# Treating Hepatitis C in Veterans Affairs (VA): Early Experience with Sofosbuvir-based Regimens

*VA Office of Public Health/Population Health and VA Pharmacy Benefits Management Services*

VA HEALTH CARE | Defining EXCELLENCE in the 21st Century

October 31, 2014

Veterans Health Administration

# Table of Contents

# Executive Summary

VA maintains a comprehensive Hepatitis C treatment program which incorporates simultaneous safety, effectiveness and quality surveillance reporting in alignment with VA medication criteria for use.

This multifaceted approach demonstrates a collaborative action between VA Office of Public Health and Pharmacy Benefits Management Services spanning all VA levels (national, VISN, and station) which provides insight into HCV treatment patterns and outcomes across this large healthcare system.

VA presents our early experience in using sofosbuvir-based treatment regimens for Veterans with chronic hepatitis C (HCV) infection. Given the public health impact of HCV, and the importance of effective treatment, providing early outcomes with treatments will help inform clinicians and policy makers within and outside of VA.

Findings include:

- Combination therapy with sofosbuvir and simeprevir is frequently used for treatment of HCV genotype 1
- Treatment discontinuation rates in VA (13.6% overall) are significantly higher than observed in clinical trials
- Among veterans who discontinued treatment early, 34% discontinued due to presumed virologic failure, and death in 3.8%
- Estimated sustained virologic response (SVR) rates were lower than reported in clinical trials

These data highlight differences between efficacy observed in clinical trials and real-world effectiveness observed in clinical practice

# Background

Antiviral therapy for chronic hepatitis C virus (HCV) infection is rapidly evolving. Understanding the effectiveness of antiviral regimens in real-world settings is necessary for informed treatment decisions. Information derived from HCV antiviral clinical trials, like other clinical trials, may be limited in applicability to clinical practice where variations in patient characteristics, care coordination, and management cannot be controlled. Differences between real-world HCV care outcomes (“effectiveness”) and clinical trials (“efficacy”) often become apparent once these medications are prescribed to a broader population.[1-3] Such real-world

experiences are essential to provide practical information that may better inform HCV treatment decisions in this rapidly changing environment.

While sustained virologic response (SVR) rates reported in clinical trials with sofosbuvir- and simeprevir-based regimens represent a substantial improvement over previous direct-acting antiviral regimens, gaps in the evidence remain. For example, the Food and Drug Administration (FDA) approval of sofosbuvir for treatment-experienced patients was based on modeling and not evaluated in clinical trials. Limited or no data exists in important subgroups of patients including those with other co-morbidities, active substance abuse, active mental illness, prior protease inhibitor failure, or cirrhosis. Use of the non-FDA approved combination of sofosbuvir and simeprevir stems from open-label phase II studies with only 14 to 30 patients per treatment arm.

With the rapid uptake of sofosbuvir-based regimens across VA, and the underrepresentation of the Veteran population in clinical trials, we examined the real world experience of the diverse Veteran population receiving these regimens. Monitoring and optimizing the uptake, appropriate use, tolerance and toxicity, and outcomes related to the use of sofosbuvir-based regiments is a priority for VA.[4]

# Methods

The data source for this analysis was the VA's national HCV Clinical Case Registry maintained by the Office of Public Health/Population Health.[5] The population included all Veterans in VA care with chronic HCV who filled at least one VA prescription for a sofosbuvir-based regimen through 25 September 2014. Cohorts of this population were created based on HCV genotype and medication regimen dispensed to the Veteran. Treatment completion and discontinuation rates were determined in those Veterans for whom adequate time had passed to complete a full treatment course or where review of prescription fills indicated that treatment stopped prior to the recommended full treatment course. To assess treatment completion rates, we considered all Veterans with genotype 1 or 2 who initiated treatment by 1 July 2014 to allow sufficient follow-up time to complete the recommended 12 week course of therapy. For Veterans with genotype 3, we considered patients who initiated treatment by 8 April 2014 to allow sufficient time to complete the recommended 24 week course of therapy.

