Title

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Effectiveness of All-Oral Antiviral Regimens in 996 Genotype 1 HIV/HCV Coinfected Patients treated in Routine Practice

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Short Running Title: Efficacy of DAAs in an HIV/HCV Cohort

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Summary: SVR rates for HIV/HCV coinfected individuals were similarly high among African-

Americans and non-African Americans, even with efavirenz-based therapy. Renal function did

not worsen on LDV/SOF regimens with tenofovir. PPI use did not impact SVR. **In ITT analysis,**

cirrhosis predicted treatment failure..

Abstract

Background: Large cohorts are needed to assess HIV/HCV real-world treatment outcomes. We examined the effectiveness of ledipasvir/sofosbuvir±ribavirin (LDV/SOF±RBV) and ombitasvir/paritaprevir/ritonavir+dasabuvir (OPrD)±RBV in HIV/HCV genotype 1 (GT 1) patients initiating HCV therapy in clinical practice.

Methods: Observational intent-to-treat cohort analysis using Veterans Affairs' Clinical Case Registry to identify HIV/HCV GT1 veterans initiating 12 weeks of LDV/SOF±RBV or OPrD±RBV. Multivariate models of **sustained virologic response** (SVR) included age, race, cirrhosis, CD4 count, HCV viral load, proton pump inhibitor (PPI) prescription, prior HCV treatment, body mass index, genotype subtype, and HCV treatment regimen.

Results: 996 GT1 HIV/HCV veterans initiated therapy; 757 LDV/SOF, 138 LDV/SOF+RBV, 28 OPrD, and 73 OPrD+RBV. Overall SVR was 90.9% (823/905); LDV/SOF 92.1% (631/685), LDV/SOF+RBV 86.3% (113/131), OPrD 88.9% (24/27), OPrD+RBV 88.7% (55/62). SVR was 85.9% (176/205) and 92.4% (647/700) in those with and without cirrhosis (p=0.006). SVR was similar between African Americans (90.5% [546/603]) and all others (91.7% [277/302]). PPI use with LDV/SOF±RBV did not affect SVR (89.7% [131/146] with and 91.5% [613/670] without PPI). Cirrhosis was predictive of reduced SVR (OR 0.50, 95% CI 0.30-0.85, p=0.008). Median creatinine change did not differ among patients receiving LDV/SOF and tenofovir (TDF) without a protease inhibitor (PI) (0.18 (IQR 0.22) n=372), LDV/SOF and TDF/PI (0.17 (IQR 0.26) n=100) and LDV/SOF without TDF (0.15 (IQR 0.30) n=423).

Conclusions: SVR rates in genotype 1 HIV/HCV patients were high. African American race or PPI use with LDV/SOF±RBV was not associated with lower SVR rates but cirrhosis was. Renal function did not worsen on LDV/SOF regimens with TDF.

Introduction

HCV coinfection is common in HIV-infected individuals, affecting 15-30% of those with HIV in the US and Europe [1]. As compared with monoinfected patients, HIV/HCV coinfected individuals have higher rates of cirrhosis, hepatocellular carcinoma, and mortality [2, 3] and, in the interferon era, had lower overall sustained virologic response (SVR) rates [4]. With the advent of direct acting antiviral (DAA) therapy, SVR rates have been relatively equivalent in clinical trials of HCV mono- and HIV/HCV co-infection [5-7]. There is, however, limited data in larger real-world cohorts of HIV/HCV co-infected individuals where populations are likely to be enriched for African American race and cirrhosis, both factors previously associated with decreased SVR rates [8-10].

In the DAA era, African American race has been associated with lower SVR rates including those receiving 8 week LDV/SOF regimens [11-12] and in one 12-week clinical trial of HIV/HCV coinfection, both in genotype 1 (GT1) infections [5]. In ION-4, a study of LDV/SOF in HIV/HCV coinfection, the overall SVR rate was 96% but was only 90% in African-Americans, reflecting all 10 relapses in the study, eight of whom received efavirenz-containing regimens [5]. This finding from exploratory subgroup analyses has raised questions about the co-administration of LDV/SOF and efavirenz in African Americans.

Real-world data on the impact of proton pump inhibitor (PPI) use and changes in renal function in HIV/HCV coinfected individuals receiving ledipasvir/sofosbuvir (LDV/SOF) is limited. LDV concentrations are decreased in the setting of PPI use [13]. Observational cohorts of predominantly HCV-monoinfected patients have been inconsistent, demonstrating decreased

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SVR rates with PPI use in some cohorts but not others [14, 15]. Presently, the extent of clinically meaningful changes in renal function in HIV/HCV coinfected patients receiving tenofovir and protease inhibitors is unknown. LDV increases the plasma Cmax of tenofovir by 47-64% when coadministered with ritonavir-boosted atazanavir or darunavir [13, 16]. The ION-4 study of LDV/SOF in HIV/HCV coinfection excluded participants on protease inhibitor-containing therapy [5], thus real-world use of tenofovir and protease inhibitor-containing regimens is needed to inform complicated treatment decisions.

