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12 Weeks of Daclatasvir in Combination with Sofosbuvir for HIV-HCV Coinfection (ALLY-2 study): Efficacy and Safety by HIV Combination Antiretroviral Regimens

Anne F. Luetkemeyer[1], Cheryl McDonald[2], Moti Ramgopal[3], Stephanie Noviello[4], Rafia Bhore[5], Peter Ackerman[6]

[1]University of California, San Francisco, CA

[2]Tarrant County Infectious Disease Associates, Fort Worth, TX

[3]Midway Immunology and Research Center, Fort Pierce, FL

[4]Bristol-Myers Squibb, Lawrenceville, NJ

[5]Bristol-Myers Squibb, Hopewell, NJ

[6]Bristol-Myers Squibb, Wallingford, CT

Correspondence: Anne F Luetkemeyer, MD, Division of HIV, Infectious Diseases and Global Medicine, San Francisco General Hospital, University of California, San Francisco, CA 941104, USA. Email: aluetkemeyer@php.ucsf.edu

Key points: : In HIV-HCV coinfected patients, daclatasvir + sofosbuvir once daily for 12 weeks resulted in a 97% SVR12, with high SVR rates demonstrated across a broad range of antiretroviral regimens. Treatment was well tolerated and did not compromise HIV virologic control.

ClinicalTrials.Gov Number: NCT02032888

Abstract

BACKGROUND: Highly-effective hepatitis C virus (HCV) direct-acting antiviral therapies are needed that do not require modification of human immunodeficiency virus (HIV) antiretroviral regimens. This analysis evaluates the efficacy and safety of the combination of daclatasvir+sofosbuvir (DCV+SOF) for 12 weeks by antiretroviral regimen in HIV-HCV coinfected patients.

METHODS: In the randomized, open-label ALLY-2 study (NCT02032888), HIV-HCV coinfected patients received 8 or 12 weeks of once-daily (QD) DCV 60mg + SOF 400mg. Results were stratified by antiretroviral class for the 151 patients who received 12 weeks of DCV+SOF.

RESULTS: Fifty-one patients were HCV treatment-experienced, 100 were treatment-naïve, 89% were male, 33% were black. HCV genotypes were GT1a (69%), GT1b (15%), GT2 (8%), GT3 (6%), GT4 (2%). Sustained virologic response 12 weeks post-treatment (SVR12) was 97% and was similar across antiretroviral regimens (p=0.774): protease inhibitor-based, 97% (95% CI: 90%-99.7%); non-nucleoside reverse transcriptase inhibitor-based, 100% (95% CI: 91%-100%); and integrase inhibitor-based, 95% [95% CI: 83%-99.4%]). SVR12 by NRTI backbone containing either tenofovir disoproxil fumarate or abacavir was 98% [95% CI: 93%-99.5%] and 100% [95% CI: 85%-100%], respectively. Age, gender, race, cirrhosis, HCV treatment history, HCV genotype, baseline HCV viral load and CD4 cell count did not affect SVR12. HIV virologic control was not compromised. There were no treatment-related serious adverse events (SAEs) or AEs leading to discontinuation.

CONCLUSION: DCV+SOF QD for 12 weeks led to high SVR rates (97%) across a broad range of antiretroviral regimens and was safe and well tolerated. DCV+SOF is a highly efficacious, all-oral, pangenotypic HCV treatment for HIV-HCV coinfection.

Introduction

In the US and Europe, approximately one-third of all HIV infected individuals are coinfected with HCV, and liver disease has become the most common cause of morbidity and mortality in HIV-HCV infected patients [1–3]. Thus, successful treatment of HCV is a priority for HIV-HCV coinfected individuals.

