# Real World Effectiveness of Ledipasvir/Sofosbuvir in 4365 Treatment-Naïve Genotype 1 Hepatitis C Infected Patients

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# Real-World Effectiveness of Ledipasvir/Sofosbuvir in 4,365 Treatment-Naive, Genotype 1 Hepatitis C-Infected Patients

Lisa I. Backus, Pamela S. Belperio, Troy A. Shahoumian, Timothy P. Loomis, and Larry A. Mole

**Real-world effectiveness data are needed to inform hepatitis C virus (HCV) treatment decisions. The uptake of ledipasvir/sofosbuvir (LDV/SOF) regimens across health care settings has been rapid, but variations often occur in clinical practice. The aim of this study was to assess sustained virologic response (SVR) of LDV/SOF±ribavirin (RBV) in routine medical practice. This observational, intent-to-treat cohort was comprised of 4,365 genotype 1, treatment-naive, HCV-infected veterans treated with LDV/SOF±RBV. SVR rates were 91.3% (3,191/3,495) for LDV/SOF and 92.0% (527/573) for LDV/SOF+RBV ($P = 0.65$). African American race (odds ratio 0.70, 95% confidence interval 0.54-0.90, $P = 0.004$) and FIB-4 >3.25 (odds ratio 0.56, 95% confidence interval 0.43-0.71, $P < 0.001$) were independently associated with decreased likelihood of SVR; age, sex, body mass index, decompensated liver disease, diabetes, genotype 1 subtype, and regimen did not predict SVR. In models limited to those who completed 12 weeks of treatment, African American race was no longer a significant predictor of SVR but FIB-4 >3.25 (odds ratio 0.35, 95% confidence interval 0.24-0.50, $P < 0.001$) remained. Among those without cirrhosis (defined by FIB-4 $\leq$3.25) and with baseline HCV RNA<6,000,000 IU/mL, SVR rates were 93.2% (1,020/1,094) for those who completed 8 weeks of therapy and 96.6% (875/906) for those who completed 12 weeks of therapy ($P = 0.001$). *Conclusions:* In this real-world cohort, SVR rates with LDV/SOF±RBV nearly matched the rates reported in clinical trials and were consistently high across all subgroups; those without cirrhosis but with HCV RNA<6,000,000 IU/mL were less likely to achieve SVR with 8 weeks compared to 12 weeks of therapy, although the numeric difference in SVR rates was small.** (HEPATOLOGY 2016; 00:000–000)

Antiviral therapy for chronic hepatitis C virus (HCV) infection continues to rapidly evolve. Sustained virologic response (SVR) rates reported in clinical trials with the newest regimens are consistently above 90% for most HCV-infected patient populations. The promise of such results in clinical trials has created similarly high expectations among both providers and patients. However, studies examining real-world effectiveness with interferon-based HCV regimens and, more recently, sofosbuvir plus simeprevir regimens revealed differences in outcomes compared to clinical trials.[1-7] These differences may reflect the wide heterogeneity in clinical practice where patient characteristics, care coordination, and management are not uniform. Only when prescribed to a broader population do these variances become apparent. Understanding the effectiveness of antiviral regimens in real-world settings is essential to provide practical information to better inform HCV treatment decisions.

The use of ledipasvir/sofosbuvir (LDV/SOF) for varying treatment durations has been extensively evaluated in clinical trials of treatment-naive, genotype 1 HCV-infected individuals. The phase 3 ION-1 clinical

*Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; BMI, body mass index; CI, confidence interval; EOT, end of treatment; FDA, US Food and Drug Administration; HCV, hepatitis C virus; IL, interleukin; LDV/SOF, ledipasvir/sofosbuvir; OR, odds ratio; RBV, ribavirin; SVR, sustained virologic response; VA, Department of Veterans Affairs.*

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trial comparing 12-week and 24-week regimens resulted in SVR rates of 97%-100% in all treatment arms including subgroups defined by race, genotype subtype, and presence of cirrhosis.[8] The high SVRs observed in this study led to the exploration of shortening treatment duration even further. In ION-3, LDV/SOF ± ribavirin (RBV) regimens of 8 and 12 weeks' duration were compared in treatment-naive, HCV genotype 1-infected patients without cirrhosis.[9] While SVR rates were high in all treatment arms (93%-95%), relapse rates were higher in the 8-week treatment arms (5%) compared to the 12-week arms (1%). *Post hoc* analysis of baseline predictors revealed higher relapse rates only in patients receiving the 8-week regimen with a baseline HCV RNA above 6 million IU/mL. Based on data from this trial, current US Food and Drug Administration (FDA) labeling indicates that an 8-week regimen of LDV/SOF can be considered in patients who are treatment-naive without cirrhosis and have a baseline HCV RNA below 6,000,000 IU/mL. Though the generalizability of this approach may be viewed as limited, it is being widely used in clinical practice.

