (38)	8 (31)	8 (19)
60	246 (60)	50 (57)	9 (56)	158 (61)	27 (64)
90	39 (10)	9 (10)	1 (6)	22 (8)	7 (17)
Treatment experienced#	330 (82)	58 (68)	10 (63)	221 (85)	39 (95)
HIV RNA <50 copies/mL	322 (95)	69 (95)	14 (100)	203 (95)	34 (97)
CD4 cells/mm^3, median (IQR)	555 (335–765)	617 (387–912)	457 (230–628)	569 (350–763)	363 (230–588)
<200 cells/mm^3	32 (9)	7 (9)	3 (20)	16 (7)	6 (16)
ARV regimen**					
PIs††	136 (35)	33 (40)	7 (47)	86 (34)	10 (24)
Non-nucleoside RTIs‡‡	91 (23)	18 (22)	3 (20)	61 (24)	9 (22)
Integrase inhibitors§§	255 (65)	50 (60)	8 (53)	162 (64)	33 (80)
Maraviroc	17 (4)	2 (2)	1 (7)	13 (5)	1 (2)
Other	2 (1)	1 (1)	0	1 (<1)	0
Laboratory results at TAR, median (IQR)					
Platelets, $\times 10^9$/L	135 (87–193)	154 (99–203)	105 (71–152)	137 (87–191)	116 (70–183)
Albumin, g/L	39 (35–43)	39 (34–42)	41 (38–43)	40 (35–43)	37 (32–42)
ALT, IU/L	62 (43–102)	64 (41–105)	61 (42–97)	61 (43–96)	67 (44–108)
AST, IU/L	64 (42–95)	64 (41–89)	58 (43–93)	66 (42–96)	62 (42–93)
Total bilirubin, μmol/L	13 (8–24)	13 (8–24)	9 (6–13)	13 (9–26)	16 (10–25)
Gamma GT, IU/L	106 (60–176)	103 (66–166)	130 (77–164)	99 (56–171)	122 (81–215)

Percentages are of patients with available data in indicated category. Missing data: sex (n = 9); HCV GT (n = 5); previous HCV treatment (n = 4); cirrhosis (n = 4); Child-Pugh (n = 42); MELD (n = 175); hepatocellular carcinoma (n = 4); extrahepatic manifestations (n = 4); fibrosis stage (n = 10); HIV RNA (n = 69); CD4 cells (n = 39); ARV regimen (n = 14).

*Includes 2 patients with missing regimen data.

†Also one GT 2, one GT 4, and one mixed GT 1b/3 infection (DCV+SOF, 24 weeks).

‡Includes unspecified subtype (n = 7).

§Excludes patients reported as F3/F4 (n = 10).

‖Cirrhotic patients only.

¶Cirrhotic and/or pretransplant patients only.

#SOF-experienced, n = 4.

**Excludes nucleoside analogs; patients could receive more than one agent or class of agent.

††With or without reported use of ritonavir boosting: darunavir (n = 53); atazanavir (n = 60); lopinavir/ritonavir (n = 13); fosamprenavir (n = 8); saquinavir (n = 3); nelfinavir (n = 1).

‡‡Etravirine (n = 38); rilpivirine (n = 35); efavirenz (n = 17); nevirapine (n = 2).

§§Raltegravir (n = 235); dolutegravir (n = 17); raltegravir + dolutegravir (n = 3).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GT, glutamyl transferase; IQR, interquartile (25th–75th) range; NR, not reported; RTI, reverse transcriptase inhibitor.