Viral response was determined by HCV viral load which was categorized as undetectable or detectable based on the locally reported result and the type of test used. Veterans were presumed to have on-treatment virologic failure if they had either a detectable HCV viral load on their last HCV viral load test while on treatment *or* a detectable HCV viral load after stopping treatment before completing a full course. Because a substantial proportion of Veterans have not had HCV viral load testing at least 12 weeks after the end of a full treatment course which is necessary for definitive SVR determination, SVR estimates are presented as a range. The high-

end of the range includes Veterans who had post-treatment viral load testing which was undetectable as well as Veterans who had an undetectable HCV viral load on their last test while still on treatment (and who are presumed likely to go on to SVR). The low-end of the range includes only those Veterans with undetectable post-treatment viral load testing.

# Uptake

Simeprevir and sofosbuvir were approved by the FDA in November and December 2013, respectively, and the first VA prescriptions were dispensed in January 2014. As of 25 September 2014, a total of 5,285 Veterans have been prescribed sofosbuvir-based regimens of whom 2,246 received sofosbuvir and simeprevir. Utilization of specific regimens, by genotype, is shown in Table 1. In August and September of 2014, an average of 225 Veterans started on sofosbuvir-based regimens each week; approximately half of these Veterans received the combination of sofosbuvir and simeprevir.

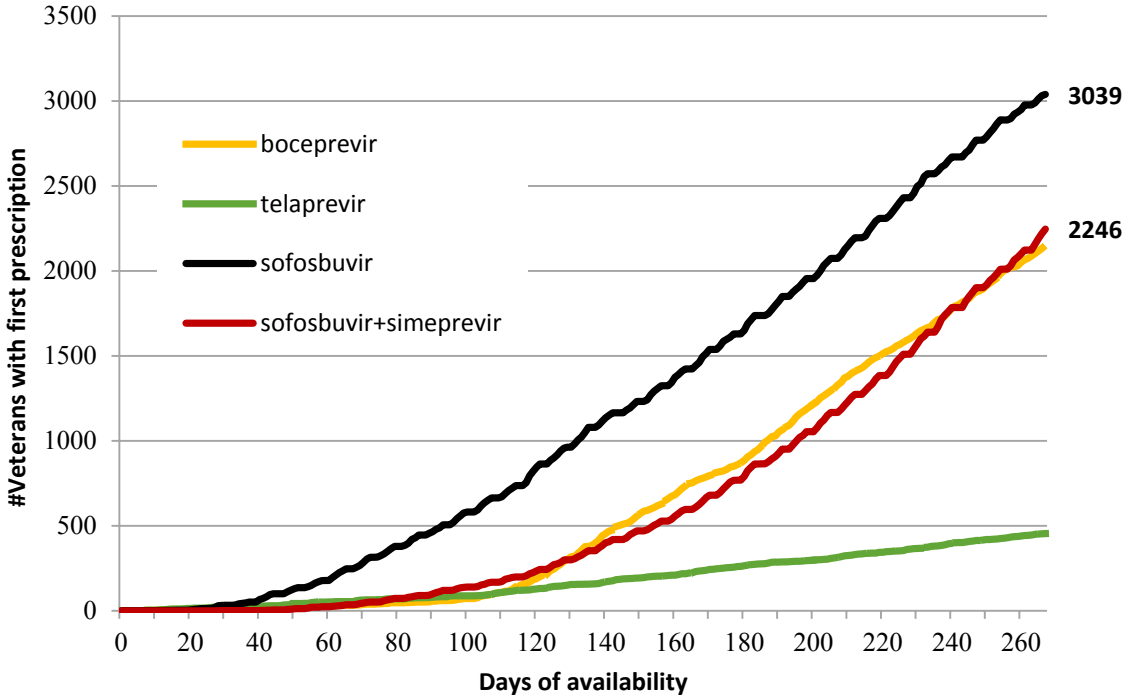
*Table 1. Treatment Regimen by Genotype*

