Comparative Treatment Effectiveness of Direct Acting Antiviral Regimens for Hepatitis C: Data from the Veterans Administration

Short title: Effectiveness of Hepatitis C Direct Acting Antiviral Regimens

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Abbreviations

Direct acting antiviral (DAA) combination regimens

Fibrosis-4 score [FIB4]

Hepatitis C virus (HCV)

Hepatocellular carcinoma (HCC),

Human immunodeficiency virus [HIV]

Ledipasvir/sofosbuvir (LDV/SOF)

Ombitasvir/paritaprevir/ritonavir/dasabuvir (3D)

Ribivirin [RBV]

Simeprevir and sofosbuvir (SIM+SOF),

Sustained virologic response 12-weeks post-treatment (SVR12)

Veterans Health Administration [VHA]

Abstract

Background and Aims: Data addressing real world effectiveness of direct acting antiviral agents in hepatitis C infected patients are now emerging. This study compared the sustained virologic response rates achieved 12 weeks post-treatment in patients treated with three such agents by the Veterans Health Administration.

Methods: A retrospective cohort study was conducted using patients who terminated treatment by July 1, 2015. Data were retrieved from the Veterans Health Administration electronic medical records system. Patients were included if sufficient viral load laboratory data were available to determine sustained virologic response. Applying an intention to treat approach and logistic regression analysis, the sustained virologic response rates achieved were compared across drug regimens.

Results: A total of 11,464 patients met study selection criteria. Without controlling for other risk factors, sustained virologic response at least 12 weeks post treatment was achieved in 92% of ledipasvir/ sofosbuvir, 86% of ombitasvir/paritaprevir/ritonavir/dasabuvir, and 83% of simeprevir/sofosbuvir patients. After adjusting for patient characteristics, simeprevir/sofosbuvir (93.3%) and ledipasvir/sofosbuvir (96.2%) patients were statistically more likely than ombitasvir/paritaprevir/ritonavir/dasabuvir (91.8%) patients to demonstrate sustained virologic response. Human immunodeficiency virus, hepatitis B infection, diabetes, obesity, previous treatment history and augmentation therapy using ribavirin did not impact sustained virologic response rates. Sustained virologic response rates were lower for patients under age 65, with cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, indications of fibrosis or a non-genotype 1 infection. Women and Caucasian patients were more likely to achieve a sustained virologic response.

Conclusions: All three direct acting antiviral regimens appear highly effective in achieving sustained virologic response.

Key Words: Hepatitis C, Antiviral Agents, Simeprevir, Ledipasvir, Ombitasvir

Introduction

Chronic infection with hepatitis C virus (HCV) in the United States caused more than 19,000 deaths in 2014 alone.[1] Complications from HCV infection include cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), and liver transplantation.[2-6] In the United States, approximately 2.7 million persons have been estimated to have HCV infection.[7] Among U.S. Veterans, prevalence of HCV is 5.4% which significantly exceeds that of the general population.[8] Multiple highly effective direct acting antiviral (DAA) combination regimens have recently been developed to treat HCV infection, with three of the most widely prescribed being simeprevir and sofosbuvir (SIM+SOF), ledipasvir/sofosbuvir (LDV/SOF), and ombitasvir/paritaprevir/ritonavir/dasabuvir (3D). All three regimens have demonstrated high efficacy rates in clinical trials, achieving a sustained virologic response 12-weeks post-treatment (SVR12) in the 80-100% of patients. In the phase II COSMOS study, SIM+SOF±RBV was randomly assigned to genotype 1 HCV patients with varying degrees of disease severity and achieved SVR12 in 90-94% of treated patients.[9] Similarly, the efficacy of LDV/SOF±RBV has been demonstrated in various clinical trials, most notably the phase III ION studies, which yielded SVR12 in 82-100% of patients.[10-12] Finally, in the SAPPHIRE and TURQUOISE studies 3D±RBV achieved SVR12 in 87-100% of patients, depending on disease severity, treatment history, and treatment duration.[13-15]

Although the efficacy of these regimens has proven impressively high in controlled studies, research documenting their effectiveness in large real-world practices is only starting to emerge. The earliest of the studies focused on SIM+SOF±RBV[16,17], the earliest all-oral DAA combination in the market. More recently, Backus *et al.*[18,19] compared SVR12 rates for LDV/SOF±RBV and 3D±RBV for genotype 1 patients treated within the Veterans Health Administration [VHA]. Finally, Ioannou, *et al.*[20] compared SVR12 rates across a sample of VHA patients treated with SOF, LDV/SOF±RBV or 3D±RBV. All of these studies have found that the new DAAs are highly effective at achieving SVR12 but have been limited in scope or imputed values for missing clinical data, including the patient's HCV genotype and/or a final SVR12.