Our objectives were to characterize SVR rates in HIV/HCV coinfected veterans receiving LDV/SOF- and OPrD-based regimens, to identify predictors of SVR, and to characterize changes in renal function particularly in those receiving LDV/SOF-containing regimens in a real-world cohort of HIV/HCV coinfected veterans.

MATERIALS AND METHODS

This was an observational intent-to-treat cohort analysis of genotype 1 HIV/HCV coinfected veterans receiving LDV/SOF±RBV or OPrD±RBV from any **Veterans' Affairs (VA)** facility. This study used data from the VA's Clinical Case Registry for HCV, an extract of the VA electronic medical record for HCV-infected veterans seen at all VA medical facilities [17].

Eligible subjects included all genotype 1 HIV/HCV-infected veterans from any VA facility nationwide who initiated VA-prescribed LDV/SOF±RBV or OPrD±RBV by 30 September 2015 with an end of treatment (EOT) by 15 January 2016 and a days' supply of greater than 1 week and less than or equal to 91 days. For patients who received multiple courses of therapy, only the

first course was included. Regimen selection and timing of follow-up visits and laboratory testing was at the discretion of the provider as patients were treated in routine practice. Patients were excluded if they had a baseline HCV RNA $\leq$ 1000 IU/ml (n=32), had a liver transplant (n=1), or received OPrD alone and had subtype 1a (n=3).

Treatment Outcome

Patients were considered to have SVR if they had HCV RNA results below the limit of quantification on all HCV RNA tests after the EOT including at least one test 10 weeks or more after the EOT; a 10-week time point was used to account for the realities of variability in timing of laboratory testing in clinical practice. Patients were categorized as no SVR if they had HCV RNA above the limit of quantification after the EOT and no subsequent test $\geq$10 weeks after EOT, had no HCV RNA testing after the EOT and HCV RNA above the limit of quantification on their last HCV RNA test while on treatment, or died on treatment or within 10 weeks of the EOT. Patients with HCV RNA below the limit of quantification on their last HCV viral load test while on treatment or after the EOT, but no test 10 weeks of more after the EOT were excluded from the SVR analysis. The EOT was calculated as the last day covered by prescriptions of LDV/SOF or OPrD using the dates the medication was dispensed and the days' supply. HCV RNA was categorized as above or below the lower limit of quantification of which 98% of sites utilized assays with a lower limit of quantification of 15 IU/mL or less. Patients were followed from the initiation of LDV/SOF±RBV or OPrD±RBV through 30 April 2016. Patients were considered to have completed 12 weeks of LDV/SOF±RBV or OPrD±RBV if they received between 77-91 days of medication.

Control Variables

Demographic and other baseline variables were determined at the time of treatment initiation and included age, sex, race, cirrhosis (defined by ICD-9 codes), history of decompensated liver disease (defined by ICD-9 codes for esophageal variceal hemorrhage, hepatic coma, hepatorenal syndrome or spontaneous bacterial peritonitis), PPI prescription, and prior HCV antiviral treatment experience. Prior virologic response was based on the most recent VA course of HCV antiviral treatment. Because HIV antiretroviral prescriptions are generally filled for 90 days in VA, the HIV antiretroviral regimen for a patient was identified as including any antiretrovirals filled in both the 89 days before and the 89 days after start of HCV treatment or any antiretrovirals filled on the date of starting HCV treatment. Patients with no antiretrovirals meeting these criteria are categorized as "Unstable/None" for HIV antiretroviral regimen.

Baseline values for height and weight were used to calculate body mass index (BMI) and the baseline laboratory tests for alanine aminotransferase, aspartate aminotransferase, creatinine, platelets, HCV RNA, HIV viral load and CD4 count were defined as the value within 1 year before and closest to the HCV treatment start date. IL28B polymorphism and HCV genotype 1 subtype was determined from the most recent result. Subtype 1a included patients with reported results of 1a, mixed 1a/1b or 1 with subtype unspecified. Maximum creatinine change was calculated as the maximum absolute change in creatinine from the baseline creatinine until 7 days after the EOT.

Statistical Analysis

Univariate comparisons used the Pearson Chi-square test with Yates' continuity correction for categorical variables. The Kruskal-Wallis H-Test was used for comparing median maximum

creatinine changes. Multivariate logistic regression models were constructed to model SVR. Models included variables selected *a priori* of age, race, **CD4,** cirrhosis, PPI, treatment experience, BMI, genotype 1 subtype, **HCV viral load**, and HCV treatment. **For the models, race/ethnicity was divided into two categories, African-American race and non- African- American race.** A set of models with the above variables was constructed with all patients and with only patients who completed 12 weeks of treatment. An additional model included a variable for PI-based, NNRTI-based and INSTI-based antiretroviral regimens.

For all comparisons, a p value <0.05 was considered statistically significant. All analyses were performed using R version 3.1 (R Foundation for Statistical Computing, Vienna, Austria).

The protocol was approved by the Stanford University Institutional Review Board and the VA Palo Alto Health Care System Research and Development Committee.