Current HIV treatment guidelines recommend initiation of antiretroviral therapy in all HIV-HCV coinfected patients [4, 5]. However, simultaneous treatment of HIV and HCV can be complicated by drug interactions between antiretroviral therapy and current all-oral direct-acting antivirals (DAAs) [4–9]. HIV-HCV coinfected patients may require modification of their stable antiretroviral regimens before starting some current DAA regimens, which is neither desirable for patients with long-term HIV suppression on a specific regimen, nor possible for some treatment-experienced patients with limited alternative antiretroviral options. Therefore, there is a need in HIV-HCV coinfection for all-oral DAA regimens that combine high efficacy with good tolerability, simple dosing, and few or easily manageable drug interactions with concomitant antiretrovirals.

Daclatasvir (DCV, an NS5A inhibitor) and sofosbuvir (SOF, an NS5B polymerase inhibitor) are both oral, once-daily, pangenotypic DAAs with limited potential for interactions with antiretroviral drugs [10,11]. DCV is approved for use in the US, Europe, Japan, and multiple countries across the Americas, Middle East and Asia Pacific region, and SOF is approved for use in the US, Europe, and other countries. After 12 weeks of DCV + SOF, 98% and 97% of HCV treatment-naïve, mono-infected and HIV-HCV coinfected patients achieved sustained virologic response 12 weeks after stopping therapy (SVR12), respectively [12, 13]. However, following 8 weeks of treatment, SVR12

rates were 76% in HIV-HCV coinfected patients [13], suggesting that 12 weeks of DCV + SOF therapy is preferred. To investigate the impact of antiretroviral regimens on DCV + SOF efficacy and safety, we evaluated 12 weeks of DCV + SOF in HIV-HCV coinfected patients stratified according to antiretroviral regimen.

Methods

Patients

Eligible patients were HIV-HCV coinfected adults who were HCV treatment-naive or treatment-experienced. All HCV genotypes were allowed, but the number of patients with non-GT1 virus was capped at 20% per cohort. Compensated cirrhosis was permitted and was capped at 50% per cohort. Patients receiving antiretroviral therapy were required to have HIV-1 RNA of <50 copies/mL and a CD4 cell count ≥100 cells/mm^3 at screening. Those not receiving antiretroviral therapy were required to have a CD4 cell count >350 cells/mm^3. The following antiretroviral agents were permitted: ritonavir-boosted darunavir (DRV/r), ritonavir-boosted atazanavir (ATV/r), ritonavir-boosted lopinavir (LPV/r), efavirenz (EFV), nevirapine (NVP), rilpivirine (RPV), dolutegravir (DTG), raltegravir (RAL), enfuvirtide, maraviroc, tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), abacavir (ABC), lamivudine, and zidovudine (AZT). Coadministration of a boosted protease inhibitor (PI) and a non-nucleoside reverse transcriptase inhibitor (NNRTI) was not permitted, with the exception of RPV + PI; all other combinations of permitted antiretrovirals were allowed.

Study design

This was a Phase 3, randomized, open-label study (ALLY-2, ClinicalTrials.gov number NCT02032888). Patients were randomized to receive either 8 or 12 weeks of DCV 60 mg + SOF 400 mg (both once daily; QD). On the basis of initial pharmacokinetic drug–drug interaction data [11] the standard 60 mg dose of DCV was adjusted to 30 mg in patients receiving ritonavir-boosted PIs, and to 90 mg in those receiving EFV or NVP. Patients who had received 12 weeks of DCV + SOF were stratified into PI, NNRTI, or integrase inhibitor (INSTI) regimen groups based on their antiretroviral therapy. Patients receiving more than one class of antiretroviral agent were listed as: PI regimen if receiving any boosted PI (PI/r); listed as NNRTI if receiving an NNRTI but not a PI/r; listed as INSTI if receiving an INSTI but not a PI/r or NNRTI; and listed as nucleosides only if receiving combination nucleoside therapy without any other antiretroviral class. Two patients who were not receiving antiretroviral therapy were excluded from this analysis. Patients were also evaluated according to nucleoside reverse transcriptase inhibitor (NRTI) backbone, categorized as tenofovir-based or abacavir-based. Further details on study design and data from the two patients who were not receiving antiretroviral therapy and from those who received DCV + SOF for 8 weeks have been described previously [13].