HCV disproportionately affects the veteran population, and this population is often underrepresented in clinical trials, largely due to complicating comorbidities.[10] Thus, evaluating the effectiveness of HCV antiviral regimens remains a priority for the Department of Veterans Affairs (VA).[11] With the rapid uptake of LDV/SOF regimens across health care settings and variations that often occur in clinical practice, we examined real-world outcomes in the diverse HCV-infected veteran population receiving this regimen. Our aim was to assess the effectiveness of LDV/SOF±RBV in treatment-naïve, genotype 1 HCV-infected veterans treated in routine medical practice.

# Materials and Methods

This was an observational intent-to-treat cohort analysis of HCV-infected veterans receiving LDV/SOF±RBV from the 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* diagnosis codes from inpatient hospitalizations, outpatient visits, and problem lists of HCV-infected veterans seen at all VA medical facilities.[12]

Eligible subjects included all treatment-naive, genotype 1 HCV-infected veterans from any VA facility nationwide who initiated VA-prescribed LDV/SOF± RBV with a recommended duration of 8 or 12 weeks between November 1, 2014, and March 31, 2015, and stopped treatment by July 14, 2015. The choice of regimen and timing of follow-up visits and laboratory testing were at the discretion of the provider as patients were treated in routine practice. Patients were excluded if they changed regimens (n = 8), had baseline HCV RNA ≤1000 IU/mL (n = 82), had undergone liver transplantation (n = 113), or had received more than 91 days of LDV/SOF±RBV (n = 266).

## TREATMENT OUTCOME

SVR was defined as an undetectable HCV RNA on all HCV RNA tests after the end of treatment (EOT) including at least one test 10 weeks or more after the EOT. This 10-week time point was chosen to account for variability of clinic visits and timing of lab draws in clinical practice. Patients were categorized as not achieving SVR if they had a detectable HCV RNA after the EOT, had no viral load testing after the EOT, and had a detectable HCV RNA on their last HCV viral load test while on treatment or died while on treatment or within 10 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 10 weeks of more after the EOT were excluded from the SVR analysis. The EOT was calculated as the last day covered by prescriptions of LDV/SOF using the dates the medication was dispensed and the

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number of days of supply. HCV RNA was categorized as detectable or undetectable based on the locally reported HCV RNA result of which 98% used assays with a lower limit of detection of 7 IU/mL or less. Patients were followed from the initiation of LDV/SOF±RBV through February 29, 2016, allowing for more than 32 weeks of follow-up after the 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 as esophageal variceal hemorrhage, hepatic coma, hepatorenal syndrome, or spontaneous bacterial peritonitis), diabetes, human immunodeficiency virus coinfection, and HCV genotype 1 subtype. Baseline values for height and weight, which were used to calculate body mass index (BMI), and laboratory tests for alanine aminotransferase, aspartate aminotransferase, platelets, and baseline HCV RNA were defined as the value within 1 year before and closest to the treatment start date. A FIB-4 score >3.25 or an aspartate aminotransferase-to-platelet ratio index (APRI) score >2 at the start of treatment using baseline laboratory values was used as a marker of advanced liver disease.[13-15] Patients with FIB-4 ≤3.25 or APRI ≤2 were considered to not have cirrhosis.

The percentage of patients on treatment was calculated from the cumulative days' supply of all LDV/SOF prescriptions starting with the first prescription for LDV/SOF through the last day of treatment covered by LDV/SOF. In the VA, LDV/SOF prescriptions are frequently filled for quantities less than 28 days, particularly for the first 1 or 2 months of treatment. Patients were considered to have completed 8 and 12 weeks of LDV/SOF±RBV if they had received between 49-63 and 77-91 days' worth of medication, respectively.

On-treatment HCV RNA at 4 weeks was 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 categorized as undetectable, detectable <15 IU/mL, and detectable ≥15 IU/mL.

## STATISTICAL ANALYSIS

Univariate comparisons used the Pearson chi-squared test with Yates' continuity correction for categorical variables and analysis of variance for continuous variables. Multivariate logistic regression models were constructed to model SVR. Variables included in the multivariate regression were selected *a priori* based on variables that had been previously shown to impact SVR or were of clinical interest. Models included age, sex, race/ethnicity, history of decompensated liver disease, diabetes, genotype 1 subtype, regimen, and FIB-4. A set of models with the above baseline variables was constructed with patients who completed 12 weeks of treatment. These models were rerun also including HCV RNA at 4 weeks. In addition, a set of models with the baseline variables was constructed with only patients who completed 8 or 12 weeks of LDV/SOF and then further restricted to those patients who met the criteria for not having cirrhosis based on FIB-4 ≤3.25 and baseline HCV RNA <6,000,000 IU/mL.

For all comparisons, $P < 0.01$ was considered statistically significant. All analyses were performed using R, version 3.1 (R Foundation for Statistical Computing, Vienna, Austria).