| Regimen | Genotype 1<br>N =3927<br>n (%) | Genotype 2<br>N = 877<br>n (%) | Genotype 3<br>N=481<br>n (%) | Total<br>N=5285<br>n (%) |
|---|---|---|---|---|
| Sofosbuvir + Peginterferon + Ribavirin | 1470 (37%) | 27 (3%) | 96 (20%) | 1593 (30%) |
| Sofosbuvir + Ribavirin | 223 (6%) | 842 (96%) | 381 (79%) | 1446 (27%) |
| Sofosbuvir + Simeprevir | 1729 (44%) | 4 (<1%) | 1 (<1%) | 1734 (33%) |
| Sofosbuvir + Simeprevir + Ribavirin | 433 (11%) | 4 (<1%) | 2 (<1%) | 439 (8%) |
| Sofosbuvir + Simeprevir + Peginterferon + Ribavirin* | 72 (2%) | 0 (0%) | 1 (<1%) | 73 (2%) |

**This non-standard combination reflects Veterans who started on sofosbuvir+peginterferon+ ribavirin who then developed peginterferon intolerance and switched to sofosbuvir+simeprevir±ribavirin*

Comparing the uptake of sofosbuvir-based regimens after FDA approval in 2014 to the uptake of boceprevir- and telaprevir-based regimens after FDA approval in 2011, the trajectory of uptake differs substantially (Figure 1). Uptake of sofosbuvir regimens has been more rapid and more than doubles what was observed with boceprevir- and telaprevir-based regimens.

*Figure 1. Comparison of Simeprevir and Sofosbuvir Uptake in 2014 to Boceprevir and Telaprevir Uptake in 2011 Once Available in VA*




# Veteran Characteristics

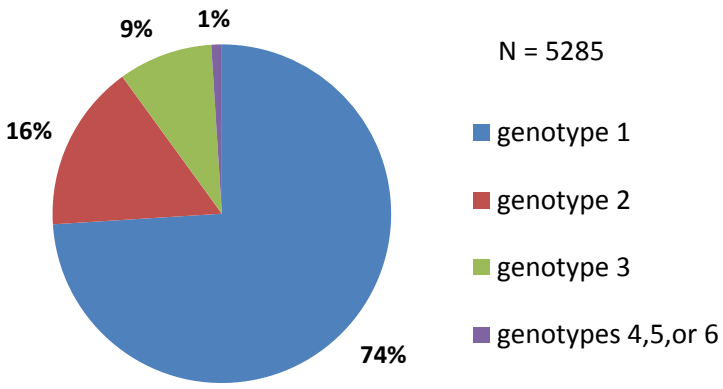
Veterans receiving treatment in clinical practice typically represent a broader spectrum of patients than those included in clinical trials. Veterans treated have been older (average age of 61 years old) than those treated in clinical trials in which the average age ranged from 46 to 52 years old. Over a quarter of Veterans treated were African Americans compared to only 3%-17% of those included in clinical trials. Over half of Veterans (53%) treated with sofosbuvir-based regimens had advanced liver disease. This represents a much higher proportion than those enrolled in clinical trials where cirrhosis was present in only 4%-17% of sofosbuvir patients and 22%-33% of simeprevir patients.7-10. Historically, patients with advanced liver disease have had lower SVR rates.

Veterans with prior HCV treatment experience constituted 36% of those initiating sofosbuvir-based regimens, and are a group that was not evaluated in sofosbuvir clinical trials. Small proportions of treated Veterans were HIV/HCV co-infected (3.5%) or post-liver transplant (3%), both populations where clinical trial data is limited.

