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Effectiveness of sofosbuvir-based regimens in genotype 1 and 2 hepatitis C virus infection in 4026 U.S. Veterans

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SUMMARY

Background
Real-world effectiveness data are needed to inform hepatitis C virus (HCV) treatment decisions.

Aim
To assess sustained virological response (SVR) of sofosbuvir (SOF)-based regimens in routine medical practice.

Methods
Observational, intent-to-treat cohort analysis of genotype 1 and 2 HCV-infected veterans initiating SOF-based regimens with recommended treatment duration of 12 weeks.

Results
Four thousand and twenty-six veterans with genotype 1 ($N = 3203$) and genotype 2 ($N = 823$) comprise the cohort. SVR rates for genotype 1 were 66.8% for SOF + peginterferon + ribavirin (RBV), 75.3% for SOF + simeprevir (SIM), 74.1% for SOF + SIM + RBV and for genotype 2 were 79.0% for SOF + RBV. Genotype 1 patients were less likely to achieve SVR with BMI ≥30 (OR 0.64, 95% CI 0.49–0.84, $P < 0.001$), a history of decompensated liver disease (OR 0.51, 95% CI 0.36–0.71, $P < 0.001$), treatment experience (OR 0.58, 95% CI 0.48–0.71, $P < 0.001$), APRI >2 (OR 0.44, 95% CI 0.36–0.55, $P < 0.001$) and with SOF + PEG + RBV compared with SOF + SIM (OR 0.50, 95% CI 0.40–0.62, $P < 0.001$). Age, sex, race/ethnicity, diabetes and genotype subtype did not predict SVR. Odds of achieving SVR with SOF + SIM + RBV did not differ compared with SOF + SIM (OR 1.03, 95% CI 0.75–1.44, $P = 0.86$). Genotype 2 patients were less likely to achieve SVR with prior treatment experience (OR 0.55, 95% CI 0.35–0.88, $P = 0.009$) and APRI >2 (OR 0.39, 95% CI 0.25–0.62, $P < 0.001$).

Conclusions
In this real-world cohort, SVR rates were lower than in clinical trials. Genotype 1 and 2 HCV-infected patients with advanced liver disease by APRI >2 or FIB-4 > 3.25 were significantly less likely to achieve SVR. For genotype 1, a SOF + SIM ± RBV regimen was associated with a higher likelihood of SVR.

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INTRODUCTION

Anti-viral therapy for chronic hepatitis C virus (HCV) infection is rapidly evolving. Information derived from HCV anti-viral clinical trials may be limited in applicability to clinical practice where variations in patient characteristics, care coordination and management cannot be as tightly controlled. Differences between real-world HCV care outcomes and clinical trials often become apparent once these medications are prescribed to a broader population.[1–4] Understanding the effectiveness of anti-viral regimens in real-world settings is essential to provide practical information to better inform HCV treatment decisions.

While sustained virological response (SVR) rates reported in clinical trials with sofosbuvir (SOF)-based regimens represent a substantial improvement over previous direct acting anti-viral regimens, gaps in the evidence remain. For example, the US Food and Drug Administration (FDA) approval of SOF for genotype 1 treatment-experienced patients was based on modelling, as this group was not evaluated in clinical trials. Furthermore, use of the widely accepted combination of SOF and simeprevir (SIM) was based on open-label phase II studies with only 14–30 patients per treatment arm.[5]

Monitoring and optimising uptake, appropriate use and outcomes of HCV anti-viral regimens is a priority for the Department of Veterans Affairs (VA).[6] With the rapid uptake of SOF-based regimens across healthcare settings, and the underrepresentation of important populations in clinical trials, we examined the real-world outcomes of the diverse HCV-infected veteran population receiving these regimens. Our aim was to assess the effectiveness of SOF-based regimens in genotype 1 and 2 HCV-infected veterans treated in routine medical practice.

MATERIALS AND METHODS

This is an observational intent-to-treat cohort analysis of HCV-infected veterans receiving SOF-based treatment from VA. Data for this study were obtained from the VA's Clinical Case Registry for HCV, an extract of the VA electronic medical record that contains demographics, laboratory results, pharmacy information and International Classification of Diseases – Ninth Revision (ICD-9) diagnosis codes from in-patient hospitalisations, out-patient visits and problem lists of HCV-infected veterans seen at all VA medical facilities.[7]

Eligible subjects included all veterans from any VA facility nationwide with HCV genotype 1 or 2 who initiated a VA-prescribed SOF-based anti-viral treatment regimen with a recommended duration of 12 weeks between 1 January 2014 and 9 October 2014 and had stopped treatment by 31 December 2014. Twelve week regimens included SOF + peginterferon (PEG) + ribavirin (RBV) for genotype 1 and 2, SOF + SIM ± RBV for genotype 1 and SOF + RBV for genotype 2. As the recommended duration for SOF + RBV in genotype 1 is 24 weeks, it was not included. The choice of regimen 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 changed regimens (n = 65), had SOF added to an existing regimen (n = 76), had a baseline HCV RNA ≤1000 IU/mL (n = 133), had HIV infection (n = 156) or had a liver transplant (n = 162).

Treatment outcome

Patients were considered to have SVR if they had undetectable HCV RNA on all HCV RNA tests after the end of treatment (EOT) including at least one test at least 12 weeks or more after the EOT. Patients were considered 'nonresponders' (no SVR) if they had a detectable HCV RNA at any time after the EOT, had no viral load testing after the EOT and a detectable HCV RNA on their last HCV viral load test while on treatment or died while on treatment or within 12 weeks of the EOT. Patients with undetectable HCV RNA on their last HCV viral load test, either on treatment or after the EOT, but no test 12 weeks of more after the EOT were excluded from the SVR analysis. The EOT was calculated as the last day covered by prescriptions of SOF using the dates the medication was dispensed and the days supply. HCV RNA was categorised as detectable or undetectable based on the locally reported HCV RNA result of which 98% utilised assays with a lower limit of detection of 18 IU/mL or less. Patients were followed from the initiation of SOF-based treatment through 8 April 2015, allowing for more than 14 weeks of follow-up after EOT for all patients in the cohort.

Control variables

Demographic and other baseline variables were determined at the time of treatment initiation and included age, sex, race/ethnicity, history of decompensated liver disease (defined by oesophageal variceal haemorrhage, hepatic coma, hepatorenal syndrome or spontaneous bacterial peritonitis), diabetes, prior HCV anti-viral treatment experience and HCV genotype subtype for genotype 1 patients. Prior virological response was based on the most recent previous VA course of HCV anti-viral treatment and categorised as prior relapse (undetectable

HCV RNA at the end of a previous course of therapy with subsequent detectable HCV RNA during follow-up), prior partial response (at least a 2 $\log_{10}$ reduction in HCV RNA at week 12 of therapy but still HCV RNA detectable by week 24), prior null response (less than 2 $\log_{10}$ reduction in HCV RNA after 12 weeks of prior therapy) and not defined (lacked baseline or 12 week HCV RNA or received less than 12 weeks of prior therapy). Baseline values for height and weight which were used to calculate body mass index (BMI) and the laboratory tests for alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelets and baseline HCV RNA were defined as the value within 1 year before and closest to the treatment start date. An APRI score >2 or a FIB-4 score >3.25 at the start of treatment using baseline laboratory values was used as a marker of advanced liver disease.[8–10]

Kaplan–Meier curves of the percentage of patients on treatment were calculated from the cumulative days' supply of all SOF prescriptions starting with the first prescription for SOF through the last day of treatment covered by SOF. In VA, SOF prescriptions are frequently filled for quantities less than 28 days particularly for the first one or 2 months of treatment.

On-treatment HCV RNA at 4 weeks was also determined using the locally reported result closest to and within 2 weeks prior to and 2 weeks after the specified time point. HCV RNA results at 4 weeks were categorised as undetectable, detectable <43 IU/mL and detectable ≥43 IU/mL. Detectable ≥43 IU/mL was used because variation in HCV RNA assays across facilities prevented consistent reporting to a lower level of quantification.