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

# Results

In total, 4,834 treatment-naive patients with HCV genotype 1 initiated LDV/SOF±RBV at 124 VA facilities. After applying exclusion criteria, 4,365 remained. The mean age for the cohort overall was 61.3 years, 96.1% were male, 36.6% were African American, 3.3% had a history of decompensated liver disease, 34.2% had a BMI ≥30 kg/m$^2$, 30.5% had diabetes, and 29.2% had FIB-4 >3.25.

Baseline characteristics for the cohort by regimen appear in Table 1. For the cohort, 86.3% (n = 3,763) received LDV/SOF and 13.7% (n = 602) received LDV/SOF+RBV. Patients who received LDV/SOF+RBV were more likely to have markers of advanced liver disease including lower mean platelet count, higher mean APRI score, APRI >2, higher mean FIB-4 score, FIB-4 >3.25, and a history of decompensated liver disease. T1

Among patients who received LDV/SOF, 3.6% (n = 134) discontinued treatment before 8 weeks, 37.0% (n = 1,392) received 8 weeks, 1.7% (n = 65) discontinued treatment between 8 and 12 weeks, and 57.7% (n = 2,172) received 12 weeks. In total,

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**TABLE 1. Baseline Characteristics and 4 Week On-Treatment Response of Treatment-Naive Genotype1 Patients Receiving LDV/SOF-Based Regimens**

| | LDV/SOF (n = 3,763) | LDV/SOF+RBV (n = 602) | P* |
|---|---|---|---|
| Age (years) | 61.1 ± 6.7 (25.3-90.8) | 62.1 ± 5.2 (37.0-86.2) | |
| Sex, male | 95.9% | 97.2% | |
| Race/ethnicity | | | <0.001 |
| African American | 37.9% | 28.1% | |
| Caucasian | 50.8% | 57.1% | |
| Hispanic | 4.3% | 6.8% | |
| Other/multiple | 7.0% | 8.0% | |
| Decompensated liver disease | 2.1% | 10.3% | <0.001 |
| Diabetes | 29.6% | 36.2% | 0.001 |
| HIV coinfected | 5.4% | 3.5% | |
| BMI (kg/m$^2$) | 28.4 ± 5.1 (15.8-65.2) | 29.5 ± 5.4 (17.9-60.1) | <0.001 |
| BMI (kg/m$^2$) | | | <0.001 |
| <25 | 25.2% | 20.1% | |
| 25-29 | 41.8% | 38.0% | |
| ≥30 | 33.0% | 41.9% | |
| ALT (U/L) | 72.3 ± 56.6 (8-659) | 83.4 ± 56.9 (16-445) | <0.001 |
| AST (U/L) | 61.2 ± 43 (6-614) | 80.2 ± 49.7 (11-427) | <0.001 |
| Platelets (K/$\mu$L) | 193.8 ± 68.7 (6-661) | 148.2 ± 70.7 (22-759) | <0.001 |
| APRI | 1.0 ± 1.2 (0.1-20.4) | 1.9 ± 1.8 (0.1-11.5) | <0.001 |
| APRI >2 | 12.0% | 31.3% | <0.001 |
| FIB-4 | 2.9 ± 2.7 (0.1-51.4) | 5.1 ± 4.4 (0.6-34.7) | <0.001 |
| FIB-4 >3.25 | 24.8% | 56.7% | <0.001 |
| HCV RNA (log IU/mL) | 6.2 ± 0.7 (3.1-7.9) | 6.2 ± 0.7 (3.9-7.8) | |
| HCV RNA <6,000,000 IU/mL | 83.2% | 83.9% | |
| HCV subtype 1b | 24.0% | 21.1% | |
| IL28B polymorphism | n = 462 | n = 69 | |
| CC | 25.8% | 14.5% | |
| CT | 50.2% | 56.5% | |
| TT | 24.0% | 29.0% | |
| 4-week HCV RNA | n = 3265 | n = 557 | |
| Undetectable | 76.4% | 75.6% | |
| Detectable <15 IU/mL | 9.1% | 8.4% | |
| Detectable ≥15 IU/mL | 14.6% | 16.0% | |

Continuous variables reported as mean ± standard deviation (range). Categorical variables reported as percentage.
*$P$ values listed if <0.01 between LDV/SOF and LDV/SOF+RBV.
Abbreviations: ALT, alanine amino transferase; AST, aspartate aminotransferase; HIV, human immunodeficiency virus.

94.7% completed either an 8-week or a 12-week course. Among people who received LDV/SOF+RBV, 90.0% (n = 542) completed 12 weeks of treatment.