# HCV Genotype of Veterans Treated

The HCV genotype distribution of Veterans initiating treatment with sofosbuvir-based regimens is shown in Figure 2. Three-quarters of Veterans initiating treatment in 2014 had HCV genotype 1. This is consistent with the distribution of HCV genotypes within the US and among Veterans in which genotype 1 is the most prevalent affecting 70-80% of those infected.[6]

*Figure 2. HCV Genotype Distribution among Veterans Receiving Sofosbuvir-based Regimens*




# Treatment Completion by Regimen

Table 2 presents the number of Veterans with adequate time to complete a sofosbuvir-based regimen by genotype and regimen, the proportion of Veterans who completed a full treatment course and the proportion that stopped treatment before completing a full treatment course. Of 1,587 Veterans with genotype 1 with adequate time to receive a recommended 12 week treatment course, 182 (11%) discontinued treatment early. Of those that discontinued treatment early, 101 (55%) were prescribed sofosbuvir+peginterferon+ribavirin, 64 (35%) sofosbuvir+simeprevir, 14 (8%) sofosbuvir+simeprevir+ribavirin, and 3 (2%) sofosbuvir+simeprevir+peginterferon+ribavirin. More patients discontinuing treatment early were treatment naïve (n=98, 54%) than treatment experienced (n=84, 46%).

Of 90 Veterans with genotype 1 who received sofosbuvir+ribavirin and had adequate time to complete 24 weeks of treatment, 25 (28%) discontinued treatment early. Treatment discontinuations occurred equally among treatment naïve (n=13, 52%) and treatment experienced individuals (n=12, 48%).

Of 393 Veterans with genotype 2 who had adequate time to receive a 12-week treatment course with sofosbuvir+ribavirin or sofosbuvir+peginterferon+ribavirin, 58 (15%) discontinued

treatment early. Early treatment discontinuation occurred more frequently in genotype 2 Veterans who were treatment naïve (n=40, 69%) than those who were treatment experienced (n=18, 31%).

Of 53 Veterans with genotype 3 who had adequate time to receive a 24-week course of treatment with sofosbuvir + ribavirin, 23 (43%) discontinued treatment early. Early treatment discontinuation occurred at a similar frequency in those who were treatment naïve (n=12, 52%) and those who were treatment experienced (n=11, 48%). Of 50 Veterans who had adequate time to receive a 12-week course of sofosbuvir+peginterferon+ribavirin, 8 (16%) discontinued treatment early and all but 1 individual were treatment-experienced.

Overall, the proportions of Veterans who discontinued treatment early were similar for the 12-week sofosbuvir-based regimens, irrespective of genotype, and ranged from 11%-16%; rates were higher for genotype 2 patients who also received peginterferon but the number of patients on this regimen was small. Early discontinuation rates for the 24-week sofosbuvir + ribavirin regimen were higher and ranged from 28%-43%, highlighting the difficulty of maintaining patients on regimens with longer duration. These discontinuation rates are higher than those observed in either clinical trials (0-3.6%) or by CVS Health (4.2%-10.2%).[11]

*Table 2. Treatment Completion and Discontinuations, by Genotype and Regimen*

| Genotype, Regimen, Usual treatment course duration | Veterans with sufficient time to complete treatment N | Veterans completing a full treatment course n (%) | Veterans NOT completing a full treatment course n (%) |
|---|---|---|---|
| Genotype 1 | | | |
| Sofosbuvir + Peginterferon + Ribavirin, 12 weeks | 818 | 716 (88%) | 101 (12%) |
| Sofosbuvir + Simeprevir ± Ribavirin,* 12 weeks | 769 | 688 (89%) | 81 (11%) |
| Sofosbuvir + Ribavirin, 24 weeks | 90 | 65 (72%) | 25 (28%) |
| Genotype 2 | | | |
| Sofosbuvir + Ribavirin, 12 weeks | 371 | 319 (86%) | 52 (14%) |
| Sofosbuvir + Peginterferon + Ribavirin, 12 weeks | 22 | 16 (73%) | 6 (27%) |
| Genotype 3 | | | |
| Sofosbuvir + Ribavirin, 24 weeks | 53 | 30 (57%) | 23 (43%) |
| Sofosbuvir + Peginterferon + Ribavirin, 12 weeks | 50 | 42 (84%) | 8 (16%) |
| TOTAL | 2173 | 1876 (86.4%) | 296 (13.6%) |