Baseline characteristics for the mITT efficacy population are shown in Table 1. Patients were primarily cirrhotic (72%, of whom 18% were decompensated) and infected with HCV genotype (GT) 1 (69%; 53% GT 1a, 14% GT 1b), GT 3 (12%), or GT 4 (19%). Most were treatment experienced (82%), of whom almost all had previously received pegIFN/RBV with (23%) or without (77%) an NS3 protease inhibitor (PI). Most previous failures were for null or partial response (76%) or relapse (23%). Model for end-stage liver disease (MELD) scores were >10 in 47% of patients with available data, baseline albumin <35 g/L in 25%, and 55% had baseline HCV-RNA ≥6 $\log_{10}$ IU/mL. All patients with data (n = 393) were receiving cART with a wide variety of PIs, nonnucleoside reverse transcriptase inhibitors, and integrase inhibitors; 9% had a baseline CD4 cell count <200 cells/mm^3, and 95% had plasma HIV RNA <50 copies/mL at baseline. Eight patients (2%) were HIV/HCV/HBV coinfected.

Baseline characteristics between the mITT efficacy population and the 183 intention-to-treat patients excluded from the primary analysis for missing data not related to treatment failure were comparable (Supplemental Digital Content, Table 2, http://links.lww.com/QAI/A979). Compared with the mITT population, the only differences with $P < 0.05$ among excluded patients were lower RBV use (7% vs 14% receiving RBV), a shorter duration of actual treatment among those with a derived duration of 12 weeks (13% treated <10 weeks vs 4% in mITT patients) or 24 weeks (10% vs 3% treated 14 to <20 weeks), and a higher use of nucleoside-sparing HIV treatment (17% vs 10%).

The median duration of treatment in the mITT population was 168 days (range 11–215). Most patients (86%) received DCV+SOF without RBV, of whom 75% received an analyzed duration of 24 weeks. Of the 14% who received RBV, most (72%) were in the 24-week group. In the 24-week group, those who received RBV had more advanced baseline markers of both HCV and HIV disease (Supplemental Digital Content, Table 3, http://links.lww.com/QAI/A979) as shown by more posttransplant HCV recurrence (12% vs 3% of those not receiving RBV), more hepatic encephalopathy (8% vs 1%), higher gamma GT (median 138 vs 96 IU/mL), and lower CD4 cell counts (median 363 vs 569 cells/mm^3, with 47% vs 25% <350 cells/mm^3), and were more likely to be receiving HIV integrase inhibitors (80% vs 64%; all comparisons $P < 0.05$). Trends ($P < 0.1$) were also noted for more ascites, a higher proportion with previous HCV treatment, more total bilirubin >60 μmol/L, and lower median albumin among patients who received RBV.

Virologic Response

SVR12 outcomes are shown in Table 2 for all patients, and broken down by cirrhosis status. Among all treated patients, SVR12 (mITT) was 92% (95% without cirrhosis; 90% with cirrhosis). Among patients who received DCV+SOF without RBV for 24 weeks, SVR12 was 96% overall (98% without cirrhosis; 95% with cirrhosis), and 100% both with and without cirrhosis in the smaller group who received DCV+SOF+RBV for 24 weeks.

SVR12 was numerically lower among the 103 patients analyzed as having received 12 weeks of treatment [78% (80/103) with or without RBV], driven primarily by a high proportion (17%; 17/103) with very short (<10 weeks) actual durations (Fig. 1). Among this subgroup with short treatment, the incidence of both nonvirologic treatment failure [12% (2/17)] and undefined virologic failure for missing HCV-RNA data after week 2 or 4 (9 of 10 undefined failures) was substantially higher than among patients treated for longer. Among 13 treatment failures in patients with less than 10 weeks of treatment, 8 (62%) were treated for ≤6 weeks.

In patients with compensated (Child–Pugh A) cirrhosis treated for 24 weeks, SVR12 was 95% (134/141) without RBV and 100% (22/22) with RBV (Supplemental Digital Content, Table 4, http://links.lww.com/QAI/A979). Only 4 patients with decompensated cirrhosis (Child–Pugh B or C) received RBV; among the 33 decompensated patients treated for 24 weeks with or without RBV, SVR12 was 94% (31/33).