Statistical analysis

Univariate comparisons used the Pearson χ^2 test with Yates' continuity correction for categorical variables. The log-rank test was used to compare the Kaplan–Meier curves of on-treatment percentage. Multivariate logistic regression models were constructed to model SVR for genotype 1 and genotype 2 patients separately. Model A – the main model – included age, sex, race/ethnicity, treatment experience, decompensated liver disease, diabetes, BMI, advanced liver disease by APRI >2 or FIB-4 > 3.25, and, for genotype 1, treatment regimen and genotype 1 subtype. Two additional sets of models were constructed with the above baseline variables with the prior treatment response in place of the binary variable of treatment experience (Model B) and with HCV RNA at 4 weeks on treatment added to the main model (Model C). Given the number of comparisons, a $P \leq 0.01$ was considered statistically significant. In addition, P values were not reported when a small number in any subgroup meant that the minimum expected value in any cell was less than 5.

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, the VA Palo Alto Health Care System Research and Development Committee, and the VA Clinical Case Registry Data Use Committee.

RESULTS

In total, 4637 veterans with HCV genotype 1 or genotype 2 initiated SOF-based treatment with recommended 12 week duration by 9 October 2014 and stopped treatment by 31 December 2014. After applying exclusion criteria, 4045 remained. Only 19 genotype 2 patients received SOF + PEG + RBV who were subsequently excluded given the extremely small sample. Baseline characteristics for the final cohort of 4026 patients – 3203 genotype 1 and 823 genotype 2 – appear in Table 1.

Among genotype 1 patients the mean age was 61 years, 96% were male, 31% were African American, 7% had a history of decompensated liver disease, 34% had diabetes, 37% were treatment experienced, 13% had prior protease inhibitor (PI) experience, 31% had an APRI >2 and 53% had a FIB-4 > 3.25; 40.6% received SOF + PEG + RBV, 48.7% received SOF + SIM and 10.7% received SOF + SIM + RBV. In comparing patients on the three regimens, patients receiving SOF + SIM or SOF + SIM + RBV were generally very similar and differed on some key characteristics from patients receiving SOF + PEG + RBV. In particular, patients on SOF + SIM or SOF + SIM + RBV compared with those on SOF + PEG + RBV appeared more likely to have advanced liver disease based on APRI >2 (38.2% vs. 46.5% vs. 18.1% respectively, $P < 0.001$) or FIB-4 ≥ 3.25 (63.1% vs. 68.4% vs. 38.2% respectively, $P < 0.001$) and more likely to have a history of decompensated liver disease compared with SOF + PEG + RBV (10.6% vs. 9.6% vs. 2.8% respectively, $P < 0.001$).

Among genotype 2 patients the mean age was 61 years, 97% were male, 9% were African American, 6% had a history of decompensated liver disease, 27% had diabetes, 23% were treatment experienced, 21% had an APRI >2 and 38% had a FIB-4 > 3.25.

The Kaplan–Meier on-treatment curves for SOF + PEG + RBV, SOF + SIM and SOF + SIM + RBV for

Table 1 | Baseline characteristics and 4 week on-treatment response of patients starting sofosbuvir-based regimens

	All genotype 1 (*N* = 3203)	Genotype 1 SOF + PEG + RBV (*N* = 1302)	Genotype 1 SOF + SIM (*N* = 1559)	Genotype 1 SOF + SIM + RBV (*N* = 342)	*P**	Genotype 2 SOF + RBV (*N* = 823)
Age (years)	60.9 ± 5.6 (24.4–82.4)	60.2 ± 5.8 (24.7–78.5)	61.6 ± 5.3 (30.2–82.4)	60.6 ± 5.9 (24.4–80.1)	–	60.9 ± 7.0 (27.1–82.9)
<55	349 (10.9)	178 (13.7)	133 (8.5)	38 (11.1)	<0.001	108 (13.1)
55–64	2184 (68.2)	901 (69.2)	1041 (66.8)	242 (70.8)		508 (61.7)
≥65	670 (20.9)	223(17.1)	385 (24.7)	62 (18.1)		207 (25.2)
Sex, male	3068 (95.8)	1244 (95.5)	1500 (96.2)	324 (94.7)	NS	795 (96.6)
Race/ethnicity						
African American	994 (31.0)	428 (32.9)	461 (29.6)	105 (30.7)	NS	73 (8.9)
Caucasian	1775 (55.4)	713 (54.8)	872 (55.9)	190 (55.6)		639 (77.6)
Hispanic	217 (6.8)	69 (5.3)	128 (8.2)	20 (5.8)		47 (5.7)
Other/multiple	217 (6.8)	92 (7.1)	98 (6.3)	27 (7.9)		64 (7.8)
Treatment-experienced	1184 (37.0)	488 (37.5)	566 (36.3)	130 (38.0)	NS	189 (23.0)
PI experienced	415 (13.0)	256 (19.7)	130 (8.3)	29 (8.5)	<0.001	–
Prior treatment response						
Relapse	271 (22.9)	150 (30.7)	97 (17.1)	24 (18.5)	<0.001	79 (41.8)
Partial	239 (20.2)	113 (23.2)	102 (18.0)	24 (18.5)		17 (9.0)
Null	207 (17.5)	70 (14.3)	110 (19.4)	27 (20.8)		7 (3.7)
Cannot determine	467 (39.4)	155 (31.8)	257 (45.4)	55 (42.3)	86 (45.5)	
Decompensated liver disease	234 (7.3)	36 (2.8)	165 (10.6)	33 (9.6)	<0.001	46 (5.6)
Diabetes	1092 (34.1)	381 (29.3)	584 (37.5)	127 (37.1)	<0.001	220 (26.7)
BMI (kg/m^2)	29.2 ± 5.2 (14.9–54.2)	29.2 ± 5.1 (14.9–54.2)	29.1 ± 5.3 (15.4–53.4)	29.6 ± 5.3 (17.4–53.6)	–	29.3 ± 5.8 (17.4–56.0)
<25	647 (20.3)	254 (19.5)	332 (21.3)	61 (18.0)	NS	189 (23.0)
25–29	1296 (40.6)	540 (41.5)	623 (40.0)	133 (39.2)		315 (38.4)
≥30	1252 (39.2)	506 (38.9)	601 (38.6)	145 (42.8)		316 (38.5)
ALT (U/L)	82.4 ± 59.0 (8–585)	81.1 ± 57.7 (8–573)	82.7 ± 58.9 (9–520)	86.1 ± 64.3 (13–585)		85.8 ± 78.0 (7–777)
AST (U/L)	79.1 ± 52.9 (12–547)	70.9 ± 47.8 (13–345)	83.8 ± 53.9 (12–509)	88.6 ± 61.6 (15–547)		70.9 ± 56.2 (10–475)
Platelets (K/μL)	148.4 ± 68.5 (12–739)	169.2 ± 62.5 (47–615)	135.3 ± 67.2 (12–559)	128.7 ± 75.5 (30–739)		169.4 ± 68.4 (19–385)
APRI	1.9 ± 1.9 (0.1–26.7)	1.3 ± 1.3 (0.1–9.4)	2.2 ± 2.2 (0.1–26.7)	2.5 ± 2.4 (0.2–16.1)	–	1.5 ± 2.0 (0.1–22.4)
≤2	2207 (69.1)	1066 (81.9)	958 (61.8)	183 (53.5)	<0.001	646 (78.6)
>2	988 (30.9)	236 (18.1)	593 (38.2)	159 (46.5)		176 (21.4)
FIB-4	4.9 ± 4.3 (0.3–61.6)	3.3 ± 2.4 (0.3–19.6)	5.9 ± 5.0 (0.5–61.6)	6.4 ± 5.1 (0.5–30.9)	–	3.8 ± 4.0 (0.3–33.4)
≤3.25	1486 (46.5)	805 (61.8)	573 (36.9)	108 (31.6)	<0.001	514 (62.5)
>3.25	1709 (53.5)	497 (38.2)	978 (63.1)	234 (68.4)		308 (37.5)
HCV RNA (log IU/mL)	6.2 ± 0.7 (3.0–8.1)	6.2 ± 0.7 (3.0–7.8)	6.1 ± 0.7 (3.0–7.8)	6.3 ± 0.6 (4.2–8.1)	–	6.2 ± 0.8 (3.0–7.7)
<800 000 IU/mL	900 (28.1)	330 (25.3)	490 (31.4)	80 (23.4)	<0.001	233 (28.3)
800 000–1 999 999 IU/mL	790 (24.7)	324 (24.9)	389 (25.0)	77 (22.5)		156 (19.0)
2 000 000–5 999 999 IU/mL	980 (30.6)	413 (31.7)	451 (28.9)	116 (33.9)		248 (30.1)
≥6 000 000 IU/mL	533 (16.6)	235 (18.0)	229 (14.7)	69 (20.2)		186 (22.6)
HCV subtype						
1 no subtype	360 (11.2)	162 (12.4)	169 (10.8)	29 (8.5)	<0.001	–
1a	1936 (60.4)	797 (61.2)	893 (57.3)	246 (71.9)		
1b	907 (28.3)	343 (26.3)	497 (31.9)	67 (19.6)		
IL28B polymorphism	*N* = 702	*N* = 322	*N* = 323	*N* = 57		*N* = 69
CC	155 (22.1)	71 (22.0)	73 (22.6)	11 (19.3)	NS	26 (37.7)