RESULTS

In total, 996 patients with HIV/HCV genotype 1 infection initiated LDV/SOF±RBV or OPrD±RBV treatment at 126 VA facilities. Baseline characteristics for the cohort by regimen appear in Table 1. As this was a real-world cohort with no restrictions on antiretroviral regimen, a wide variety of antiretroviral regimens were identified, particularly among patients receiving LDV/SOF±RBV. The majority of patients (76%, n=757) received LDV/SOF. Patients receiving the LDV/SOF+RBV regimen (14%, n=138) were more likely to have cirrhosis and be treatment-experienced. Most patients receiving OPrD±RBV received integrase strand transfer inhibitor-based regimens. Fewer African Americans received regimens which included RBV.

Treatment discontinuations before 12 weeks occurred in 16% (124/757), 9% (12/138), 14% (4/28) and 11% (8/73) receiving LDV/SOF, LDV/SOF+RBV, OPrD, and OPRD+RBV regimens, respectively. Treatment discontinuations of LDV/SOF regimens included patients who received 8 weeks of therapy. VA guidance recommends 12 weeks of LDV/SOF for HIV/HCV coinfected patients, however, some providers chose to use 8 weeks of LDV/SOF given the FDA labeling consideration for this regimen. Among patients who received LDV/SOF, 4.2% (n=32/757) discontinued treatment before 8 weeks, 10.6% (80/757) received 8 weeks, and 1.6% (12/757) discontinued between 8 and 12 weeks. **For the people who did not complete a 12-week course of treatment, where we could assign an outcome, 72.7% (101/139) nevertheless had a SVR, 20.1% (28/139) had confirmed treatment failure with a detectable HCV RNA after the end of treatment, and 7.2% (10/139) did not have testing after the EOT and were categorized as not having a SVR since their last documented HCV RNA – while on treatment – was still detectable.**

SVR results were available for 90.9% (n=905/996) of patients in the cohort, including 5 patients who died while on treatment or shortly after who were categorized as no SVR. There were 91 patients whose last HCV RNA was undetectable, but occurred while still on treatment (n=30) or less than 10 weeks after the EOT (n=61), who were excluded from the SVR analysis. Fifty patients had an undetectable HCV RNA obtained 10 to 11 weeks after the EOT and were included in the SVR analysis

Overall, among 905 genotype 1 HIV/HCV coinfected patients 90.9% (823/905) achieved SVR (Table 2). Among 685 LDV/SOF patients and 131 LDV/SOF+RBV patients, 92.1% (631/685) and 86.3% (113/131) achieved SVR, respectively; SVR rates for OPrD were 88.9% (24/27) and for OPrD+RBV, 88.7% (55/62). In the overall cohort and for patients who received LDV/SOF, SVR rates differed statistically based on the presence of cirrhosis. No statistically significant differences in SVR were observed according to baseline patient characteristics among patients receiving LDV/SOF+RBV, OPrD or OPrD+RBV, though there were few patients in the OPrD±RBV subgroups to detect differences.

Rates of response were similar in patients receiving various HIV antiretroviral regimens. No difference in SVR was observed in African Americans receiving LDF/SOF±RBV with antiretroviral regimens containing efavirenz (92.5%, 124/134) compared to antiretroviral regimens without efavirenz (91.0%, 376/413, p=0.72) and these responses were similar in non-African Americans (89.3%, 50/56 with efavirenz-containing regimens; 91.1%, 194/213 without efavirenz-containing regimens, p=0.88). Among the potentially harder to treat subgroup of African Americans with cirrhosis receiving LDV/SOF±RBV, SVR rates did not differ between those with antiretroviral regimens containing efavirenz (88.0%, 22/25) and antiretroviral regimens without efavirenz (85.9%, 73/85, p=1.00). Similarly, no difference in SVR rates was observed in treatment-experienced African Americans, with or without cirrhosis, who did or did not receive efavirenz-containing regimens.

For patients who completed a 12 week course of LDV/SOF±RBV or OPrD±RBV, SVR rates were consistently higher when compared to the intention-to-treat SVR rates (Table 3). An SVR

of 95.3% (542/569) was achieved in patients completing 12 weeks of LDV/SOF, 90.8% (108/119) with LDV/SOF+RBV, 95.7% (22/23) with OPrD, and 90.9% (50/55) with OPrD+RBV.   No differences in SVR were observed overall in patients who received LDV/SOF for 8 weeks (94.6%, 70/74) and those who received LDV/SOF for 12 weeks (95.3% 542/569, p=0.96) including patients who met the criteria for shortened course and received LDV/SOF for 8 weeks (98.1%, 51/52) compared to those patients who met the criteria for shortened course and received LDV/SOF for 12 weeks (95.7%, 310/324).

