Research Article
Viral Hepatitis

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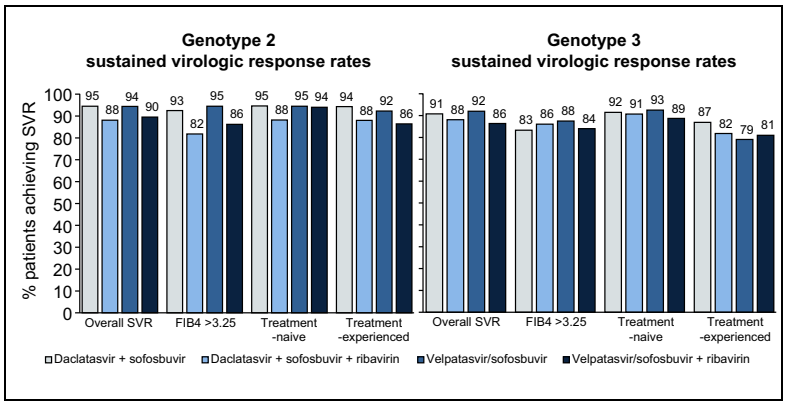
Real-world effectiveness of daclatasvir plus sofosbuvir and velpatasvir/sofosbuvir in hepatitis C genotype 2 and 3

Graphical abstract



Highlights

- In HCV genotype 2 or 3 patients, SVR rates with DCV + SOF were comparable to VEL/SOF.
- SVR with DCV + SOF + RBV was comparable to SVR with VEL/SOF + RBV.
- Regimen did not impact the odds of SVR for either HCV genotype 2 or genotype 3.
- Results support using either DCV + SOF or VEL/SOF for HCV genotypes 2 and 3.
- As guidelines have changed, some of the patients in this cohort were treated outside the current guidelines.

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Lay summary

In clinical practice, cure rates for hepatitis C virus (HCV) genotype 2 were 94% and cure rates for HCV genotype 3 were 90%. The chance of achieving cure was the same whether a person received daclatasvir plus sofosbuvir or velpatasvir/sofosbuvir. Ribavirin did not affect cure rates. The chance of a cure was lowest in people who had received HCV medication in the past.

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Real-world effectiveness of daclatasvir plus sofosbuvir and velpatasvir/sofosbuvir in hepatitis C genotype 2 and 3

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Background & Aim: Understanding the real-world effectiveness of all-oral hepatitis C virus (HCV) regimens informs treatment decisions. We evaluated the effectiveness of daclatasvir + sofosbuvir ± ribavirin (DCV + SOF ± RBV) and velpatasvir/sofosbuvir (VEL/SOF) ± RBV in patients with genotype 2 and genotype 3 infection treated in routine practice.

Methods: This observational analysis was carried out in an intent-to-treat cohort of patients with HCV genotype 2 and genotype 3. Sustained virologic response (SVR) analysis was performed in 5,400 patients initiated on DCV + SOF ± RBV or VEL/SOF ± RBV at any Department of Veterans Affairs facility.

Results: For genotype 2, SVR rates did not differ between DCV + SOF (94.5%) and VEL/SOF (94.4%) or between DCV + SOF + RBV (88.1%) and VEL/SOF + RBV (89.5%). For genotype 3, SVR rates did not differ between DCV + SOF (90.8%) and VEL/SOF (92.0%) or between DCV + SOF + RBV (88.1%) and VEL/SOF + RBV (86.4%). In multivariate models of patients with genotype 2 and 3 infection, the treatment regimen was not a significant predictor of the odds of SVR. For genotype 3, significant predictors of reduced odds of SVR were prior HCV treatment-experience (odds ratio [OR] 0.51, 95% CI 0.36–0.72; p <0.001), FIB-4 >3.25 (OR 0.60; 95% CI 0.43–0.84; p = 0.002) and a history of decompensated liver disease (OR 0.68; 95% CI 0.47–0.98; p = 0.04). For patients with genotype 2 and 3, treated with VEL/SOF ± RBV, 89% and 85% received 12-weeks of treatment, respectively. For DCV + SOF ± RBV, 56% and 20% of patients with HCV genotype 2 received 12-weeks and 24-weeks of treatment, respectively; while 53% and 23% of patients with HCV genotype 3 received 12-weeks and 24-weeks, with most direct-acting antiviral experienced patients receiving 24-weeks.

Conclusions: In patients infected with HCV genotype 2 and 3, DCV + SOF ± RBV and VEL/SOF ± RBV produced similar SVR rates within each genotype, and the regimen did not have a significant impact on the odds of SVR. For patients with genotype 3, prior treatment-experience and advanced liver disease were significant predictors of reduced odds of SVR regardless of regimen.

Lay summary: In clinical practice, cure rates for hepatitis C virus (HCV) genotype 2 were 94% and cure rates for HCV genotype 3 were 90%. The chance of achieving cure was the same whether a person received daclatasvir plus sofosbuvir or velpatasvir/sofosbuvir. Ribavirin did not affect cure rates. The chance of a cure was lowest in people who had received HCV medication in the past.

Introduction

Approximately 71.1 million people are estimated to be chronically infected with hepatitis C virus (HCV) worldwide, with 2.9 million infected in the United States.[1] Genotype 2 accounts for 11% of chronic HCV infections both worldwide and in the United States, while genotype 3 accounts for 18% of HCV infections worldwide and 9% in the United States.[1,2]

Daclatasvir (DCV), an NS5A inhibitor, has been evaluated in combination with sofosbuvir (SOF), an NS5B polymerase inhibitor, in phase III and early access clinical trials in patients with HCV genotype 2 and genotype 3. Sustained virologic response (SVR) rates of 92%–100% were obtained with 12 or 24-week regimens in treatment-naïve and peginterferon/ribavirin (RBV)-experienced patients with HCV genotype 2.[3] In genotype 3, SVR rates varied based on patient characteristics, duration, and RBV use, ranging from 86% to 97% with 12 weeks of DCV + SOF ± RBV in treatment-naïve and peginterferon, protease inhibitor, or SOF-experienced patients without cirrhosis and from 70% to 89% with 12 or 24 weeks in patients with cirrhosis.[4–7] The co-formulated NS5A and NS5B inhibitor velpatasvir (VEL)/SOF was approved approximately one year after DCV for genotype 2 and genotype 3. In phase III clinical trials of patients with HCV genotype 2, SVR was achieved in 99%–100% of treatment-naïve and interferon-experienced patients with and without cirrhosis.[8–10] In a mix of treatment-naïve and interferon-experienced patients with genotype 3, with and without cirrhosis, 12 weeks of VEL/SOF resulted in SVRs of 89% to 97%, and VEL/SOF + RBV resulted in an SVR rate of 85% in patients with decompensated cirrhosis.[9,11]

Several expert-developed recommendations for HCV management exist, including those from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA), the European Association for the Study of the Liver (EASL), and the Department of Veterans Affairs (VA).[12–14] Given rapid advances in HCV treatment, these HCV guidelines have changed as new data have

Keywords: Daclatasvir; Hepatitis C; Sofosbuvir; Sustained virologic response; Velpatasvir.
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emerged.[12,15] In real-world practice, treatment does not always follow guidelines and providers make individualized decisions to use regimens where evidence is evolving.