Table 1 | (Continued)

	All genotype 1 (N = 3203)	Genotype 1 SOF + PEG + RBV (N = 1302)	Genotype 1 SOF + SIM (N = 1559)	Genotype 1 SOF + SIM + RBV (N = 342)	P*	Genotype 2 SOF + RBV (N = 823)
CT	376 (53.6)	165 (51.2)	175 (54.2)	36 (63.2)		34 (49.3)
TT	171 (24.4)	86 (26.7)	75 (23.2)	10 (17.5)		9 (13)
4 week HCV RNA	N = 2599	N = 1022	N = 1307	N = 270		N = 659
Undetectable	1959 (75.4)	819 (80.1)	933 (71.4)	207 (76.7)	<0.001	533 (80.9)
Detectable <43 IU/mL	452 (17.4)	137 (13.4)	268 (20.5)	47 (17.4)		80 (12.1)
Detectable ≥43 IU/mL	188 (7.2)	66 (6.5)	106 (8.1)	16 (5.9)		46 (7.0)

Continuous variables reported as mean ± s.d. (range). Categorical variables reported as n (%).

ALT, alanine amino transferase; AST, aspartate aminotransferase; BMI, body mass index; PEG, peginterferon; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir.

* P-value reported for chi-squared test for categorical variables.

genotype 1 and SOF + RBV for genotype 2 appear in Figure 1. For genotype 1, log-rank tests showed that the trajectories of the curves for SOF + SIM and SOF + SIM + RBV did not differ but did differ significantly from the curve for SOF + PEG + RBV (SOF + PEG + RBV vs. SOF + SIM, $P < 0.001$ and SOF + PEG + RBV vs. SOF + SIM + RBV, $P < 0.001$). Overall, 13.7% of SOF + PEG + RBV, 11.8% of SOF + SIM and 9.9% of SOF + SIM + RBV-treated genotype 1 patients discontinued therapy prior to completing a full 12 weeks, and 14.3% of SOF + RBV-treated genotype 2 patients discontinued therapy prior to completing a full 12 weeks.

SVR results were available for 2417 genotype 1 patients which includes 24 patients who died while on treatment or within 12 weeks after the EOT who were categorised as no SVR. Seven hundred eighty-six patients whose last HCV RNA was undetectable, but occurred while still on treatment (n = 156) or less than 12 weeks after the EOT (n = 630), were excluded from the SVR analysis. SVR rates were 66.8% for SOF + PEG + RBV, 75.3% for SOF + SIM and 74.1% for SOF + SIM + RBV (Table 2). Overall SVR rates did not differ for SOF + SIM compared with SOF + SIM + RBV (P = 0.75). SVR rates were higher for patients receiving SOF + SIM ± RBV compared with SOF + PEG + RBV (75.1% vs. 66.8%, $P < 0.001$). APRI ≤ 2 compared to APRI >2 was the one baseline characteristic with significantly higher SVR rates for all three regimens (SOF + PEG + RBV 71.1% vs. 48.5%, $P < 0.001$, SOF + SIM 80.6% vs. 67.5%, $P < 0.001$ and SOF + SIM + RBV 83.2% vs. 63.9%, $P < 0.001$). In patients receiving SOF + PEG + RBV, significant differences in SVR rates were observed between treatment-naïve and treatment-experienced patients (55.6% vs. 73.7%, $P < 0.001$). For patients receiving SOF + SIM, SVR rates again differed between treatment-naïve and treatment-experienced patients although the magnitude of the difference and the statistical significance was reduced (77.8% vs. 71.2%, P = 0.02). For patients receiving SOF + SIM + RBV, SVR rates differed little between treatment-naïve and treatment-experienced patients (74.7% vs. 73.3%, P = 0.91).

Given the differential effect of treatment-experience across the three regimens, SVR rates are also presented separately for treatment-naïve (Table 3) and treatment-experienced patients (Table 4). For treatment-naïve genotype 1 patients, APRI ≤2 compared to APRI >2 continued to be the one baseline characteristic with significantly higher SVR rates for all three regimens (SOF + PEG + RBV 77.5% vs. 56.9%, $P < 0.001$; SOF + SIM 82.1% vs. 71.5%, P = 0.001; SOF + SIM + RBV 85.0% vs. 64.1%, P = 0.005). Among treatment-naïve genotype 1 patients, SVR rates also differed for those with FIB-4 ≤ 3.25 compared to >3.25 for patients on SOF + PEG + RBV (82.9% vs. 58.4%, $P < 0.001$) and for those on SOF + SIM (84.9% vs. 74.0%, P = 0.002) but did not differ statistically for those on SOF + SIM + RBV (81.6% vs. 71.6%, P = 0.25) despite an apparent numeric difference. SVR rates differed based on HCV RNA at 4 weeks on treatment for the same two regimens (SOF + PEG + RBV 81.3% undetectable vs. 63.6% detectable <43 IU/mL vs. 56.8% detectable ≥43 IU/mL, $P < 0.001$; SOF + SIM 85.5% undetectable vs. 69.7% detectable <43 IU/mL vs. 62.7% detectable ≥43 IU/mL, $P < 0.001$). Given the small sample, the

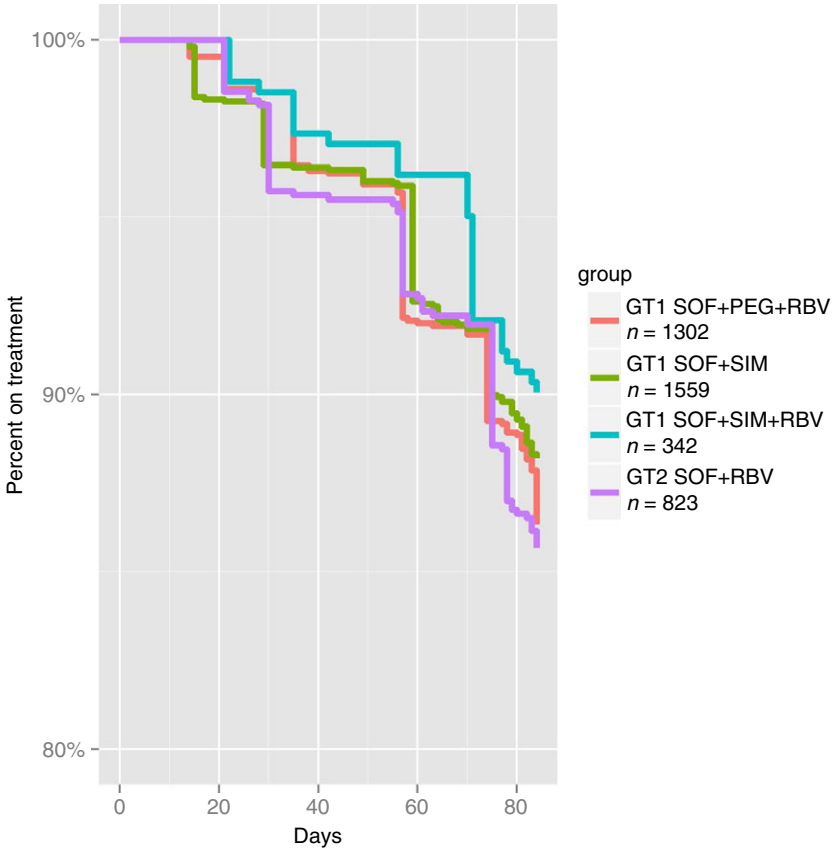

Figure 1 | Kaplan–Meier plot of on-treatment rates from sofosbuvir start date to end of treatment based on total days supply*. *Represents duration of treatment from sofosbuvir start date through the last day of treatment covered by sofosbuvir using pharmacy records of total days' supply. GT1, genotype 1; GT2, genotype 2; PEG, peginterferon; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir.

rates could not be compared for SOF + SIM + RBV. In addition, for those on SOF + PEG + RBV with genotype 1 subtype or IL-28B testing available, SVR rates were numerically higher although not significantly different for those with 1a compared to 1b with (75.4% vs. 66.7%, $P = 0.04$) and SVR was achieved in 92.1% with CC genotype, 67.1% with CT genotype and 51.2% with TT genotype ($P < 0.001$).