Study endpoints

The primary efficacy endpoint was SVR (HCV RNA < LLOQ; <25 IU/mL) at post-treatment Week 12 (SVR12) among previously untreated patients with GT1 infection treated for 12 weeks. Secondary endpoints included efficacy among HCV treatment-experienced patients and overall safety. Exploratory endpoints included the proportion of patients receiving antiretroviral therapy who maintained HIV-1 suppression (<50 copies/mL at end of DCV + SOF treatment) or experienced HIV

virologic failure (defined as a confirmed or last available measurement of HIV-1 RNA ≥400 copies/mL), and the change in absolute CD4 cell count throughout the treatment phase.

Efficacy and safety assessments

Serum HCV and HIV-1 RNA and CD4 cell counts were assessed at screening, baseline and Weeks 1, 2, 4, 6, 8 and 12. HCV RNA was measured by the Roche COBAS TaqMan HCV Test v2.0. Virologic response was defined as undetectable HCV RNA (<20 IU/mL) during the treatment period and as unquantifiable HCV RNA post-treatment (<25 IU/mL). Adverse events (AEs) and laboratory abnormalities were graded using NIH DAIDS criteria (v1.0 2009 clarification).

Resistance monitoring

Polymorphisms associated with DCV resistance in the HCV NS5A region (at positions M28, Q30, L31 and Y93) were assessed in all patients at baseline and at the time of virologic failure (when HCV RNA was ≥1000 IU/mL) using population-based (≥20%) sequencing of plasma samples. NS5B resistance testing was performed in each sample obtained from patients with virologic failure that could be evaluated (plus a matched baseline comparator) and in comparator samples from two patients who achieved SVR.

Statistical Analysis

Safety and antiviral activity were assessed for all treated patients using descriptive and exploratory analyses. For the primary endpoint, SVR12 was summarized for patients in each cohort (PI, NNRTI, and INSTI regimens).The primary statistical objective was to determine whether the SVR12 rate

among previously untreated patients with HCV GT 1 was higher after 12 weeks of DCV + SOF than the historical response rate of 29% observed in similar patients after 48 weeks of treatment with peginterferon–ribavirin [14].

Results

Study population

Overall, 153 patients were treated with DCV + SOF for 12 weeks, of whom 151 were receiving concomitant antiretroviral therapy (100 were HCV treatment-naïve, and 51 were HCV treatment-experienced). Patient demographics and HCV and HIV disease characteristics are summarized in **Table 1.** Median age was 53 years, 49/151 (32.5%) patients were black and 96/151 (63.6%) white, 23/151 (15.2%) had cirrhosis, and 24/151 (15.9%) were infected with non-GT1 HCV (12/151 [7.9%] GT2; 9/151 [6.0%] GT3; and 3/151 [2%] GT4). Approximately half (70/151 [46.4%]) of the patients receiving antiretroviral therapy were on a PI regimen; 40/151 (26.5%) were on an NNRTI regimen; 39/151 (25.8%) were on an INSTI regimen, and 2/151 (1.3%) were taking nucleosides only. Sixteen patients (10.5%) were taking a complex antiretroviral regimen containing three or more antiretroviral classes (among PI, NNRTI, INSTI and NRTI). In total, 120/151 (79.5%) patients were receiving TDF as part of their NRTI backbone (five [4.2%] received both ABC and TDF). An additional 23 of 151 patients (15.2%) were receiving ABC without TDF, four patients (2.7%) were receiving other NRTIs (FTC +/- AZT) and four patients (2.7%) were on antiretroviral therapy that did not include an NRTI. Two patients (1.3%) were not receiving any antiretroviral therapy (and were thus excluded from this analysis). Patients with HCV GT1a were evenly distributed across antiretroviral groups. Overall, 143 of 151 patients (95%) on antiretroviral therapy had HIV RNA <50 copies/mL at baseline, which was similar between treatment groups.