In multivariate analysis, the only significant independent predictor of SVR **in the ITT group** was cirrhosis **(OR 0.51, 95% CI 0.31-0.87, p=0.01)** (Table 4). **The use of LDV/SOF+ RBV was associated with a statistically significant increased risk of non-SVR in those who completed 12 weeks of therapy (0.42 (0.18-0.97) p 0.03, and there was a similar non-significant trend in both ITT groups. Similarly, there was a borderline statistically significant finding of HCV RNA > 6 million IU/ml associated with non-SVR in the ITT group including major antiretroviral regimens and similar non-significant trends in the other groups.**   Age, race, **CD4,** PPI, treatment experience, BMI, genotype 1 subtype, and HCV treatment regimen did not predict SVR. In models limited to patients receiving 12 weeks of treatment, cirrhosis no longer predicted SVR (OR 0.62, 95% CI 0.31-1.27, p=0.17). In additional sensitivity analysis, use of HIV PI-based or non-nucleotide reverse transcriptase inhibitor (NNRTI)-based antiretroviral regimens compared to use of integrase strand transfer inhibitor (INSTI)-based regimens was not associated with a difference in the odds of achieving SVR.

Median baseline creatinine values did not differ among the four regimens (Table 1). Median

maximum creatinine change also did not differ among the four regimens (LDV/SOF 0.16 mg/dL,

IQR 0.25, range -3.85 – 12.25; LDV/SOF+RBV 0.13 mg/dL, IQR 0.23, range -0.84 – 1.70;

OPrD 0.11 mg/dL, IQR 0.28, range -0.20 – 1.10; OPrD+RBV 0.13 mg/dL, IQR 0.26, range

-0.71-15.20)(p=0.30). In patients receiving LDF/SOF±RBV, concomitant use of tenofovir-

containing regimens with or without a HIV PI did not result in clinically meaningful changes in

median creatinine over the course of HCV treatment. Median baseline creatinine values were

minimally higher in patients not receiving tenofovir-containing antiretroviral regimens (1.10

mg/dL, IQR 0.40, range 0.34-5.34, n=423) compared to those who were receiving tenofovir-

containing regimens with a HIV PI (1.00 mg/dL, IQR 0.26, range 0.58-2.23, n=100) or without a

HIV PI (0.99 mg/dL, IQR 0.28, range 0.50 – 1.70, n=372). The median maximum creatinine

changes for patients in all three groups were generally very small and did not differ (p=0.30).

Median maximum creatinine changes were 0.17 mg/dL (IQR 0.26, range -0.58 - 1.21), 0.18

mg/dL (IQR 0.22, range, -0.3 - 1.7), and 0.15 (IQR 0.30, range -3.85 - 12.25) for patients

receiving tenofovir-containing regimens with an HIV PI, tenofovir- containing regimens without

an HIV PI, and non-tenofovir containing regimens, respectively. (Figure 1).

DISCUSSION

In this large real-world cohort of HIV/HCV coinfected veterans, SVR rates were 92.1% for

LDV/SOF, 86.3% for LDV/SOF+RBV, 88.9% for OPrD and 88.7% for OPrD+RBV. Limited to

those who completed 12 weeks of treatment, SVR rates were even higher. SVR rates for

HIV/HCV coinfected African-Americans, who represented 67% of this cohort, did not differ

from non-African Americans. Of note, SVR rates in African-Americans who received efavirenz-

based therapy and LDV/SOF did not differ from SVR rates in non-African Americans on efavirenz-based therapy and LDV/SOF. The only predictor of treatment failure in multivariate analysis was cirrhosis. PPI prescriptions were not associated with reduced SVR in this HIV/HCV coinfection cohort.

In the interferon-era, African-American race was associated with decreased SVR rates [18], in part because of a high prevalence of the IL28B CT/TT genotypes that conferred reduced interferon susceptibility in persons of African descent [19]. More recently, in an integrated analysis of all phase III LDV/SOF studies, African American race was associated with decreased SVR rates in those receiving 8-week regimens of LDV/SOF [11]. A VA real-world cohort that included HCV monoinfected and HIV/HCV coinfected patients showed similar results in African Americans [12]. In a HIV/HCV co-infection clinical trial, Naggie and colleagues found that, when compared to non-black patients, black patients had lower SVR12 rates, 90% vs 99% $p<0.001$, respectively, and higher relapse rates [5]. Eight of the 10 black patients failing treatment received efavirenz. LDV plasma levels, however, were equivalent in those receiving efavirenz versus other antiretroviral containing regimens and in those with or without SVR. In our larger cohort of HIV/HCV coinfected African American veterans, there was no impact of African American race on SVR rates in patients receiving LDV/SOF. Furthermore, we found equivalent SVR rates in African Americans on efavirenz- and non-efavirenz-based therapy (92.5% and 91.0%), respectively.

In those who received LDV/SOF, there was no difference in creatinine change among those receiving tenofovir and non-tenofovir-containing regimens, including those also receiving PIs.

This is the first study to report renal outcomes of HIV/HCV coinfected patients and reassures providers that in patients with normal renal function, tenofovir/PI-containing regimens can be used with LDV/SOF. This may have positive implications for velpatasvir which also increases tenofovir concentrations.

