



Effectiveness of Sofosbuvir, Ledipasvir/Sofosbuvir, or Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir Regimens for Treatment of Patients With Hepatitis C in the Veterans Affairs National Health Care System

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BACKGROUND & AIMS: We investigated the real-world effectiveness of sofosbuvir, ledipasvir/sofosbuvir, and paritaprevir/ritonavir/ombitasvir and dasabuvir (PrOD) in treatment of different subgroups of patients infected with hepatitis C virus (HCV) genotypes 1, 2, 3, or 4. **METHODS:** We performed a retrospective analysis of data from 17,487 patients with HCV infection (13,974 with HCV genotype 1; 2131 with genotype 2; 1237 with genotype 3; and 135 with genotype 4) who began treatment with sofosbuvir (n = 2986), ledipasvir/sofosbuvir (n = 11,327), or PrOD (n = 3174), with or without ribavirin, from January 1, 2014 through June 20, 2015 in the Veterans Affairs health care system. Data through April 15, 2016 were analyzed to assess completion of treatments and sustained virologic response 12 weeks after treatment (SVR12). Mean age of patients was 61 ± 7 years, 97% were male, 52% were non-Hispanic white, 29% were non-Hispanic black, 32% had a diagnosis of cirrhosis (9.9% with decompensated cirrhosis), 36% had a Fibrosis-4 index score >3.25 (indicator of cirrhosis), and 29% had received prior antiviral treatment. **RESULTS:** An SVR12 was achieved by 92.8% (95% confidence interval [CI], 92.3%–93.2%) of subjects with HCV genotype 1 infection (no significant difference between ledipasvir/sofosbuvir and PrOD regimens), 86.2% (95% CI, 84.6%–87.7%) of those with genotype 2 infection (treated with sofosbuvir and ribavirin), 74.8% (95% CI, 72.2%–77.3%) of those with genotype 3 infection (77.9% in patients given ledipasvir/sofosbuvir plus ribavirin, 87.0% in patients given sofosbuvir and pegylated-interferon plus ribavirin, and 70.6% of patients given sofosbuvir plus ribavirin), and 89.6% (95% CI 82.8%–93.9%) of those with genotype 4 infection. Among patients with cirrhosis, 90.6% of patients with HCV genotype 1, 77.3% with HCV genotype 2, 65.7% with HCV genotype 3, and 83.9% with HCV genotype 4 achieved an SVR12. Among previously treated patients, 92.6% with genotype 1; 80.2% with genotype 2; 69.2% with genotype 3; and 93.5% with genotype 4 achieved SVR12. Among treatment-naïve patients, 92.8% with genotype 1; 88.0% with genotype 2; 77.5% with genotype 3; and 88.3% with genotype 4 achieved SVR12. Eight-week regimens of ledipasvir/sofosbuvir produced an SVR12 in 94.3% of eligible

patients with HCV genotype 1 infection; this regimen was underused. **CONCLUSIONS:** High proportions of patients with HCV infections genotypes 1–4 (ranging from 75% to 93%) in the Veterans Affairs national health care system achieved SVR12, approaching the results reported in clinical trials, especially in patients with genotype 1 infection. An 8-week regimen of ledipasvir/sofosbuvir is effective for eligible patients with HCV genotype 1 infection and could reduce costs. There is substantial room for improvement in SVRs among persons with cirrhosis and genotype 2 or 3 infections.

Keywords: Harvoni; Viekira; DAA; VA.

The introduction of sofosbuvir (SOF) in December of 2013 and ledipasvir/sofosbuvir (LDV/SOF) and paritaprevir/ritonavir/ombitasvir and dasabuvir (PrOD) in October and December of 2014, respectively, made highly effective, well-tolerated, non-interferon-based antiviral regimens for hepatitis C virus (HCV) infection available for the first time. These regimens were reported in clinical trials to have sustained virologic response (SVR) rates well in excess of 90%,^{1–9} with the exception of certain subgroups, such as patients with Child's B or C cirrhosis¹⁰ and those infected with genotype 3 HCV.¹¹

Prior interferon-based antiviral regimens had significantly lower SVR rates in real-world clinical practice than in clinical trials.^{12–17} It is unclear if this is the case for current interferon-free regimens, or whether the relative ease of administration of these regimens has narrowed the SVR gap

Abbreviations used in this paper: CI, confidence interval; DAA, direct antiviral agent; FDA, US Food and Drug Administration; FIB-4, Fibrosis-4 Index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD-9, International Classification of Diseases, 9th revision; LDV, ledipasvir; PEG, pegylated interferon; PrOD, paritaprevir/ritonavir/ombitasvir and dasabuvir; RIBA, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; VA, Veterans Affairs.

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between clinical trials and clinical practice. Some non-US Food and Drug Administration (FDA)-approved regimens have been used widely in clinical practice, but it is unclear if they are as effective as FDA-approved regimens and whether they are used in appropriate patient groups. Finally, for HCV genotypes and patient subgroup for which multiple regimens exist, it is uncertain whether there are substantial differences in effectiveness between regimens.

We aimed to describe and compare the real-world effectiveness of SOF, LDV/SOF, and PrOD-based regimens among clinically relevant patient subgroups in a national health care system. Such data on effectiveness are important for guiding patients and providers in making decisions about treatment regimens and timing of treatment, as well as informing policy around treatment coverage.

Methods

Data Source: The Veterans Affairs Corporate Data Warehouse

The Veterans Affairs (VA) health care system includes 167 medical centers and 875 ambulatory care and community-based outpatient clinics throughout the United States. It is the largest integrated health care provider for HCV-infected patients in the United States. There were 174,889 patients with diagnosed HCV infection in VA care in 2014 and an estimated additional 45,000 patients with undiagnosed HCV infection.¹⁵ The VA utilizes electronic medical records almost exclusively. We extracted electronic data on all patients in VA care who received HCV antiviral treatments using the VA Corporate Data Warehouse, a national, continually updated repository of data from the VA's computerized patient records.¹⁸ Data extracted included all patient pharmacy prescriptions, demographic characteristics, inpatient and outpatient visits, problem lists, procedures, vital signs, diagnostic tests, and laboratory tests.

Study Population and Antiviral Regimens

Of 24,089 HCV antiviral regimens initiated in the VA nationally during the 18-month period from January 1, 2014 (the month after SOF was approved by the FDA) to June 30, 2015 and completed before October 1, 2015, we excluded 6193 regimens that were no longer used or recommended by the time we analyzed our data (eg, SOF and simeprevir±ribavirin or SOF+pegylated interferon [PEG]/RIBA for genotype 1-infected patients) (Figure 1A). We additionally excluded 409 duplicate regimens, in which the same patient appeared to have received one very short regimen (eg, 14-day regimen) followed at a later date by a longer course of the same regimen (these short, duplicate regimens were most likely erroneous or postponed prescriptions) leaving 17,487 patients in the current analysis, all of which included the direct antiviral agents (DAAs) SOF, LDV/SOF, or PrOD.

Duration of therapy was determined as the total duration of the DAA prescriptions filled. A course was considered terminated if medications were not refilled within 45 days after the final prescription was exhausted. Data extended backward to October 1, 1999, in order to allow determination of previous antiviral treatments and medical history, and forward until April 15, 2016, in order to allow completion of treatments and ascertainment of SVR.

Baseline Characteristics

All baseline characteristics were ascertained using data recorded before the initiation of antiviral treatment. We ascertained age race, ethnicity, sex, receipt of a prior antiviral regimen since 1999 (treatment experienced); diagnosis of cirrhosis (defined by International Classification of Diseases, 9th revision (ICD-9) codes for cirrhosis with alcoholism (571.2) or cirrhosis no mention of alcohol (571.5) or by the presence of decompensated cirrhosis defined by the ICD-9 codes for esophageal varices with or without bleeding (456.0–456.21), ascites (789.5), spontaneous bacterial peritonitis (567.23), hepatic encephalopathy (572.2), and hepatorenal syndrome (572.4); hepatocellular carcinoma (defined by ICD-9 code 155.0^{19–22}); diabetes (ICD-9 codes 250.0–250.92 or prescription of diabetes medications); and liver transplantation (ICD-9 code 996.82, V42.7). Patients with cirrhosis or hepatocellular carcinoma (HCC) who underwent liver transplantation were excluded from the cirrhosis or HCC categories. We used ICD-9 codes to define depression (311.0–311.9), post-traumatic stress disorder (309.81), anxiety or panic (300.0–300.9), and schizophrenia (295.0–295.9). Alcohol use disorders were identified by ICD-9 codes for alcohol abuse (305.00–305.03), dependence (303.90–303.93), and withdrawal (291.81). Substance use disorders were defined by codes for substance abuse (305.2–305.9), dependence (304.0–304.9), or drug withdrawal (292.0). These conditions were noted only if recorded at least twice before treatment initiation in any inpatient or outpatient encounter. These ICD-9-based definitions of cirrhosis and HCC,^{19–24} as well as the other comorbidities,^{14,21,25–28} have been widely used and validated in VA medical records.