SVR results were available for 4,068 patients, including 12 patients who died while on treatment or shortly after who were categorized as no SVR. Patients whose last HCV RNA was undetectable but occurred while still on treatment (n = 86) or less than 10 weeks after the EOT (n = 211) were excluded from the SVR analysis. Patients with an undetectable HCV RNA obtained 10 or 11 weeks after the EOT were included in the SVR analysis for reasons described previously (n = 197). In additional support for categorizing these individuals as achieving SVR, 98 other patients in this cohort had undetectable HCV RNA test results in week 10 or 11 with subsequent HCV RNA testing at 12 weeks or later. All 98 patients remained undetectable on the later HCV RNA testing, further validating the acceptance of testing at 10 weeks or later as a practical accommodation for the realities of clinical practice while providing an accurate assessment of virologic response that would be seen if testing were conducted strictly at 12 weeks.

Overall SVR rates were similar for LDV/SOF and LDV/SOF+RBV (91.3% versus 92.0% respectively, $P$ = 0.65) (Table 2). For patients who received LDV/SOF, SVR rates were significantly lower in African Americans compared to Caucasians, patients with APRI >2, and patients with FIB-4 >3.25 but for no other baseline characteristics examined. Significantly lower SVR rates were observed in those receiving LDV/SOF who had a 4-week on-treatment detectable HCV RNA ≥15 IU/mL compared to those who were



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**TABLE 2. SVR Rates by Regimen for Genotype 1, Treatment-Naive Patients Receiving LDV/SOF-Based Regimens**

| | LDV/SOF (n = 3,495) | *P** | LDV/SOF+RBV (n = 573) | *P** |
|---|---|---|---|---|
| Overall SVR | 91.3% (3,191/3,495) | | 92.0% (527/573) | |
| Age (years) | | | | |
| <55 | 93.8% (361/385) | | 95.1% (39/41) | |
| 55-64 | 90.3% (1,918/2,124) | | 90.7% (323/356) | |
| ≥65 | 92.5% (912/986) | | 93.8% (165/176) | |
| Sex | | | | |
| Male | 91.1% (3,052/3,349) | | 92.1% (512/556) | |
| Female | 95.2% (139/146) | | 88.2% (15/17) | |
| Race/ethnicity | | | | |
| African American | 89.8% (1,185/1,320) | 0.003 | 93.2% (151/162) | |
| Caucasian | 92.8% (1,657/1,785) | | 92.0% (298/324) | |
| Hispanic | 88.2% (134/152) | | 90.0% (36/40) | |
| Other/multiple | 90.3% (215/238) | | 89.4% (42/47) | |
| Decompensated liver disease | | | | |
| No | 91.3% (3,125/3,421) | | 92.6% (476/514) | |
| Yes | 89.2% (66/74) | | 86.4% (51/59) | |
| Diabetes | | | | |
| No | 91.3% (2,236/2,448) | | 93.7% (344/367) | |
| Yes | 91.2% (955/1,047) | | 88.8% (183/206) | |
| HIV coinfection | | | | |
| No | 91.3% (3,013/3,300) | | 92.1% (510/554) | |
| Yes | 91.3% (178/195) | | 89.5% (17/19) | |
| BMI (kg/m$^2$) | | | | |
| <25 | 89.8% (791/881) | | 93.3% (111/119) | |
| 25-29 | 92.8% (1,356/1,461) | | 93.0% (200/215) | |
| ≥30 | 90.5% (1,044/1,153) | | 90.4% (216/239) | |
| APRI | | | | |
| ≤2 | 92.0% (2,814/3,059) | <0.001 | 93.6% (368/393) | |
| >2 | 86.7% (372/429) | | 88.2% (157/178) | |
| FIB-4 | | | | |
| ≤3.25 | 92.6% (2,407/2,599) | <0.001 | 94.4% (234/248) | |
| >3.25 | 87.6% (779/889) | | 90.1% (291/323) | |
| HCV RNA (log IU/mL) | | | | |
| <6,000,000 IU/mL | 91.4% (2,657/2,908) | | 91.9% (440/479) | |
| ≥6,000,000 IU/mL | 91.0% (534/587) | | 92.6% (87/94) | |
| HCV subtype | | | | |
| 1a† | 90.9% (2,402/2,642) | | 91.6% (414/452) | |
| 1b | 92.5% (789/853) | | 93.4% (113/121) | |
| IL28B polymorphism | n = 441 | | n = 65 | |
| CC | 92.2% (107/116) | | 90.0% (9/10) | |
| CT | 91.8% (202/220) | | 94.4% (34/36) | |
| TT | 93.3% (98/105) | | 89.5% (17/19) | |
| 4-week HCV RNA | n = 3,036 | | n = 532 | |
| Undetectable | 95.3% (2,204/2,312) | NS | 95.3% (384/403) | NS |
| Detectable <15 IU/mL | 93.2% (260/279) | <0.001 | 88.6% (39/44) | <0.001 |
| Detectable ≥15 IU/mL | 84.8% (393/445) | | 88.2% (75/85) | |

*$P$ values only listed if <0.01 between categories of each baseline variable for the same regimen.
†Subtype 1a includes 1a, mixed 1a/1b, and 1 with subtype unspecified.
Abbreviations: HIV, human immunodeficiency virus; NS, not significant.

undetectable by week 4. For patients who received LDV/SOF+RBV, SVR rates were numerically lower in those with high FIB-4 or APRI scores; but these differences were not statistically significant. SVR rates were also significantly lower in those receiving LDV/SOF+RBV who had a 4-week on-treatment detectable HCV RNA ≥15 IU/mL compared to those who were undetectable by week 4.