In the 368 patients with baseline CD4 data, SVR12 (mITT) was 81% (26/32; 95% CI: 64.7%–91.1%) in those <200 cells/mm^3 vs 92% (309/336; 95% CI: 88.6%–94.4%) in those ≥200 cells/mm^3.

SVR12 was consistent across HCV GTs and broadly comparable across cART regimens (Fig. 2). A slightly lower SVR12 was observed among patients receiving PIs, driven primarily by higher rates of nonvirologic failure [4% (6/136) vs <1% (1/257)] and undefined virologic failure due to missing data after treatment week 2 or 4 [5% (7/136) vs 2% (4/257)] than those not receiving PIs. Restricting the denominator to virologic breakthroughs or relapses resulted in SVR12 rates of 93% (115/123) for those taking PIs vs 97% (244/252) for those who were not.

Treatment Failure

Thirty-four patients in the mITT population did not achieve SVR12 for virologic (n = 27) or nonvirologic (n = 7) failure. Virologic failures comprised one breakthrough, 15 relapses, and 11 undefined failures (10 for missing HCV-RNA after a quantifiable result at treatment week 2 or 4). Nonvirologic failures consisted of 5 deaths and 2 discontinuations for AEs, detailed below.

Individual characteristics of the 34 patients with treatment failure are shown in Supplemental Digital Content, Table 5, http://links.lww.com/QAI/A979, and aggregated baseline characteristics for patients with virologic or nonvirologic failure and those with SVR12 in Supplemental Digital Content, Table 6, http://links.lww.com/QAI/A979. Overall, patients with treatment failure, particularly nonvirologic failure, showed more advanced indicators of liver and/or HIV disease than those who achieved SVR12, with trends toward more decompensated liver disease, higher MELD scores, more baseline laboratory abnormalities, and lower CD4 cells.

Evolution of Liver Disease and HIV-Associated Parameters

Paired data at baseline and PT12 were available for Child–Pugh class in 42 patients and MELD score in 21

TABLE 2. Sustained Virologic Response and Treatment Failure by Derived Treatment Regimen and Cirrhosis Status

	Overall (All Treated)	DCV+SOF 12 wk	DCV+SOF+RBV 12 wk	DCV+SOF 24 wk	DCV+SOF+RBV 24 wk
All patients					
N					
mITT	407*†	87‡	16§	260	42
Observed values‖	400*†	84	15	257	42
SVR12, n (%) (95% CI)					
mITT	373 (92) (88.6–94.0)	67 (77) (67.1–84.6)	13 (81) (57.0–93.4)	249 (96) (92.6–97.6)	42 (100) (91.6–100)
Observed values‖	373 (93) (90.4–95.3)	67 (80) (70.0–87.0)	13 (87) (62.1–96.3)	249 (97) (94.0–98.4)	42 (100) (91.6–100)
Treatment failures, n	34	20	3	11	0
Virologic breakthrough	1	1	0	0	—
Relapse	15	6	1	8	—
Undefined virologic failure	11¶	10	1	0	—
Nonvirologic failure	7	3	1	3	—
Patients without cirrhosis					
N					
mITT	113	39	2	65	7
Observed values	112	38	2	65	7
SVR12, n (%) (95% CI)					
mITT	107 (95) (88.9–97.5)	34 (87) (73.3–94.4)	2 (100) (34.2–100)	64 (98) (91.8–99.7)	7 (100) (64.6–100)
Observed values‖	107 (96) (90.0–98.1)	34 (89) (75.9–95.8)	2 (100) (34.2–100)	64 (98) (91.8–99.7)	7 (100) (64.6–100)
Treatment failures, n	6	5	0	1	0
Virologic breakthrough	0	0	—	0	—
Relapse	4	3	—	1	—
Undefined virologic failure	1	1	—	0	—
Nonvirologic failure	1	1	—	0	—
Patients with cirrhosis					
N					
mITT	290*	46	14	195	33
Observed values‖	284*	44	13	192	33
SVR12, n (%) (95% CI)					
mITT	262 (90) (86.4–93.2)	31 (67) (53.0–79.1)	11 (79) (52.4–92.4)	185 (95) (90.8–97.2)	33 (100) (89.6–100)
Observed values‖	262 (92) (88.6–94.8)	31 (70) (55.8–81.8)	11 (85) (57.8–95.7)	185 (96) (92.7–98.2)	33 (100) (89.6–100)
Treatment failures, n	28	15	3	10	0
Virologic breakthrough	1	1	0	0	—
Relapse	11	3	1	7	—
Undefined virologic failure	10	9	1	0	—
Nonvirologic failure	6	2	1	3	—