This study evaluates the real-world treatment effectiveness of these three most widely prescribed DAA combination regimens used to treat HCV patients within the VHA using an intent-to-treat analysis which included both initial and secondary treatment episodes. We control for the impact of various patient, disease, and treatment characteristics on treatment effectiveness when comparing effectiveness across the regimens.

Methods

Data for this retrospective cohort study were retrieved from the Veterans Health Administration's Corporate Data Warehouse, and included patient demographics, disease diagnoses (inpatient, outpatient, problem lists), pharmacy, and laboratory data. We included all HCV infected patients, nationwide, who initiated treatment on any of the three study regimens, and stopped treatment prior to July 1, 2015. This cutoff date allowed for sufficient post-treatment follow-up to document if SVR12 was achieved. Potential study patients were then screened for availability of post-treatment HCV viral load labs. Given the heterogeneity of viral load lab types in the VHA data, and result reporting behavior, significant care was taken to accurately interpret viral load lab results. Viral load lab results were defined as "not detected" if the result was reported either qualitatively as "not detected", or quantitatively as below that lab's lower limit of quantification. Viral load lab results were defined as "detected" if they met the converse conditions. Inconsistent results were adjudicated manually. Finally, a patient was defined as having achieved SVR12 if all available post-treatment viral load lab results were defined as "not detected", with at least one viral load lab tests occurring 12 or more weeks after the end-of-treatment. Patients with any "detected" lab results post-treatment were classified as treatment failures. Patients with no post-treatment viral load labs available were excluded from the analysis, as were patients with post-treatment results of "not detected" but with no test performed at least 12 weeks after end-of-treatment. (By contrast, Ioannou, *et al.*[20] imputed these missing values based on SVR4 results, implicitly assuming a 100% concordance.)

Each patient's treatment initiation date was defined as their earliest recorded DAA prescription release date, and end-of-treatment was calculated as the last recorded prescription release date plus the days of supply released in the last recorded prescription. Patients who initiated treatment on more than one DAA on the same date were excluded; however, patients who were treated with more than one regimen sequentially were included in the SVR12 analysis. Treatment duration was defined as the sum of all days' supply released across the entire treatment episode.

Baseline control variables included demographics, disease severity, comorbidities, previous treatment status, and ribavirin use. Disease severity measures included prior diagnoses of cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and/or history of liver transplantation prior to DAA treatment. Baseline FIB4 fibrosis scores were also used as a secondary measure of disease severity.[21] Comorbidities included HIV, hepatitis B, diabetes and obesity [See Supplementary Material].

Logistic regression analysis was used to estimate the impact of the control variables on the likelihood of achieving SVR12, as well as to compare the likelihood of achieving SVR12 across DAA regimens. Statistical analyses were carried out in SAS 9.2. [SAS Corporation, Cary N.C.] This study was approved by the Institutional Review Board of the Veterans Administration Healthcare System at Long Beach, California.

Results

In total, 3,549 SIM+SOF±RBV patients, 7,952 LDV/SOF±RBV patients, and 1,579 3D±RBV patients were identified [Table 1]. A high proportion of these patients had adequate follow-up laboratory data to determine SVR12: 92% of SIM+SOF±RBV, 86% of LDV/SOF±RBV, and 88% of 3D±RBV patients. An additional six patients who initiated treatment on two different regimens on the same date were excluded from the analysis. The final study population was comprised of 3,263 SIM+SOF±RBV, 6,816 LDV/SOF±RBV, and 1,385 3D±RBV patients. This included patients who were treated, sequentially, with more than one DAA. For example, 398 patients had a SIM+SOF±RBV episode followed by LDV/SOF±RBV. For patients with sequential DAA regimens, all of their initial treatment episodes were defined as treatment failures. Their second episode of DAA treatment was entered into the analysis if sufficient data were available to determine SVR12.