Among patients who completed a full 12 weeks of treatment, SVR rates did not differ between LDV/SOF and LDV/SOF+RBV (94.3% [1,924/2,040] versus 94.2% [485/515], respectively; $P = 1.00$). Among patients who completed a full 12 weeks of LDV/SOF, SVR rates remained significantly lower in those with APRI >2, FIB-4 >3.25, and 4-week on-treatment HCV RNA ≥15 IU/mL compared to those



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**TABLE 3. ORs for SVR in Multivariable Model for Treatment-Naive Genotype 1 Patients Treated With LDV/SOF-Based Regimens**

| | OR (95% CI) (n = 4,059) | Completed 12 weeks OR (95% CI) (n = 2,533) |
|---|---|---|
| Age <55 years (ref. 55-64) | 1.43 (0.95-2.24) | 1.31 (0.69-2.75) |
| Age ≥65 years (ref. 55-64) | 1.39 (1.07-1.82) | 1.31 (0.89-1.96) |
| Female (ref. male) | 1.83 (0.94-4.12) | 2.72 (0.83-16.8) |
| African American (ref. Caucasian) | **0.70 (0.54-0.90)*** | 0.85 (0.57-1.26) |
| Hispanic (ref. Caucasian) | 0.62 (0.39-1.03) | 0.77 (0.38-1.71) |
| Other/multiple (ref. Caucasian) | 0.73 (0.48-1.16) | 0.50 (0.29-0.91) |
| BMI <25 kg/m$^2$ (ref. BMI 25-29 kg/m$^2$) | 0.71 (0.53-0.96) | 0.86 (0.54-1.38) |
| BMI ≥30 kg/m$^2$ (ref. BMI 25-29 kg/m$^2$) | 0.73 (0.55-0.95) | 0.68 (0.45-1.00) |
| Diabetes | 0.97 (0.76-1.25) | 0.93 (0.65-1.35) |
| FIB-4 >3.25 (ref. FIB-4 ≤3.25) | **0.56 (0.43-0.71)†** | **0.35 (0.24-0.50)†** |
| History of decompensated liver disease (ref. no) | 0.88 (0.51-1.59) | 0.89 (0.47-1.84) |
| Subtype 1b | 1.26 (0.96-1.68) | 1.13 (0.75-1.77) |
| LDV/SOF+RBV (ref. LDV/SOF) | 1.34 (0.96-1.91) | 1.31 (0.86-2.06) |

*$P < 0.01$.
†$P < 0.001$.
Abbreviation: ref., reference.

with undetectable 4-week HCV RNA (Supporting Table S1).

In multivariate analysis, significant independent predictors of SVR were African American race compared to Caucasian (odds ratio [OR] 0.70, 95% confidence interval [CI] 0.54-0.90, $P = 0.004$) and FIB-4 >3.25 compared to FIB-4 ≤3.25 (OR 0.56, 95% CI 0.43-0.71, $P < 0.001$) (Table 3). Age, sex, BMI, diabetes, history of decompensated liver disease, genotype 1 subtype, and regimen did not predict SVR. When restricted to those patients who completed 12 weeks of treatment, only FIB-4 >3.25 remained a significant predictor of decreased odds of SVR (OR 0.35, 95% CI 0.24-0.50, $P < 0.001$). In both models the substitution of APRI with a cut point of 2 in place of FIB-4 produced similar ORs (data not shown).

Four-week on-treatment HCV RNA was an independent predictor of SVR when included as a variable in the models (Supporting Table S2). Having a detectable HCV RNA ≥15 IU/mL was associated with reduced odds of SVR compared to undetectable in the full model (OR 0.40, 95% CI 0.29-0.56, $P < 0.001$) and in the model limited to those who completed 12 weeks of treatment (OR 0.38, 95% CI 0.25-0.58, $P < 0.001$).

With regard to treatment duration, as noted above, among patients who received LDV/SOF, 37.0% (n = 1392) received 8 weeks and 57.7% (n = 2172) received 12 weeks. Of the 1,392 receiving 8 weeks, 86.9% (n = 1209) met FDA criteria of a baseline HCV RNA <6,000,000 IU/mL when "without cirrhosis" was defined as FIB-4 ≤3.25 and 92.7% (n = 1291) met FDA criteria when "without cirrhosis" was defined as APRI ≤2. Of the 2,172 patients who received 12 weeks of LDV/SOF, 45.0% (n = 977) also met the FDA criteria for 8 weeks of treatment using the FIB-4 definition of "without cirrhosis" and 58.4% (n = 1268) met the FDA criteria using the APRI definition of "without cirrhosis."