We extracted all laboratory tests shown in Table 1 and recorded the value of each test closest to the treatment starting date within the preceding 6 months. We calculated the Fibrosis-4 Index (FIB-4) score²⁹ ($FIB-4 = [age \times aspartate \text{ amino-transferase}] / [platelets \times alanine \text{ aminotransferase}]^{1/2}$), which is associated with advanced fibrosis and cirrhosis. Of 17,487 regimens, 678 had missing genotype information. These patients were treated with either PrOD±ribavirin (n = 130) or LDV/SOF monotherapy (n = 548) and were assigned genotype 1 because these regimens are used almost exclusively for genotype 1 HCV. Among patients with known genotype treated with these regimens 11,761 of 11,871 (99%) had genotype 1 HCV.

Sustained Virologic Response

SVR was defined by a viral load below the limit of quantification performed >12 weeks after the end of treatment.³⁰ If no viral load test was available >12 weeks after the end of treatment, then SVR was defined by a viral load performed 4 to 12 weeks after the end of treatment, which accounted for only 996 additional SVR determinations. This was justified because SVR ascertained based on viral load 4 weeks after the end of treatment was shown to have 98% concordance (positive predictive value 98%; negative predictive value 100%) with SVR ascertained based on viral load >12 weeks after the end of treatment in SOF-treated patients.³⁰

Statistical Analysis

We determined SVR rates and their 95% confidence intervals (CIs) by regimen, genotype, and clinically significant

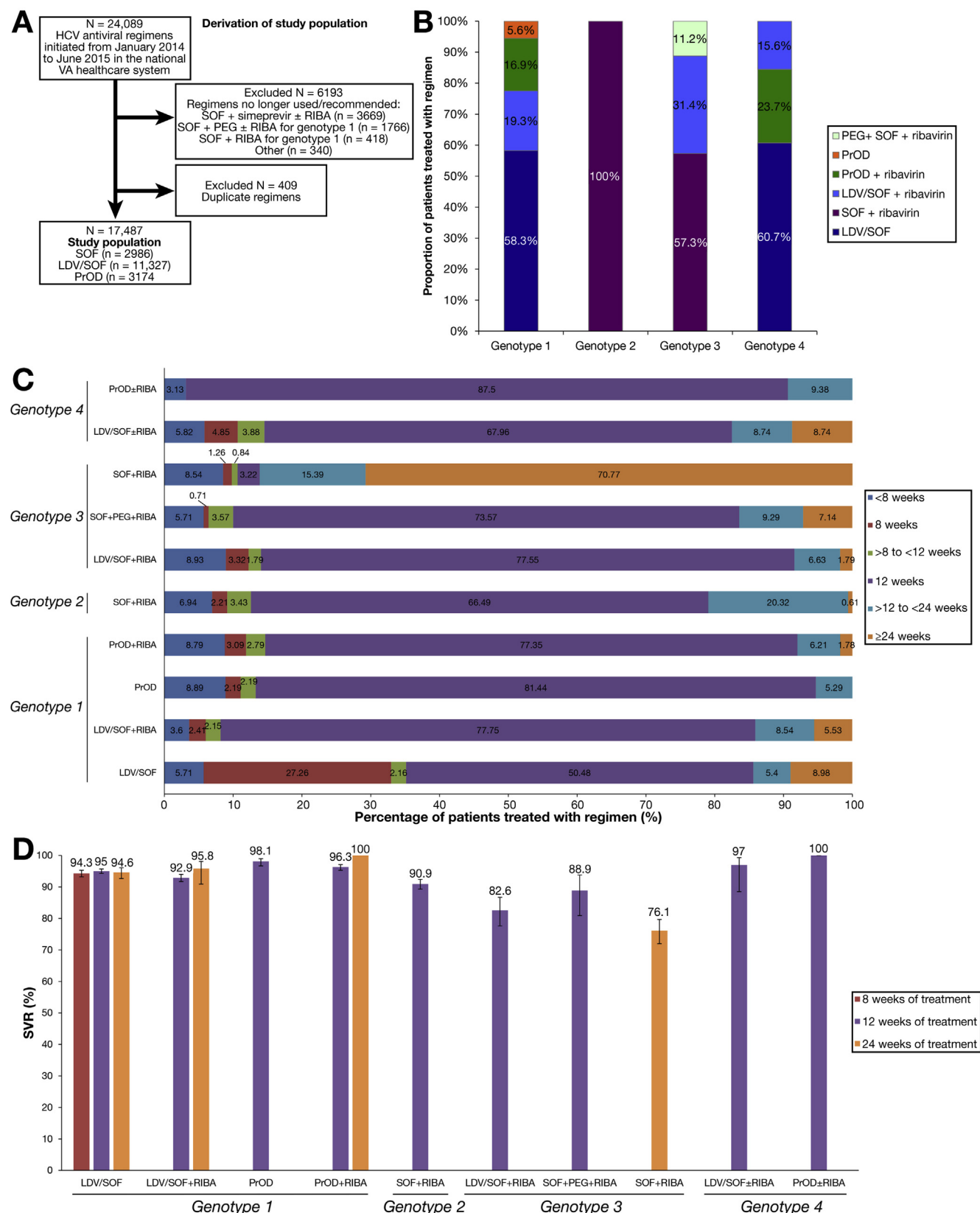


Figure 1. Study population, duration of antiviral treatment and SVR. (A) Derivation of study population. (B) Distribution of HCV antiviral regimens by genotype during period January 2014 to June 2015. (C) Proportions of patient completing treatment durations of <8 weeks, 8 weeks, >8 to <12 weeks, >12 to <24 weeks, and ≥24 weeks, by genotype and treatment regimen. (D) SVR in patients completing 8 weeks, 12 weeks, or 24 weeks of treatment, by genotype and treatment regimen.

Table 1. Baseline Characteristics of 17,487 Patients Who Initiated Antiviral Treatment in the Veterans Affairs Nationally From January 2014 to June 2015

Characteristic	All patients, n (%) ^a	Genotype 1, % ^b				Genotype 2, % ^b		Genotype 3, % ^b			Genotype 4, % ^b	
		LDV/ SOF	LDV/SOF+ RIBA	PrOD	PrOD+ RIBA	SOF+ RIBA		LDV/SOF+ RIBA	SOF+PEG+ RIBA	SOF+ RIBA	LDV/SOF± RIBA	PrOD± RIBA
All patients	17,487 (100)	8140	2692	776	2366	2131		392	140	715	103	32
Age, y, mean (SD)	61 (7)	61 (6)	62 (5)	62 (6)	61 (6)	61 (7)		58 (8)	58 (5)	58 (8)	60 (7)	60 (8)
Male	16,920 (97)	96	97	97	98	97		98	97	98	94	100
Race/ethnicity												
White, non-Hispanic	9141 (52)	46	52	40	48	70		74	68	77	58	48
Black, non-Hispanic	5043 (29)	36	27	45	32	8.9		2.0	6.1	3.4	32	39
Hispanic	913 (5.3)	4.3	6.8	3.0	5.6	6.1		7.8	8.2	7.3	6.6	0
Asian, Pacific Islander, American Indian	280 (1.6)	1.4	1.6	0.6	2.0	1.6		3.2	2.7	2.7	0	3.0
Declined to answer, missing	2110 (12)	12	13	11	13	13		13	15	9.8	2.8	9.0
Treatment experienced	5109 (29)	25	56	21	26	23		26	48	31	26	24
Prior interferon	4680 (27)	22	51	20	24	21		23	48	28	24	24
Prior boceprevir	929 (5.3)	5.4	17	0.9	1.6	0		0	0	0	0	0
Prior telaprevir	225 (1.3)	1.3	4.5	0.1	0.04	0		0	0	0	0	0
Prior simeprevir+SOF	306 (1.8)	1.5	6.5	0.6	0.9	0		0	0	0	0	0
Prior SOF	741 (4.2)	2.9	14	1.2	2.2	2.6		5.4	2.7	2.6	3.8	0
Prior LDV/SOF	142 (0.8)	1.2	1.2	0.6	0.4	0		0.5	0	0.5	0.9	0
Prior PrOD	68 (0.4)	0.2	0.4	0.6	1.5	0		0	0	0	0	0
HCV RNA viral load >6 million IU/mL	3248 (19)	17	16	22	23	24		15	15	15	14	6
HIV co-infection	713 (4.1)	6.0	3.7	2.1	1.4	2.4		2.0	4.1	1.8	8.5	3.0
Cirrhosis	5250 (30)	23	58	6.8	29	25		35	54	43	25	25
Decompensated cirrhosis	1448 (8.3)	5.9	18	0.9	4.5	7.9		13	11	16	7.8	9.4
Hepatocellular carcinoma	482 (2.8)	2.1	6.1	0.6	2.0	1.6		4.9	4.3	4.3	1.9	3.1
Liver transplantation	391 (2.2)	1.7	7.5	0.1	0.2	1.5		3.2	0.7	3.2	1.9	0
Diabetes	5106 (29)	30	38	29	25	27		25	20	25	27	18
Alcohol use disorder	7720 (44)	44	45	38	40	45		53	50	51	37	42
Substance use disorder	6466 (37)	39	33	33	34	35		43	40	43	41	36
Depression	8284 (47)	49	51	41	43	45		49	51	51	52	48
PTSD	4689 (27)	28	27	23	25	26		26	18	26	28	15
Anxiety/panic	5961 (34)	35	34	28	31	35		37	32	38	41	33
Schizophrenia	941 (5.4)	6.1	4.5	4.7	4.5	5.4		4.2	2.0	4.4	3.8	9.1
Laboratory results												
Anemia ^c	2541 (15)	17	17	13	9	13		11	11	13	14	6
Platelet count <100 k/ μ L	2368 (14)	11	26	1	11	14		21	22	26	7.6	9.1
Creatinine >1.1 mg/dL	3384 (20)	22	21	22	18	17		12	8.2	12	23	17
Bilirubin >1.1 g/dL	294 (14)	12	24	6	11	14		17	14	22	11	9