Nonvirologic failure: treatment discontinuation for AEs or death before posttreatment week 12.
*Includes 2 cirrhotic patients with missing regimen details; both achieved SVR12.
†Includes 4 patients with missing cirrhosis status.
‡Fourteen patients received <10 weeks of treatment (9 for <6 weeks), of whom 11 were treatment failures.
§Three patients received <10 weeks of treatment (1 for <6 weeks), of whom 2 were treatment failures.
‖Excludes nonvirologic treatment failure.
¶Last reported HCV-RNA through posttreatment week 12 was at treatment week 2 or 4 (quantifiable) in 10 of 11 undefined virologic failures.
CI, confidence interval; SVR12, sustained virologic response at posttreatment week 12; wk, weeks.

patients. Improved Child–Pugh results at PT12 were observed in 14% (6/42) of patients (5 class B to class A, and 1 class C to class A); 83% remained unchanged, and one deteriorated (class A to class B). For MELD score, 19% (4/21) had a reduction in score category at PT12 from 10–<15 to <10 (n = 1), or from ≥15 to 10–<15 (n = 1) or to <10 (n = 2); 67% (14/21) had an unchanged category, and 14% (3/21) had worsened.

CD4 cell count was stable between baseline and EOT in 153 patients with paired data, with a median change of 9 cells/mm^3 and an interquartile range of −10 to 29 cells/mm^3. Of patients with paired HIV RNA data, 93% (141/152) of those who had <50 copies/mL at day 0 were <50 copies/mL at EOT, and 97% (150/154) of those <200 copies/mL at day 0 remained <200 copies/mL at EOT.

Safety

On-treatment AEs in the overall safety population (N = 617) are summarized in Table 3. Fifty-five patients