The distribution of treatment duration varied significantly across regimens. Over 70% of SIM+SOF±RBV episodes were 12 weeks in duration, with an additional 17% being longer than 12 weeks. For LDV/SOF±RBV, approximately 61% of episodes were 12 weeks in duration and nearly 26% were 8 weeks, which is an FDA indicated duration for certain patients.[12] Approximately 80% of 3D±RBV patients were treated for 12 weeks, while approximately 18% completed less than 12 weeks of treatment.

Baseline patient characteristics are presented in Table 2. Several factors are consistent across regimens, and reflective of the general VHA HCV population. For example, most patients were male [96%] and over the age of 60 [64%]. Approximately 55% of the population was white, 35% black, and the remainder were of other or unknown race. Genotype 1 was the

predominant genotype, representing approximately 97% of all infections with a recorded genotype.

Some characteristics varied across DAA regimens, potentially reflecting triage of earlier treatment to the most severely ill patients, the evolving VHA national guidelines provided to VHA clinicians as new evidence emerged, and potential cost savings to the VHA resulting from ongoing drug price negotiations. Specifically, patients treated with SIM+SOF±RBV exhibited significantly higher rates of cirrhosis, decompensated cirrhosis, HCC and history of a liver transplant at the time of treatment. This is likely due to it having been the first DAA available and aggressive triage of more ill patients to early treatment. Baseline FIB4 also showed a similar pattern, as did the rates of prior HCV treatment experience.

Table 3 presents data on the *unadjusted* SVR12 rates, categorized by patient characteristics and regimen. Overall unadjusted SVR12 rates were 83.2% for SIM+SOF±RBV, 91.6% for LDV/SOF±RBV, and 85.7% for 3D±RBV. Among patients who completed 12 weeks of treatment the SVR12 rates were 85.8%, 93.0%, and 96.5%, respectively. The SVR12 rate for those treated with 8 weeks of LDV/SOF±RBV was 93.0%.

For DAA regimens that included ribavirin, rates of SVR12 were 85.3% for SIM+SOF+RBV, 89.3% for LDV/SOF+RBV, and 84.2% for 3D+RBV. The SVR12 rates for patients treated without ribavirin were 82.8%, 92.4%, and 90.2%, respectively. SVR12 rates were lower for patients with cirrhosis, decompensated cirrhosis and HCC and, correspondingly, were also significantly lower among those with a FIB4 score greater than 3.25 (78.2%, 87.6%, and 82.7%, respectively).

Multivariable logistic regression results are reported in Table 4. They estimate the impact of various patient, disease, and treatment characteristics on the likelihood of achieving SVR12. The primary findings were:

1. Patients treated with LDV/SOF±RBV (96.2%) and SIM + SOF±RBV (93.3%) were significantly more likely to achieve SVR12 than patients treated with 3D±RBV (91.8%), after controlling for other variables in the analysis by holding them at their reference group levels.
2. Females (vs. males), and those with a history of liver transplantation were *more* likely to achieve SVR12, while those who were less than 60 years of age (vs. 65+), black (vs. white), non-genotype 1 (vs. genotype 1), or obese were *less* likely to achieve SVR12.
3. Cirrhosis, decompensated cirrhosis, HCC, and having a FIB4 score > 3.25 were associated with a significantly lower likelihood of achieving SVR12.
4. Notable factors that *did not* significantly impact the likelihood of achieving SVR12 were: coinfection with HIV, hepatitis B, or diabetes, as well as ribavirin use, and previous treatment status.

Discussion

Our study augments the findings reported in previous studies using VHA data[18-20] by applying clinically relevant differences in research methods. First, we include SIM+SOF±RBV which is currently not used often in the VHA system but is often used in other clinical settings. Second, we include patients with multiple DAA episodes, and analyze all their treatment episodes for which sufficient data were available to determine SVR12.