Table 1. Continued

Characteristic	All patients, n (%) ^a	Genotype 1, % ^b				Genotype 2, % ^b		Genotype 3, % ^b				Genotype 4, % ^b			
		LDV/ SOF	LDV/SOF + RIBA	PrOD + RIBA	PrOD	SOF + RIBA		LDV/SOF + RIBA	SOF + PEG + RIBA	SOF + RIBA		LDV/SOF + RIBA	LDV/SOF + RIBA	PrOD + RIBA	PrOD
Albumin <3.6 g/dL	3564 (20)	19	35	17	10	16		21	20	25		19	18	18	
INR >1.1	3653 (22)	20	31	18	9.8	24		29	25	33		18	9.3	21	
FIB-4 ^c score >3.25	5960 (36)	31	55	34	12	35		49	53	58		26	21		

INR, international normalized ratio; PTSD, post-traumatic stress disorder.

^aData are n (%) except age, which is mean (SD).

^bData are percentages, except age, which is mean (SD), and all patients, which is n (%).

^cAnemia is defined as a hemoglobin concentration <13 g/dL in men or <12 g/dL in women.

^dFIB-4 score²⁹ = [age × aspartate aminotransferase] / [platelets × alanine aminotransferase^{1/2}].

subgroup. We developed multivariable logistic regression models predicting SVR using age, sex, race/ethnicity, history of alcohol use disorders, HCV genotype and subgenotype, HCV regimen, baseline HCV viral load, diabetes, treatment naïve/experienced, cirrhosis, decompensated cirrhosis, HCC, liver transplantation, platelet count, serum bilirubin and albumin levels, separately for each genotype or for all patients combined in order to identify significant predictors of SVR.

Genotypes 1 and 3 have multiple treatment regimen options available requiring additional analytical methods to determine the association between regimen and SVR, because the regimens were not randomly assigned. We chose to use an augmented inverse-probability-weighted method using propensity scores as weights to estimate the average treatment effect of different regimens on achieving SVR for these genotypes.³¹ Augmented inverse-probability-weighted estimators are doubly robust and provide consistent estimates in the case of correct specification of either the treatment assignment propensity score model (multinomial logit) or the SVR outcome model (logit). After the removal of 304 (2%) genotype 1 and 34 (3%) genotype 3 patients without sufficient overlap, positivity was assumed. Exchangeability was assumed by the inclusion of the following confounders in the regimen assignment model: race/ethnicity, baseline HCV viral load, diabetes, treatment naïve/experienced, cirrhosis, decompensated cirrhosis, HCC, platelet count, serum bilirubin, and albumin levels. The same predictors were used in the SVR outcome model as those listed here for the multivariable logistic regression.

We anticipated that viral load testing necessary to ascertain SVR might be missing in a proportion of patients. To estimate the impact that missing SVR data might have, we used multiple imputation to impute missing SVR values in secondary analyses. Missing SVR values were imputed using a logistic regression model that included duration of treatment together with 24 baseline patient characteristics shown in Table 1, including regimen, genotype, treatment experience/naïve, cirrhosis, and HCC. The number of imputations was varied from 10 to 200, resulting in estimates that were identical up to 4 significant digits. The model was determined stable and an $m = 20$ imputations were used. Data were assumed to be missing at random. This assumption was verified using observed data.

Analyses were performed using STATA MP version 14 (StataCorp, College Station, TX).

Results

Treatment Regimens by Genotype

Among HCV genotype 1-infected patients ($n = 13,974$), the majority were treated with LDV/SOF alone (58%) or in combination with ribavirin (19%), while PrOD regimens with (17%) or without (5.5%) ribavirin were used much less frequently (Figure 1B). Genotype 2-infected patients ($n = 2131$) were all treated with SOF and ribavirin. The majority of genotype 3-infected patients ($n = 1247$) were treated with SOF and ribavirin (57%), followed by LDV/SOF and ribavirin (31%) and SOF+PEG+ribavirin (11%). Genotype 4-infected patients ($n = 135$) were treated mostly with LDV/SOF alone (61%) or in combination with ribavirin (16%), while the remaining 23% received PrOD with ribavirin.

Patient Characteristics

The mean age of antiviral treatment recipients was 61 ± 7 years, 97% were male, 52% were non-Hispanic white, 29% were non-Hispanic black, 32% had a diagnosis of cirrhosis (including 9.9% with decompensated cirrhosis), 36% had an FIB-4 score >3.25 (suggestive of cirrhosis), 3.7% had HCC and 29% were treatment-experienced (Table 1). Among genotype 1-infected patients, those treated with LDV/SOF and ribavirin were more than twice as likely to be treatment-experienced and to have cirrhosis, decompensated cirrhosis, or HCC than patients treated with LDV/SOF monotherapy or PrOD regimens. Almost all liver transplantation recipients with genotype 1 infection were treated with LDV/SOF rather than PrOD regimens. Among genotype 3-infected patients, those treated with SOF+PEG+ribavirin were more likely to be treatment-experienced and to have cirrhosis than those treated with SOF+ribavirin or LDV/SOF+RIBA. Genotype 2- and 3-infected patients were much more likely to be white and less likely to be black than genotype 1- and 4-infected patients.

Early Discontinuation of Treatment

Early discontinuation of treatment in <8 weeks occurred in 6.3% ($n = 1098$) among all patients who initiated antiviral treatment ($n = 17,487$) and in 4.4% ($n = 700$) among those with available SVR data ($n = 15,884$). Among genotype 1-infected patients, early discontinuation in <8 weeks was more common in PrOD (8.9%) and PrOD plus ribavirin (8.8%) regimens than in LDV/SOF (5.7%) or LDV/SOF plus ribavirin (3.6%) regimens ($P < .001$) (Figure 1C and Supplementary Table 1). Early discontinuation in <8 weeks was more common in genotype 3-infected patients (8.3%) than in genotype 2 (7.0%) or genotype 1 (6.0%) patients. Early discontinuation was not more common in patients with cirrhosis (5.2%), decompensated cirrhosis (6.1%), or age ≥ 65 years (6.5%), but was slightly more common in black (7.0%), Hispanic (8.4%), and Asian/Pacific Islander/American Indian/Alaska Native (7.9%) patients than in white patients (5.7%).

Overall Sustained Virologic Response Rates by Genotype

Of 17,487 patients, SVR data were available in 15,884 (91%) and are reported here and in Tables 2–5 and Figures 1 and 2.

SVR rates were 90.7% overall and were higher in genotype 1 (SVR 92.8%; 95% CI, 92.3%–93.2%) and genotype 4-infected patients (SVR 89.6%; 95% CI, 82.8%–93.9%) than genotype 2 (SVR 86.2%; 95% CI, 84.6%–87.7%) or 3 (SVR 74.8%; 95% CI, 72.2%–77.3%) patients. Among genotype 1-infected patients, all 4 regimens studied had similarly high SVR rates, ranging from 92.0% to 94.9%, with no significant difference between LDV/SOF and PrOD regimens in unadjusted SVR rates (Table 2 and Figure 2A). Although paradoxically the LDV/SOF and PrOD regimens without ribavirin seemed to have slightly higher SVR rates than the regimens with ribavirin, this can be explained by

the higher prevalence of adverse predictors in the combination regimens and by the fact that almost all patients treated with PrOD monotherapy had genotype 1b infection, as shown in Supplementary Table 2. Genotype 1b patients had slightly higher SVR than genotype 1a patients treated with PrOD+ribavirin regimens (94.2% vs 91.7%), but there was almost no difference between genotype 1a and 1b for LDV/SOF regimens (Supplementary Table 2).

Among genotype 3-infected patients, the best SVR was achieved in those treated with SOF+PEG+RIBA (SVR, 86.5%; 95% CI, 79.2%–91.5%), followed by LDV/SOF and ribavirin (SVR, 79.5%; 95% CI, 74.6%–83.7%) and last SOF plus ribavirin (SVR, 70.1%; 95% CI, 66.2%–73.7%), even though SOF plus ribavirin is a 24-week regimen.