VA is the largest provider of healthcare to HCV-infected individuals in the United States and has provided all-oral HCV treatment to more than 100,000 veterans.[16] We evaluated the real-world effectiveness of DCV + SOF ± RBV and VEL/SOF ± RBV in patients infected with HCV genotype 2 and genotype 3 treated in routine practice.

Patients and methods

This observational intent-to-treat cohort analysis used the VA's HCV Clinical Case Registry, a VA electronic medical record extract.[17] Eligible individuals included all patients infected with HCV genotype 2 and genotype 3 who initiated VA-prescribed DCV + SOF ± RBV or VEL/SOF ± RBV by the 31st March 2017 with an end of treatment (EOT) by 30th June 2017. DCV, SOF, and VEL/SOF were available on the VA national formulary. DCV was FDA approved on the 24th July 2015 for genotype 3 and first prescribed in VA on the 20th August 2015. VEL/SOF was FDA approved on the 28th June 2016 for genotype 2 and 3 and first prescribed in VA on the 14th July 2016. During the time of this observation, for genotype 2, VA guidance recommended 12 weeks of VEL/SOF, adding RBV for patients with decompensated cirrhosis, and extending treatment duration to 24 weeks in NS5A-experienced patients.[14] Although not FDA approved for genotype 2, VA guidance included DCV + SOF for 12 weeks as an alternative, with the addition of RBV and consideration of 16–24 weeks in patients with cirrhosis or prior SOF-experience.[14,18] For genotype 3, 12 weeks of DCV + SOF or VEL/SOF was recommended for patients without cirrhosis; VEL/SOF ± RBV for 12 weeks was recommended for cirrhotic patients with 24 weeks recommended for prior NS5A-experience; DCV + SOF + RBV was recommended for 12–16 weeks in patients with cirrhosis, with the option for 24 weeks based on data available at the time.[3–7] Regimen choice and follow-up laboratory testing were at the discretion of the provider. Patients were excluded if their baseline HCV RNA ≤1,000 IU/ml (n = 43) or they had undergone a liver transplant (n = 30).

SVR required an HCV RNA below the lower limit of quantification (LLOQ) ≥12 weeks after the EOT. Approximately 16.4% and 83.6% of patients were tested with an HCV RNA assay with an LLOQ of 12 and 15 IU/ml, respectively. Patients whose most recent HCV RNA was >LLOQ and those who died on treatment or within 12 weeks of the EOT were categorized as having no SVR. Patients whose most recent HCV RNA was <LLOQ but had no test ≥12 weeks after the EOT were excluded from the SVR analysis. The EOT was calculated as the last day covered by prescriptions of DCV or VEL/SOF using dispensing dates and quantity dispensed. Patients were followed through to the 30th June 2018.

Demographic and baseline variables were determined at the time of treatment initiation and included age, sex, race/ethnicity, body mass index (BMI), cirrhosis (by International Classification of Diseases (ICD)-9/10 codes or a history of decompensated liver disease), history of decompensated liver disease (by ICD-9/10 codes for ascites, esophageal variceal hemorrhage, hepatic coma, hepatic encephalopathy, hepatorenal syndrome, or spontaneous bacterial peritonitis), history of hepatocellular carcinoma (HCC), proton pump inhibitor (PPI) prescription, prior HCV treatment with peginterferon- or DAA-based regimens, alanine aminotransferase (ALT), albumin, aspartate aminotransferase (AST), estimated glomerular filtration rate (eGFR), platelets, FIB-4 score, treatment regimen and start date. Albumin, ALT, AST, creatinine, platelets and baseline HCV RNA used the value within 1 year before and closest to the treatment start date.

Univariate comparisons used the Pearson Chi-square test with Yates' continuity correction or Fisher's exact test as appropriate for categorical variables and *t* tests for continuous variables. Multivariate logistic regression models were constructed with all patients to identify predictors of SVR. Models included variables selected *a priori* of age, sex, race/ethnicity, BMI, history of decompensated disease, history of HCC, prior HCV treatment, eGFR, FIB-4, and regimen with VEL/SOF as the reference. Two additional models with the same baseline variables were constructed: one replacing FIB-4 with a clinical diagnosis of cirrhosis, and another with only patients who completed at least 12 weeks of treatment. To examine the impact of regimen, four multivariate models for each genotype were constructed separately for patients who received DCV + SOF or VEL/SOF and had FIB-4 ≤3.25 or no diagnosis of cirrhosis and for patients who received any of the four regimens and had FIB-4 >3.25 or a diagnosis of cirrhosis. Multivariate models excluded patients with eGFR <30 ml/min/1.73 m^2 in whom SOF is not recommended. A p value <0.05 was considered statistically significant. Analyses were performed using R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

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

Results

A total of 2,939 patients with HCV genotype 2 and 2,824 patients with HCV genotype 3 were initiated on DCV + SOF ± RBV or VEL/SOF ± RBV at 128 VA facilities. The median start date for DCV + SOF ± RBV was several months earlier than for VEL/SOF ± RBV because DCV + SOF received FDA approval 11 months earlier. For both genotype 2 and 3, patients starting DCV + SOF + RBV and VEL/SOF + RBV had higher rates of cirrhosis, decompensated disease, prior HCV treatment, lower platelets and higher FIB-4 compared to those starting DCV + SOF or VEL/SOF (Tables 1 and 2).