For treatment-experienced genotype 1 patients, SVR rates for patients with APRI ≤2 were significantly higher compared to APRI >2 for SOF + PEG + RBV (60.5% vs. 35.9%, $P < 0.001$) and for those on SOF + SIM (78.1% vs. 60.9%, $P < 0.001$) but did not differ statistically for those on SOF + SIM + RBV (80.7% vs. 63.6%, $P = 0.09$). Patients with FIB-4 ≤ 3.25 similarly had significantly higher SVR rates compared to FIB-4 > 3.25 for the same two regimens (SOF + PEG + RBV 64.0% vs. 54.5%, $P < 0.001$; SOF + SIM 86.1% vs. 63.6%, $P < 0.001$).

SVR results were available for 619 genotype two patients including four patients who died while on treatment or within 12 weeks after EOT. Two hundred four patients whose last HCV RNA was undetectable but occurred while still on treatment ($n = 56$) or less than 12 weeks after the EOT ($n = 148$) were excluded from the SVR analysis. The SVR rate was 79.0% for SOF + RBV overall (Table 2). Among treatment-naïve genotype 2 patients, the SVR rate was 81.6%. Among naïve patients, SVR rates were significantly higher in patients with APRI ≤2 (85.5% vs. 69.8%, $P < 0.001$) and patients with FIB-4 ≤ 3.25 (85.9% vs. 74.9%, $P = 0.004$; Table 3). Among treatment-experienced genotype 2 patients, SVR rates were significantly higher in patients with FIB-4 ≤ 3.25 (81.0% vs. 58.2%, $P = 0.004$) and higher with borderline statistical significance in patients with APRI ≤2 (75.6% vs. 53.1%, $P = 0.02$; Table 4).

In multivariate analysis Model A including APRI score, genotype 1 patients were less likely to achieve SVR with BMI ≥30 (OR 0.64, 95% CI 0.49–0.84, $P < 0.001$), a history of decompensated liver disease (OR 0.51, 95% CI 0.36–0.71, $P < 0.001$), treatment experience (OR 0.58, 95% CI 0.48–0.71, $P < 0.001$), APRI >2 (OR 0.44, 95% CI 0.36–0.55, $P < 0.001$) and with SOF + PEG + RBV compared with SOF + SIM (OR 0.50, 95% CI 0.40–0.62, $P < 0.001$; Table 5). Age, sex, race/ethnicity, diabetes and genotype 1 subtype did not predict SVR. The odds of achieving SVR with SOF + SIM + RBV did not differ compared with SOF + SIM (OR 1.03, 95% CI 0.74–1.44, $P = 0.86$). The substitution of FIB-4 for APRI score in Model A produced virtually identical odds ratios for all variables.

Table 2 | SVR rates by regimen for genotype 1 and genotype 2 patients

	Genotype 1 SOF + PEG + RBV (*N* = 1028)	*P*	Genotype 1 SOF + SIM (*N* = 1130)	*P*	Genotype 1 SOF + SIM + RBV (*N* = 259	*P*	Genotype 2 SOF + RBV (*N* = 619)	*P*
Overall SVR	66.8 (687/1028)		75.3 (851/1130)		74.1 (192/259)		79.0 (489/619)	
Age (years)								
<55	69.5 (89/128)	NS	71.3 (72/101)	NS	75.0 (21/28)	NS	76.5 (52/68)	NS
55–64	67.8 (486/717)		74.3 (554/746)		73.2 (134/183)		79.8 (312/391)	
≥65	61.2 (112/183)		79.5 (225/283)		77.1 (37/48)		78.1 (125/160)	
Sex								
Male	66.7 (652/977)	NS	74.9 (810/1082)	NS	72.8 (179/246)	–*	78.8 (476/604)	–*
Female	68.6 (35/51)		85.4 (41/48)		100 (13/13)		86.7 (13/15)	
Race/ethnicity								
African American	65.5 (220/336)	NS	73.4 (235/320)	NS	79.3 (65/82)	–*	80.0 (44/55)	NS
Caucasian	67.7 (386/570)		75.6 (484/640)		71.3 (102/143)		78.5 (379/483)	
Hispanic	70.2 (40/57)		85.6 (83/97)		64.3 (9/14)		83.8 (31/37)	
Other/multiple	63.1 (41/65)		67.1 (49/73)		80 (16/20)		79.5 (35/44)	
Treatment experience								
Naive	73.7 (469/636)	<0.001	77.8 (544/699)	NS	74.7 (118/158)	NS	81.6 (382/468)	0.007
Experienced	55.6 (218/392)		71.2 (307/431)		73.3 (74/101)		70.9 (107/151)	
Non-PI experienced	–58.0 (105/181)		–72.5 (229/316)		–71.8 (56/78)			
PI experienced	–53.6 (113/211)		–67.8 (78/115)		–78.3 (18/23)			
Prior treatment response								
Relapse	70.6 (84/119)	<0.001	75.3 (55/73)	NS	77.8 (14/18)	–*	79.4 (50/63)	–*
Partial	62.2 (56/90)		70.1 (54/77)		84.2 (16/19)		46.2 (6/13)	
Null	24.1 (14/58)		71.1 (59/83)		61.5 (16/26)		100.0 (6/6)	
Cannot determine	51.2 (64/125)		70.2 (139/198)		73.7 (28/38)		65.2 (45/69)	
Decompensated liver disease								
No	67.2 (671/998)	NS	77.3 (775/1002)	<0.001	76.0 (177/233)	NS	80.0 (463/579)	NS
Yes	53.3 (16/30)		59.4 (76/128)		57.7 (15/26)		65.0 (26/40)	
Diabetes								
No	68.4 (498/728)	NS	76.0 (538/708)	NS	68.7 (114/166)	NS	80.0 (349/436)	NS
Yes	63.0 (189/300)		74.2 (313/422)		83.9 (78/93)		76.5 (140/183)	
BMI (kg/m^2)								
<25	68.9 (131/190)	0.008	80.4 (185/230)	0.001	84.1 (37/44)	NS	85.2 (115/135)	0.01
25–29	71.1 (303/426)		78.5 (350/446)		74.3 (78/105)		81.3 (196/241)	
≥30	61.3 (252/411)		69.6 (314/451)		71.0 (76/107)		72.9 (175/240)	
APRI								
≤2	71.1 (593/834)	<0.001	80.6 (535/664)	<0.001	83.2 (114/137)	<0.001	83.0 (390/470)	<0.001
>2	48.5 (94/194)		67.5 (312/462)		63.9 (78/122)		66.2 (98/148)	
FIB-4								
≤3.25	76.3 (467/612)	<0.001	85.3 (326/382)	<0.001	81.7 (67/82)	NS	84.8 (312/368)	<0.001
>3.25	52.9 (220/416)		70.0 (521/744)		70.6 (125/177)		70.4 (176/250)	
HCV RNA								
<800 000 IU/mL	71.3 (179/251)	NS	73.5 (258/351)	NS	67.7 (44/65)	NS	75.1 (130/173)	NS
800 000–1 999 999 IU/mL	68.7 (180/262)		72.3 (193/267)		75.0 (45/60)		74.8 (89/119)	
2 000 000–5 999 999 IU/mL	63.0 (209/332)		76.6 (255/333)		76.5 (62/81)		80.8 (156/193)	
≥6 000 000 IU/mL	65.0 (119/183)		81.0 (145/179)		77.4 (41/53)		85.1 (114/134)	
HCV subtype								
1 no subtype	70.5 (93/132)		72.0 (95/132)		71.4 (15/21)		–	
1a	69.8 (435/623)	1a vs. 1b	73.3 (463/632)	1a vs. 1b	74.1 (143/193)	1a vs. 1b		
1b	58.2 (159/273)	<0.001	80.1 (293/366)	NS	75.6 (34/45)	NS		
IL28B Polymorphism	*N* = 283		*N* = 256		*N* = 46		*N* = 51	