Utilization and Sustained Virologic Response Rates of 8-Week Ledipasvir/Sofosbuvir Regimens

VA guidelines recommended that treatment-naïve, non-cirrhotic, genotype 1-infected patients with a viral load <6 million IU/mL can be treated with LDV/SOF monotherapy for only 8 weeks, rather than 12 weeks. However, this regimen is based on a post-hoc analysis of the ION-3 study,³ is not FDA-approved, and it is unclear if it is widely utilized. We found that of 8140 patients who received LDV/SOF monotherapy, 2219 (27.3%) received only 8 weeks of treatment and had an overall SVR of 94.3% (Table 2 and Figure 1). However, of 4066 treatment-naïve, non-cirrhotic patients with a viral load <6 million IU/mL who received LDV/SOF monotherapy, only a minority ($n = 1975$ [48.6%]) received 8 weeks of treatment and achieved an SVR of 95.1% (95% CI, 94.0%–96.0%), and 1556 (38%) received 12 weeks of treatment and achieved a very similar SVR of 95.8% (95% CI, 94.7%–96.8%; $P = .6$).

Utilization and Sustained Virologic Response Rates of 24-Week Ledipasvir/Sofosbuvir and Paritaprevir/Ritonavir/Ombitasvir Regimens

Although 24-week LDV/SOF or PrOD regimens are FDA-approved and American Association for the Study of Liver Diseases/Infectious Diseases Society of America-recommended³² for cirrhotic patients (PrOD, genotype 1) or for treatment-experienced cirrhotic patients (LDV/SOF, genotype 1), they were rarely used in practice. Among all genotype 1-infected patients, only 1.8% of PrOD+ribavirin regimens, 9.5% of LDV/SOF regimens, and 5.0% of LDV/SOF+ribavirin regimens extended to 24 weeks (Table 3), and there was little difference in SVR between 12-week and 24-week regimens overall (Table 3 and Figure 1). Limiting to the specific subpopulations for which 24-week regimens are recommended, PrOD+ribavirin regimens extended to 24 weeks only in 5.9% of cirrhotic patients, which was too small a number to allow robust estimates of SVR; however, 12 weeks of PrOD+ribavirin resulted in very high SVR rates in both treatment-naïve (97.4%) and treatment-experienced (98.5%) cirrhotic patients (Table 3), leaving little room for further improvement in SVR by extending to 24 weeks.

Table 2. Sustained Virologic Response Rates (95% Confidence Intervals) in 15,884^a Patients Who Initiated Antiviral Treatment in the Veterans Affairs Nationally From January 2014 to June 2015

	n	All patients	Genotype 1, SVR, % (95% CI)				Genotype 2, SVR, % (95% CI)		Genotype 3, SVR, % (95% CI)			Genotype 4, SVR, % (95% CI)	
			LDV/SOF	LDV/SOF+ RIBA	PrOD	PrOD+ RIBA	SOF+ RIBA		LDV/SOF+ RIBA	SOF+ PEG+ RIBA	SOF+ RIBA	LDV/SOF± RIBA	PrOD± RIBA
n		15,884	7412	2500	704	2128	1910		344	131	630	97	28
All patients	15,884	90.7 (90.2–91.1)	92.9 (92.2–93.3)	92.0 (90.9–93.0)	94.9 (92.9–96.3)	92.5 (91.3–93.5)	86.2 (84.6–87.7)		77.9 (73.1–82.0)	87.0 (80.0–91.8)	70.6 (66.9–74.1)	87.6 (79.3–92.9)	96.4 (76.3–99.5)
Patients who completed 8-wk treatment	2027	NA	94.3 (93.2–95.3)	NA	NA	NA	NA		NA	NA	NA	NA	NA
12-wk treatment	9921	94.0 (93.5–94.4)	95.0 (94.3–95.7)	92.9 (91.7–94.0)	98.1 (96.7–99.0)	96.3 (95.3–97.1)	90.9 (89.3–92.4)		82.6 (77.6–86.7)	88.9 (80.9–93.8)	NA	97.0 (88.5–99.3)	100
24-wk treatment	1383	88.1 (86.3–89.7)	94.6 (92.7–96.1)	95.8 (90.9–98.1)	NA	100	NA		NA	NA	76.1 (72.0–79.7)	NA	NA
SVR in the following subgroups													
No cirrhosis	11,111	92.3 (91.8–92.8)	93.5 (92.8–94.1)	95.6 (94.1–96.7)	94.8 (92.8–96.3)	92.1 (90.6–93.5)	89.1 (89.1–90.6)		84.8 (79.4–88.9)	93.4 (83.4–97.6)	77.6 (72.9–81.6)	90.3 (80.7–95.4)	95.5 (70.4–99.5)
Cirrhosis	4773	86.8 (85.8–87.7)	90.5 (88.9–91.9)	89.4 (87.7–90.9)	95.7 (83.8–99.0)	93.4 (91.1–95.1)	77.3 (73.3–80.8)		65.3 (56.3–73.3)	81.4 (70.3–89.0)	61.9 (56.0–67.4)	80.0 (58.3–92.0)	100
FIB-4 score ≤3.25	9695	92.5 (92.0–93.0)	93.7 (93.0–94.3)	93.7 (92.1–95.0)	95.2 (93.1–96.6)	92.2 (90.6–93.5)	89.2 (87.3–90.9)		85.6 (79.4–90.2)	92.9 (82.0–97.4)	80.4 (74.9–84.9)	90 (80.2–95.2)	95.5 (70.4–99.5)
FIB-4 score >3.25	5418	87.4 (86.7–88.3)	90.9 (89.6–92.1)	90.7 (89.0–92.2)	92.6 (84.2–96.7)	93.1 (90.9–94.8)	80.8 (77.6–83.7)		69.0 (61.2–75.9)	81.0 (69.0–89.0)	62.7 (57.5–67.7)	80.8 (59.6–92.3)	100
Treatment-naïve	11,159	91.1 (90.6–91.6)	92.7 (92.0–93.4)	92.9 (91.2–94.3)	95.8 (93.8–97.2)	92.0 (90.6–93.3)	88.0 (86.3–89.6)		78.1 (72.3–82.7)	90.6 (80.3–95.9)	75.1 (70.8–79.0)	86.1 (75.8–92.5)	95.5 (70.4–99.5)
Treatment-experienced	4725	89.7 (88.7–90.5)	93.2 (91.9–94.3)	91.4 (89.8–92.7)	91.4 (85.7–95.0)	93.8 (91.4–95.5)	80.2 (76.2–83.6)		77.4 (67.0–85.2)	83.6 (72.4–90.8)	61.1 (54.0–67.6)	92.0 (70.9–98.2)	100

NA, not available.

^aThe number of patients is different from that in Table 1 because Table 2 includes only 15,884 patients with available SVR data (of 17,487 patients who initiated antiviral treatment).

Table 3. Sustained Virologic Response Rates in Genotype 1–Infected Patients by Duration of Treatment, Cirrhosis, and Prior Treatment

	LDV/SOF		LDV/SOF+RIBA		PrOD		PrOD+RIBA	
	n	SVR, % (95% CI)	n	SVR, % (95% CI)	n	SVR, % (95% CI)	n	SVR, % (95% CI)
Treatment-naïve								
No cirrhosis								
All durations	4485	93.4 (92.6–94.0)	522	96.7 (94.8–98.0)	519	95.8 (93.6–97.2)	1135	91.6 (89.9–93.1)
12 wk	2101	95.6 (94.7–96.4)	404	98.5 (96.7–99.3)	448	97.8 (95.9–98.8)	930	95.8 (94.3–96.9)
24 wk	NR	NR	NR	NR	NR	NR	NR	NR
Cirrhosis								
All durations	1131	90.1 (88.2–91.7)	579	89.5 (86.7–91.7)	34	97.1 (80.2–99.6)	445	93.0 (90.3–95.1)
12 wk	798	92.0 (89.9–93.7)	468	91.2 (88.3–93.5)	23	100	350	97.4 (95.1–98.7)
24 wk	141	92.2 (86.4–95.7)	22	95.5 (70.4–99.5)	NR	NR	NA ^a	NA ^a
Treatment-experienced								
No cirrhosis								
All durations	1237	94.1 (92.6–95.3)	538	94.4 (92.1–96.1)	138	91.3 (85.2–95.0)	373	93.6 (90.6–95.7)
12 wk	806	96.7 (95.2–97.7)	424	95.0 (92.5–96.8)	114	99.1 (93.9–99.9)	298	95.6 (92.6–97.5)
24 wk	147	96.6 (92.0–98.6)	NR	NR	NR	NR	NR	NR
Cirrhosis								
All durations	559	91.2 (88.6–93.3)	861	89.4 (87.2–91.3)	13	92.3 (53.1–99.2)	175	94.3 (89.6–96.9)
12 wk	127	94.5 (88.8–97.4)	668	89.4 (86.8–91.5)	NA	NA ^a	132	98.5 (94.0–99.6)
24 wk	332	93.7 (90.5–95.8)	85	94.1 (86.4–97.6)	NR	NR	NA	NA ^a

NA, not available; NR, not recommended for the specific subpopulation.

^aRegimens with <20 patients.

Among cirrhotic, treatment-experienced, genotype 1–infected patients, LDV/SOF regimens extended to 24 weeks in 58% of patients (SVR 94.1% for 24 weeks and 94.2% for 12 weeks), and LDV/SOF+ribavirin regimens in 11.5% of cases (SVR 95.8% for 24 weeks and 89.2% for 12 weeks) (Table 3).