Among patients with genotype 2, comparable percentages discontinued treatment before 12 weeks with a higher early discontinuation rate for those who received DCV + SOF + RBV. The discontinuation rates were 8.1% (22/271) for DCV + SOF, 13.6% (6/44) for DCV + SOF + RBV, 7.4% (175/2,368) for VEL/SOF and 7.0% (18/256) for VEL/SOF + RBV. Among patients with genotype 3 infection, discontinuation rates before 12 weeks were similar regardless of regimen: 7.0% (30/431) for DCV + SOF, 8.8% (45/514) for DCV + SOF + RBV, 8.8% (126/1,424) for VEL/SOF and 7.9% (36/455) for VEL/SOF + RBV. Given the latitude of DCV + SOF treatment recommendations with 16 and 24-week options, observed treatment durations for DCV + SOF ± RBV varied more than the durations observed with VEL/SOF ± RBV. Among patients with genotype 2 infection, 36.4% (16/44) of those treated with DCV + SOF + RBV received 24 weeks of treatment compared to 3.9% (10/256) of those treated with VEL/SOF + RBV. Among patients with genotype 3 infection, 30.2% (155/514) of those treated with DCV + SOF + RBV received

Table 1. Baseline characteristics of patients with HCV genotype 2.

	GT2 DCV + SOF n = 271	GT2 DCV + SOF + RBV n = 44	GT2 VEL/SOF n = 2,368	GT2 VEL/SOF + RBV n = 256
Age (years)	62.9 ± 8.2	62.5 ± 7.0	62.9 ± 8.1	63.4 ± 6.4
Sex male	259 (95.6%)	44 (100%)	2,273 (96.0%)	252 (98.4%)
Race/ethnicity				
African-American	45 (16.6%)	3 (6.8%)	282 (11.9%)	28 (10.9%)
Caucasian	191 (70.5%)	34 (77.3%)	1,686 (71.2%)	190 (74.2%)
Hispanic	19 (7.0%)	4 (9.1%)	218 (9.2%)	23 (9.0%)
Other/multiple	16 (5.9%)	3 (6.8%)	182 (7.7%)	15 (5.9%)
Body Mass Index (kg/m^2)	28.6 ± 5.5	30.7 ± 6.4	28.0 ± 5.5	29.5 ± 5.9
Cirrhosis	54 (19.9%)	24 (54.5%)	355 (15.0%)	124 (48.4%)
Decompensated liver disease	26 (9.6%)	13 (29.5%)	72 (3.0%)	61 (23.8%)
Hepatocellular carcinoma	6 (2.2%)	2 (4.5%)	7 (0.3%)	17 (6.6%)
PPI	73 (26.9%)	8 (18.2%)	344 (14.5%)	49 (19.1%)
Prior HCV treatment	55 (20.3%)	27 (61.4%)	93 (3.9%)	152 (59.4%)
Ledipasvir/SOF ± RBV	0 (0.0%)	0 (0.0%)	6 (0.3%)	2 (0.8%)
PegIFN + RBV	34 (12.5%)	6 (13.6%)	14 (0.6%)	39 (15.2%)
SOF + PegIFN + RBV	0 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.4%)
SOF + RBV	27 (10.0%)	26 (59.1%)	89 (3.8%)	148 (57.8%)
Albumin (g/dl)	3.9 ± 0.5	3.7 ± 0.6	4.0 ± 0.4	3.8 ± 0.5
ALT (U/L)	70.0 ± 74.1	70.1 ± 66.5	65.3 ± 65.5	70.9 ± 79.4
AST (U/L)	56.1 ± 46.6	70.2 ± 60	51.9 ± 42.3	71.1 ± 74.4
eGFR (ml/min/1.73 m^2)	81.3 ± 19.4	81.7 ± 17.5	82.8 ± 18.0	86.3 ± 15.5
≥60	225 (83.0%)	38 (86.4%)	2,093 (88.4%)	239 (93.4%)
30–59	44 (16.2%)	6 (13.6%)	261 (11.0%)	17 (6.6%)
<30	2 (0.7%)	0 (0.0%)	14 (0.6%)	0 (0.0%)
Platelets (K/μl)	197.1 ± 83.3	147.9 ± 77.2	204.5 ± 65.8	157.6 ± 71.4
FIB-4	2.9 ± 2.8	5.3 ± 5.0	2.3 ± 1.9	4.8 ± 5.0
<1.45	83 (30.6%)	10 (22.7%)	766 (32.3%)	56 (21.9%)
1.45–3.25	114 (42.1%)	11 (25.0%)	1,194 (50.4%)	82 (32.0%)
>3.25	74 (27.3%)	23 (52.3%)	408 (17.2%)	118 (46.1%)
HCV RNA (log IU/ml)	6.2 ± 0.8	6.1 ± 0.8	6.2 ± 0.9	6.1 ± 0.9
Start date (YYYY-MM-DD) median [25%, 75%]	2016–05-17 [2016–04-05, 2016–06-23]	2016–03-23 [2015–11-12, 2016–05-18]	2016–11-07 [2016–09-16, 2017–01-20]	2016–10-20[2016–09-10, 2017–01-04]

Continuous variables reported as mean ± standard deviation.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCV, daclatasvir; eGFR, estimated glomerular filtration rate; PPI, proton pump inhibitor; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.

24 weeks of treatment compared to 8.6% (39/455) of those treated with VEL/SOF + RBV.

SVR results were available for 94.4% (n = 2,774) of patients with HCV genotype 2 and 93.0% (n = 2,626) with HCV genotype 3 (Fig. 1). For both genotype 2 and genotype 3, patients excluded from the SVR analysis were statistically younger but generally did not differ from those included in the SVR analysis (Table S1).

SVR was achieved in 93.9% of 2,774 patients with HCV genotype 2. SVR rates did not differ between those who received DCV + SOF (94.5%, 241/255) and VEL/SOF (94.4%, 2,105/2,230) ($p = 0.94$) or between those who received DCV + SOF + RBV (88.1%, 37/42) and VEL/SOF + RBV (89.5%, 221/247) ($p = 1.00$) (Table 3). SVR rates were generally lower in patients with cirrhosis, in those with FIB-4 >3.25 and in those with a history of decompensation, although not statistically so. Use of RBV did not improve SVR. Extending DCV + SOF treatment duration from 12 weeks to 16 or 24 weeks in those with FIB-4 >3.25 achieved higher SVR rates (82.6% (19/23) *vs.* 100.0% (13/13), and 95.8% (23/24), respectively).