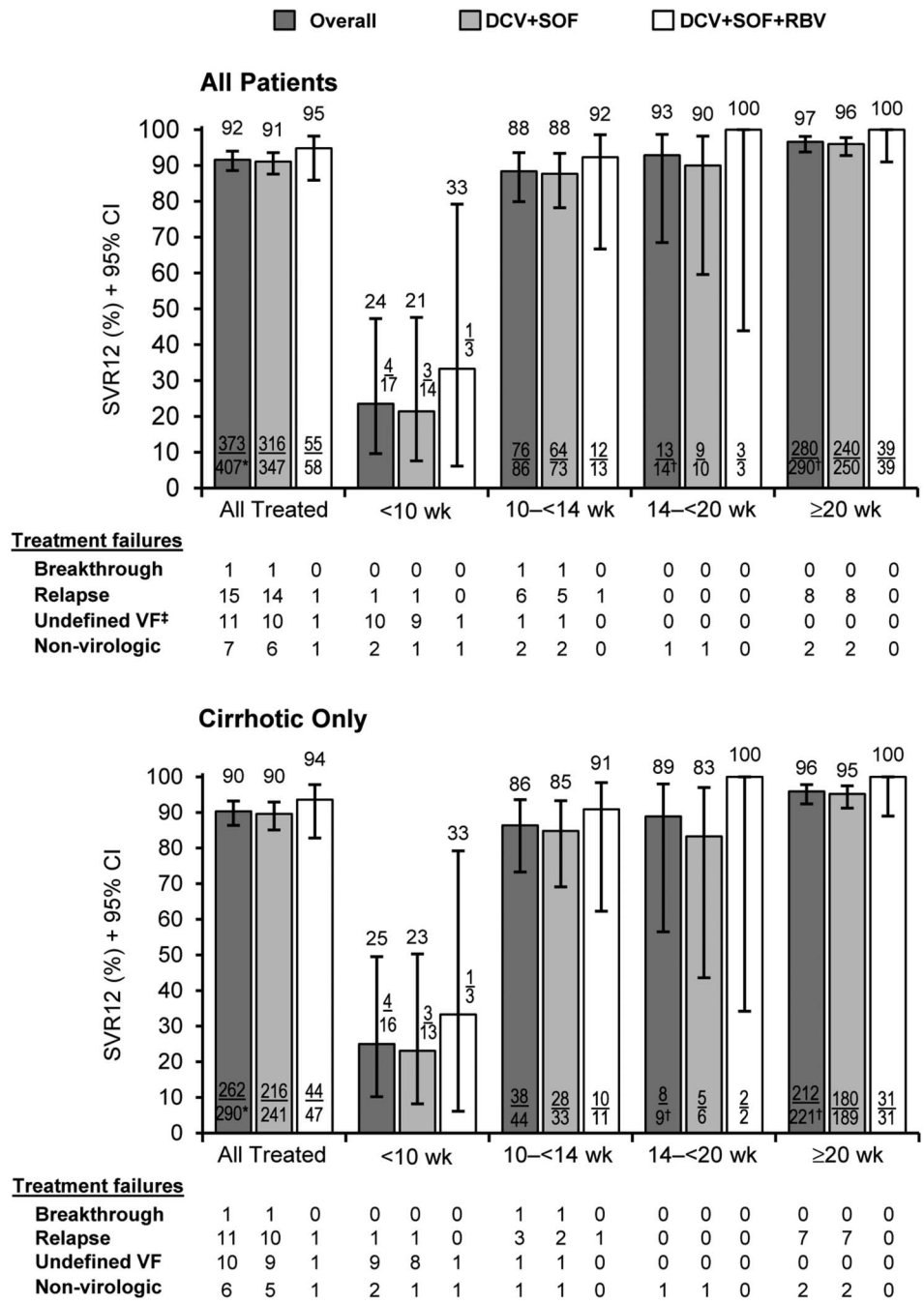

FIGURE 1. Sustained virologic response (mITT) according to actual duration of treatment. CI, confidence interval; SVR12, sustained virologic response at posttreatment week 12; VF, virologic failure; wk, weeks. Missing regimen details: *n = 2 and †n = 1. ‡Ninety-one percent (10/11) of undefined VFs were patients whose last reported HCV-RNA through posttreatment week 12 was a detectable measure at treatment week 2 or 4.

(9%) experienced one or more serious AEs (Supplemental Digital Content, Table 7, http://links.lww.com/QAI/A979), and 26 (4%) experienced one or more AEs of severity grade 3 or 4 (Supplemental Digital Content, Table 8, http://links.lww.com/QAI/A979). There were 10 on- or off-treatment deaths, mostly for causes consistent with complications of advanced liver disease (Supplemental Digital Content, Table 9, http://links.lww.com/QAI/A979); one (decompensated cirrhosis in a patient who also had multiorgan failure) was considered possibly related to HCV or HIV treatment by the physician, and 2 (multiorgan failure plus septic shock plus intestinal obstruction, and hepatic carcinoma) were imputed as treatment-related for unreported causality. The remaining 7 deaths were not considered treatment related. Five deaths were classed as nonvirologic treatment failures. There were 7 discontinuations for AEs, of which 3 were subsequently fatal (hepatic carcinoma, decompensated cirrhosis/multiorgan failure, respiratory distress) and 4 nonfatal—lymphopenia, renal insufficiency (both reported as related to treatment), attempted suicide (imputed as treatment-related for missing causality), and anxiety/ascites/hepatocellular carcinoma/