Limitations to our study included the predominantly male population thus limiting generalizability to women. Few patients received OPrD, likely a result of drug-drug interaction concerns, thus interpretations are limited in this group. In addition, there may be other unidentified cofounders not included in the multivariate models. The finding of reduced odds of SVR with LDV/SOF+RBV compared to LDV/SOF suggests that providers appropriately identified patients as less likely to respond and opted for a more intensive regimen with ribavirin. As such, the reduced odds of SVR with LDV/SOF+RBV likely does not reflect an intrinsic increased risk of treatment failure with LDV/SOF+RBV but rather that receipt of this regimen identifies patients less likely to respond even controlling for the other factors included in the models which included the diagnosis of cirrhosis. Inherent to large administrative health record analyses, we were unable to assess prescriber intent for duration of therapy and reasons for discontinuation. We did not assess 24 week regimens, although they are used rarely in VA. We could not assess the impact of IL28B status or baseline resistance associated variants as these were performed on very few patients during this time. **Finally, we could not assess the impact of HIV viral load on HCV treatment response as the majority were HIV virologically suppressed.**

In conclusion, SVR rates were comparable to those of clinical trials in this large real-world cohort of HCV treatment-naïve and treatment-experienced HIV/HCV coinfected veterans receiving 12 weeks of LDV/SOF or OPrD-based regimens. African Americans had SVR rates comparable to non-African Americans, including in those receiving efavirenz-based regimens. In multivariate analysis, only cirrhosis was associated with reduced odds of SVR. There was no clinically meaningful difference in creatinine change in those receiving tenofovir versus non-tenofovir-containing antiretroviral regimens, including in those receiving tenofovir/PI-containing regimens. Data from this cohort provide further evidence of the efficacy of DAA-based therapy in HIV/HCV coinfection, particularly in African Americans, and reassurance on the use of tenofovir containing regimens when co-administered with LDV/SOF.

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Table 1. Baseline Characteristics and 4 Week On-Treatment Response of Genotype 1 HIV/HCV Coinfected Patients Receiving LDV/SOF- or OPrD-Based Regimens with Durations of 12 Weeks or Less

	GT1 N=996, (%)	LDV/SOF N=757 (%)	LDV/SOF+RBV N=138 (%)	OPrD N=28 (%)	OPrD+RBV N=73 (%)
Age (years) < 55 55-64 ≥ 65	60.8±6.3 (27.7-81.0) 140 (14.1) 598 (60.0) 258 (25.9)	60.6±6.5 (27.7-81.0) 112 (14.8) 458 (60.5) 187 (24.7)	61.7±5.1 (46.8-76.0) 12 (8.7) 87 (63.0) 39 (28.3)	61.4±6.1 (41.1-69.7) 4 (14.3) 15 (53.6) 9 (32.1)	61.4±6.8 (36.4-77.8) 12 (16.4) 38 (52.1) 23 (31.5)
Male	981 (98.5)	745 (98.4)	135 (97.8)	28 (100.0)	73 (100.0)
African American	667 (67.0)	530 (70.0)	77 (55.8)	21 (75.0)	39 (53.4)
Cirrhosis	225 (22.6)	143 (18.9)	63 (45.7)	3 (10.7)	16 (21.9)
Decompensated liver disease	16 (1.6)	10 (1.3)	5 (3.6)	1 (3.6)	0 (0.0)
PPI	178 (17.9)	129 (17.0)	27 (19.6)	8 (28.6)	14 (19.2)
Treatment Experienced DAA experienced* *-simeprevir/sofosbuvir* *-sofosbuvir* *-boceprevir* *-telaprevir*	160 (16.1) 27/160 (16.9) 5 8 8 8	87 (11.5) 8/87 (9.2) - 2 3 3	62 (44.9) 17/62 (27.4) 5 5 4 5	3 (10.7) 0/3 (0.0) - - - -	8 (11.0) 2/8 (25.0) - 1 1 -

Prior Treatment Response
  Relapse
  Partial
  Null
  Unknown
	N=160
	22 (13.8)
	13 (8.1)
	37 (23.1)
	88 (55.0)
		N=87
		8/87 (9.2)
		7/87 (8.0)
		17/87 (19.5)
		55/87 (63.2)
			N=62
			14/62 (22.6)
			6/62 (9.7)
			19/62 (30.6)
			23/62 (37.1)
				N=3
				0/3 (0.0)
				2/3 (66.7)
				1/3 (33.3)
				0/3 (0.0)
					N=8
					0/8 (0.0)
					0/8 (0.0)
					8/8 (100.0)
					0/8 (0.0)

BMI (kg/m^2) <25 25-29 ≥30	26.1±4.7 (15.8-48.6) 447 (44.9) 369 (37.0) 180 (18.1)	26.0±4.7 (16.1-48.6) 347 (45.8) 275 (36.3) 135 (17.8)	27.1±5.1 (18.6-44.4) 58 (42.0) 47 (34.1) 33 (23.9)	24.6±3.8 (15.8-31.7) 13 (46.4) 14 (50.0) 1 (3.6)	26.2±4.4 (17.2-38.8) 29 (39.7) 33 (45.2) 11 (15.1)
ALT (U/L)	59.5±41.7 (8-478)	58.9±41.2 (8-478)	63.3±42 (11-266)	63.9±50.7 (17-224)	57±42.8 (13-222)
AST (U/L)	58.5±37.3 (16-345)	57.6±35.9 (16-345)	63.9±42.7 (17-270)	57.2±35 (17-163)	57.4±41.3 (21-242)
Median Creatinine (mg/dL)	1.01 (0.30)(0.34-8.83)	1.01 (0.30)(0.34-5.34)	1.00 (0.30)(0.58-2.43)	1.11 (0.40)(0.74-1.76)	1.03 (0.34)(0.55-8.83)
Platelets (K/µL)	186.8±67.9 (27-782)	187.4±62.9 (27-564)	178.9±89.9 (27-782)	189.1±57 (95-317)	195.3±72.6 (85-523)