The overall SVR rate for genotype 3 was 90.2% (2,369/2,626) and rates did not differ between DCV + SOF (90.8%, 366/403) and VEL/SOF (92.0%, 1,203/1,307) ($p = 0.50$), or between DCV + SOF + RBV (88.1%, 430/488) and VEL/SOF + RBV (86.4%, 370/428) ($p = 0.51$) (Table 4). In univariate comparisons, prior HCV treatment and indicators of advanced liver disease (cirrhosis, decompensation, HCC, and FIB-4 >3.25) were generally associated with lower SVR rates. When combined with FIB-4 >3.25, both prior peginterferon and prior DAA treatment were associated with even lower SVR rates. Adding RBV to DCV + SOF and extending treatment duration from 12 weeks to 24 weeks marginally increased SVR rates in patients with FIB-4 >3.25 from 90.0% (27/30) to 93.9% (107/114), but did not impact VEL/SOF SVR rates.

In multivariate models for all patients with HCV genotype 2, the only significant predictor of decreased odds of SVR was age <55 (odds ratio (OR) 0.45; 95% CI 0.27–0.77; $p = 0.002$). Other baseline demographic and clinical characteristics including treatment regimen, clinical diagnosis of cirrhosis or FIB-4 category were not significant predictors. In a model limited to patients with HCV genotype 2 who received at least 12 weeks of treatment, receipt of DCV + SOF + RBV (OR 0.27; 95% CI 0.08–0.99; $p = 0.04$) or VEL/SOF + RBV (OR 0.45; 95% CI 0.20–0.99; $p = 0.04$) compared to VEL/SOF predicted reduced odds of SVR but receipt of DCV + SOF compared to VEL/SOF did not (OR 0.92; 95% CI 0.42–2.34; $p = 0.85$). This suggests that providers accurately identified patients less likely to respond and added RBV to their regimen, but the odds of SVR were still significantly reduced.

In multivariate models for all patients with HCV genotype 3, significant predictors of decreased odds of SVR were FIB-4 >3.25 compared to FIB-4 1.45–3.25 (OR 0.60; 95% CI 0.43–0.84; $p = 0.002$), decompensated disease (OR 0.68; 95% CI 0.47–0.99; $p = 0.04$), and prior HCV treatment (OR 0.51, 95% CI 0.36–0.72,

Table 2. Baseline characteristics of patients with HCV genotype 3.

	GT3 DCV + SOF n = 431	GT3 DCV + SOF + RBV n = 514	GT3 VEL/SOF n = 1,424	GT3 VEL/SOF + RBV n = 455
Age (years)	57.0 ± 10.0	60.9 ± 5.6	56.9 ± 10.9	61.0 ± 6.7
Sex male	416 (96.5%)	505 (98.2%)	1,360 (95.5%)	442 (97.1%)
Race/ethnicity				
African-American	53 (12.3%)	31 (6.0%)	95 (6.7%)	19 (4.2%)
Caucasian	321 (74.5%)	388 (75.5%)	1,114 (78.2%)	362 (79.6%)
Hispanic	34 (7.9%)	55 (10.7%)	102 (7.2%)	40 (8.8%)
Other/multiple	23 (5.3%)	40 (7.8%)	113 (7.9%)	34 (7.5%)
Body Mass Index (kg/m^2)	27.9 ± 5.6	28.5 ± 5.3	27.3 ± 5.2	28.7 ± 5.7
Cirrhosis	84 (19.5%)	310 (60.3%)	224 (15.7%)	267 (58.7%)
Decompensated liver disease	45 (10.4%)	137 (26.7%)	64 (4.5%)	119 (26.2%)
Hepatocellular carcinoma	6 (1.4%)	21 (4.1%)	18 (1.3%)	28 (6.2%)
PPI	63 (14.6%)	106 (20.6%)	170 (11.9%)	74 (16.3%)
Prior HCV treatment	66 (15.3%)	151 (29.4%)	48 (3.4%)	131 (28.8%)
Ledipasvir/SOF ± RBV	2 (0.5%)	32 (6.2%)	26 (1.8%)	52 (11.4%)
PegIFN + RBV	54 (12.5%)	96 (18.7%)	10 (0.7%)	20 (4.4%)
SOF + PegIFN + RBV	0 (0.0%)	1 (0.2%)	0 (0.0%)	2 (0.4%)
SOF + RBV	14 (3.2%)	51 (9.9%)	23 (1.6%)	77 (16.9%)
Albumin (g/dl)	4.0 ± 0.4	3.8 ± 0.5	4.0 ± 0.4	3.7 ± 0.5
ALT (U/L)	92.7 ± 80.1	104.8 ± 72.2	92.6 ± 81.5	96.3 ± 65.4
AST (U/L)	69.2 ± 53.2	96.5 ± 62.4	68.4 ± 50	86.3 ± 52.6
eGFR (ml/min/1.73 m^2)	88.4 ± 18.9	88.6 ± 15.9	88.9 ± 17.1	87.5 ± 15.9
≥60	403 (93.5%)	486 (94.6%)	1,340 (94.1%)	424 (93.2%)
30–59	23 (5.3%)	26 (5.1%)	78 (5.5%)	31 (6.8%)
<30	5 (1.2%)	2 (0.4%)	6 (0.4%)	0 (0.0%)
Platelets (K/μl)	201.9 ± 74.7	133 ± 60.5	202.5 ± 69.8	146 ± 65.8
FIB-4	2.8 ± 3.3	5.5 ± 4.3	2.5 ± 2.1	5.1 ± 4.3
<1.45	152 (35.3%)	31 (6.0%)	474 (33.3%)	48 (10.5%)
1.45–3.25	195 (45.2%)	136 (26.5%)	657 (46.1%)	146 (32.1%)
>3.25	84 (19.5%)	347 (67.5%)	293 (20.6%)	261 (57.4%)
HCV RNA (log IU/ml)	6.0 ± 0.8	6.1 ± 0.7	6.0 ± 0.8	6.1 ± 0.8
Start date (YYYY-MM-DD) (median [25%, 75%])	2016–04-15 [2016–01-25, 2016–06-16]	2016–03-03 [2016–01-05, 2016–04-27]	2016–11-01 [2016–09-15, 2017–01-18]	2016–10-04 [2016–09-06, 2016–12-06]

Continuous variables reported as mean ± standard deviation.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCV, daclatasvir; eGFR, estimated glomerular filtration rate; GT, genotype; PPI, proton pump inhibitor; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.