Table 2 | (Continued)

	Genotype 1 SOF + PEG + RBV (*N* = 1028)	*P*	Genotype 1 SOF + SIM (*N* = 1130)	*P*	Genotype 1 SOF + SIM + RBV (*N* = 259	*P*	Genotype 2 SOF + RBV (*N* = 619)	*P*
CC	83.6 (51/61)	<0.001	91.4 (53/58)	NS	83.3 (5/6)	–*	73.7 (14/19)	–*
CT	62.3 (91/146)		77.9 (109/140)		80.6 (25/31)		84.6 (22/26)	
TT	52.6 (40/76)		72.4 (42/58)		88.9 (8/9)		83.3 (5/6)	
4 week HCV RNA	*N* = 798		*N* = 937		*N* = 212		*N* = 495	
Undetectable	71.5 (454/635)	0.003	81.4 (540/663)	<0.001	79.4 (131/165)	–*	88.5 (345/390)	<0.001
Detectable <43 IU/mL	61.3 (65/106)		70.5 (136/193)		63.9 (23/36)		68.7 (46/67)	
Detectable ≥43 IU/mL	52.6 (30/57)		61.7 (50/81)		72.7 (8/11)		63.2 (24/38)	

BMI, body mass index; PEG, peginterferon; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response. Values are expressed in percentage.

* *P* values not reported when small sample size means that the minimum expected value in any cell of the χ^2 is <5.

In multivariate analysis Model B including the prior treatment response categories, genotype 1 patients were additionally less likely to achieve SVR with a prior null treatment response (OR 0.37, 95% CI 0.26–0.52, $P < 0.001$) or with a prior treatment response that could not be determined (OR 0.53, 95% CI 0.41–0.69, $P = 0.001$).

In multivariate analysis Model C including the 4 week on-treatment HCV RNA, having a detectable 4 week on-treatment HCV RNA <43 IU/mL was associated with a lower likelihood of achieving SVR (OR 0.59, 95% CI 0.45–0.78, $P < 0.001$) and a detectable 4 week on-treatment HCV RNA ≥43 IU/mL was associated with an even lower likelihood of achieving SVR (OR 0.42, 95% CI 0.29–0.62, $P < 0.001$). Higher BMI, prior treatment experience, advanced liver disease by APRI >2 or FIB-4 > 3.25 and SOF + PEG + RBV compared with SOF + SIM remained significant predictors of decreased likelihood of achieving SVR.

In multivariate analysis Model A for genotype 2, patients were less likely to achieve SVR with prior treatment experience (OR 0.55, 95% CI 0.35–0.88, $P = 0.009$) and APRI >2 (OR 0.39, 95% CI 0.25–0.62, $P < 0.001$) or with a FIB-4 > 3.25 (OR 0.42, 95% CI 0.27–0.65, $P < 0.001$). Age, sex, race/ethnicity, a history of decompensated liver disease, diabetes and BMI did not predict SVR. Because of small numbers of treatment-experienced patients in the individual response categories, Model B was not estimated for genotype 2.

As with genotype 1, having a detectable 4 week on-treatment HCV RNA <43 IU/mL was associated with a lower likelihood of achieving SVR (OR 0.29, 95% CI 0.15–0.56, $P < 0.001$) and a detectable 4 week on-treatment HCV RNA ≥43 IU/mL was associated with an even lower likelihood of achieving SVR (OR 0.21, 95% CI 0.09–0.49, $P < 0.001$).

DISCUSSION

In this cohort of genotype 1 and 2 HCV-infected veterans treated with SOF-based therapy at any VA facility nationwide, we observed SVR rates lower than reported in clinical trials for either genotype although still substantially higher than rates reported previously in similar VA cohorts with boceprevir- or telaprevir-based regimens.[1, 11–13] This represents real-world effectiveness in a diverse population consisting of historically more difficult to treat patients where more than a quarter were African American, almost 90% were over the age of 55, over a third were overweight, and substantial proportions were treatment experienced and had advanced liver disease.

In genotype 1 treatment-naïve patients receiving SOF + PEG + RBV, SVR rates were 73.7% overall. Rates were higher for treatment-naïve patients with less advanced liver disease defined by FIB-4 ≤ 3.25 (82.9%) or by APRI ≤2 (77.5%) but were still substantially lower than the 91% overall SVR rate reported in clinical trials of naïve patients and the 92% SVR rate reported in those without cirrhosis.[14] Part of this apparent decrement in effectiveness may be explained by differences in patient populations as our cohort consisted of older patients, with generally higher BMI and a greater proportion with advanced liver disease. Furthermore, there are likely differences in practice patterns, patient motivation, provider

Table 3 | SVR rates for treatment naïve by regimen for genotype 1 and genotype 2 patients

	Genotype 1 SOF + PEG + RBV (*N* = 636)	*P*	Genotype 1 SOF + SIM (*N* = 699)	*P*	Genotype 1 SOF + SIM + RBV (*N* = 158)	*P* value	Genotype 2 SOF + RBV (*N* = 468)	*P*
Overall SVR	73.7 (469/636)		77.8 (544/699)		74.7 (118/158)		81.6 (382/468)	
Age (years)								
<55	78.3 (65/83)	NS	72.7 (48/66)	NS	88.2 (15/17)	–*	77.6 (45/58)	NS
55–64	73.5 (330/449)		77.4 (356/460)		73.0 (84/115)		82.1 (238/290)	
≥65	71.2 (74/104)		80.9 (140/173)		73.1 (19/26)		82.5 (99/120)	
Sex								
Male	73.6 (448/609)	NS	77.5 (519/670)	NS	73.7 (112/152)	–*	81.5 (369/453)	–*
Female	77.8 (21/27)		86.2 (25/29)		100.0 (6/6)		86.7 (13/15)	
Race/ethnicity								
African American	73.1 (147/201)	NS	77.0 (151/196)	NS	80.8 (42/52)	–*	89.1 (41/46)	–*
Caucasian	74.5 (269/361)		78.0 (308/395)		71.1 (64/90)		79.9 (286/358)	
Hispanic	73.2 (30/41)		86.0 (49/57)		75.0 (3/4)		96.2 (25/26)	
Other/multiple	69.7 (23/33)		70.6 (36/51)		75.0 (9/12)		78.9 (30/38)	
Decompensated liver disease								
No	73.9 (459/621)	–*	79.3 (497/627)	NS	75.9 (107/141)	–*	82.4 (360/437)	NS
Yes	66.7 (10/15)		65.3 (47/72)		64.7 (11/17)		71.0 (22/31)	
Diabetes								
No	74.0 (342/462)	NS	79.1 (353/446)	NS	68.3 (71/104)	NS	80.7 (276/342)	NS
Yes	73.0 (127/174)		75.5 (191/253)		87.0 (47/54)		84.1 (106/126)	
BMI (kg/m^2)								
<25	75.0 (96/128)	NS	78.5 (113/144)	NS	92.3 (24/26)	NS	84.2 (96/114)	NS
25–29	77.0 (208/270)		79.5 (229/288)		71.9 (46/64)		84.6 (159/188)	
≥30	69.2 (164/237)		75.8 (200/264)		72.3 (47/65)		76.1 (124/163)	
APRI								
≤2	77.5 (403/520)	<0.001	82.1 (335/408)	0.001	85.0 (68/80)	0.005	85.5 (300/351)	<0.001
>2	56.9 (66/116)		71.5 (206/288)		64.1 (50/78)		69.8 (81/116)	
FIB-4								
≤3.25	82.9 (330/398)	<0.001	84.9 (202/238)	0.002	81.6 (40/49)	NS	85.9 (244/284)	0.004
>3.25	58.4 (139/238)		74.0 (339/458)		71.6 (78/109)		74.9 (137/183)	
HCV RNA								
<800 000 IU/mL	78.8 (119/151)	NS	74.9 (161/215)	NS	75.0 (33/44)	NS	77.1 (108/140)	NS
800 000–1 999 999 IU/mL	75.9 (123/162)		74.9 (125/167)		65.7 (23/35)		81.8 (72/88)	
2 000 000–5 999 999 IU/mL	67.0 (138/206)		80.6 (174/216)		82.9 (34/41)		83.2 (119/143)	
≥6 000 000 IU/mL	76.1 (89/117)		83.2 (84/101)		73.7 (28/38)		85.6 (83/97)	
HCV subtype								
1 no subtype	82.5 (52/63)		78.5 (51/65)		70.0 (7/10)			
1a	75.4 (301/399)	1a vs. 1b	77.3 (317/410)	1a vs. 1b	76.0 (95/125)	1a vs. 1b		
1b	66.7 (116/174)	NS	78.6 (176/224)	NS	69.6 (16/23)	NS		
IL28B Polymorphism	*N* = 157		*N* = 155		*N* = 26		*N* = 35	
CC	92.1 (35/38)	<0.001	90.7 (39/43)	NS	50.0 (1/2)	–*	68.8 (11/16)	–*
CT	67.1 (51/76)		80.2 (65/81)		88.2 (15/17)		92.9 (13/14)	
TT	51.2 (22/43)		71.0 (22/31)		85.7 (6/7)		80.0 (4/5)	
4 week treatment HCV RNA	*N* = 488		*N* = 568		*N* = 129		*N* = 365	