The overall SVR rate in those who completed 8 weeks of LDV/SOF treatment was 92.1% compared to 94.3% in those who completed 12 weeks of treatment (Table 4). Among patients in the subgroups who met the FDA criteria, SVR rates were statistically lower for those who received 8 weeks of LDV/SOF than for those who received 12 weeks of LDV/SOF, regardless of whether "without cirrhosis" was defined by APRI ≤2 or FIB-4 ≤3.25. The numeric difference in SVR between those receiving 8 or 12 weeks was 2.8% and 3.4% when "without cirrhosis" was defined by APRI ≤2 or FIB-4 ≤3.25, respectively. SVR rates for other baseline characteristics in patients who completed 8 or 12 weeks of LDV/SOF treatment are available in Supporting Table S1.

In multivariate analysis of patients who completed 8 or 12 weeks of LDV/SOF, significant independent predictors of SVR were African American race (OR 0.66, 95% CI 0.48-0.90, $P = 0.008$), FIB-4 >3.25 (OR 0.45, 95% CI 0.32-0.62, $P < 0.001$), and 8-week treatment duration compared to 12-week treatment duration (OR 0.56, 95% CI 0.41-0.76, $P < 0.001$) (Table 5). In models limited to patients with baseline HCV RNA <6,000,000 IU/mL and FIB-4 ≤3.25, only 8-week treatment duration remained a significant



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**TABLE 4. SVR Rates by Regimen for Genotype 1 Treatment-Naive Patients Who Completed 8 or 12 Weeks of LDV/SOF**

| | LDV/SOF 8 weeks | LDV/SOF 12 weeks | *P** |
|---|---|---|---|
| Overall SVR | 92.1% (1,169/1,269) | 94.3% (1,924/2,040) | |
| HCV RNA <6,000,000 IU/mL | 92.7% (1,138/1,227) | 94.1% (1,431/1,520) | |
| APRI ≤2 | 92.1% (1,124/1,220) | 95.5% (1,603/1,679) | <0.001 |
| FIB-4 ≤3.25 | 92.5% (1,043/1,128) | 96.3% (1,285/1,335) | <0.001 |
| HCV RNA <6,000,000 IU/mL and APRI ≤2 | 92.8% (1,095/1,180) | 95.6% (1,139/1,191) | 0.004 |
| HCV RNA <6,000,000 IU/mL and FIB-4 ≤3.25 | 93.2% (1,020/1,094) | 96.6% (875/906) | 0.001 |

*$P$ values listed if <0.01 between 8 weeks and 12 weeks.

predictor of reduced odds of SVR (OR 0.47, 95% CI 0.30-0.72, $P < 0.001$). Similar results were obtained in models limited to patients with baseline HCV RNA <6,000,000 IU/mL and APRI ≤2 (data not shown).

# Discussion

In this real-world cohort of treatment-naive, genotype 1 HCV-infected veterans treated with LDV/SOF-based therapy at any VA facility nationwide, we observed SVR rates over 90%, nearly matching the rates reported in clinical trials.[8,9] The response rates were consistently high across all subgroups evaluated, regardless of regimen or duration, and ranged from 86% to 97%. Use of RBV did not appear to offer general benefit and was associated with higher early discontinuation rates, although overall more veterans were able to successfully complete treatment with LDV/SOF-based regimens compared to regimens previously evaluated.[1,5] Shorter, 8-week, regimens of LDV/SOF were widely used in patients with baseline HCV RNA below 6,000,000 IU/mL without cirrhosis; however, SVR rates were significantly lower in those treated with 8 weeks compared to 12 weeks.

The large differences between real-world effectiveness and clinical trial efficacy previously observed have now been almost eliminated with the use of potent all-oral regimens, which are well-tolerated and easily administered for shorter durations. The remaining small decrement in effectiveness in this real-world cohort may be explained by differences in patient populations as our cohort consisted of mostly older male patients with generally higher BMI, a greater proportion of African Americans, and more prevalent evidence of advanced liver disease. Furthermore, there are persistent variations in practice patterns, patient motivation, provider knowledge, provider resources, and ancillary services in routine medical practice compared to highly structured, highly resourced clinical trials.