**Includes 162 patients who received sofosbuvir+simeprevir+ribavirin and 29 patients that received sofosbuvir+ simeprevir+peginterferon+ribavirin*

Table 3 describes the reasons for early discontinuation of sofosbuvir-based regimens which could be determined from the HCV Clinical Case Registry. Due to the nature of the electronic data, a specific reason for early discontinuation could not be determined in Veterans who appeared to be virologically suppressed at the time of early treatment discontinuation. Besides virologic failure, early discontinuation may have been related to adverse effects, tolerance, a Veteran not returning for follow-up, Veteran choice to stop therapy, or provider choice where the Veteran is non-adherent with taking the medications or other social and behavioral factors make completion of the treatment course unlikely.

Among Veterans who discontinued sofosbuvir-based treatment before completing a full treatment course, 30%-38% of Veterans were not virologically suppressed when treatment was stopped. These rates of presumed virologic failure are higher than the rates reported in clinical trials with sofosbuvir or sofosbuvir+simeprevir which were between 0%-4%.[12] A small number of patients died while on treatment, each of whom had advanced liver disease and/or cirrhosis at the time of treatment initiation. Most Veterans that did not complete a full treatment course, however, discontinued treatment for reasons other than virologic failure or death. As observed, the greatest challenges in completing a successful course of treatment may not be recognized until the medication regimen is used outside of the clinical trial setting. This highlights the challenges of treating real-world populations and differences between clinical trial results and results achieved in clinical practice.

*Table 3. Reasons for Early Discontinuation of Sofosbuvir-based Regimens, by Genotype*

| Genotype, Regimen, Usual treatment course duration | Veterans NOT completing a full treatment course, N | Reason for discontinuation: Presumed virologic failure* | Reason for discontinuation: Death | Other reason for early dis-continuation |
|---|---|---|---|---|
| Genotype 1 | | | | |
| Sofosbuvir + Peginterferon + Ribavirin, 12 weeks | 101 | 32 (32%) | 0 (0%) | 69 (68%) |
| Sofosbuvir + Simeprevir± Ribavirin 12 weeks | 81 | 30 (37%) | 5 (6%) | 46 (57%) |
| Sofosbuvir + Ribavirin, 24 weeks | 25 | 8 (32%) | 2 (8%) | 15 (60%) |
| Genotype 2 | | | | |
| Sofosbuvir + Ribavirin, 12 weeks | 52 | 19 (36%) | 2 (4%) | 31 (60%) |
| Genotype 3 | | | | |
| Sofosbuvir + Peginterferon + Ribavirin, 12 weeks | 8 | 3 (38%) | 0 (0%) | 5 (62%) |
| Sofosbuvir + Ribavirin, 24 weeks | 23 | 7 (30%) | 2 (9%) | 14 (61%) |
| TOTAL | 290 | 99 (34.1%) | 11 (3.8%) | 180 (62.1%) |

*Detectable HCV viral load on the last HCV viral load test while on treatment *or* on a HCV viral load test obtained after early treatment discontinuation

# Estimated SVR

As noted earlier, because a substantial proportion of Veterans have not had post-treatment HCV viral load testing to be able to assess SVR, an estimated range of SVR is provided in Table 4. Given the higher rates of early discontinuation observed in clinical practice than in clinical trials, SVR rates are expected to be lower than in clinical trials. Indeed, the high-end of the SVR ranges estimated for each regimen and genotype are lower than the overall SVR rates reported in sofosbuvir or sofosbuvir+simeprevir trials.[12] This may be reflective of the treated Veteran population having more characteristics which historically have been associated with lower SVR

rates. The estimated SVR rates among Veterans prescribed sofosbuvir-based regimens signals the decrement in efficacy when moving from the clinical trial to clinical practice. These SVR rates, however, are still substantially higher than the rates observed with the prior antiviral regimens in Veterans.[1,13]