Sustained Virologic Response Rates in Patients With Cirrhosis

Patients with a diagnosis of cirrhosis had lower SVR (86.8%) than patients without a diagnosis of cirrhosis (SVR 92.3%) (Table 2). The gap in SVR between cirrhotics and non-cirrhotics was much smaller among genotype 1 (90.6% vs 93.6% or 3% difference) than genotype 2 (77.3% vs 89.1% or 11.8% difference) or genotype 3 (65.7% vs 81.6% or 15.6% difference) infected patients (Figure 2B, Table 2 and Supplementary Table 3). Similar findings were observed when comparing patients with FIB-4 >3.25 vs ≤3.25. Consequently, among cirrhotic patients, there were large differences in SVR between genotype 1 (90.6%; 95% CI, 89.7%–91.5%), genotype 2 (77.3%; 95% CI, 73.3%–80.9%), and genotype 3 (65.7%; 95% CI, 61.2%–69.8%) infected patients. These findings demonstrate the high effectiveness of LDV/SOF and PrOD regimens in cirrhotic, genotype 1–infected patients and the relatively poor effectiveness of SOF regimens in genotype 2 and LDV/SOF and SOF regimens in genotype 3–infected cirrhotic patients.

Among genotype 1–infected cirrhotic patients, there was little difference in SVR between LDV/SOF±ribavirin and PrOD±ribavirin regimens (Figure 2C, Table 2). However,

among genotype 3–infected cirrhotic patients, there were great differences in SVR among SOF+PEG+RIBA (81.4%), LDV/SOF+RIBA (65.3%), and SOF+RIBA (61.9%).

Sustained Virologic Response Rates in Treatment-Experienced vs Treatment-Naïve Patients

There was almost no difference in SVR between treatment-experienced (92.6%; 95% CI, 91.7%–93.3%) and treatment-naïve (92.8%; 95% CI, 92.2%–93.3%) patients with genotype 1 infection, whereas this difference was more pronounced in genotype 2 (80.2% vs 88%) and genotype 3 patients (69.2% vs 77.5%) (Figure 2B, Table 2, and Supplementary Table 3). Among treatment-experienced patients, there were large differences in SVR between genotype 1 (92.6%; 95% CI, 91.7%–93.3%), genotype 2 (80.2%; 95% CI, 76.2%–83.6%), and genotype 3 (69.2%; 95% CI, 64.2%–73.9%) infected patients.

Among genotype 1–infected, treatment-experienced patients there was little difference in SVR between LDV/SOF±ribavirin and PrOD±ribavirin regimens (Figure 2D, Table 2). Among genotype 3–infected treatment-experienced patients, SVR was especially low in SOF+RIBA-treated patients (61.1%) compared with PEG+SOF+RIBA (83.6%) and LDV/SOF+RIBA (77.4%).

Among genotype 1–infected, treatment-experienced patients, SVR rates were >90% for patients previously treated with interferon (92.8%), boceprevir (94.7%), telaprevir (90.1%), or PrOD (96.8%), but they were <90% for patients previously treated with SOF (88.7%), simeprevir+SOF (87.0%), or LDV/SOF (87.7%) (Supplementary Table 4).

Independent Predictors of Sustained Virologic Response

Among all patients, the following characteristics were independent predictors of failure to achieve SVR in multivariable models: male sex, black race, Hispanic ethnicity, genotype 2 or 3 HCV, cirrhosis, diabetes, low platelet count,

low serum albumin level, and elevated serum bilirubin level (Table 4). Notable characteristics that were not associated with SVR included age, baseline HCV viral load, and history of alcohol use disorders. Treatment experience was associated with reduced likelihood of SVR only among genotype 2- and 3-infected patients, but not among genotype

Table 4. Predictors of Sustained Virologic Response by Genotype^a in Multivariable Logistic Regression Models

	All patients		Genotype 1		Genotype 2		Genotype 3	
	AOR ^b	P value	AOR ^b	P value	AOR ^b	P value	AOR ^b	P value
Age								
<55 y	1		1		1		1	
55 to <60 y	0.88	.2	0.87	.3	1.37	.2	0.58	.01
60 to <65 y	0.95	.6	0.84	.2	1.61	.05	0.73	.2
65 to <70 y	0.95	.6	0.86	.3	1.20	.5	1.12	.7
70 to <75 y	0.91	.6	0.86	.5	1.41	.4	0.81	.7
≥75 y	1.62	.2	1.22	.7	3.04	.09	NA	
Race/ethnicity								
White, non-Hispanic	1		1		1		1	
Black, non-Hispanic	0.81	.004	0.83	.02	0.49	.001	0.76	.5
Hispanic	0.79	.05	0.72	.04	1.14	.7	0.80	.4
Asian, Pacific Islander, American Indian	0.93	.7	0.84	.5	0.67	.4	1.77	.3
Declined to answer, missing	0.92	.4	0.76	.01	1.42	.1	1.31	.3
Sex								
Female	1		1		1		1	
Male	0.58	.01	0.55	.02	0.42	.1	0.98	.97
Alcohol use disorder								
No	1		1		1		1	
Yes	0.93	.2	0.91	.2	1.0	1.0	0.98	.9
Diabetes								
No	1		1		1		1	
Yes	0.81	.001	0.89	.1	0.69	.01	0.66	.01
Regimen ^c								
LDV/SOF	NA	NA	1		NA	NA	NA	NA
LDV/SOF+ribavirin	NA	NA	1.51	.001	NA	NA	1	
PrOD	NA	NA	0.63	.3	NA	NA	NA	NA
PrOD+ribavirin	NA	NA	1.04	.9	NA	NA	NA	NA
SOF+ribavirin	NA	NA	NA	NA	NA	NA	0.78	.04
PEG+SOF+ribavirin	NA	NA	NA	NA	NA	NA	2.65	.001
Genotype								
1	1		NA	NA	NA	NA	NA	NA
2	0.43	<.001	NA	NA	NA	NA	NA	NA
3	0.23	<.001	NA	NA	NA	NA	NA	NA
4	0.59	.08	NA	NA	NA	NA	NA	NA
Subgenotype								
a	NA		1		1		1	
b	NA	NA	1.33	.001	0.82	.7	NA	NA
None	NA	NA	1.42	.006	0.65	.4	NA	NA
HCV RNA viral load								
≤6 million IU/mL	1		1		1		1	
>6 million IU/mL	0.92	.3	0.83	.04	1.53	.02	0.83	.4
Cirrhosis								
No	1		1		1		1	
Yes	0.80	.002	0.88	.1	0.62	.007	0.67	.03
Prior treatment								
Treatment-naïve	1		1		1		1	
Treatment-experienced	0.92	.2	1.02	.8	0.59	.001	0.69	.02
Platelet count								
≥100 k/μL	1		1		1		1	
<100 k/μL	0.74	<.001	0.81	.06	0.46	<.001	0.84	.4

Table 4. Continued

	All patients		Genotype 1		Genotype 2		Genotype 3	
	AOR ^b	P value	AOR ^b	P value	AOR ^b	P value	AOR ^b	P value
Serum bilirubin								
≤1.1 g/dL	1		1		1		1	
>1.1 g/dL	0.81	.01	0.86	.06	0.83	.3	0.78	.2
Serum albumin								
≥3.6 g/dL	1		1		1		1	
<3.6 g/dL	0.81	.003	0.79	.007	1.13	.5	0.60	.007

NA, not available.

^aGenotype 4–infected patients were not modeled separately as there were too few for robust multivariable models.

^bAOR, adjusted odds ratio, by multivariable logistic regression modeling including the following variables: age, sex, race/ethnicity, history of alcohol use disorders, HCV genotype and subgenotype, HCV regimen, baseline HCV viral load, diabetes, treatment naïve/experienced, cirrhosis, decompensated cirrhosis, HCC, liver transplantation, platelet count, serum bilirubin and albumin levels.

^cThe effect of regimen on SVR was estimated using augmented inverse-probability-weighted logistic regression to account for the propensity of receiving each regimen.

1–infected patients. Also, cirrhosis was more strongly associated with reduced likelihood of SVR in genotypes 2 and 3 than in genotype 1.

We employed augmented inverse-probability-weighted methods using propensity scores specifically to look at the association between regimen and SVR among genotype 1– or 3–infected patients. Among genotype 1–infected patients, there was no significant difference between LDV/SOF±ribavirin regimens and PrOD±ribavirin regimens (Table 4). Addition of ribavirin to LDV/SOF, which was much more common in cirrhotic and treatment-experienced patients, was associated with a significantly higher likelihood of SVR (adjusted odds ratio, 1.51; $P = .001$), suggesting that

ribavirin was appropriately used more commonly in patients with cirrhosis and treatment experience. Among genotype 3–infected patients, PEG+SOF+ribavirin was significantly better, while SOF+ribavirin was significantly worse than LDV/SOF+ribavirin.