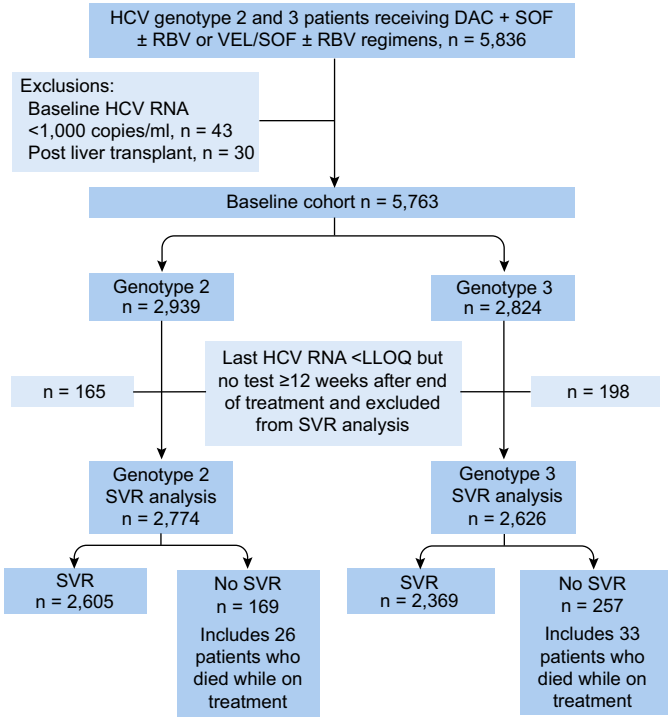

Fig. 1. Study flow design.

p <0.001). When limited to patients who received at least 12 weeks of treatment, the significant predictors remained the same, with HCC (OR 0.45; 95% CI 0.23–0.89; p = 0.02) additionally associated with significantly reduced odds of SVR. Treatment regimen was not a significant predictor.

Odds of SVR did not significantly differ based on genotype and regimen in multivariate models constructed separately for patients who received DCV + SOF or VEL/SOF with FIB-4 ≤3.25, or for patients with FIB-4 >3.25 who received any of the four regimens (Table S2). Although not significant, in patients with genotype 2 the odds of SVR were consistently higher for DCV + SOF compared to VEL/SOF. In patients with genotype 3, the odds of SVR were higher with DCV + SOF + RBV in patients with cirrhosis and with DCV + SOF + RBV or VEL/SOF + RBV in patients who were HCV-treatment experienced, suggesting some benefit from RBV.

Patients with HCV genotype 3, receiving VEL/SOF + RBV and a PPI, had lower SVR rates than patients not receiving a PPI (78.5% (51/65) *vs.* 87.9% (319/363), p = 0.049). SVR rates were numerically (but not statistically) lower in those receiving VEL/SOF and a PPI compared to those not receiving a PPI (89.5% (145/162) *vs.* 92.4% (1058/1145), p = 0.26). Patients with HCV genotype 3, receiving VEL/SOF ± RBV and PPIs, had non-significantly reduced odds of SVR in a multivariate model including PPI use (OR 0.66; 95% CI 0.43–1.03; p = 0.06). PPI use had no impact in patients with HCV genotype 2.

Table 3. SVR rates in patients with HCV genotype 2.

	GT2 DCV + SOF n = 255	GT2 DCV + SOF + RBV n = 42	GT2 VEL/SOF n = 2,230	GT2 VEL/SOF RBV n = 247
Overall SVR	94.5% (241/255)	88.1% (37/42)	94.4% (2,105/2,230)	89.5% (221/247)
Age (years)				
<55	86.2% (25/29)	66.7% (2/3)	89.7% (175/195)*	100.0% (12/12)
55–64	98.2% (112/114)	90.9% (20/22)	94.9% (1,054/1,111)	87.3% (117/134)
≥65	92.9% (104/112)	88.2% (15/17)	94.8% (876/924)	91.1% (92/101)
Sex				
Male	94.3% (230/244)	88.1% (37/42)	94.3% (2,017/2,139)	89.3% (217/243)
Female	100.0% (11/11)	–	96.7% (88/91)	100.0% (4/4)
Race/ethnicity				
African-American	92.7% (38/41)	100.0% (3/3)	93.9% (248/264)	85.7% (24/28)
Caucasian	94.0% (173/184)	84.4% (27/32)	94.1% (1,496/1,590)	89.5% (162/181)
Hispanic	100.0% (16/16)	100.0% (4/4)	94.1% (190/202)	87.0% (20/23)
Other/multiple	100.0% (14/14)	100.0% (3/3)	98.3% (171/174)	100.0% (15/15)
Cirrhosis				
No	95.1% (195/205)	91.3% (21/23)	94.5% (1,789/1,894)	92.1% (117/127)
Yes	92.0% (46/50)	84.2% (16/19)	94.0% (316/336)	86.7% (104/120)
Decompensated liver disease				
No	95.2% (219/230)	90.0% (27/30)	94.5% (2,043/2,162)	89.4% (168/188)
Yes	88.0% (22/25)	83.3% (10/12)	91.2% (62/68)	89.8% (53/59)
Hepatocellular carcinoma				
No	94.8% (236/249)	87.5% (35/40)	94.4% (2,100/2,225)	90.4% (208/230)
Yes	83.3% (5/6)	100.0% (2/2)	100.0% (5/5)	76.5% (13/17)
Prior HCV treatment^				
No	94.6% (191/202)	88.2% (15/17)	94.5% (2,021/2,139)	94.0% (94/100)
Yes	94.3% (50/53)	88.0% (22/25)	92.3% (84/91)	86.4% (127/147)
Prior PegIFN + RBV◇	96.9% (31/32)	83.3% (5/6)	85.7% (12/14)	83.8% (31/37)
Prior SOF + RBV◇	92.6% (25/27)	87.5% (21/24)	93.1% (81/87)	86.8% (125/144)
FIB-4				
<1.45	95.0% (76/80)	88.9% (8/9)	94.7% (673/711)	90.9% (50/55)
1.45–3.25	95.4% (103/108)	100.0% (11/11)	94.2% (1,070/1,136)	93.4% (71/76)
>3.25	92.5% (62/67)	81.8% (18/22)	94.5% (362/383)	86.2% (100/116)
Treatment duration				
<12 weeks	63.2% (12/19)	80.0% (4/5)	50.6% (82/162)	37.5% (6/16)
12 weeks	96.1% (148/154)	90.9% (10/11)	97.9% (1,956/1,997)	93.0% (186/200)
16 weeks	100.0% (27/27)	80.0% (4/5)	93.2% (41/43)	100.0% (15/15)
24 weeks	97.7% (43/44)	100.0% (16/16)	100.0% (8/8)	88.9% (8/9)
Other duration	100.0% (11/11)	60.0% (3/5)	89.5% (18/20)	85.7% (6/7)
FIB-4 >3.25	n = 67	n = 22	n = 383	n = 116
<12 weeks	100.0% (2/2)	66.7% (2/3)	42.3% (12/27)	33.3% (3/9)
12 weeks	82.6% (19/23)	100.0% (4/4)	98.2% (330/336)	90.0% (81/90)
16 weeks	100.0% (13/13)	80.0% (4/5)	100.0% (14/14)	100.0% (7/7)
24 weeks	95.8% (23/24)	100.0% (7/7)	100.0% (3/3)	87.5% (7/8)
Other duration	100.0% (5/5)	33.3% (1/3)	100.0% (3/3)	100.0% (2/2)
Prior PegIFN and FIB-4 ≤3.25				
12 weeks	100.0% (12/12)	0.0% (0/1)	100.0% (7/7)	94.4% (17/18)
24 weeks	100.0% (6/6)	100.0% (2/2)	100.0% (1/1)	–
Prior PegIFN and FIB-4 >3.25				
12 weeks	66.7% (2/3)	100.0% (1/1)	75.0% (3/4)	84.6% (11/13)
24 weeks	100.0% (3/3)	–	–	100.0% (1/1)
Prior DAA and FIB-4 ≤3.25				
12 weeks	100.0% (1/1)	66.7% (2/3)	98.4% (61/62)	93.6% (76/78)
24 weeks	100.0% (10/10)	100.0% (9/9)	100.0% (2/2)	100.0% (1/1)
Prior DAA and FIB-4 >3.25				
12 weeks	100.0% (3/3)	100.0% (1/1)	88.2% (15/17)	84.1% (37/44)
24 weeks	75.0% (3/4)	100.0% (7/7)	100.0% (1/1)	80.0% (4/5)