Table 3 | (Continued)

	Genotype 1 SOF + PEG + RBV (*N* = 636)	*P*	Genotype 1 SOF + SIM (*N* = 699)	*P*	Genotype 1 SOF + SIM + RBV (*N* = 158)	*P* value	Genotype 2 SOF + RBV (*N* = 468)	*P*
Undetectable	81.3 (313/385)	<0.001	85.5 (349/408)	<0.001	79.4 (81/102)	–*	91.0 (263/289)	–*
Detectable <43 IU/mL	63.6 (42/66)		69.7 (76/109)		63.6 (14/22)		69.4 (34/49)	
Detectable ≥43 IU/mL	56.8 (21/37)		62.7 (32/51)		80.0 (4/5)		74.1 (20/27)	

BMI, body mass index; PEG, peginterferon; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response. Values are expressed in percentage.

* *P* values not reported when small sample size means that the minimum expected value in any cell of the Chi-square is <5.

knowledge, provider resources and ancillary services in routine medical practice compared with highly structured, highly resourced clinical trials.

The SOF + PEG + RBV regimen has not been evaluated in clinical trials in treatment-experienced genotype 1 patients and thus, this analysis represents one of the first reports of SVR in this population. The observed SVR in treatment-experienced patients on SOF + PEG + RBV was 55.6%, much lower than the estimated 71% which was predicted using data from treatment-naïve patients with multiple baseline factors traditionally associated with a lower response to interferon-based therapy.[14]

Our analysis also provides information concerning the comparative effectiveness of SOF + SIM and SOF + SIM + RBV. In genotype 1 treatment-naïve patients SVR rates overall did not differ between SOF + SIM (77.8%) and SOF + SIM + RBV (74.7%). Overall SVR rates for treatment-experienced patients were also similar between the two regimens (SOF + SIM 71.2%; SOF + SIM + RBV 73.3%) and only marginally decreased compared with the SVR rates for treatment-naïve patients. In multivariate models the likelihood of having SVR with SOF + SIM + RBV did not differ from SOF + SIM, which is consistent with what has been reported in the Phase 2 study evaluating SOF + SIM ± RBV.[5] SVR rates observed in our cohort, however, were notably less than the observed in this trial. This was particularly true in those with more advanced liver disease where 66.8% of patients with APRI >2 and 70.1% of patients with FIB-4 > 3.25 treated with SOF + SIM ± RBV achieved SVR compared to 93% in the smaller subgroup evaluated in the COSMOS clinical trial. Although our SVR rates were lower than observed in the Phase 2 study, the SVR rates associated with SOF + SIM ± RBV were consistent, in the mid-70s, among most subgroups. As noted above, the apparent decrement in effectiveness of SOF + SIM ± RBV likely represents differences in structure and resources available in routine medical practice compared to clinical trials.

Our analysis also provides information concerning the comparative effectiveness between SOF + PEG + RBV and SOF + SIM ± RBV in genotype 1. For treatment-naïve patients, SVR rates did not differ between SOF + PEG + RBV (73.7%), SOF + SIM (77.8%) and SOF + SIM + RBV (74.7%). For treatment-experienced patients, however, the SVR rate was substantially lower for SOF + PEG + RBV (55.6%) compared with SOF + SIM (71.2%) or SOF + SIM + RBV (73.3%). For treatment-experienced patients, SVR rates with SOF + PEG + RBV were lower than SVR rates with SOF + SIM ± RBV for every patient subgroup based on baseline characteristics. In multivariate models to control for differences in baseline patient characteristics, SOF + PEG + RBV was associated with more than a 50% decrease in the odds of achieving SVR compared with SOF + SIM. One small prior study in 82 genotype 1 patients with Child's grade A cirrhosis showed a similar 18 percentage point difference between the SVR rates with SOF + PEG + RBV (75%) and SOF + SIM (93%).[15] These comparative effectiveness data provide further support for the use of interferon-free regimens over triple therapy with a direct acting anti-viral plus PEG + RBV.

Our genotype 1 cohort included patients with prior PI (boceprevir or telaprevir) experience. While significantly more of these patients received SOF + PEG + RBV, some did receive SOF + SIM ± RBV and, notably, this represents a population that was not included in the COSMOS trial. Although no statistical differences in

Table 4 | SVR rates for treatment experienced by regimen for genotype 1 and genotype 2 patients