Third, we do not impute values for missing data such as genotype or SVR12 for patients with insufficient data.

This analysis of the three all-oral DAA regimens as used by the VHA found overall unadjusted SVR12 rates between 83% and 92%. These rates are lower than rates reported by other researchers using the VHA data[18-20] for two reasons. First, we include patients who switched therapy, and assumed that the initial treatment episode was a treatment failure. Ioannou, *et al.*[20] argue that early switching could be related to factors other than drug effectiveness, and dropped these patients from their analysis. Second, we applied a strict interpretation of SVR12 which required a confirmed undetectable viral load 12 or more weeks post-treatment. Ioannou *et al.*[20] relaxed this requirement and assumed that patients achieved treatment success if they had only 'undetectable' viral load tests post-treatment, but no result beyond 12 weeks post-treatment to confirm SVR12. While concordance between SVR12 and SVR24 is quite high, concordance between SVR4 and SVR12 appears somewhat lower: 78-98% (even in controlled trials).[26-30] We maintained the more conservative clinical trial standard of requiring confirmed SVR12. The limited fraction of patients who lacked confirmed SVR12 (or a confirmed failure sooner) were excluded from analysis, rather than imputed to be treatment successes, since including them would inflate the observed SVR12 rate by some modest but unknown percentage. Regardless of those differences in the methods and assumptions, these studies using VHA data found real-world SVR12 rates for DAA therapy which approach those found in clinical trials.

However, the *statistically* significant differences between SVR12 rates estimated here may not be *clinically* significant. It is also no surprise that these observed rates are lower than those found in *controlled* trials, most likely due to a less selected patient population, and lower treatment adherence. Furthermore, while the VHA HCV population skews more male and less ethnically diverse than the general U.S. HCV population, our results for non-white, non-black patients did not differ radically from those for black patients. The very strong statistical difference in SVR12 for female patients suggests that it may also be clinically significant, albeit based on a total sample of 405 female patients. Patients with specifically identified genotypes other than genotype 1 represented a smaller proportion than in other published non-VHA studies, prompting the decision to pool those patients rather than attempt a statistically suspect regression on small sub-groups.[16,20] We did not deem it reliable to impute genotype based on regimen. However, it was clearly necessary to use 'non-genotype 1' as a control factor, given that VHA clinicians' choice of DAA was not evenly distributed across genotype and treatment failures in non-genotype 1 patients could be due to inappropriate regimen selection. In general, the VHA population spans the spectrum of comorbidities and the regression analysis results do allow the SVR12 estimates to be adjusted for specific comorbidities prevalent in non-VHA populations.

This study estimated SVR12 for genotype 1 patients as: 83.3% for SIM+SOF±RBV; 85.8% for 3D±RBV; and 92.3% for LDV/SOF±RBV. These results are in line with other studies that used VHA data. Backus *et al.*[18,19] reported overall SVR12 rates for genotype 1 patients of 90.0-92.0% for LDV/SOF±RBV, and 85.8-95.1% for 3D±RBV. Ioannou *et al.*[20] reported an SVR12 rate of 92.7% for LDV/SOF±RBV and 93.8% for 3D±RBV. The apparent discrepancy between our 3D SVR12 rate and that of Ioannou probably lies in our analytic approach, which assumed switching to a second DAA regimen constituted treatment failure

for the initial regimen; this occurred in a significant proportion of 3D patients (93/1,385 = 6.7%). While some of those switches may have been for financial reasons, others were likely ITT treatment failures, either due to failure to suppress viral replication, or intolerable side effects. Finally, our study is the only large study to date that evaluates the effectiveness of SIM+SOF±RBV for genotype 1 patients alongside of LDV/SOF±RBV and 3D±RBV in a real-world setting.

Since the unadjusted SVR12 rates reflected differences in average patient comorbidities between treatment regimens, we also report adjusted SVR12 rates. These can be calculated by inverting the regression coefficients to generate the estimated absolute SVR12 probabilities for patients with specific comorbidities levels. We used the reference baseline comorbidities (e.g., male, >65 years, no cirrhosis, etc.), as noted in Table 4 for our adjustments.