DAA, direct-acting antiviral; DCV, daclatasvir; GT, genotype; PEG, peginterferon; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.
Univariate comparisons used the Pearson Chi-square test with Yates' continuity correction or Fisher's exact test as appropriate for categorical variables and t-tests for continuous variables.
^ Prior HCV treatment includes prior peginterferon and prior DAA.
◇ For statistical testing, those with prior regimen compared to treatment-naïve.

Discussion

In this large diverse real-world population, overall SVR rates were approximately 94% for patients with HCV genotype 2 and 90% for those with HCV genotype 3, treated with either DCV + SOF ± RBV or VEL/SOF ± RBV. Within genotype, overall SVR rates with 12 weeks of DCV + SOF were comparable to VEL/SOF and rates with 12 weeks of DCV + SOF + RBV were comparable to VEL/SOF + RBV, with RBV more likely to be used in

Table 4. SVR rates in patients with HCV genotype 3.

	GT3 DCV + SOF n = 403	GT3 DCV + SOF + RBV n = 488	GT3 VEL/SOF n = 1,307	GT3 VEL/SOF + RBV n = 428
Overall SVR	90.8% (366/403)	88.1% (430/488)	92.0% (1,203/1,307)	86.4% (370/428)
Age (years)				
<55	89.9% (89/99)	94.1% (48/51)	91.4% (288/315)	93.3% (42/45)
55–64	90.9% (219/241)	87.6% (282/322)	92.3% (646/700)	85.9% (225/262)
≥65	92.1% (58/63)	88.0% (103/117)	91.0% (233/256)	87.6% (99/113)
Sex				
Male	90.7% (353/389)	88.1% (422/479)	92.0% (1,146/1,246)	86.3% (359/416)
Female	92.9% (13/14)	88.9% (8/9)	93.4% (57/61)	91.7% (11/12)
Race/ethnicity				
African-American	95.8% (46/48)	93.3% (28/30)	94.3% (83/88)	94.1% (16/17)
Caucasian	90.4% (272/301)	88.6% (326/368)	91.6% (930/1,015)	87.9% (299/340)
Hispanic	90.6% (29/32)	83.0% (44/53)	92.9% (91/98)	78.9% (30/38)
Other/multiple	86.4% (19/22)	86.5% (32/37)	93.4% (99/106)	75.8% (25/33)
Cirrhosis				
No	92.3% (299/324)	89.6% (172/192)	93.1% (1,023/1,099)	89.3% (158/177)
Yes	84.8% (67/79)	87.2% (258/296)	86.5% (180/208)**	84.5% (212/251)
Decompensated liver disease				
No	92.0% (333/362)	90.2% (323/358)	92.5% (1,153/1,247)	88.6% (280/316)
Yes	80.5% (33/41)*	82.3% (107/130)*	83.3% (50/60)*	80.4% (90/112)*
Hepatocellular carcinoma				
No	91.2% (362/397)	88.0% (418/475)	92.3% (1,193/1,292)	87.0% (349/401)
Yes	66.7% (4/6)	90.5% (19/21)	66.7% (10/15)**	77.8% (21/27)
Prior HCV treatment^				
No	91.5% (313/342)	90.7% (313/345)	92.5% (1,169/1,264)	88.7% (268/302)
Yes	86.9% (53/61)	81.8% (117/143)**	79.1% (34/43)**	81.0% (102/126)*
Prior ledipasvir/SOF◇	100.0% (2/2)	80.6% (25/31)	78.3% (18/23)*	80.8% (42/52)
Prior PegIFN + RBV◇	84.3% (43/51)	83.3% (75/90)	80.0% (8/10)	70.0% (14/20)*
Prior SOF + RBV◇	100.0% (12/12)	80.4% (37/46)*	76.2% (16/21)*	81.9% (59/72)
FIB-4				
<1.45	92.9% (130/140)	92.9% (26/28)	94.1% (398/423)	89.1% (41/46)
1.45–3.25	92.4% (171/185)	92.3% (120/130)	92.6% (566/611)	89.9% (125/139)
>3.25	83.3% (65/78)*	86.1% (284/330)	87.5% (239/273)**	84.0% (204/243)
Treatment duration				
<12 weeks	67.9% (19/28)	56.8% (25/44)	61.6% (69/112)	50.0% (16/32)
12 weeks	93.6% (276/295)	89.8% (158/176)	95.3% (1,099/1,153)	90.3% (287/318)
16 weeks	93.8% (15/16)	89.4% (84/94)	88.5% (23/26)	82.1% (23/28)
24 weeks	90.9% (50/55)	94.6% (141/149)	80.0% (4/5)	89.5% (34/38)
Other duration	66.7% (6/9)	88.0% (22/25)	72.7% (8/11)	83.3% (10/12)
FIB-4 >3.25	n = 78	n = 330	n = 273	n = 243
<12 weeks	66.7% (4/6)	48.1% (13/27)	59.3% (16/27)	42.1% (8/19)
12 weeks	90.0% (27/30)	86.4% (95/110)	91.3% (210/230)	89.0% (154/173)
16 weeks	100.0% (2/2)	88.5% (54/61)	100.0% (9/9)	81.2% (13/16)
24 weeks	84.8% (28/33)	93.9% (107/114)	75.0% (3/4)	83.2% (22/27)
Other duration	57.1% (4/7)	83.3% (15/18)	33.3% (1/3)	75.0% (6/8)
Prior PegIFN and FIB-4 ≤3.25				
12 weeks	90.0% (27/30)	100.0% (11/11)	100.0% (3/3)	85.7% (6/7)
24 weeks	100.0% (5/5)	100.0% (4/4)	–	–
Prior PegIFN and FIB-4 >3.25				
12 weeks	66.7% (2/3)	71.4% (10/14)	60.0% (3/5)	57.1% (4/7)
24 weeks	60.0% (3/5)	85.2% (23/27)	100.0% (1/1)	50.0% (1/2)
Prior DAA and FIB-4 ≤3.25				
12 weeks	100.0% (3/3)	100.0% (3/3)	86.7% (13/15)	84.6% (33/39)
24 weeks	100.0% (2/2)	100.0% (15/15)	–	100.0% (10/10)
Prior DAA and FIB-4 >3.25				
12 weeks	100.0% (2/2)	83.3% (5/6)	88.2% (15/17)	75.0% (24/32)
24 weeks	100.0% (4/4)	86.7% (26/30)	100.0% (1/1)	83.3% (20/24)