	Genotype 1 SOF + PEG + RBV (*N* = 392)	*P*	Genotype 1 SOF + SIM (*N* = 431)	*P*	Genotype 1 SOF + SIM + RBV (*N* = 101)	*P*	Genotype 2 SOF + RBV (*N* = 151)	*P*
Overall SVR	55.6 (218/392)		71.2 (307/431)		73.3 (74/101)		70.9 (107/151)	
Age (years)								
<55	53.3 (24/45)	NS	68.6 (24/35)	NS	54.5 (6/11)	–*	70.0 (7/10)	–*
55–64	58.2 (156/268)		69.2 (198/286)		73.5 (50/68)		73.3 (74/101)	
≥65	48.1 (38/79)		77.3 (85/110)		81.8 (18/22)		65.0 (26/40)	
Sex								
Male	55.4 (204/368)	NS	70.6 (291/412)	NS	71.3 (67/94)	–*	70.9 (107/151)	–*
Female	58.3 (14/24)		84.2 (16/19)		100.0 (7/7)		–	
Race/ethnicity								
African American	54.1 (73/135)	NS	67.7 (84/124)	NS	76.7 (23/30)	–*	33.3 (3/9)	–*
Caucasian	56.0 (117/209)		71.8 (176/245)		71.7 (38/53)		74.4 (93/125)	
Hispanic	62.5 (10/16)		85.0 (34/40)		60.0 (6/10)		54.5 (6/11)	
Other/multiple	56.2 (18/32)		59.1 (13/22)		87.5 (7/8)		83.3 (5/6)	
Treatment experience								
Non-PI experienced	58.0 (105/181)	NS	72.5 (229/316)	NS	71.8 (56/78)	NS	70.9 (107/151)	–
PI experienced	53.6 (113/211)		67.8 (78/115)		78.3 (18/23)			
Prior treatment response								
Relapse	70.6 (84/119)	<0.001	75.3 (55/73)	NS	77.8 (14/18)	–*	79.4 (50/63)	–*
Partial	62.2 (56/90)		70.1 (54/77)		84.2 (16/19)		46.2 (6/13)	
Null	24.1 (14/58)		71.1 (59/83)		61.5 (16/26)		100.0 (6/6)	
Cannot determine	51.2 (64/125)		70.2 (139/198)		73.7 (28/38)		65.2 (45/69)	
Decompensated liver disease								
No	56.2 (212/377)	NS	74.1 (278/375)	0.001	76.1 (70/92)	–*	72.5 (103/142)	–*
Yes	40.0 (6/15)		51.8 (29/56)		44.4 (4/9)		44.4 (4/9)	
Diabetes								
No	58.6 (156/266)	NS	70.6 (185/262)	NS	69.4 (43/62)	NS	77.7 (73/94)	NS
Yes	49.2 (62/126)		72.2 (122/169)		79.5 (31/39)		59.6 (34/57)	
BMI (kg/m^2)								
<25	56.5 (35/62)	NS	83.7 (72/86)	<0.001	72.2 (13/18)	–*	90.5 (19/21)	NS
25–29	60.9 (95/156)		76.6 (121/158)		78.0 (32/41)		69.8 (37/53)	
≥30	50.6 (88/174)		61.0 (114/187)		69.0 (29/42)		66.2 (51/77)	
APRI								
≤2	60.5 (190/314)	<0.001	78.1 (200/256)	<0.001	80.7 (46/57)	NS	75.6 (90/119)	NS
>2	35.9 (28/78)		60.9 (106/174)		63.6 (28/44)		53.1 (17/32)	
FIB-4								
≤3.25	64.0 (137/214)	<0.001	86.1 (124/144)	<0.001	81.8 (27/33)	NS	81.0 (68/84)	0.004
>3.25	45.5 (81/178)		63.6 (182/286)		69.1 (47/68)		58.2 (39/67)	
HCV RNA								
<800 000 IU/mL	60.0 (60/100)	NS	71.3 (97/136)	NS	52.4 (11/21)	–*	66.7 (22/33)	
800 000–1 999 999 IU/mL	57.0 (57/100)		68.0 (68/100)		88.0 (22/25)		54.8 (17/31)	
2 000 000–5 999 999 IU/mL	56.3 (71/126)		69.2 (81/117)		70.0 (28/40)		74.0 (37/50)	
≥6 000 000 IU/mL	45.5 (30/66)		78.2 (61/78)		86.7 (13/15)		83.8 (31/37)	
HCV subtype								
1 no subtype	59.4 (41/69)		65.7 (44/67)	1a vs. 1b	72.7 (8/11)	–*	–	
1a	59.8 (134/224)	1a vs. 1b	65.8 (146/222)	<0.001	70.6 (48/68)			
1b	43.4 (43/99)	0.009	82.4 (117/142)		81.8 (18/22)			
IL28B Polymorphism	*N* = 126	NS	*N* = 101	–*	*N* = 20	–*	*N* = 16	–*
CC	69.6 (16/23)		93.3 (14/15)		100.0 (4/4)		100.0 (3/3)	

Table 4 | (Continued)

	Genotype 1 SOF + PEG + RBV (*N* = 392)	*P*	Genotype 1 SOF + SIM (*N* = 431)	*P*	Genotype 1 SOF + SIM + RBV (*N* = 101)	*P*	Genotype 2 SOF + RBV (*N* = 151)	*P*
CT	57.1 (40/70)		74.6 (44/59)		71.4 (10/14)		75.0 (9/12)	
TT	54.5 (18/33)		74.1 (20/27)		100.0 (2/2)		100.0 (1/1)	
4 week on treatment HCV RNA	*N* = 310		*N* = 369		*N* = 83		*N* = 130	
Undetectable	56.4 (141/250)	NS	74.9 (191/255)	NS	79.4 (50/63)	–*	81.2 (82/101)	–*
Detectable <43 IU/mL	57.5 (23/40)		71.4 (60/84)		64.3 (9/14)		66.7 (12/18)	
Detectable ≥43 IU/mL	45.0 (9/20)		60.0 (18/30)		66.7 (4/6)		36.4 (4/11)	

BMI, body mass index; PEG, peginterferon; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response. Values are expressed in percentage.

* *P* values not reported when small sample size means that the minimum expected value in any cell of the χ^2 is <5.

SVR exists among experienced patients with PI experience and those with other non-PI treatment experience, the numerically higher SVR rate with SOF + SIM + RBV (78.3%) compared with SOF + SIM (67.8%) suggests that there may be some benefit to the SOF + SIM + RBV regimen in patients with prior PI experience.

These data represent the largest cohort of genotype 2 patients treated with SOF + RBV in the published literature to date. The 81.6% SVR rate among genotype 2 treatment-naive patients and the 70.9% SVR rate among treatment-experienced patients are lower than the 92–97% and 82–90% reported from smaller published cohorts of naïve and experienced patients, respectively.[14, 16, 17] There has been some discordance in the SVR rates among genotype 2 treatment-experienced patients with cirrhosis in the clinical trials with one study reporting SVRs of 60% (6/10) and another reporting SVRs of 88% (7/8).[16, 17] In our cohort, we observed a SVR rate of 58.2% in those with FIB-4 > 3.25, 53.1% in those with APRI >2 and 44.4% in those with a history of decompensated liver disease suggesting SVR rates lower than those in the clinical trials in those with treatment experience and more advanced fibrosis. In multivariate analysis, the odds of achieving SVR were reduced by 45% in those with prior treatment experience and by approximately 60% in those with advanced disease by APRI or FIB-4 score. This suggests that while SOF + RBV may be very effective in patients with less advanced disease, the presence of advanced liver disease has a dramatic effect on SVR and may identify a gap in currently available treatment. As recommended in the AASLD/IDSA/IAS-USA guidelines, extending SOF + RBV treatment to 16 weeks in patients with cirrhosis may improve treatment effectiveness, however, evaluation in larger real-world populations is currently lacking.[18]

Unlike in clinical trials where the stage of liver disease is often determined by biopsy or, more recently, fibroscan, few patients in VA undergo liver biopsy and fibroscan is not yet widely available. Our analysis thus included the laboratory markers of fibrosis or cirrhosis that are often used in clinical practice.[9, 10] For genotype 1 patients with APRI scores >3.25 compared to those with APRI ≤3.25, SVR rates were 10.6–20.6% lower for treatment-naïve patients and 17.1–24.6% lower for treatment-experienced patients. For genotype 2 patients with APRI scores >3.25 compared to those with APRI ≤3.25, SVR rates were 15.7% lower for treatment-naïve patients and 22.5% lower for treatment-experienced patients. Similar reductions were observed using FIB-4 > 3.25. In multivariate models, across genotype and regimens, the presence of advanced liver disease as assessed by these simple laboratory tests independently reduced the likelihood of achieving SVR by more than half. Thus, in clinical practice, calculation of APRI and/or FIB-4 scores may be useful in discussions with patients regarding the likelihood of treatment success.

Detectable 4 week on-treatment HCV RNA≥43 IU/mL was independently associated with an even greater reduction in the odds of SVR, for both genotype 1 and genotype

Table 5 | Significant predictors of SVR in multivariable model for genotype 1 and genotype 2 patients treated with sofosbuvir-based regimens