FIB-4
  ≤3.25
  >3.25
	3.0±2.7 (0.5-28.7)
	726 (72.9)
	270 (27.1)
		3.0±2.5 (0.5-28.1)
		567 (74.9)
		190 (25.1)
			3.7±3.8 (0.8-28.7)
			90 (65.2)
			48 (34.8)
				2.6±1.2 (0.9-5.2)
				19 (67.9)
				9 (32.1)
					2.9±2.1 (0.8-13.7)
					50 (68.5)
					23 (31.5)

HCV RNA (log IU/mL) <6,000,000 IU/mL ≥6,000,000 IU/mL	6.3±0.6 (4.0-8.1) 800 (80.3) 196 (19.7)	6.2±0.6 (4.0-7.8) 615 (81.2) 142 (18.8)	6.3±0.6 (4.3-8.1) 112 (81.2) 26 (18.8)	6.3±0.7 (4.2-7.3) 21 (75.0) 7 (25.0)	6.4±0.7 (4.2-7.6) 52 (71.2) 21 (28.8)
Subtype 1b	260 (26.1)	189 (25.0)	33 (23.9)	28 (100.0)	10 (13.7)

Continuous variables reported as mean±standard deviation (range) except for creatinine and CD4 count which are reported as median (IQR)(range). Categorical variables reported as % (n).

*Some patients received more than one prior DAA regimen and are included in the count for each regimen they received.

Abbreviations: ALT, alanine aminotransferase; ARV, antiretroviral; AST, aspartate aminotransferase; BMI, body mass index; DAA, direct-acting antiviral; INSTI integrase strand transfer inhibitor; LDV/SOF, ledipasvir/sofosbuvir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; OPrD, ombitasvir/paritaprevir/ritonavir+dasabuvir; PI, protease inhibitor; PPI, proton pump inhibitor; RBV, ribavirin.

Table 2. SVR Rates by Regimen for Genotype 1 HIV/HCV coinfected Patients Receiving Ledipasvir/Sofosbuvir- or OPrD-Based Regimens with Durations of 12 Weeks or Less

	GT1 N=905, %	P	LDV/SOF N=685, %	P	LDV/SOF+RBV N=131, %	P	OPrD N=27, %	P	OPrD+RBV N=62, %	P
Overall SVR	90.9 (823/905)		92.1 (631/685)		86.3 (113/131)		88.9 (24/27)		88.7 (55/62)	
Age (years)		0.76		0.67		#		#		#
< 55	91.3 (116/127)		93.0 (93/100)		83.3 (10/12)		75.0 (3/4)		90.9 (10/11)	
55-64	91.4 (497/544)		92.5 (385/416)		87.7 (71/81)		85.7 (12/14)		87.9 (29/33)	
≥ 65	89.7 (210/234)		90.5 (153/169)		84.2 (32/38)		100.0 (9/9)		88.9 (16/18)	
Sex		#		#		#				
Male	90.8 (808/890)		92.0 (619/673)		85.9 (110/128)		88.9 (24/27)		88.7 (55/62)	
Female	100.0 (15/15)		100.0 (12/12)		100.0 (3/3)		---		---	
Race		0.65		1.00		0.90		#		#
African American	90.5 (546/603)		92.0 (438/476)		87.3 (62/71)		85.0 (17/20)		80.6 (29/36)	
Non-African American	91.7 (277/302)		92.3 (193/209)		85.0 (51/60)		100.0 (7/7)		100.0 (26/26)	
Cirrhosis		0.006		0.05		0.62		#		#
No	92.4 (647/700)		93.2 (518/556)		88.4 (61/69)		87.5 (21/24)		92.2 (47/51)	
Yes	85.9 (176/205)		87.6 (113/129)		83.9 (52/62)		100.0 (3/3)		72.7 (8/11)	
Liver decompensation		#		#		#		#		#
No	90.9 (809/890)		92.2 (623/676)		85.7 (108/126)		88.5 (23/26)		88.7 (55/62)	
Yes	93.3 (14/15)		88.9 (8/9)		100.0 (5/5)		100.0 (1/1)		---	
PPI		0.64		0.70		#		#		#
No	91.2 (675/740)		92.4 (522/565)		86.7 (91/105)		84.2 (16/19)		90.2 (46/51)	
Yes	89.7 (148/165)		90.8 (109/120)		84.6 (22/26)		100.0 (8/8)		81.8 (9/11)	
Treatment Experienced		1.00		0.23		1.00		#		#
No	91.0 (687/755)		91.6 (555/606)		85.7 (60/70)		87.5 (21/24)		92.7 (51/55)	
Yes	90.7 (136/150)		96.2 (76/79)		86.9 (53/61)		100.0 (3/3)		57.1 (4/7)	
DAA experienced vs other experienced		#		#		#				#
No	94.4 (117/124)		97.2 (69/71)		93.3 (42/45)		100.0 (3/3)		60.0 (3/5)	
Yes	73.1 (19/26)		87.5 (7/8)		68.8 (11/16)		---		50.0 (1/2)	
Prior Treatment Response		#		#		#				
Relapse	100.0 (13/13)		100.0 (7/7)		100.0 (6/6)		---		---	
Partial	88.9 (32/36)		93.8 (15/16)		84.2 (16/19)		100.0 (1/1)		---	
Null	---		---		---		---		---	
Unknown	85.7 (18/21)		100.0 (7/7)		78.6 (11/14)		---		---	
BMI (kg/m^2)		0.59		0.52		#		#		#
<25	89.8 (353/393)		90.8 (277/305)		83.3 (45/54)		92.3 (12/13)		90.5 (19/21)	
25-29	91.9 (316/344)		93.0 (238/256)		91.1 (41/45)		84.6 (11/13)		86.7 (26/30)	
≥30	91.7 (154/168)		93.5 (116/124)		84.4 (27/32)		100.0 (1/1)		90.9 (10/11)	
FIB-4		0.05		0.21		0.22		#		#
≤3.25	92.1 (609/661)		93.0 (476/512)		89.5 (77/86)		89.5 (17/19)		88.6 (39/44)	