Reported virologic response rates to other direct-acting antiviral and prior interferon-based regimens showed wide variability in clinical practice, particularly

**TABLE 5. ORs for SVR in Multivariable Model for Genotype 1 Treatment-Naive Patients Who Completed 8 or 12 Weeks of LDV/SOF**

| | OR (95% CI) (n = 3,303) | Baseline FIB-4 ≤3.25 and HCV <6,000,000 IU/mL OR (95% CI) (n = 1,989) |
|---|---|---|
| Age <55 years (ref. 55-64) | 1.27 (0.77-2.19) | 1.38 (0.71-2.92) |
| Age ≥65 years (ref. 55-64) | 1.25 (0.90-1.75) | 1.22 (0.76-2.00) |
| Female (ref. male) | 3.22 (1.19-13.3) | ‡ |
| African American (ref. Caucasian) | **0.66 (0.48-0.90)*** | 0.75 (0.48-1.17) |
| Hispanic (ref. Caucasian) | 0.67 (0.36-1.37) | 0.60 (0.26-1.63) |
| Other/multiple (ref. Caucasian) | 0.59 (0.36-1.03) | 1.12 (0.50-3.00) |
| BMI <25 kg/m$^2$ (ref. BMI 25-29 kg/m$^2$) | 0.79 (0.55-1.14) | 0.79 (0.48-1.34) |
| BMI ≥30 kg/m$^2$ (ref. BMI 25-29 kg/m$^2$) | 0.73 (0.52-1.01) | 0.78 (0.49-1.26) |
| Diabetes | 1.01 (0.74-1.40) | 0.74 (0.47-1.18) |
| FIB-4>3.25 (ref. FIB-4≤3.25) | **0.45 (0.32-0.62)†** | § |
| History of decompensated liver disease (ref. no) | 0.91 (0.40-2.42) | § |
| Subtype 1b | 1.32 (0.94-1.90) | 1.28 (0.80-2.10) |
| 8 weeks (ref. 12 weeks) | **0.56 (0.41-0.76)†** | **0.47 (0.30-0.72)†** |

*$P < 0.01$.
†$P < 0.001$.
‡Female not included as a variable because of small numbers of females.
§FIB-4 and history of decompensated liver disease not included in the model as patients had to have FIB-4 ≤3.25 to be included.

in patients with specific baseline characteristics including African American race, genotype subtype 1a, interleukin-28B (IL28B) non-CC subtype, and high baseline HCV RNA.[16-20] A strength of the current study is the large number of patients evaluated, which allows for the detection of differences in subgroups that might not otherwise be identified in smaller studies or clinical trials. Nearly 1,500 African Americans were evaluated in this cohort study, and our results indicate that response rates may still be reduced in African Americans compared to Caucasians. African American race was a predictor of reduced likelihood of SVR in multivariate models of the overall cohort but not in models of those patients completing a full treatment course, suggesting that perhaps tolerability or adherence may be a contributing factor, though we did not specifically evaluate this. While in general RBV did not offer any benefit overall in achieving SVR, there is an indication that its use in African Americans may improve SVR rates as evidenced by the 89.8% SVR rate in those who did not receive RBV and the 93.2% SVR in those that did. Furthermore, treating for 12 weeks may also overcome this difference as SVR rates in African Americans completing 12 weeks of LDV/SOF therapy were higher than in those completing 8 weeks (94.0% versus 89.8%) and were similar to SVR rates achieved in Caucasians (12 weeks 95.2%, 8 weeks 93.9%). This finding of lower SVR rates in African Americans receiving an 8-week treatment course of LDV/SOF is consistent with results from the ION clinical trials, which showed higher relapse rates among black patients receiving 8 weeks of treatment compared with those receiving 12 and 24 weeks of treatment.[16] The largest difference between blacks and nonblacks occurred in those who received 8 weeks of LDV/SOF therapy with baseline HCV RNA $\geq$6,000,000 (83% versus 92%). This aligns with our findings of those completing 8 or 12 weeks of LDV/SOF treatment in which African American race predicted decreased odds of achieving SVR overall but no longer predicted decreased odds of SVR when limited to those who did not have cirrhosis with baseline HCV RNA <6,000,000.

Clinical trials suggested that an 8-week treatment course of LDV/SOF could be used in patients with specific baseline characteristics, namely treatment-naive patients without cirrhosis and with a pretreatment HCV RNA <6,000,000 IU/mL; and these criteria are included in FDA labeling.[8,9,21] The use of an 8-week treatment course, however, is not recommended in the American Association for the Study of Liver Diseases/Infectious Diseases Society of America hepatitis C guidance due to the higher relapse rate.[22] Our analysis highlights the complexity of the treatment duration decision. SVR rates were statistically lower with 8 weeks of treatment compared to 12 weeks of treatment, and patients had approximately 53% reduced odds of achieving SVR in multivariable models with 8 weeks of treatment compared to 12 weeks. The absolute numeric SVR difference, however, was small at only 3.4%; and SVR rates were debatably high with either duration. From a patient perspective, the benefit of even marginally increased SVR rates may outweigh the inconvenience of an additional 4 weeks of treatment. From a payer perspective, however, the calculus is likely more complex and depends not only on the initial drug cost but also on variables regarding the cost and success rate of retreatment. In our cohort, for example, we identified 977 patients out of a total of 2,303 patients with low baseline HCV RNA and FIB-4 $\leq$3.25 who met criteria for 8 weeks of treatment but nevertheless completed 12 weeks of treatment. Had these patients who qualified for an 8-week regimen actually received 8 weeks rather than 12 weeks, over $11 million in initial drug costs could have been avoided; but this would be offset to an unknown degree by the approximately 3%-4% of patients failing to achieve SVR who received the shorter course. These patients would require retreatment at a higher cost to the patients and the health care system in terms of not only drug cost but also treatment duration, potential for toxicity and drug resistance, and overall health care resources. Given current resource constraints, the high cost of LDV/SOF, and emerging data regarding retreatment options, additional study will be needed to assess whether from a health care system perspective it may be more cost-effective to treat all patients who qualify for an 8-week course with an 8-week course and retreat the small proportion who may fail.