There were 398 patients who had a SIM+SOF±RBV treatment episode followed by an episode of LDV/SOF±RBV. There were also 93 patients who had a 3D±RBV episode followed by LDV/SOF±RBV. The reason(s) why these patients switched therapies is unknown. It is doubtful that the second episode was initiated due to re-infection, given the short interval between treatment episodes for the majority of patients. It is conceivable that some SIM+SOF±RBV patients were switched to LDV/SOF±RBV to reduce cost – in which case defining these patients as treatment failures would bias downward the reported SVR12 rate for SIM+SOF±RBV. Conversely, restricting the analysis to single DAA episode patients upwardly biases SVR12 rates - in this study that would result in notably higher SVR12 rates of 94.9% for SIM/SOF±RBV, 92.4% for LDV/SOF±RBV, and 91.9% for 3D±RBV. Our

results thus allow the reader to better interpret the SVR12 rates reported in prior studies[16-20], some of which specifically excluded multiple regimen patients from analysis.

The reader should also note that both SIM-SOF and 3D are now contraindicated for patients with decompensated cirrhosis. Our analysis included patients with decompensated cirrhosis treated under those regimens prior to those indication changes.

Treatment with SIM+SOF±RBV appears to have been prioritized to sicker patients, as evidenced by their higher rates of cirrhosis, decompensated cirrhosis and HCC [Table 2]. However, our results also demonstrate that the likelihood of achieving SVR12 is inversely related liver-related illness severity of illness. Those findings are consistent with our pre-DAA research using VHA data which demonstrated that achieving viral load suppression after significant fibrosis has occurred reduced the effectiveness of even successful treatment in reducing the risks of future liver complications.[22,23]

Limitations This study was a retrospective cohort analysis, and thus has several potential limitations. The selection of which patients received treatment, and the specific DAA regimen used, was at the discretion of individual VHA physicians, subject to VHA policy. However, we controlled for any differences in observed patient characteristics across the three alternative DAA regimens using well established analytic methods, made conservative assumptions regarding missing data, and also adjusted for observable potential risk factors. Post-treatment follow-up viral load lab data was also incomplete, mostly due to limited time following the last recorded DAA prescription; patients with a SVR at 4 to 11 weeks post-treatment often failed to re-visit the clinic for their final viral load test. Nonetheless, more

than 86% of patients in each group who initiated treatment during the study period had sufficient laboratory data to identify the treatment outcome.

A significant proportion of patients switched to a second regimen, usually before completing a full course of the first regimen. The cause for these switches was not readily ascertainable. While it may have been due to cost or other non-clinical considerations, we took the conservative approach consistent with an intention to treat analysis and assumed that switching was due to treatment failure. Other published analyses have either ignored the second treatment attempt for patients switching regimens or excluded switchers from analysis altogether.[18-20] Data on some relevant risk factors were incomplete (e.g., HCV genotype, and patient race). Our regression analysis results found these factors, when known, were significantly correlated with the likelihood of the patient achieving SVR12. However, given the frequency of incomplete data, caution should be used when interpreting these results. For similar reasons, and to promote appropriate parsimony, we also did not separately analyze second order cofactor interactions, for example between the influence of cirrhosis and ribavirin use.

The definition of SVR12 used in this study conforms with the standard definition of a 'cure' by requiring all post-treatment viral load tests to be negative, including at least one performed 12 *or more* weeks post-treatment. Patients with all negative post-treatment viral load tests, but without a viral load at or beyond 12 weeks post-treatment (741 in total) were excluded from the analysis. Conversely, Ioannou, *et al.*[20] imputed a final SVR12 for patients with missing data based on a confirmed SVR at 4 or more weeks which likely overstates the true SVR12 rate.[26-30] Both approaches violate the strictest definition of an intention to treat analysis. Nevertheless, both approaches report similar cure rates for the new DAA

combination therapies. Excluding the additional 861 patients with NO post treatment viral load is more problematic. Including those patients as presumed treatment failures could be done, but would significantly depress observed SVR12 rates. However, since many of those patients likely lacked VL follow-up labs due to insufficient elapsed time, not treatment failure, this approach seems unreasonably pessimistic. It seems plausible that many patients simply fail to return for scheduled testing once an SVR4 is achieved.