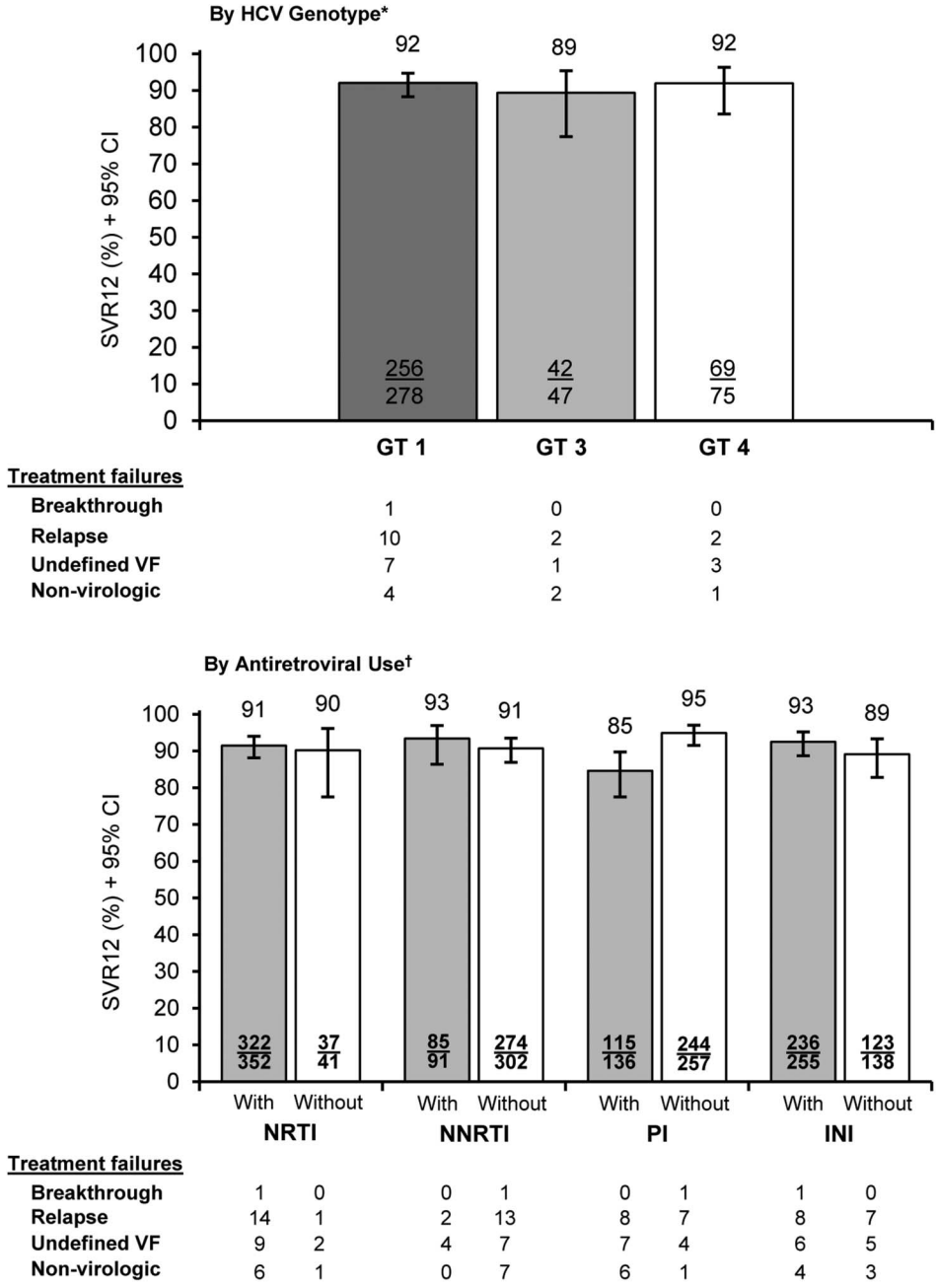

FIGURE 2. Sustained virologic response (mITT) by HCV GT and use of ARV drug classes. CI, confidence interval; INI, integrase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; SVR12, sustained virologic response at posttreatment week 12; VF, virologic failure; wk, weeks. *Excludes 1 GT 2 (achieved SVR12), 1 GT 6 (SVR12), and 5 missing GT (4 SVR12) patients. †Excludes 14 patients without ARV usage data (all SVR12).