Efficacy

Following 12 weeks of DCV + SOF treatment SVR12 rates were similarly high across all groups, regardless of concomitant antiretroviral therapy **(Figure 1, Table 2)**. SVR12 was achieved by 97.1% (95% CI: 90%-99.7%), 100% (95% CI: 91%-100%) and 94.9% (95% CI: 83%-99.4%) of patients receiving PI, NNRTI, and INSTI therapy, respectively. Within the PI group, SVR12 was achieved by all 31 (100%) patients receiving ATV/r, 28/30 (93.3%) receiving DRV/r and all 9 (100%) of those receiving LPV/r. Within the NNRTI group, SVR12 was achieved by all 26 patients (100%) receiving EFV, all 8 receiving NVP and all 6 receiving RPV. In the INSTI group, 30/32 (93.8%) of patients receiving RAL and 7/7 (100%) receiving DTG, achieved SVR12. In total, 117/120 (97.5%; [95% CI: 92.9%-99.5%]) of patients receiving TDF and all 23 patients (100%; [95% CI: 85.2%-100%]), receiving ABC (without TDF) achieved SVR12. Of the patients receiving a complex antiretroviral regimen containing three or more antiretroviral classes, 15/16 (93.8%) achieved SVR12.

When stratified by antiretroviral regimen, SVR12 rates were similar regardless of gender, age or race (**Figure 2a**); HCV treatment history or baseline HCV RNA levels (**Figure 2b**); or HCV genotype or *IL28B* genotype (**Figure 2c**). SVR12 was achieved by 21/23 (91.3%) and 126/128 (98.4%) of patients with and without cirrhosis, respectively (**Figure 2c**).

Resistance associated variants

Of the four patients who did not achieve SVR12 (**Table 2**), three had no DCV-resistance-associated variants at baseline. One of these three patients relapsed with an emergent Q30R mutation detected

at time of failure. The fourth patient had a detectable DCV polymorphism (Y93N mutation) both at baseline and at time of HCV relapse.

Safety

On-treatment safety is summarized in **Table 3**. A similar number of patients experienced ≥ 1 AE across groups (70.7–77.5%). Common AEs (experienced by ≥10% in any group) were fatigue, nausea, headache, diarrhea and rash. Similar proportions of patients reported these AEs across groups and were similar to those observed in DCV + SOF-treated HCV-monoinfected patients [17]. No patient discontinued treatment for AEs. Serious AEs (SAEs) during treatment included priapism in a patient receiving medication for erectile dysfunction, presyncope plus chest pain, drug abuse plus pulmonary embolism, and syncope plus hypertensive crisis. No SAE was considered related to study treatment. There was one death among patients in the 12-week treatment groups: a 53 year-old black male died of cardiomyopathy and multi-organ failure at Post-treatment Day 194. There was one additional death across the entire study: a 52 year-old white male in the 8-Week treatment group suffered cardiac arrest at post-treatment Day 40. Neither death was judged by the investigator to be related to study treatment.

Treatment-emergent increases in the international normalized ratio of ≥2.1 x upper limit of normal (ULN) were observed in 2/70 (2.9%) patients in the PI group: one patient had a history of aortic-valve replacement and was receiving anticoagulation therapy; and one patient had an isolated Grade 3 elevation at Week 6 that was within normal limits on repeat testing at Week 8. Treatment-emergent increases in total bilirubin of ≥2.6 x ULN were observed among patients receiving ATV/r only; eight patients (5.3%) presented with this laboratory abnormality. Overall, transient Grade 3–4 increases in lipase (≥3.1 x ULN) were observed in 4% of patients, but there were no reported cases

of clinical pancreatitis.