DAA, direct-acting antiviral; DCV, daclatasvir; GT, genotype; PEG, peginterferon; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.
Univariate comparisons used the Pearson Chi-square test with Yates' continuity correction or Fisher's exact test as appropriate for categorical variables and t-tests for continuous variables.
*p <0.05,
**p <0.01.
^Prior HCV treatment includes prior peginterferon and prior DAA.
◇For statistical testing, those with prior regimen compared to treatment-naïve.

those with HCV treatment-experience and advanced liver disease. In cohorts of those with and without cirrhosis and treatment-experience, controlling for baseline characteristics, regimen did not have a significant impact on odds of SVR for either genotype 2 or genotype 3. Although VEL/SOF and DCV/SOF regimens have not been compared directly in clinical trials,

higher SVR rates achieved in clinical trials with VEL/SOF have led to the assumption of greater efficacy.[3–13] The present data show that DCV + SOF and VEL/SOF achieve similar SVR rates even among difficult subgroups, and generally irrespective of RBV use.

This study covers treatment initiation from August 2015 through March 2017 when data on optimal regimens were emerging, guidelines were rapidly changing, and the most recently approved medications (glecaprevir/pibrentasavir and VEL/SOF/voxilaprevir) were not yet available. Prior to the availability of glecaprevir/pibrentasivir and VEL/SOF/voxilaprevir, retreatment of patients with prior DAA-failure was less certain, often involving empiric decisions to add RBV or extend treatment duration. Notably, while some of the regimens used during the time of this evaluation are not recommended in current 2018 guidelines, these regimens were recommended in the 2015–2016 guidelines, which were in place at the time the regimens were prescribed.[12,14,15]

Our analysis supports DCV + SOF and VEL/SOF as effective treatment options for genotypes 2 and 3, with some nuances. Current EASL guidelines recommend either DCV + SOF or VEL/SOF for 12 weeks in patients with genotype 2, whereas AASLD recommends VEL/SOF for 12 weeks and lists DCV + SOF as an alternative for treatment-naïve and peginterferon + RBV-experienced patients with genotype 2.[13,15] In the present analysis, DCV + SOF and VEL/SOF SVR rates in treatment-naïve patients with HCV genotype 2 did not differ (94.6% and 94.5%, respectively) and peginterferon + RBV-experienced patients receiving DCV + SOF achieved higher SVR rates than those receiving VEL/SOF (96.9% *vs.* 85.7%, respectively), although the sample size was too small for statistical comparison. There appeared to be some benefit in extending DCV + SOF duration in patients with genotype 2 infection and cirrhosis, in accordance with current AASLD guidance, as SVR rates increased to 96%–100% in those treated for 16 to 24 weeks. Adding RBV did not improve SVR in any genotype 2 subgroup evaluated and regimen was not a significant predictor of SVR in multivariate models, supporting the EASL stance of both DCV + SOF and VEL/SOF as recommended regimens for genotype 2.

For genotype 3, EASL guidance recommends DCV + SOF ± RBV or VEL/SOF ± RBV, with RBV administration and duration dependent upon treatment-experience and cirrhosis status.[15] AASLD now recommends 12 weeks of VEL/SOF for treatment-naïve and peginterferon + RBV-experienced patients without cirrhosis, and VEL/SOF + RBV as an alternative for peginterferon + RBV-experienced patients with cirrhosis.[13] Twelve weeks of DCV + SOF is an alternative for treatment-naïve and peginterferon + RBV-experienced patients without cirrhosis and 24 weeks of DCV + SOF ± RBV for naïve patients with cirrhosis.[13] We observed similar SVR rates for treatment-naïve patients with HCV genotype 3 receiving DCV + SOF (91.5%) or VEL/SOF (92.5%, $p = 0.63$) and numerically higher SVR rates in peginterferon + RBV-experienced patients receiving DCV + SOF or DCV + SOF + RBV than patients receiving VEL/SOF or VEL/SOF + RBV (84.3% and 83.3% *vs.* 80.0% and 70.0%, respectively). In multivariate analysis of patients with genotype 3, as a whole or separately based on advanced liver disease status, regimen was not a significant predictor of SVR, supporting EASL's stance of both DCV + SOF and VEL/SOF as recommended regimens.