Abbreviations: BMI, body mass index; DAA, direct-acting antiviral; INSTI integrase strand transfer inhibitor; LDV/SOF, ledipasvir/sofosbuvir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; OPrD, ombitasvir/paritaprevir/ritonavir+dasabuvir; PI, protease inhibitor; PPI, proton pump inhibitor; RBV, ribavirin; SVR, sustained virologic response
*Subtype 1a includes 1a, mixed 1a/1b and 1 with subtype unspecified; # P value not reported when minimum expected value in any cell is <5

Table 3. SVR Rates by Regimen for Genotype 1 HIV/HCV coinfected Patients Receiving LDV/SOF- or OPrD-Based Regimens who Completed 12 Weeks of Treatment

	All N=766 12 Weeks, %	P	LDV/SOF N=569 12 Weeks, %	P	LDV/SOF+RBV N=119 12 Weeks, %	P	OPrD N=23 12 Weeks, %	P	OPrD+RBV N=55 12 weeks, %	P
Overall SVR	94.3 (722/766)		95.3 (542/569)		90.8 (108/119)		95.7 (22/23)		90.9 (50/55)	
Age (years)		0.40		#		#		#		#
< 55	93.6 (102/109)		94.3 (82/87)		90.9 (10/11)		100.0 (3/3)		87.5 (7/8)	
55-64	95.2 (433/455)		96.5 (328/340)		91.8 (67/73)		90.9 (10/11)		90.3 (28/31)	
≥ 65	92.6 (187/202)		93.0 (132/142)		88.6 (31/35)		100.0 (9/9)		93.8 (15/16)	
Sex		#		#		#				
Male	94.1 (707/751)		95.2 (530/557)		90.5 (105/116)		95.7 (22/23)		90.9 (50/55)	
Female	100.0 (15/15)		100.0 (12/12)		100.0 (3/3)		---		---	
Race/ethnicity		0.44		1.00		#		#		#
African-American	93.7 (475/507)		95.4 (372/390)		88.2 (60/68)		94.1 (16/17)		84.4 (27/32)	
Non-African American	95.4 (247/259)		95.0 (170/179)		94.1 (48/51)		100.0 (6/6)		100.0 (23/23)	
Cirrhosis		0.19		0.85		#		#		#
No	94.9 (563/593)		95.4 (440/461)		90.9 (60/66)		95.2 (20/21)		95.6 (43/45)	
Yes	91.9 (159/173)		94.4 (102/108)		90.6 (48/53)		100.0 (2/2)		70.0 (7/10)	
Liver decompensation		#		#		#		#		
No	94.2 (709/753)		95.2 (535/562)		90.4 (103/114)		95.5 (21/22)		90.9 (50/55)	
Yes	100.0 (13/13)		100.0 (7/7)		100.0 (5/5)		100.0 (1/1)		---	
PPI		0.61		#		#		#		#
No	94.5 (589/623)		95.3 (447/469)		91.5 (86/94)		93.3 (14/15)		93.3 (42/45)	
Yes	93.0 (133/143)		95.0 (95/100)		88.0 (22/25)		100.0 (8/8)		80.0 (8/10)	
Treatment Experienced		0.61		#		1.00		#		#
No	94.0 (593/631)		94.6 (471/498)		90.5 (57/63)		95.0 (19/20)		92.0 (46/50)	
Yes	95.6 (129/135)		100.0 (71/71)		91.1 (51/56)		100.0 (3/3)		80.0 (4/5)	
DAA experienced vs other experienced		#		#		#				#
No	99.1 (111/112)		100.0 (64/64)		97.6 (41/42)		---		100.0 (3/3)	
Yes	78.3 (18/23)		100.0 (7/7)		71.4 (10/14)		100.0 (3/3)		50.0 (1/2)	
Prior Treatment Response		#		#		#				
Relapse	100.0 (13/13)		100.0 (7/7)		100.0 (6/6)		---		---	
Partial	93.9 (31/33)		100.0 (14/14)		88.9 (16/18)		100.0 (1/1)		---	
Null	---		---		---		---		---	
Unknown	85.0 (17/20)		100.0 (6/6)		78.6 (11/14)		---		---	
BMI (kg/m^2)		0.91		#		#		#		#
<25	93.9 (309/329)		94.8 (235/248)		88.2 (45/51)		100.0 (10/10)		95.0 (19/20)	
25-29	94.3% (281/298)		95.4 (209/219)		95.1 (39/41)		91.7 (11/12)		84.6 (22/26)	
≥30	95.0% (132/139)		96.1 (98/102)		88.9 (24/27)		100.0 (1/1)		100.0 (9/9)	
FIB-4		0.13		0.27		#		#		#