Finally, there are other potential confounding risk factors not captured in our analysis including the use of proton pump inhibitors, baseline viral load, and the presence of resistance associated variants of HCV. Additional research into such factors is warranted.

Conclusions and Policy Implications Among genotype 1 patients, all three study regimens worked well in real world practice, achieving SVR12 rates comparable to those observed in pre-approval randomized clinical trials. The LDV/SOF±RBV regimen appears to have performed best, after adjusting for severity and other risk factors. Some potential risk factors, including diabetes and concurrent HIV or HBV infection, did not prove to have an impact on the likelihood of achieving SVR12. Conversely, obesity, cirrhosis, decompensated cirrhosis, and HCC were found to significantly impact the likelihood of achieving SVR12. The FIB4 results point to a similar conclusion: that initiating treatment after significant fibrosis has occurred is associated with a lower likelihood of achieving SVR12. Prior research also suggests that achieving viral load suppression later is associated with significant progression to end stage liver disease and death.[22].[23] Therefore, physicians should not wait until HCV complications arise to treat patients' infections.[24] It is not surprising that other health economic studies project that treating *all* HCV+ patients is cost effective; reinforcing the advantages of at least treating patients with an elevated FIB4.[25] Conversely, immediately

treating all HCV+ patients would consume nearly the entire annual prescription drug spending in the U.S., while ethical concerns dictate that the most severely ill patients are treated first. The implication is that society should establish clinical parameters for HCV treatment that allocate scare resources first to advanced HCV patients, but then adjust guidelines over time to also treat less severely ill patients, and monitor completely asymptomatic patients for any progression of the disease. Expanding treatment eligibility over time should prove increasingly feasible as prices drop, especially following competition from newer, pan-genotypic DAA regimens now entering the market.

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Table 1. Selection of Treatment Episodes and Treatment Duration

Selection of Treatment Episodes	SIM+SOF ± RBV	LDV/SOF ± RBV	3D ± RBV
Patient episodes terminating treatment prior to July 1st, 2015	3549	7952	1579
Patient episodes with at least 1 post-treatment viral load lab test	3405	7335	1479
Patient episodes with undetected viral load post-treatment, but none occurring ≥ 12 weeks after treatment (excluded)	142	517	90
Patient episodes eligible for analysis	3263	6818	1389
Patients initiating episodes with 2 DAAs on the same date (excluded)	0	2	4
Total patient episodes included in the analysis	3263	6816	1385
Patients with > 1 DAA Episode			
SIM+SOF±RBV then LDV/SOF±RBV	398	116	-
LDV/SOF±RBV then SIM+SOF±RBV	2	29	-
SIM+SOF±RBV then 3D±RBV	4	-	1
3D±RBV then SIM+SOF±RBV	0	-	0
LDV/SOF±RBV then 3D±RBV	-	12	2
3D±RBV then LDV/SOF±RBV	-	17	93
SIM+SOF±RBV, LDV/SOF±RBV, 3D±RBV	1	2	1
Duration of Treatment	N = 3263	N = 6816	N = 1385
< 8 weeks	124 (3.8%)	203 (3.0%)	152 (11.0%)
8 weeks	95 (2.9%)	1747 (25.6%)	52 (3.7%)
9 - 11 weeks	148 (4.5%)	131 (1.9%)	41 (3.0%)
12 weeks	2324 (71.2%)	4137 (60.7%)	1108 (80.0%)
> 12 weeks	572 (17.5%)	598 (8.8%)	32 (2.3%)

† DAA = direct-acting antiviral, RBV = ribavirin, SIM = simeprevir, SOF = sofosbuvir, LDV = ledipasvir, 3D = ombitasvir/paritaprevir/ritonavir+dasabuvir