While regimen was not a predictor of SVR for genotype 3, prior HCV treatment was associated with significantly (49%) reduced odds of SVR, and FIB-4 >3.25 or cirrhosis, with (40%) reduced odds of SVR. The size of this cohort allowed differentiation of these subgroups to better assess the impact of RBV and treatment duration than in other cohorts.[5,7,19,20] Genotype 3 clinical trials demonstrated a varying negative impact of treatment-experience on SVR for both DCV + SOF ± RBV and VEL/SOF ± RBV. In 2016 only a few studies including a small number of selected patients underpinned the re-treatment recommendations.[12] In the current analysis, for HCV genotype 3, SVR rates were 4% to 13% lower overall in treatment-experienced patients compared to naïve patients and as much as 16% lower in SOF + RBV failures retreated with VEL/SOF, a regimen not recommended in 2018 guidelines, and 19% lower in peginterferon + RBV failures retreated with VEL/SOF + RBV. Lower SVRs were also reported from the German hepatitis C registry where SVR in patients with any DAA experience was 72.7% (n = 8/11) overall, and 88.9% (n = 8/9) in SOF-experienced patients retreated with VEL/SOF + RBV.[19] We observed a 3–6% increase in SVR in SOF-experienced patients retreated with VEL/SOF + RBV overall which, in patients without cirrhosis, was maximized when treatment was extended to 24 weeks, as supported by 2016 EASL guidelines. For non-cirrhotic DAA-experienced patients with HCV genotype 3, SVR rates of 100% were observed with DCV + SOF ± RBV for 12 weeks, DCV + SOF ± RBV for 24 weeks and VEL/SOF + RBV for 24 weeks. In general, SVR rates were lowest in treatment-experienced cirrhotic patients with genotype 3 infection, particularly those with prior peginterferon-experience, where SVRs ranged from 57% to 71% with 12-week VEL/SOF ± RBV and DCV + SOF ± RBV regimens, though some benefits were observed by extending treatment duration, as recommended in current guidelines.

In difficult-to-treat populations where less evidence-based guidance may be available, real-world providers may make empiric decisions to extend treatment, add RBV, or both. In our analysis for genotype 3, adding RBV to DAC + SOF or VEL/SOF improved SVR rates in patients with HCC. While in patients with HCV genotype 3 and cirrhosis, previously treated with DCV + SOF, we observed incremental SVR increases by regimen: DCV + SOF for 24 weeks (84.8%, 28/33), DCV + SOF + RBV for 12 weeks (86.4%, 95/110), and DCV + SOF + RBV for 24 weeks (93.9%, 107/114). A similar trend was observed in the German registry among patients with cirrhosis, where overall SVR rates were 87% (13/15) with DCV + SOF for 24 weeks, 92% (11/12) for DCV + SOF + RBV for 12 weeks, and 98% (44/45) for DCV + SOF + RBV for 24 weeks.[20] For DCV + SOF, a possible benefit was also observed by extending treatment in patients with HCV genotype 3, without cirrhosis, who had prior peginterferon-experience (12 weeks 90.0%, 27/30) *vs.* 24 weeks 100%, 5/5) and with the addition of RBV and extending treatment duration in patients with HCV genotype 3 and cirrhosis, with prior peginterferon-experience (12 weeks 71.4%, 10/14 *vs.* 24 weeks 85.2%, 23/27). Extending treatment duration of VEL/SOF + RBV potentially improved SVR rates in patients with HCV genotype 3 and prior DAA experience, without cirrhosis (12 weeks 84.6%, 33/39 *vs.* 24 weeks 100.0%, 10/10) and with cirrhosis (12 weeks 75.0%, 24/32 *vs.* 24 weeks 85.3%, 20/24), however numbers in these subgroups are small.

Although the 2018 guidelines recommend VEL/SOF for 24 weeks in the cirrhotic DAA-experienced population, 2016 guidelines had recommended VEL/SOF + RBV for 24 weeks and thus we were unable to assess VEL/SOF for 24 weeks since this regimen was rarely used.[12,15] One-third of patients with prior

DAA-treatment experience and cirrhosis received the EASL 2016 recommended regimen of SOF/VEL + RBV for 24 weeks and 83.3% (20/24) achieved SVR. Almost half received the 2016 AASLD/IDSA recommended regimen of SOF/VEL + RBV for 12 weeks and 75% (24/32) achieved SVR. One-quarter of DAA-experienced patients with cirrhosis received VEL/SOF for 12 weeks (a regimen not recommended by guidelines) however 88% achieved SVR, suggesting no benefit of RBV in this scenario. Since only one DAA-experienced patient with cirrhosis received VEL/SOF for 24 weeks, no comparison of VEL/SOF and VEL/SOF + RBV for 24 weeks could be made beyond what might be extrapolated from the 12-week results.

While this study represents one of the largest real-world cohorts of HCV-infected male patients treated with these regimens, there are limitations. As this was real-world, some patients received regimens outside of current guidelines.[13–15] Prior treatment history could be determined only for patients previously treated within VA, though treatment outside VA was likely minimal given the lower cost and more rapid uptake of DAAs within VA.[14] We cannot determine the intended duration, nor could we capture reasons for discontinuation. Differential selection of regimens by providers may not be fully addressed although multivariate models provide adjustment for numerous differences in baseline characteristics. We were unable to assess the impact of resistance testing because it was not uniformly performed nor were results uniformly captured in the electronic data. Although patients lacking definitive SVR data were excluded from the SVR analysis the impact was likely minimal given the small number and that such excluded patients differed minimally from patients with definitive SVR results.

In this large, diverse real-world cohort of patients infected with HCV genotype 2 or 3, treatment with DCV + SOF ± RBV or VEL/SOF ± RBV produced SVR rates that were similar within genotype and were consistently high across most subgroups evaluated. The results support current evidence-based guidelines for the use of either DCV + SOF or VEL/SOF as effective treatment options for genotypes 2 and 3. Among patients with genotype 2 infection and cirrhosis, extending DCV + SOF duration resulted in higher SVR rates. Among patients with genotype 3, prior treatment-experience predicted reduced odds of SVR and lower SVR rates were observed for all four regimens in this subgroup. For genotype 3, adding RBV and extending treatment duration potentially improved SVR rates in patients with cirrhosis and prior peginterferon-experience treated with DCV + SOF, and in those with prior DAA experience with and without cirrhosis treated with VEL/SOF. Indicators of more advanced disease such as increased FIB-4 and a history of decompensated disease were significant predictors of reduced odds of SVR in patients with HCV genotype 3, strongly advocating for earlier treatment of such patients, prior to the onset of advanced liver disease.

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Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: Drs. Backus, Belperio; analysis and interpretation of data: Drs. Backus, Belperio, Loomis, Mole, and Shahoumian; drafting of the manuscript: Drs. Backus, Belperio; critical revision of the manuscript for important intellectual content: Drs. Backus, Belperio and Mole; statistical analysis: Dr. Shahoumian. This statement acknowledges that all authors approved the final version of the article.

Supplementary data

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