In clinical trials, the stage of liver disease is often determined by biopsy or, more recently, transient elastography. In clinical practice, however, practitioners may conclude that a patient does not have cirrhosis based on biopsy, transient elastography, FIB-4, APRI, imaging, or platelet count depending on the available resources and information. This variability means that guidance recommending specific treatment for those "without cirrhosis" may be applied in heterogeneous ways. In the VA, few patients undergo liver biopsy and transient elastography is not yet widely available, nor are such results captured in standardized data fields in the electronic medical record. Thus, in our analysis advanced fibrosis or cirrhosis was assessed using

laboratory markers which are commonly used in clinical practice.[9,10,22] In multivariate models, the presence of advanced liver disease as assessed by these simple laboratory tests independently predicted reduced odds of achieving SVR by nearly half. In the resource-restrained environment surrounding HCV, our study suggests that simple calculations of FIB-4 or APRI from inexpensive laboratory tests can be useful in discussions with patients regarding the likelihood of treatment success. These same inexpensive, readily available laboratory markers can be used in a wide variety of settings to determine whether a patient might meet criteria for shortened 8-week treatment.

In this analysis, 4-week viral kinetics predicted SVR with a greater effect in those who received LDV/SOF. Significant reductions of 10.5% and 7.1% in SVR rates were observed in patients receiving LDV/SOF and LDV/SOF+RBV, respectively, who had a detectable 4-week HCV RNA ≥15 IU/mL compared to those with undetectable 4-week HCV RNA. In patients who completed 12-week courses of LDV/SOV there remained a significant 6.4% reduction in SVR rates between those with detectable 4-week HCV RNA ≥15 IU/mL and those with undetectable 4-week HCV. For those who completed 12 weeks of LDV/SOF+RBV the difference in SVR rates was no longer statistically significant. In multivariable analysis, having a HCV RNA ≥15 IU/mL after 4 weeks of treatment was associated with a 60% reduced odds of achieving SVR for the cohort and a 62% reduced odds of achieving SVR for those who completed 12 weeks of treatment. The VA guidance recommends obtaining 4-week HCV RNA testing, thus providing a large sample size to evaluate this variable which has not generally been assessed in prior LDV/SOF studies. The clinical implications of this finding on treatment decisions, such as potentially adding RBV or extending treatment duration based on 4-week on-treatment HCV RNA, warrant further study.

While this study includes a large cohort of diverse patients treated in clinical practice, there are limitations. Due to the nature of the electronic data, we could not determine the original intended duration of treatment. It is possible that some patients who received 12 weeks of treatment were originally planned to receive 8 weeks and vice versa. In addition, specific reasons for early discontinuation (i.e., adverse events or poor tolerability) could not be determined. Treatment duration and 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. In the VA, many prescriptions are filled for small quantities (e.g., 7-14 days at a time), which would limit the extent of the overestimation. Few patients underwent IL28B testing, and no patients underwent resistant associated variant testing; thus, we were unable to assess the impact of these factors. From the univariate analysis, IL28B did not appear to have an impact on SVR rates. Approximately 6.8% (297/4,365) of the cohort lacked definitive laboratory data to determine SVR status and may represent a potential source of bias, although all were undetectable on their most recent HCV RNA occurring while still on treatment or less than 10 weeks after the EOT. If all of these patients in fact had SVR, the maximum overall SVR rate for LDV/SOF would be 91.9% and that for LDV/SOF+RBV would be 92.4%, similar to the reported SVR rates of 91.3% and 92.0%, respectively. With this scenario significant predictors of SVR do not change and the ORs in multivariate models are not substantially altered (data not shown).

In conclusion, in this large real-world cohort, treatment-naive, genotype 1 HCV-infected veterans treated with LDV/SOF-based therapy achieved high SVR rates, comparable to clinical trials, which were consistently high across all subgroups evaluated. SVR rates in patients without cirrhosis and with low baseline HCV RNA treated for 8 weeks were significantly lower than those achieved with 12 weeks of treatment, although the numeric difference was small. The real-world experience from large cohorts is essential to provide practical information to better inform and refine HCV management strategies.

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