	SVR Odds ratio (95% CI)	*P*	SVR Odds ratio (95% CI)	*P*
Genotype 1	APRI		FIB-4	
*Model A**	*N* = 2406		*N* = 2406	
BMI≥30 (ref. BMI<25)	0.64 (0.49–0.84)	<0.001	0.65 (0.49–0.85)	0.001
Decompensated liver disease (ref. no history)	0.51 (0.36–0.71)	<0.001	0.57 (0.40–0.79)	<0.001
Treatment experienced (ref. naïve)	0.58 (0.48–0.71)	<0.001	0.60 (0.49–0.73)	<0.001
APRI>2 (ref. APRI≤2)/FIB-4 > 3.25 (ref. FIB-4 ≤ 3.25)	0.44 (0.36–0.55)	<0.001	0.39 (0.32–0.49)	<0.001
SOF + PEG + RBV (ref. SOF + SIM)	0.50 (0.40–0.62)	<0.001	0.49 (0.39–0.61)	<0.001
Model B†	*N* = 2406		*N* = 2406	
BMI ≥30 (ref. BMI <25)	0.63 (0.48–0.82)	<0.001	0.64 (0.48–0.83)	<0.001
Decompensated liver disease (ref. no history)	0.51 (0.36–0.72)	<0.001	0.57 (0.41–0.80)	<0.001
Prior treatment response null (ref. naïve)	0.37 (0.26–0.52)	<0.001	0.38 (0.26–0.54)	<0.001
Prior treatment response not determined (ref. naïve)	0.53 (0.41–0.69)	0.001	0.54 (0.41–0.70)	<0.001
APRI >2 (ref. APRI ≤2)/FIB-4 > 3.25 (ref. FIB-4 ≤ 3.25)	0.45 (0.37–0.56)	<0.001	0.40 (0.32–0.50)	<0.001
SOF + PEG + RBV (ref. SOF + SIM)	0.48 (0.39–0.60)	<0.001	0.47 (0.38–0.58)	<0.001
Model C‡	*N* = 1937		*N* = 1937	
BMI ≥30 (ref. BMI <25)	0.59 (0.43–0.81)	<0.001	0.60 (0.44–0.83)	0.001
Treatment experienced (ref. naïve)	0.52 (0.41–0.65)	<0.001	0.54 (0.43–0.67)	<0.001
APRI >2 (ref. APRI ≤2)/FIB-4 > 3.25 (ref. FIB-4 ≤ 3.25)	0.44 (0.34–0.55)	<0.001	0.41 (0.32–0.53)	<0.001
SOF + PEG + RBV (ref. SOF + SIM)	0.46 (0.35–0.59)	<0.001	0.45 (0.35–0.57)	<0.001
4 week HCV RNA <43 IU/mL (ref. undetectable)	0.59 (0.45–0.78)	<0.001	0.58 (0.44–0.77)	<0.001
4 week HCV RNA ≥43 IU/mL (ref. undetectable)	0.42 (0.29–0.62)	<0.001	0.41 (0.28–0.60)	<0.001
Genotype 2				
*Model A**	*N* = 615		*N* = 615	
Prior treatment experience (ref. naïve)	0.55 (0.35–0.88)	0.0097		NS
APRI >2 (ref. APRI ≤2)/FIB-4 > 3.25 (ref. FIB-4 ≤ 3.25)	0.39 (0.25–0.62)	<0.001	0.42 (0.27–0.65)	<0.001
Model C‡	*N* = 494		*N* = 494	
Prior treatment experience (ref. naïve)	0.47 (0.27–0.84)	0.009		NS
APRI >2 (ref. APRI ≤2)/FIB-4 > 3.25 (ref. FIB-4 ≤ 3.25)	0.32 (0.18–0.56)	<0.001	0.34 (0.19–0.59)	<0.001
4 week HCV RNA <43 IU/mL (ref. undetectable)	0.29 (0.15–0.56)	<0.001	0.28 (0.14–0.54)	<0.001
4 week HCV RNA ≥43 IU/mL (ref. undetectable)	0.21 (0.09–0.49)	<0.001	0.21 (0.09–0.47)	<0.001

CI, confidence interval; PEG, peginterferon; ref., reference; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response.

* Model A adjusted for age, sex, race/ethnicity, treatment experience, decompensated liver disease, diabetes, BMI, APRI (or FIB-4), and, for genotype 1, subtype and regimen.

† Model B adjusted for age, sex, race/ethnicity, prior treatment response, decompensated liver disease, diabetes, BMI, APRI (or FIB-4), genotype 1 subtype, regimen.

‡ Model C adjusted for age, sex, race/ethnicity, treatment experience, decompensated liver disease, diabetes, BMI, APRI (or FIB-4), 4 week HCV RNA and, for genotype 1, subtype and regimen.

2, than advanced liver disease or prior treatment experience – a finding that has not been previously reported.

Detectable HCV RNA ≥43 IU/mL at week 4 predicted an over 60% decrease in the odds of achieving SVR for genotype 1 patients and nearly an 80% decrease in the odds of SVR for genotype 2 patients. In clinical trials where the predictive value of early response was assessed, so few patients had HCV RNA above the lower level of quantification at week 4 (only 29 genotype 1 patients and 0 genotype 2 patients) that the negative predictive value of a detectable 4 week on-treatment HCV RNA was not as apparent as in this real-world cohort which had greater numbers of patients who were still detectable after 4 weeks of treatment.[5, 17]

Another notable finding of the present analysis relating to differences between real-world experience and clinical trials is the rate of early treatment discontinuation. The discontinuation rates we observed (13.7% for SOF + PEG + RBV, 11.8% for SOF + SIM, 9.9% for SOF + SIM + RBV, 14.3% for SOF + RBV) were comparable although somewhat higher than discontinuation rates reported by CVS Health (10% for SOF + PEG

+ RBV, 4% for SOF + SIM, 9% for SOF + RBV).[19] These discontinuation rates, however, are markedly higher than those observed in clinical trials (0–3.6%).[5, 14, 16, 17] The early treatment discontinuation rates likely contributed to the lower SVR rates observed in our cohort compared to the clinical trials, highlighting that the observed effectiveness may be substantially undermined by issues such as patient tolerability, social or behavioural factors, adverse events and baseline characteristics pre-disposing patients to failure.

In univariate analysis of treatment-naïve patients, SVR rates did not differ between those with 1a and 1b subtype. For treatment-experienced patients on SOF + PEG + RBV, SVR rates were higher in those with 1a compared to 1b (59.8% vs. 43.4%, $P = 0.009$), an observation that has also been reported in clinical trials with this regimen.[12–14] For treatment-experienced patients on SOF + SIM, SVR rates were lower as expected in those with 1a compared to 1b (65.8% vs. 82.4%, $P < 0.0001$). We could not assess impact of Q80K testing as this was infrequently performed. Overall in multivariate models, subtype did not independently predict SVR rates.

While this study includes a large cohort of diverse patients treated in clinical practice, there are limitations of this data. As patients treated in routine medical practice are not randomised, the potential for differential selection of regimens exists, although the multivariate models provide adjustment for differences in included baseline characteristics. Sample size constraints particularly for those receiving SOF + SIM + RBV preclude us from reporting on the statistical significance for some characteristics. From the available electronic data elements, prior treatment could only be determined for those patients treated within VA. Thus, patients who were previously treated outside VA would be erroneously classified as naïve. Treatment duration and thus early treatment discontinuation rates were determined based on the cumulative dispensed days' supply. This may overestimate the treatment duration as patients may have discontinued treatment even with medication in their possession. Given the high cost of SOF, however, many prescriptions were filled for small quantities (e.g. 7–14 days at a time) which would limit the extent of the overestimation. Due to the nature of the electronic data, specific reasons for early discontinuation (i.e. adverse events or poor tolerability) could not be determined. As few patients underwent IL28B testing, we were unable to assess the impact of this polymorphism in multivariate models. From the univariate analysis, IL28B may still be clinically relevant for patients receiving SOF + PEG + RBV, particularly treatment-naïve patients.[20, 21] While not statistically significant, SVR rates were numerically lower in IL28B-TT patients treated with SOF + SIM regardless of treatment experience, though numbers of patients in these groups were small. There did not appear to be any impact of IL28B on SVR in patients treated with SOF + SIM + RBV, though again numbers of patients in these groups were small. Approximately, a quarter of the cohort lacked definitive laboratory data to determine SVR status. Such patients did not differ statistically on nearly all baseline demographic and clinical characteristics from patients who had definitive laboratory data. Although patients with definitive laboratory testing were significantly more likely to be treatment experienced than treatment naïve and more likely to have advanced liver disease, the numerical differences were small (data not shown).

CONCLUSIONS

In this large real-world cohort, genotype 1 and 2 HCV-infected veterans with advanced liver disease, prior treatment experience or detectable week 4 on-treatment HCV RNA were significantly less likely to achieve SVR. For genotype 1, use of SOF + SIM ± RBV was associated with a higher likelihood of SVR compared with SOF + PEG + RBV. Overall, SVR rates in the VA with SOF-based regimens were substantially higher than with prior HCV anti-viral regimens but lower than the rates reported in clinical trials. The differences observed in VA with regard to patient characteristics, early treatment discontinuations and lower SVR rates reflect the differences between clinical trials and clinical practice. Thus, patient and provider expectations in real-world settings may need to be tempered accordingly depending on the population being treated. The reporting of real-world experience in VA, the largest provider of HCV care in the USA, is essential to provide practical information to better inform HCV management strategies. Given the public health impact of effective HCV treatment, real-world outcomes data will help inform clinicians and policy makers beyond VA.

AUTHORSHIP

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