Impact of Missing Sustained Virologic Response Data and Imputation for Missing Sustained Virologic Response

SVR data were missing in 1603 of the 17,487 patients who received antiviral treatment (9%). It is possible that patients lacking data on SVR were more likely to have been

Table 5. Comparison of Observed Sustained Virologic Response Among Patients With Available Sustained Virologic Response Data ($n = 15,884$) and Combined Observed or Imputed Sustained Virologic Response Among All Patients Who Initiated Antiviral Treatment ($n = 17,487$)

	Observed SVR, % (95% CI) ($n = 15,884$)	Observed SVR or Imputed SVR ^a for patients missing SVR data, % (95% CI) ($n = 17,301$)	SVR assuming all patients with missing SVR data did not achieve SVR, % (95% CI) ($n = 17,487$)
All patients	90.7 (90.2–91.1)	90.0 (90–91)	82.4 (81.8–82.9)
Genotype 1	92.8 (92.3–93.2)	92.2 (92–93)	84.6 (84.0–85.2)
LDV/SOF	92.9 (92.2–93.3)	93 (92–93)	84.5 (83.7–85.3)
LDV/SOF+RIBA	92.0 (90.9–93.0)	92 (90–93)	85.5 (84.1–86.8)
PrOD	94.9 (92.9–96.3)	94 (92–96)	86.1 (83.5–88.3)
PrOD+RIBA	92.5 (91.3–93.5)	91 (90–92)	83.2 (81.6–84.6)
Genotype 2			
SOF+RIBA	86.2 (84.6–87.7)	85 (84–87)	77.2 (75.4–79.0)
Genotype 3	74.8 (72.2–77.3)	73.9 (71–77)	66.3 (63.6–68.9)
LDV/SOF+RIBA	77.9 (73.1–82.0)	77 (73–82)	68.4 (63.6–72.8)
SOF+PEG+RIBA	87.0 (80.0–91.8)	86 (80–92)	81.4 (74.0–87.1)
SOF+RIBA	70.6 (66.9–74.1)	70 (66–73)	62.2 (58.6–65.7)
Genotype 4	89.6 (82.8–93.9)	86.9 (81–93)	83.0 (75.6–88.5)
LDV/SOF±RIBA	87.6 (79.3–92.9)	86 (78–93)	82.5 (73.8–88.8)
PrOD±RIBA	96.4 (76.3–99.5)	90 (78–100)	84.3 (66.3–93.7)

^aImputed by multiple imputation using a logistic regression model that included duration of treatment together with 24 baseline patient characteristics shown in Table 1. The number of patients is slightly less than 17,487 due to missing data in the characteristics used to impute SVR.

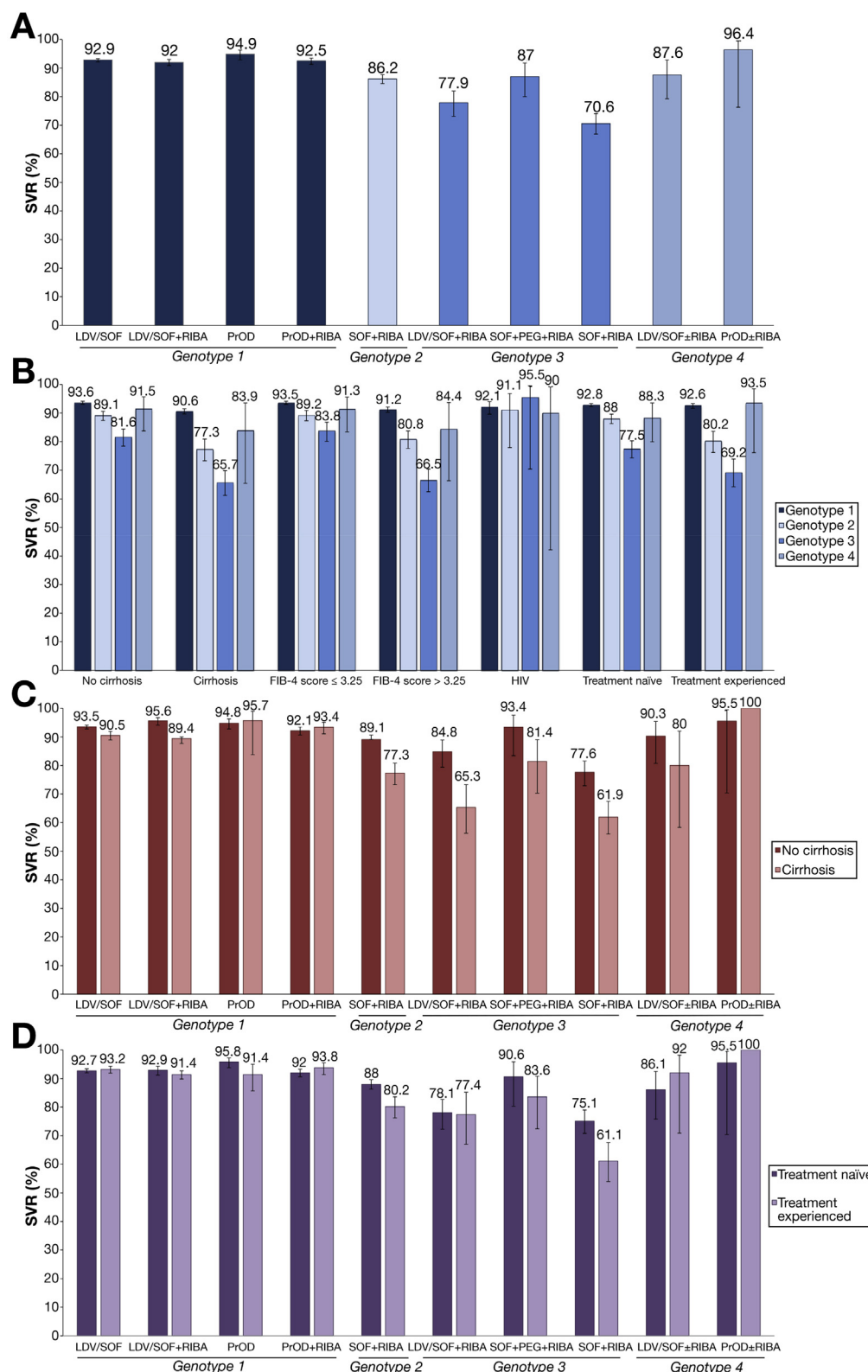


Figure 2. SVR rates by genotype and antiviral regimen. (A) SVR in all patients by genotype and treatment regimen. (B) SVR in subpopulations by genotype. (C) SVR in patients with vs without cirrhosis by genotype and treatment regimen. (D) SVR in treatment naïve vs experienced patients by genotype and treatment regimen.

lost follow-up or to discontinue therapy early or to have other predictors of poor response, which would mean that the observed SVR rates we report in [Tables 2 and 3](#) and [Figures 1B and 2](#) are overestimates. However, patients with vs without SVR data had very similar characteristics with

respect to race/ethnicity, age, HCV genotype, cirrhosis, decompensated cirrhosis, and most other baseline characteristics ([Supplementary Table 5](#)). Patients with missing SVR did indeed have a higher rate of early treatment discontinuation at <8 weeks compared with those with

available SVR data (25% vs 4.4%). However, the majority (75%) completed 8 or more weeks of treatment and the mean duration of treatment was 71 ± 38 days compared with 87 ± 31 days in patients with available SVR data. The majority of patients without SVR data were not patients who dropped out of treatment, but rather patients who simply had not yet had their follow-up HCV viral load performed in the relatively short follow-up period of our study.

When multiple imputation was used to derive missing SVR values using baseline characteristics as well as duration of treatment, the results that included imputed and observed SVR were only slightly lower than those of observed SVR (Table 5), again suggesting that it is unlikely that our results of observed SVR are biased substantially toward overestimation due to the missing SVR data. Finally, we calculated SVR rates assuming that all patients with missing SVR data did not achieve SVR, a highly unlikely worst-case scenario (Table 5).

Discussion

LDV/SOF, PrOD, and SOF-based antiviral regimens resulted in remarkably high SVR rates in the VA national health care system, approaching the rates reported in clinical trials. This is in contrast to previous interferon-based regimens, which consistently resulted in much lower SVR rates in real-world clinical practice than in clinical trials.¹²⁻¹⁷ SVR rates were higher in genotype 1- (SVR 92.8%) and genotype 4-infected patients (SVR 89.6%) than genotype 2- (SVR 86.2%) or 3-infected patients (SVR 74.8%), and these differences were even greater among cirrhotic and treatment-experienced patients. Among genotype 1-infected patients, there was no significant difference in SVR rates between LDV/SOF and PrOD regimens in either unadjusted or multivariable, propensity-score-adjusted analyses, and SVR rates >90% were achieved even in subgroups such as treatment-experienced or cirrhotic patients. The short, 8-week LDV/SOF monotherapy regimen resulted in excellent SVR rate (94.3%), but was used in only 48.6% of genotype 1-infected patients eligible for 8-week therapy (ie, treatment-naïve patients with viral load <6 million IU/mL, without cirrhosis). Long, 24-week regimens did not result in higher SVR rates and were rarely used, despite being FDA-approved and American Association for the Study of Liver Diseases/Infectious Diseases Society of America-recommended³² for certain genotype 1 patients with cirrhosis.