pneumonia/encephalopathy (not related to treatment). Two nonfatal AEs leading to discontinuation were classed as nonvirologic treatment failures.

DISCUSSION

As a regimen, DCV+SOF±RBV has several features of relevance to HIV-HCV coinfection. It is a pan-genotypic combination active against HCV GT 3—considered the most difficult GT to treat and against which many of the current DAAs have reduced or absent antiviral activity—with minimal potential as a perpetrator of drug–drug interactions and no significant impact on ARV drug exposures.[25] Although DCV is a cytochrome P450 3A4 (CYP 3A4) substrate,[27] administration of DCV and SOF as separate agents confers the flexibility to accommodate CYP 3A4–active ARVs such as efavirenz or boosted atazanavir through DCV dose adjustment. By contrast, some fixed-dose coformulation regimens for HCV are contraindicated or not recommended for use with efavirenz—eg, EPCLUSA (velpatasvir + SOF)[28] and ZEPATIER (elbasvir + grazoprevir)[29]—or with boosted PIs (eg, ZEPATIER[29]) because of alterations in exposure to one or more regimen components.

TABLE 3. On-Treatment Safety Summary (All Treated Patients)

	All Treated (N = 617)*	DCV+SOF (N = 531)	DCV+SOF+RBV (N = 74)
Patients with ≥1 AE	205 (33)	177 (33)	26 (35)
Patients with ≥1 serious AE	55 (9)	47 (9)	7 (9)
Discontinuation for AEs†	7 (1)	5 (1)	2 (3)
Deaths	10 (2)	10 (2)	0
Common AEs (all-cause ≥2% overall)			
Asthenia	42 (7)	36 (7)	6 (8)
Headache	37 (6)	37 (7)	0
Nausea	18 (3)	17 (3)	1 (1)
Fatigue	10 (2)	9 (2)	0
Diarrhea	12 (2)	11 (2)	0
Insomnia	15 (2)	12 (2)	2 (3)
Sleep disorder	13 (2)	11 (2)	2 (3)
Myalgia	11 (2)	11 (2)	0
Arthralgia	10 (2)	9 (2)	1 (1)
Anemia	11 (2)	6 (1)	5 (7)
Treatment-emergent grade 3/4 laboratory abnormalities‡			
Platelets $<50 \times 10^9$/L	20/524 (4)	20/462 (4)	0/60
ALT >175 IU/L	1/531 (<1)	1/464 (<1)	0/65
AST >200 IU/L	3/541 (1)	2/476 (<1)	1/63 (2)
Total bilirubin >60 μmol/L	21/370 (6)	19/325 (6)	2/44 (5)
Gamma GT >90 (women) or >140 (men) IU/L	36/303 (12)	32/268 (12)	4/34 (12)
Hemoglobin <8 g/dL	4/517 (1)	4/449 (1)	0/66

Values are presented as n (%) or n/N (%) unless otherwise specified.

*Includes 12 patients with missing regimen data.

†Lymphopenia, renal insufficiency, anxiety/ascites/hepatocellular carcinoma/pneumonia/encephalopathy, attempted suicide, hepatic carcinoma, decompensated cirrhosis/multiorgan failure, respiratory distress (n = 1 each).

‡Most patients had incomplete data; only available data after day 0 were considered.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; gamma GT, gamma glutamyl transferase.