Renal safety

A low proportion of patients reported AEs relating to renal function in the PI (3/70 [4.3%]) and NNRTI (1/40 [2.5%]) groups; none were reported in the INSTI group (**Table 4**). Three patients receiving TDF had a change in baseline creatinine that was ≥0.4 mg/dL. There was minimal change in mean creatinine clearance (calculated using the Cockcroft–Gault formula) through Week 12 across all groups, regardless of NRTI backbone. Three patients altered their antiretroviral regimen during the treatment period due to progression of tenofovir-related safety concerns. Two patients with reported history of chronic renal insufficiency had an increase in their serum creatinine levels (serum creatinine= 1.44 mg/dL [Grade 1] and 1.47 mg/dL [Grade 1] at baseline to 1.85 mg/dL [Grade 2] at Week 6 and 1.56 mg/dL [Grade 1] at Week 2, respectively) and one patient with a history of osteoporosis had progressive bone loss on a DEXA scan.

HIV-1 suppression

Overall, 142/151 (94.0%) patients on antiretroviral therapy had HIV-1 RNA <50 copies/mL through end of treatment (**Table 5**). The proportions of patients maintaining <50 copies/mL were 64/70 (91.4%) of those on a PI regimen, 40/40 (100%) of those on a NNRTI regimen and 36/39 (92.3%) of those on an INSTI regimen. Of the nine patients who had ≥50 copies/mL at end of treatment, six had <50 copies/mL on repeat testing without a change in antiretroviral therapy, two patients had ≥50 copies/mL on repeat testing (one had 59 copies/mL and one had 66 copies/mL), and one was lost to follow up before repeat testing could be completed. HIV-1 virologic failure (confirmed or last available HIV-1 RNA ≥400 copies/mL) was observed in 2/151 (1.3%) of patients.

One patient receiving a PI-based regimen (DRV/r, RAL, ABC/3TC) had HIV-1 RNA 4442 copies/mL at the end of treatment (Week 12) visit. HIV virologic failure was confirmed at the next visit (post-therapy follow-up Week 4; HIV-1 RNA 1755 copies/mL). The patient's HIV RNA was re-suppressed to <40 copies/mL at the post-treatment Week 12 visit without adjusting the patient's antiretroviral regimen. This patient achieved SVR12. The second patient receiving TDF/FTC/RAL had an HIV RNA of 418 copies/mL at screening but <40 copies/mL at Day 1. The patient discontinued study medications early due to incarceration (lost to follow up) following the Week 6 visit (HIV-1 RNA was 629 copies/mL at this treatment visit). For both patients, HIV resistance testing did not demonstrate any evidence of resistance (data not shown). Mean CD4 cell counts were similar between groups across the 12-week treatment period (**Figure 3**).

Discussion

Twelve weeks of DCV+ SOF resulted in high SVR12 rates (97%), comparable with SVR rates observed in similar trials of other combinations of DAAs in HIV and HCV GT1-coinfected patients [15–17]. Participants were on a wide range of antiretrovirals and SVR rates were high across all antiretroviral classes, including complex antiretroviral regimens containing drugs from three or more antiretroviral classes. The efficacy of DCV + SOF was similarly high in patients receiving TDF versus those receiving ABC (without TDF), with SVR12 rates achieved by 98% and 100% of patients, respectively. Thus DCV + SOF represents an effective HCV treatment option that does not require modification for many of the common antiretroviral regimens, including four of five DHHS-recommended and five of the six EACS-recommended first-line regimens [4, 5]. Importantly, DCV + SOF treatment in HIV-HCV coinfected patients did not compromise HIV control. CD4 cell counts remained stable and HIV RNA remained suppressed for the majority of participants throughout the study.

No differences in efficacy were observed in patients when stratified by gender, age or race. HCV treatment history, baseline HCV RNA levels, cirrhosis, HCV genotype and *IL28B* genotype also had no effect on SVR12 rates. Patients with any of the six HCV genotypes were allowed to enroll into the study; however, due to the small number of HIV-HCV coinfected patients with HCV genotypes other than GT1, definitive data on response rates across all genotypes cannot be provided.

Based on previous pharmacokinetic data with ATV/r [11], the requirement to reduce the dose of DCV to 30 mg was extrapolated to other boosted PIs (i.e. DRV/r or LPV/r). However, more recent pharmacokinetic data suggest DRV/r and LPV/r have more limited effects on systemic DCV exposures (1.41- and 1.15-fold increases, respectively) compared to the effect observed during ATV/r coadministration (2.1-fold increase in DCV levels) [18, 19]. However, the dose adjustment to DCV 30 mg in this current study did not appear to have a clinically meaningful effect on efficacy, as SVR12 was achieved by 93% and 100% of patients receiving DRV/r and LPV/r, respectively.