Table 2. Baseline Patient Characteristics

	SIM+SOF ± RBV N = 3263		LDV/SOF ± RBV N = 6816		3D ± RBV N = 1385	
	(n)	(%)	(n)	(%)	(n)	(%)
Male	3146	96.4%	6556	96.2%	1341	96.8%
Age						
< 60	1179	36.1%	2431	35.7%	460	33.2%
60 - 64	1254	38.4%	2477	36.3%	522	37.7%
65+	830	25.4%	1908	28.0%	403	29.1%
Race						
Black	1040	31.9%	2342	34.4%	485	35.0%
White	1905	58.4%	3764	55.2%	770	55.6%
Other/Unknown	318	9.7%	710	10.4%	130	9.4%
Genotype						
1	3146	96.4%	6324	92.8%	1355	97.8%
Other	50	1.5%	302	4.4%	13	1.0%
Unknown	67	2.1%	190	2.8%	17	1.2%
Disease Severity						
Cirrhosis	2099	64.3%	2466	36.2%	434	31.3%
Decompensated	1167	35.8%	1299	19.1%	175	12.6%
HCC	286	8.8%	299	4.4%	28	2.0%
Liver Transplant	221	6.8%	221	3.2%	5	0.4%
FIB4						
< 1.45	304	9.3%	1241	18.2%	287	20.7%
1.45 - 3.25	936	28.7%	2830	41.5%	635	45.8%
> 3.25	1708	52.3%	1957	28.7%	341	24.6%
Unknown	315	9.7%	788	11.6%	122	8.8%
Comorbidities						
HIV	121	3.7%	343	5.0%	31	2.2%
HBV	328	10.1%	545	8.0%	107	7.7%
Diabetes	1298	39.8%	2245	32.9%	414	29.9%
Obesity	179	5.5%	347	5.1%	68	4.9%
Prior Treatment						
Naïve	1950	59.8%	4771	70.0%	1025	74.0%
Experienced	1313	40.2%	2045	30.0%	360	26.0%
Ribavirin Use	517	15.8%	1726	25.3%	1047	75.6%
No	2746	84.2%	5090	74.7%	338	24.4%
Yes	517	15.8%	1726	25.3%	1047	75.6%

† SIM = simeprevir, SOF = sofosbuvir, LDV = ledipasvir, 3D = ombitasvir/paritaprevir/ritonavir+dasabuvir, RBV = ribavirin, HCC = hepatocellular carcinoma, HIV = human immunodeficiency virus, HBV = hepatitis B

Table 3. Unadjusted SVR12 Rates

	SIM+SOF ± RBV N = 3263		LDV/SOF ± RBV N = 6816		3D ± RBV N = 1385	
	(%)	(n)	(%)	(n)	(%)	(n)
Overall	83.2%	(2714/3263)	91.6%	(6246/6816)	85.7%	(1187/1385)
Gender						
Female	91.5%	(107/117)	94.6%	(246/260)	95.5%	(42/44)
Male	82.9%	(2607/3146)	91.5%	(6000/6556)	85.4%	(1145/1341)
Age						
< 60	80.8%	(953/1179)	91.9%	(2233/2431)	87.4%	(402/460)
60 - 64	83.0%	(1041/1254)	91.0%	(2255/2477)	86.4%	(451/522)
65+	86.8%	(720/830)	92.1%	(1758/1908)	82.9%	(334/403)
Race						
Black	83.1%	(864/1040)	91.6%	(2146/2342)	83.7%	(406/485)
White	83.3%	(1587/1905)	92.0%	(3462/3764)	87.3%	(672/770)
Other/Unknown	82.7%	(263/318)	89.9%	(638/710)	83.9%	(109/130)
Genotype						
1	83.3%	(2619/3146)	92.3%	(5839/6324)	85.8%	(1162/1355)
Other	78.0%	(39/50)	75.2%	(227/302)	76.9%	(10/13)
Unknown	83.6%	(56/67)	94.7%	(180/190)	88.2%	(15/17)
Disease Severity						
Cirrhosis	79.1%	(1660/2099)	89.0%	(2192/2466)	85.0%	(369/434)
Decompensated	76.4%	(892/1167)	87.2%	(1133/1299)	81.7%	(143/175)
HCC	75.5%	(216/286)	83.3%	(249/299)	85.7%	(24/28)
Liver Transplant	88.2%	(195/221)	93.7%	(207/221)	60.0%	(3/5)
FIB4						
< 1.45	94.4%	(287/304)	93.9%	(1165/1241)	88.5%	(254/287)
1.45 - 3.25	90.0%	(842/936)	93.3%	(2641/2830)	86.5%	(549/635)
> 3.25	78.2%	(1335/1708)	87.6%	(1714/1957)	82.7%	(282/341)
Unknown	79.4%	(250/315)	92.1%	(726/788)	83.6%	(102/122)
Comorbidities						
HIV	84.3%	(102/121)	90.7%	(311/343)	87.1%	(27/31)
HBV	84.2%	(276/328)	90.6%	(494/545)	82.2%	(88/107)
Diabetes	83.4%	(1083/1298)	90.8%	(2039/2245)	83.8%	(347/414)
Obesity	77.7%	(139/179)	89.3%	(310/347)	80.9%	(55/68)
Prior Treatment						
Naïve	84.9%	(1656/1950)	91.8%	(4378/4771)	86.2%	(884/1025)
Experienced	80.6%	(1058/1313)	91.3%	(1868/2045)	84.2%	(303/360)
Ribavirin Use						
No	82.8%	(2273/2746)	92.5%	(4705/5090)	90.2%	(305/338)
Yes	85.3%	(441/517)	89.3%	(1541/1726)	84.2%	(882/1047)