This large real-world analysis evaluated DCV+SOF±RBV in a mostly cirrhotic and treatment-experienced cohort of HIV/HCV coinfected patients receiving a broad range of cART. Most (74%) were treated for the program-recommended 24 weeks, which was also the median time on treatment. Overall, the SVR12 rate (mITT) was 92%. In those treated for 24 weeks, SVR12 was 96%–100% and broadly comparable with or without compensated or decompensated cirrhosis. These SVR12 rates are similar to 12-week treatment studies of several DAA regimens—including DCV+SOF—in coinfected patients with less advanced disease.[13,15–17] Excluding patients with very short (<10 weeks) durations of actual treatment, SVR12 in the 12-week analysis groups was 88%–92%. The incremental benefit of RBV use was small and confounded by low numbers and nonrandomized treatment allocation. The regimen was well tolerated with or without RBV, with only 1% (7/617) treatment discontinuations for fatal or nonfatal AEs, and 10 (2%) deaths, primarily from causes consistent with advanced liver disease.

Clinical data for DAA regimens in coinfected patients with advanced liver disease are sparse, particularly for decompensated cirrhosis. These real-world data are encouraging, and suggest that SVR12 rates >90% are achievable with or without RBV in decompensated patients given DCV+SOF, irrespective of HCV GT or cART regimen. These data also help address the current lack of longer duration (>16 weeks) clinical trial data for DCV+SOF±RBV. The high SVR12 rate in cirrhotic patients after 24 weeks of DCV+SOF is relevant for patients who are RBV intolerant, or for whom RBV might be considered inadvisable, such as those with relevant comorbidities or cirrhosis, or older or more clinically advanced HIV coinfected patients already receiving multiple therapeutic agents.

These ATU data are consistent with smaller cohorts of HIV/HCV coinfected patients with advanced liver disease: 92% SVR12 (48/52) was observed in a subgroup of coinfected patients treated with DCV+SOF±RBV in a Europe-wide DCV compassionate use program,[30] of whom 95% had cirrhosis, and just under half were Child–Pugh class B or C.[31] Similarly, 93% SVR12 was observed in 189 cirrhotic patients (8% Child–Pugh B or C) treated with various DAA regimens, including DCV+SOF±RBV, for 12 or 24 weeks in the French ANRS CO13 HepaVIH coinfection cohort.[32] The data are also consistent with >90% SVR12 observed in clinical DAA studies in predominantly noncirrhotic HCV monoinfected[33–37] and HIV/HCV coinfected patients,[13–17] and similarly with slightly lower rates seen in HCV monoinfection with decompensated liver disease.[38–40]

As with all real-world data, there are limitations to these analyses. Treatment allocation and duration was at the physician's discretion, and the subsequent group imbalances made it impossible to fully assess the contribution of RBV or treatment duration to outcome. Data collection was nonstandardized and based on local practice, resulting in intersite reporting variability and substantial missing data. Reporting was also voluntary, leading to potential reporting bias. Data are limited for HIV-associated parameters. Neither DCV nor SOF has any clinically relevant interactions with maintenance opioids,[41,42] and it is highly likely that many patients of this cohort would have been current or former PWID receiving opioid substitution, for whom clinical data are sparse.[43,44] Thus, it is a limitation that data on use of injection drugs and maintenance opioids were not captured. Finally, safety data were based on pharmacovigilance reporting, and it is likely that AEs were underreported.

Despite these limitations, this cohort represents the largest real-world assessment of HCV treatment efficacy yet reported in unselected patients with HIV/HCV coinfection. These patients had very limited treatment options, and their advanced disease, lifestyle characteristics, and broad range of cART regimens would have made many ineligible for randomized studies. The data indicate that

HIV/HCV coinfection with decompensated liver disease does not preclude the probability of a high response rate to DCV+SOF treatment, with or without RBV.

In conclusion, therefore, DCV+SOF±RBV was efficacious and well tolerated in this real-world HIV/HCV coinfected cohort with advanced liver disease, and this regimen is an appropriate option in this context.

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