Among a total of 17,487 patients, our study included 5250 patients with a diagnosis of cirrhosis and 5960 with a FIB-4 score >3.25 (which is highly suggestive of cirrhosis), who achieved surprisingly high overall SVR rates of 86.8% and 87.4%, respectively. These high SVR rates were driven by genotype 1-infected cirrhotic patients who had much higher SVR (90.6%; 95% CI, 89.7%–91.5%) than genotype 2 (77.3%; 95% CI 73.3%–80.9%) or genotype 3 (65.7%; 95% CI, 61.2%–69.8%). To our knowledge, this is the largest study of DAAs in cirrhotic patients and the SVR rates in genotype 1-infected patients are the highest

reported in real-world clinical practice. LDV/SOF, PrOD, and SOF regimens have allowed patients with cirrhosis to be cured of HCV in substantial numbers and proportions for the first time ever. Longer follow-up of these patients is necessary to determine whether patients with cirrhosis who achieve SVR by DAAs are protected from developing progressive liver dysfunction, liver failure, or HCC and, whether they are capable of liver remodeling and regression of cirrhosis.

American Association for the Study of Liver Diseases/Infectious Diseases Society of America guidelines during the time period of our study,³² as well as the LDV/SOF package insert,³³ recommend that LDV/SOF regimens should extend for 12 or 24 weeks, with the single exception of a short, 8-week LDV/SOF monotherapy regimen that “can be considered,”³³ “with caution and at the discretion of the practitioner”³² in treatment-naïve, genotype 1-infected patients without cirrhosis with an HCV viral load <6 million IU/mL. This is based on a post-hoc analysis of the ION-3 clinical trial showing higher relapse rates in those treated for 8 weeks who had a viral load ≥ 6 million (9 of 92 [10%]) compared with those with a viral load <6 million IU/mL (2 of 123 [2%]).³ VA treatment guidelines explicitly recommended 8 weeks of treatment for this subgroup of patients.³⁴ Indeed, our study confirmed that 8 weeks of LDV/SOF monotherapy had similarly high SVR rates (94.8%) as 12 weeks (95.3%) in this favorable subgroup. However, our results also showed that treatment was unnecessarily extended beyond 8 weeks in 1833 of 4066 patients in this subgroup, dramatically increasing the cost of treatment without increasing SVR. Our results should offer reassurance to treatment providers that 8 weeks of LDV/SOF monotherapy is sufficient duration in this subgroup.

VA treatment guidelines during the study period designated PrOD as the preferred regimen in genotype 1-infected patients except for prior null responders, those previously treated with protease inhibitors, and patients with Child’s B or C cirrhosis (in whom the preferred regimen was LDV/SOF and ribavirin for 12 weeks) and except for treatment naïve, non-cirrhotics with a viral load <6 million (in whom 8-week LDV/SOF and 12-week PrOD regimens were equally preferred). This was due to the lower cost of 12 weeks of PrOD (\$22,850) compared with 12 weeks of LDV/SOF (\$37,157) in the VA system during the study period and the absence of evidence that one is more effective than the other in the subgroups for which PrOD was preferred. Our data support the VA treatment recommendations because we found no difference in SVR between PrOD and LDV/SOF regimens in either adjusted or unadjusted analyses, in the entire population or in clinically relevant subgroups (cirrhosis or not, treatment-experienced or naïve). Despite these recommendations and the higher cost, LDV/SOF regimens constituted 77% and PrOD only 23% of regimens in genotype-1-infected patients. This could be due to higher prevalence of drug-drug interactions, higher pill burden, and more frequent requirement for co-prescription of ribavirin in PrOD regimens compared with LDV/SOF regimens. After the end of

the study period, and after FDA approval of elbasvir/grazoprevir as an additional regimen for genotype 1 HCV on January 28, 2016, regimen costs in the VA were further reduced dramatically, to approximately \$17,000 per 12-week course for LDV/SOF, PrOD, and elbasvir/grazoprevir and treatment recommendations changed to “equally recommend” all 3 agents as of March 2016.

Genotype 3-infected patients had the lowest SVR rates in our study, just as in clinical trials. We found that the non-FDA-approved regimen of LDV/SOF and ribavirin had a higher SVR rate (77.9%; 95% CI, 73.1%–82.0%) than the longer and more expensive FDA-approved regimen of SOF and ribavirin for 24 weeks (70.6%; 95% CI, 66.9%–74.1%). However, the highest SVR rate in genotype 3-infected patients was observed in the regimen that included PEG together with SOF and ribavirin (87.0%; 95% CI, 80.0%–91.8%), the only interferon-containing regimen that is still recommended.³²

Few large real-world studies of interferon-free regimens are currently available for comparison with ours. The HCV-TARGET, a prospective cohort study of patients undergoing HCV treatment in routine clinical care in academic centers, reported SVR rate to SOF and simeprevir in genotype 1-infected patients of 88% among 151 transplant recipients and 84% among 836 non-transplant recipients.^{35,36} This regimen has been superseded by LDV/SOF and PrOD-based regimens. Among 487 patients with decompensated cirrhosis treated in the United Kingdom under an Expanded Access Programme with SOF, LDV/SOF, or daclatasvir, SVR was achieved in 90.5% of genotype 1- and 68.8% of genotype 3-infected patients³⁷—very similar to our findings. A smaller VA study looked at only treatment-naïve, genotype 1-infected patients treated with LDV/SOF and reported SVR rates almost identical to ours among this subgroup.³⁸ The TRIO Network, which compiles data from participating “real-world” academic and community HCV treatment clinics in the United States, reported in an abstract an SVR rate of 94% among 1521 genotype 1-infected patients treated with LDV/SOF monotherapy.³⁹

The main limitation of our study was that SVR data were unavailable in 9% of patients, which can lead to overestimated SVR rates among those with available SVR data. We think this is unlikely for 2 reasons. First, patients with missing SVR data were similar to those with available SVR data (Supplementary Table 2). Although early discontinuation of treatment in <8 weeks was more common in patients with missing SVR data (25% vs 4.4%), the majority of patients with missing SVR completed 8 or more weeks of treatment, demonstrating that patients with missing SVR data were not patients who “dropped out” of treatment or were “lost to follow-up,” but rather patients (or physicians) who were simply delinquent in getting their SVR viral load measured after the end of their treatment—not an uncommon phenomenon outside of clinical trials. Second, we used comprehensive multiple imputation models that included duration of treatment in addition to baseline, pretreatment characteristics to impute the missing SVR data and found only a non-substantial reduction in SVR after imputation

(Table 5), suggesting that it is unlikely that our results of observed SVR are biased toward overestimation due to the missing SVR data. Important strengths of the study include the complete ascertainment of filled pharmacy prescriptions and the utilization of complete electronic medical records since 1999 from a national health care system that treats the greatest number of HCV-infected patients in the United States.

Our results demonstrate that LDV/SOF, PrOD, and SOF regimens can achieve remarkably high SVR rates in real-world clinical practice, especially in genotype 1-infected patients. The main obstacle to curing HCV infection in the maximum possible number of patients is currently the cost of HCV antiviral regimens. It is expected that cost will decline dramatically as more antiviral regimens become FDA-approved, resulting in competition between manufacturers. In fact, costs decreased dramatically within the VA after the completion of our study and after the FDA approval of elbasvir/grazoprevir in January 2016. The VA health care system has budgeted \$1.5 billion nationally for antiviral medications for fiscal year 2016, while every health care organization in the United States is faced with similar budgetary constraints due to the cost of antiviral medications. We hope that our results will be used to determine the most cost-effective ways to treat HCV-infected patients and to reassure patients, clinicians, and health care systems that current treatments for HCV, though costly, appear to be effective in the real-world setting.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <http://dx.doi.org/10.1053/j.gastro.2016.05.049>.

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Conflicts of interest

The authors disclose no conflicts.

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Supplementary Table 1. Treatment Duration by Regimen

	All patients		Genotype 1, %				Genotype 2, %	Genotype 3, %			Genotype 4, %	
Duration, wk	n	%	LDV/SOF	LDV/SOF+RIBA	PrOD	PrOD+RIBA	SOF+RIBA	LDV/SOF+RIBA	SOF+PEG+RIBA	SOF+RIB	LDV/SOF±RIBA	PrOD±RIBA
n	17,487		8140 ^a	2692 ^a	776 ^a	2366 ^a	2131 ^a	392 ^a	140 ^a	715 ^a	103 ^a	32 ^a
0 to <2	15	0.09	0.1	0	0.1	0	0.05	0	1.4	0.4	0	0
2	424	2.4	1.9	1.7	4.1	4.3	2.5	2.3	0.7	3.2	2.9	3.1
>2 to <4	15	0.09	0.07	0	0.0	0.04	0.3	0	0	0.1	0	0
4	540	3.0	2.9	1.6	4.1	4.0	3.6	5.1	2.9	4.0	1.9	0
>4 to <8	104	0.6	0.7	0.3	0.5	0.5	0.4	1.5	0.7	0.7	0.9	0
0 to <8	1098	6.3	5.7	3.6	8.9	8.8	7.0	8.9	5.7	8.5	5.8	3.1
8	2449	14	27	2.4	2.2	3.1	2.2	3.3	0.7	1.2	4.8	0
>8 to <12	412	2.4	2.2	2.2	2.2	2.8	3.4	1.8	3.6	0.8	3.9	0
12	10,609	61	50	78	81	77	66	78	74	3.2	68	88
>12 to 16	1175	6.7	4.3	7	5.0	5.5	18	6.1	9.3	3.9	7.8	6.3
>16 to 20	165	1.0	0.7	1.1	0.1	0.6	1.7	0	0	4.2	1.0	3.1
>20 to <24	112	0.6	0.5	0.4	0.1	0.2	0.1	0.5	0	7.3	0	0
≥24	1467	8.4	9.0	5.5	0	1.8	0.6	1.8	7.1	71	8.7	0

^an.