† SIM = simeprevir, SOF = sofosbuvir, LDV = ledipasvir,
3D = ombitasvir/paritaprevir/ritonavir+dasabuvir, RBV = ribavirin, HCC = hepatocellular carcinoma, HIV = human immunodeficiency virus, HBV = hepatitis B

Table 4. Logistic Analysis of Likelihood of Achieving SVR12

Parameter	Coefficient	Odds Ratio	Pr > Chi-Square
Intercept	2.4149	-	<0.0001
Treatment Type (ref. group: 3D ± RBV)			
SIM+SOF ± RBV	0.2295	1.26 (1.01 - 1.56)	0.0373
LDV/SOF ± RBV	0.8235	2.28 (1.88 - 2.77)	<0.0001
Gender (ref. group: male)			
Female	0.7360	2.09 (1.39- 3.15)	0.0004
Age (ref. group: 65+)			
< 60	-0.2196	0.80 (0.69 - 0.94)	0.0056
60 – 64	-0.1457	0.86 (0.74 - 1.01)	0.0591
Race (ref. group: white)			
Black	-0.1920	0.83 (0.72 - 0.94)	0.0047
Other/Unknown	-0.1890	0.83 (0.68 - 1.01)	0.0576
Genotype (ref. group: 1)			
Other	-1.2616	0.28 (0.22 - 0.37)	<0.0001
Unknown	0.2421	1.27 (0.82 - 1.98)	0.2829
Disease Severity			
Cirrhosis	-0.2359	0.79 (0.68 - 0.92)	0.0020
Decompensated	-0.3596	0.70 (0.60 - 0.81)	<0.0001
HCC	-0.5115	0.60 (0.48 - 0.76)	<0.0001
Liver Transplant	0.8391	2.31 (1.63 - 3.29)	<0.0001
FIB4 (ref. group: < 1.45)			
1.45 - 3.25	-0.1377	0.87 (0.70 - 1.08)	0.2091
> 3.25	-0.6694	0.51 (0.41 - 0.64)	<0.0001
Unknown	-0.4780	0.62 (0.48 - 0.80)	0.0003
Comorbidities			
HIV	0.0154	1.01 (0.75 - 1.37)	0.9193
HBV	-0.0200	0.98 (0.80 - 1.20)	0.8490
Diabetes	-0.0121	0.99 (0.87 - 1.12)	0.8508
Obesity	-0.2929	0.75 (0.59 - 0.95)	0.0171
Previous Treatment Status (ref. group: naïve)			
Experienced	-0.1096	0.90 (0.79 - 1.02)	0.0903
Ribavirin Use (ref. group: no)			
Yes	0.1083	1.11 (0.96 - 1.30)	0.1607

† SIM = simeprevir, SOF = sofosbuvir, LDV = ledipasvir,
3D = ombitasvir/paritaprevir/ritonavir+dasabuvir, RBV = ribavirin, HCC = hepatocellular carcinoma, HIV = human immunodeficiency virus, HBV = hepatitis B, ref. = reference