The DCV + SOF regimen was generally well tolerated with no treatment discontinuations due to intolerance and no treatment related serious adverse events. Grade 3–4 hyperbilirubinemia, was only observed in patients receiving ATV/r and occurred at a rate consistent with the known safety profile of ATV [20]. While healthy volunteer studies have not identified any clinically significant interactions between DCV and TDF or between SOF and TDF [11, 21], evaluation of renal function in patients receiving TDF-based regimens and DCV + SOF is important due to the complex nature of the antiretroviral regimens of some of the patients in this study, and because of known interactions between TDF and other HCV DAAs [9]. Three patients taking TDF were required to modify HIV treatment due to TDF-induced complications that were not attributed to DCV + SOF coadministration.

The main strength of this study was that a broad range of antiretrovirals, including ritonavir-boosted PIs, NRTIs, NNRTIs, INSTIs, CCR5 antagonists, and fusion inhibitors, were permitted in the ALLY-2 study. In conclusion, this comprehensive evaluation of DCV + SOF when coadministered with a broad range of antiretrovirals demonstrates that this combination was highly efficacious and generally well tolerated.

Notes

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Figure Legends

Figure 1: SVR12 by antiretroviral therapy

[a] The 60 mg standard dose of DCV was adjusted to 30 mg with ritonavir-boosted (/r) PIs. Recent data suggest that a dose of DCV 60 mg should be coadministered with darunavir/r (DRV/r) or lopinavir/r (LPV/r) [19].

[b] Two patients had HCV relapse.

[c] One patient was lost to follow up at Week 6 due to incarceration; one non-adherent patient with detectable HCV RNA at end of treatment received ~1 week of treatment.

INSTI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor PI, protease inhibitor; SVR, sustained virologic response.

Figure 2a: SVR12 by patient demographics

Figure 2b: SVR12 by baseline disease characteristics

Figure 2c: SVR12 by HCV genotype at baseline

[a] Two patients were taking NRTIs only.

[b] GT 2, n=3; GT 3, n=4.

[c] GT 2, n=5; GT 3, n=4; GT 4, n=1

[d] GT 2, n=4; GT 3, n=1; GT 4, n=2.

[e] *IL28B* TT: 16/16.

[f] *IL28B* TT: 12/12.

[g] *IL28B* TT: 6/6.

INSTI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor PI, protease inhibitor; SVR, sustained virologic response.

Figure 3: CD4 cell counts during treatment

INSTI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor PI, protease inhibitor.

Table 1: Baseline demographic and disease characteristics

Parameter	**PI regimen[a]** **N=70**	**NNRTI regimen[a]** **N=40**	**INSTI regimen[a]** **N=39**	**Total** **N=151[b]**
Median age (range), years	54.0 (27, 71)	54.0 (24, 65)	49.7 (24, 64)	53.0 (24, 71)
Male, n (%)	63 (90.0)	38 (95.0)	31 (79.5)	134 (88.7)
Race, n (%)				
White	41 (58.6)	23 (57.5)	30 (76.9)	96 (63.6)
Black/African-American	26 (37.1)	14 (35.0)	9 (23.1)	49 (32.5)
Other	3 (4.3)	3 (7.5)	0	6 (4.0)
HCV disease characteristics				
HCV genotype, n (%)				
GT1a	45 (64.3)	28 (70.0)	30 (76.9)	104 (68.9)
GT1b	18 (25.7)	2 (5.0)	3 (7.7)	23 (15.2)
GT2	3 (4.3)	5 (12.5)	3 (7.7)	12 (7.9)
GT3	4 (5.7)	4 (10.0)	1 (2.6)	9 (6.0)
GT4	0	1 (2.5)	2 (5.1)	3 (2.0)