Supplementary Table 2. Sustained Virologic Response Rates in Genotype 1–Infected Patients by Subgenotype 1a/1b, Cirrhosis, Prior Treatment and Duration of Treatment

	LDV/SOF		LDV/SOF+ RIBA		PrOD		PrOD + RIBA	
	n	SVR, % (95 CI)	n	SVR, % (95 CI)	n	SVR, % (95 CI)	n	SVR, % (95 CI)
Genotype 1a all patients	4723	92.3 (91.5–93.0)	1736	91.6 (90.2–92.9)	23	78.3 (55.2–91.3)	1500	91.7 (90.2–93.0)
Treatment-naïve								
No cirrhosis								
All durations	2870	92.8 (91.8–93.7)	378	96.6 (94.2–98.0)		NA	879	90.8 (88.7–92.5)
12 wk	1413	95.7 (94.5–96.6)	291	98.6 (96.4–99.5)		NA	725	95.0 (93.2–96.4)
24 wk						NA		
Cirrhosis								
All durations	745	89.8 (87.4–91.8)	428	89.0 (85.7–91.7)		NA	249	93.6 (89.7–96.0)
12 wk	527	91.7 (89.0–93.7)	341	91.2 (87.7–93.8)		NA	199	95.5 (91.5–97.6)
24 wk	95	93.7 (86.5–97.2)	19	94.7 (66.2–99.4)		NA		NA
Treatment-experienced								
No cirrhosis								
All durations	761	93.4 (91.4–95.0)	374	94.7 (91.8–96.5)		NA	285	93.0 (89.3–95.4)
12 wk	488	96.7 (94.7–98.0)	293	94.9 (91.7–96.9)		NA	224	94.6 (90.8–96.9)
24 wk	95	94.7 (87.8–97.8)				NA		
Cirrhosis								
All durations	347	90.8 (87.2–93.4)	556	88.3 (85.4–90.7)		NA	87	92.0 (83.9–96.2)
12 wk	75	90.7 (81.4–95.6)	421	88.8 (85.4–91.5)		NA	58	96.6 (86.7–99.2)
24 wk	205	94.1 (89.9–96.7)	60	91.7 (81.1–96.6)		NA		NA
Genotype 1b all patients	1768	93.3 (92.1–94.4)	566	93.6 (91.3–95.4)	627	95.2 (93.2–96.6)	480	94.2 (91.7–95.9)
Treatment-naïve								
No cirrhosis								
All durations	1095	94.1 (92.5–95.3)	115	96.5 (91.0–98.7)	462	96.1 (93.9–97.5)	179	93.9 (89.2–96.6)
12 wk	436	95.2 (92.7–96.8)	90	97.8 (91.3–99.5)	400	97.8 (95.7–98.8)	142	98.6 (94.5–99.7)
24 wk								
Cirrhosis								
All durations	252	90.9 (86.6–93.9)	108	92.6 (85.7–96.3)	30	96.7 (77.8–99.6)	173	93.1 (88.1–96.0)
12 wk	173	93.6 (88.8–96.5)	89	93.3 (85.6–97.0)	24	100	133	100
24 weeks	28	82.1 (62.1–92.8)		NA		NA		NA
Treatment-experienced								
No cirrhosis								
All durations	284	94.4 (91.0–96.5)	120	93.3 (87.1–96.7)	125	92.0 (85.7–95.7)	57	94.7 (84.4–98.4)
12 wk	183	95.6 (91.5–97.8)	93	94.6 (87.5–97.8)	104	99.0 (93.3–99.9)	48	97.9 (85.8–99.7)
24 wk	31	100						
Cirrhosis								
All durations	137	89.8 (83.4–93.9)	223	92.8 (88.6–95.6)		NA	71	97.2 (89.1–99.3)
12 wk	38	100	179	91.6 (86.5–94.9)		NA	60	100
24 wk	76	90.8 (81.6–95.6)		NA		NA		NA

NA, available; regimens with <20 patients. These are regimens not recommended for the specific subpopulation.

Supplementary Table 3. Sustained Virologic Response Rates by Genotype in Clinically Relevant Subpopulations

	Genotype 1	Genotype 2	Genotype 3	Genotype 4
All patients	92.8 (92.3–93.2)	86.2 (84.6–87.7)	74.8 (72.2–77.3)	89.6 (82.8–93.9)
No cirrhosis	93.6 (93.1–94.1)	89.1 (87.4–90.6)	81.6 (78.4–84.4)	91.5 (83.7–95.7)
Cirrhosis	90.6 (89.7–91.5)	77.3 (73.3–80.9)	65.7 (61.2–69.8)	83.9 (65.4–93.5)
FIB-4 score ≤ 3.25	93.5 (93.0–94.1)	89.2 (87.3–90.9)	83.8 (80.1–86.8)	91.3 (83.4–95.6)
FIB-4 score > 3.25	91.2 (90.3–92.1)	80.8 (77.6–83.7)	66.5 (62.5–70.4)	84.4 (66.3–93.7)
HIV	92.1 (89.6–94.0)	91.1 (77.9–96.8)	95.5 (70.4–99.5)	90.0 (42.2–99.1)
Liver transplantation	95.7 (92.8–97.5)	91.7 (69.8–98.1)	88.2 (71.4–95.7)	50.0 (n = 2)
Treatment-naïve	92.8 (92.2–93.3)	88.0 (86.3–89.6)	77.5 (74.3–80.3)	88.3 (79.9–93.4)
Treatment-experienced	92.6 (91.7–93.3)	80.2 (76.2–83.6)	69.2 (64.2–73.9)	93.5 (76.1–98.5)

NOTE. Values are % (95% CI) unless otherwise indicated.

Supplementary Table 4. Sustained Virologic Response Rates in Treatment-Experienced Patients According to Prior Treatment Regimen

	Genotype 1		Genotype 2		Genotype 3	
	n	SVR, % (95% CI)	n	SVR, % (95% CI)	n	SVR, % (95% CI)
Prior Interferon	3574	92.8 (91.9–93.6)	413	80.1 (76.0–83.7)	329	68.1 (62.8–72.9)
Prior Boceprevir	865	94.7 (93.0–96.0)	—	—	—	—
Prior Telaprevir	212	90.1 (85.2–93.5)	—	—	—	—
Prior SOF	592	88.7 (85.9–91.0)	45	73.3 (58.0–84.5)	—	—
Prior Simeprevir+SOF	277	87.0 (82.5–90.5)	—	—	—	—
Prior PrOD	62	96.8 (87.6–99.2)	—	—	—	—
Prior LDV/SOF	122	87.7 (80.5–92.5)	—	—	—	—

Supplementary Table 5. Characteristics of Patients With or Without Available Hepatitis C Virus Viral Load Testing to Compute Sustained Virologic Response

Characteristic	SVR data	
	Absent (n = 1603)	Present (n = 15,884)
Race/ethnicity, %		
White, non-Hispanic	47	53
Black, non-Hispanic	30	29
Hispanic	9.1	4.8
Asian/Pacific Islander/American Indian/Alaska Native	1.3	1.6
Declined to answer, missing	11.7	12.1
Treatment duration, %		
0 to <8 wk	25	4.4
8 wk	15	14
>8 to <12 wk	2.7	2.3
12 wk	43	62
>12 to <24 wk	9.5	8.2
≥24 wk	5.2	8.7
Treatment duration, d, mean (SD)	71 (38)	87 (31)
HCV genotype, %		
1	77	80
2	14	12
3	8.9	7.0
4	0.62	0.80
Age, y, mean (SD)	59.4 (7.8)	61.0 (6.3)
Male, %	96.7	96.9
Treatment-experienced, %	24	30
HCV RNA viral load >6 million IU/mL, %	20	18
HIV co-infection, %	3.4	4.1
Cirrhosis, %	30	30
Decompensated cirrhosis, %	10.2	8.1
Hepatocellular carcinoma, %	3.5	2.7
Liver transplantation, %	1.7	2.3
Diabetes, %	26	30
Alcohol use or dependence, %	51	43
Substance use disorder, %	46	36
Depression, %	53	47
Post-traumatic stress disorder, %	29	27
Anxiety/panic, %	39	34
Schizophrenia, %	6.3	5.3
Laboratory results, %		
Anemia ^a	15.9	14.4
Platelet count <100 k/μL	14.4	13.5
Creatinine >1.1 mg/dL	18.7	19.9
Bilirubin >1.1 g/dL	16.0	13.8
Albumin <3.6 g/dL	21.3	20.3
INR >1.1	25.2	21.6
FIB-4 score >3.25, %	35.2	35.9

^aAnemia is defined as a hemoglobin concentration <13 g/dL in men or <12 g/dL in women.