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Abbreviations: BMI, body mass index; DAA, direct-acting antiviral; INSTI integrase strand transfer inhibitor; LDV/SOF, ledipasvir/sofosbuvir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; OPrD, ombitasvir/paritaprevir/ritonavir+dasabuvir; PI, protease inhibitor; PPI, proton pump inhibitor; RBV, ribavirin; SVR, sustained virologic response
*Subtype 1a includes 1a, mixed 1a/1b and 1 with subtype unspecified; # P value not reported when minimum expected value in any cell is <5

Table 4. Odd Ratios for SVR in Multivariable Model for Genotype 1 Patients HIV/HCV Coinfected Patients Receiving LDV/SOF- or OPrD-Based Regimens

	Overall ITT OR (95%CI) N=905	P	Completed 12 weeks OR (95%CI) N=766	P	Overall ITT OR (95% CI) N=645	P
Age <55 years (ref. 55-64)	0.83 (0.42-1.76)	0.61	0.60 (0.25-1.59)	0.27	1.54 (0.58-5.36)	0.43
Age ≥65 years (ref. BMI 55-64)	0.83 (0.49-1.43)	0.49	0.63 (0.31-1.30)	0.20	0.68 (0.36-1.31)	0.23
African American (ref. non-African American)	0.76 (0.44-1.25)	0.28	0.63 (0.30-1.24)	0.20	0.74 (0.37-1.40)	0.37
Cirrhosis (ref. no cirrhosis)	0.50 (0.30-0.85)	0.008	0.62 (0.31-1.27)	0.17	0.65 (0.33-1.30)	0.08
PPI (ref. no PPI)	0.85 (0.49-1.56)	0.58	0.77 (0.37-1.70)	0.49	0.78 (0.39-1.68)	0.50
Treatment experienced (ref. naïve)	1.24 (0.66-2.50)	0.51	1.93 (0.79-5.47)	0.18	1.20 (0.55-2.86)	0.66
BMI <25 kg/m^2 (ref. BMI 25-29 kg/m^2)	0.73 (0.43-1.23)	0.24	0.92 (0.45-1.90)	0.80	0.76 (0.39-1.43)	0.39
BMI ≥30 kg/m^2 (ref. BMI 25-29 kg/m^2)	0.99 (0.50-2.01)	0.98	1.18 (0.48-3.17)	0.73	1.14 (0.49-2.90)	0.76
Subtype 1b (ref. 1a*)	0.79 (0.47-1.38)	0.40	0.68 (0.34-1.41)	0.28	0.70 (0.37-1.37)	0.28
LDV/SOF+RBV (ref. LDV/SOF)	0.57 (0.30-1.11)	0.09	0.42 (0.19-0.97)	0.03	0.47 (0.21-1.07)	0.06
OPrD (ref. LDV/SOF)	0.79 (0.24-3.58)	0.73	1.57 (0.27-29.67)	0.68	2.02 (0.35-38.49)	0.52
OPrD+RBV (ref. LDV/SOF)	0.62 (0.27-1.56)	0.26	0.47 (0.18-1.46)	0.14	0.44 (0.17-1.28)	0.10
PI (ref. INSTI)	-		-		0.87 (0.41-1.84)	0.70
NNRTI (ref. INSTI)	-		-		0.98 (0.47-2.05)	0.97

Abbreviations: BMI, body mass index; CI, confidence interval; INSTI, integrase strand transfer inhibitor; LDV/SOF, ledipasvir/sofosbuvir; NNRTI, non-nucleoside reverse transcriptase inhibitor; OPrD, ombitasvir/paritaprevir/ritonavir+dasabuvir; OR, odds ratio; PI, protease inhibitor; PPI, proton pump inhibitor; RBV, ribavirin; ref., reference; SVR, sustained virologic response
*Subtype 1a includes 1a, mixed 1a/1b and 1 with subtype unspecified

Figure 1. Maximum creatinine change from baseline while on HCV treatment for patients prescribed, A. tenofovir with a HIV protease inhibitor (PI), B. tenofovir without a HIV PI, and C. patients not receiving tenofovir. *One value of 12.25 mg/dl not shown.