HCV RNA, median (range), log_{10} IU/mL	6.76 (3.9, 7.9)	6.36 (3.3, 7.6)	6.69 (4.1, 7.8)	6.71 (3.3, 7.9)
Cirrhosis, n (%)	11 (15.7)	6 (15.0)	6 (15.4)	23 (15.2)
HIV-1 disease characteristics				
HIV-1 RNA <50 copies/mL, n (%)[c]	63 (90.0)	39 (97.5)	39 (100.0)	143 (94.7)
Median CD4 cells/mm^3 (range)	523.0 (122, 1115)	605.5 (143, 1087)	571.0 (212, 1318)	557.0 (122, 1318)
HIV-1 treatment, n (%)				
PI regimen				
Atazanavir/r	31 (44.3)	0	0	31 (20.5)
Darunavir/r	30 (42.9)	0	0	30 (19.9)
Lopinavir/r	9 (12.9)	0	0	9 (6.0)
NNRTI regimen				
Efavirenz	0	26 (65.0)	0	26 (17.2)
Nevirapine	0	8 (20.0)	0	8 (5.3)
Rilpivirine	0	6 (15.0)	0	6 (4.0)

INSTI regimen				
Raltegravir	0	0	32 (82.1)	32 (21.2)
Dolutegravir	0	0	7 (17.9)	7 (4.6)

[a] Patients listed as PI regimen if receiving any boosted PI; listed as NNRTI regimen if receiving an NNRTI but not a PI/r; listed as INSTI regimen if receiving an INSTI but not a PI/r or NNRTI. Patients could have received ARVs from multiple classes, except for the combination of PI+EFV or PI+NVP.

[b] Two patients were taking NRTIs only.

[c] Patients on ARV therapy with available baseline HIV-1 RNA data.

GT, genotype; INSTI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; /r, ritonavir-boosted.

Table 2: SVR12 according to HIV-1 antiretroviral regimen

Antiretroviral regimen	**Proportion of patients achieving SVR12 n/N (%)**
PI regimen	
Atazanavir/r	31/31 (100)
Darunavir/ r	28/30 (93)[a]
Lopinavir/ r	9/9 (100)
NNRTI regimen	
Efavirenz	26/26 (100)
Nevirapine	8/8 (100)
Rilpivirine	6/6 (100)
INSTI	
Raltegravir	30/32 (94)[b]
Dolutegravir	7/7 (100)

Nucleoside reverse transcriptase inhibitor	
Tenofovir disoproxil fumarate	117/120 (97.5)
Abacavir (without tenofovir disoproxil fumarate)	23/23 (100)
Complex antiretroviral regimen (≥ 3 classes)	15/16 (93.8)[c]

[a,c] Two patients who did not achieve SVR12 had a detectable NS5A-related variant at baseline and/or failure. One patient, a white male with GT1a, who was HCV treatment-naïve and cirrhotic, and had a baseline HCV viral load ≥10x10^6 IU/mL experienced HCV relapse with Y93N at baseline and at the time of failure. This patient was receiving a complex HIV regimen that included a boosted-PI along with 3 NRTIs (darunavir/ritonavir, zidovudine, tenofovir, and emtricitabine). The second patient was a black male with GT1a HCV, who was HCV-treatment-experienced with cirrhosis and baseline viral load ≥10 x 10^6 IU/mL. This patient, who also experienced HCV relapse, had no NS5A polymorphism at baseline but relapsed with an emergent Q30R mutation detected at time of failure.

[b] Two patients did not achieve SVR12. Neither patient had any NS5A-related polymorphisms (at M28, Q30, L31 or Y93). One treatment-naïve patient with GT1a, without cirrhosis and with baseline viral load of ~1x10^6 IU/mL on INSTI-based combined antiretroviral therapy (raltegravir plus zidovudine and lamivudine) had on-treatment failure (HCV RNA <LLOQ; TD at end of treatment) after early discontinuation due to non-compliance. One GT1a treatment-naïve patient without cirrhosis and with baseline viral load ~1x10^6 IU/mL on INSTI-based combined antiretroviral therapy (raltegravir plus tenofovir and emtricitabine) was lost to follow up after having undetectable HCV RNA at end of treatment.

Table 3: Summary of adverse events during treatment

Event, n (%)	PI regimen N=70	NNRTI regimen N=40	INSTI regimen N=39	Total N=151[a]
Patients with at least one AE	50 (71.4)	31 (77.5)	29 (70.7)	110 (72.8)
Serious AEs[b]	3 (4.3)	0	1 (2.6)	4 (2.6)
Death	0	0	0	0
AEs leading to discontinuation	0	0	0	0
Common AEs on treatment (≥ 10% in any treatment group)				
Fatigue	12 (17.1)	7 (17.5)	9 (23.1)	28 (18.5)
Nausea	8 (11.4)	4 (10.0)	9 (23.1)	21(13.9)
Headache	13 (18.6)	2 (5.0)	5 (12.8)	20 (13.2)
Diarrhea	9 (12.9)	3 (7.5)	2 (5.1)	14 (9.3)
Rash	3 (4.3)	1 (2.5)	5 (12.8)	9 (6.0)
Treatment-emergent Grade 3-4 laboratory abnormalities[c]				

INR ≥2.1 × ULN[d]	2 (2.9)	0	0	2 (1.3)
Total bilirubin ≥2.6 × ULN[e]	8 (11.4)	0	0	8 (5.3)
Lipase ≥3.1 × ULN[f]	2 (2.9)	3 (7.5)	1 (2.6)	6 (4.0)

[a] Two patients were taking NRTIs only.

[b] Serious AEs: PI regimen: priapism, drug abuse/pulmonary embolism and hypertensive crisis/syncope; INSTI regimen: chest pain/presyncope. Some patients presented with multiple SAEs; none were related to treatment.

[c] No Grade 3–4 ALT or AST elevations were detected.

[d] One patient had a history of aortic-valve replacement and was receiving anticoagulation therapy and one patient had an isolated Grade 3 elevation at Week 6 that was within normal limits on repeat testing at Week 8.

[e] Each event was an indirect hyperbilirubinemia in patients receiving concomitant ritonavir-boosted atazanavir.

[f] Transient hyperlipasemia without reported pancreatitis.

AE, adverse event; INR, international normalized ratio; INSTI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; ULN, upper limit of normal.

Table 4: Summary of renal safety during treatment

Event, n (%)	PI regimen N=70	NNRTI regimen N=40	Other N=41	Total N=151
Grade 1–4 renal urinary disorders	3 (4.3)	1 (2.5)	0	4 (2.6)
Hematuria	1 1.4)	1 (2.5)	0	2 (1.3)
Dysuria	1 (1.4)	0	0	1 (0.7)
Nocturia	1 (1.4)	0	0	1 (0.7)
Grade 3–4 creatinine	0	0	0	0
Mean creatinine clearance (mL/min) with Cockcroft–Gault formula at Week 12.	89.8[a]	85.7[b]	99.6[c]	91.4[d]
Change from baseline	–4.8	–3.0	–1.2	–3.3

[a] n=69; [b] n=38; [c] n=39; [d] n=146.

NNRTI, non-nucleoside reverse transcriptase inhibitor PI, protease inhibitor.

Table 5: Proportion of patients on antiretroviral therapy with HIV-1 RNA <50 copies/mL at baseline and end of treatment

Event, n (%)	PI regimen N=70	NNRTI regimen N=40	INSTI N=39	Total N=151[a]
HIV-1 RNA <50 copies/mL, n (%) at baseline	63 (90.0)	39 (97.5)	39 (100.0)	143 (94.7)
HIV-1 RNA <50 copies/mL, n (%) at end of treatment	64 (91.4)	40 (100)	36 (92.3)	142 (94.0)

[a] Two patients were taking NRTIs only.

INSTI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor PI, protease inhibitor.