*Table 4. Estimated Sustained Virologic Responses (SVR)*

| Genotype, Regimen, Usual treatment course duration | Veterans with sufficient time to complete treatment N | Estimated SVR, Range |
|---|---|---|
| Genotype 1 | | |
| Sofosbuvir + Peginterferon + Ribavirin, 12 weeks | 818 | 65%-87% |
| Sofosbuvir + Simeprevir ± Ribavirin* 12 weeks | 769 | 66%-89% |
| Sofosbuvir + Ribavirin, 24 weeks | 90 | 52%-77% |
| Genotype 2 | | |
| Sofosbuvir + Ribavirin, 12 weeks | 371 | 67%-90% |
| Sofosbuvir + Peginterferon + Ribavirin, 12 weeks | 22 | 75%-85% |
| Genotype 3 | | |
| Sofosbuvir + Ribavirin, 24 weeks | 53 | 51%-79% |
| Sofosbuvir + Peginterferon + Ribavirin, 12 weeks | 50 | 74%-92% |

# Conclusions

Overall, SVR rates in the VA with sofosbuvir-based regimens are substantially higher than with prior HCV antiviral regimens but lower than the rates reported in clinical trials. The differences observed in VA with regards to patient characteristics, early treatment discontinuations and lower SVR rates reflect the differences between clinical trials and clinical practice and may limit applicability of clinical trial outcomes to this population. Patient and provider expectations may need to be tempered accordingly. The reporting of 'real-world' experience in VA, the largest provider of HCV care in the US, is essential to provide practical information that may better inform HCV management strategies.

# Correspondence

For correspondence related to this document please contact:
Pamela S. Belperio PharmD, BCPS
National Public Health Clinical Pharmacist
VA Office of Public Health / Population Health (10P3C)
Department of Veterans Affairs
Palo Alto, California
pamela.belperio@va.gov

# References


1. Backus LI, Belperio PS, Shahoumian TA, Cheung R, Mole LA. Comparative effectiveness of the hepatitis C virus protease inhibitors boceprevir and telaprevir in a large U.S. cohort. Aliment Pharmacol Ther. 2014;39:93-103.
2. Price JC, Murphy RC, Shvachko VA, Pauly MP, Manos MM. Effectiveness of telaprevir and boceprevir triple therapy for patients with hepatitis C virus infection in a large integrated care setting. Dig Dis Sci. 2014; Aug 8. [Epub ahead of print].
3. Hezode C, Fontaine H, Dorival C, et al. Effectiveness of telaprevir or boceprevir in treatment experienced patients with HCV genotype 1 infection and cirrhosis. Gastroenterology 2014;147:132-142.
4. Belperio PS, Backus LI, Ross D, Neuhauser MM, Mole LA. A population approach to disease management: hepatitis C direct-acting antiviral use in a large health care system. J Manag Care Pharm. 2014 Jun;20(6):533-40.
5. Backus LI1, Gavrilov S, Loomis TP, Halloran JP, Phillips BR, Belperio PS, Mole LA. Clinical Case Registries: simultaneous local and national disease registries for population quality management. J Am Med Inform Assoc. 2009 Nov-Dec;16(6):775-83. Epub 2009 Aug 28.
6. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. American Association for Study of Liver Diseases. An Update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011;54:1433-44.
7. Sulkowski MS, Naggie S, Lalezari J, et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. JAMA. 2014;312(4):353-61.
8. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013;368:1878-87.
9. Forns X, Lawitz E, Zeuzem S, et al. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. Gastroenterology. 2014;146(7):1669-79.
10. Manns M, Marcellin P, Poordad F, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2014;384:414-26.
11. Brennan TA, Lotvin A, Shrank W. Analysis of 'real-world' sofosbuvir use and discontinuation rates. CVS Health. August 2014.
12. Sovaldi (sofosbuvir) tablets for oral use. Gilead Sciences, Inc. Foster City, CA. December 2013.
13. Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol. 2011;9:509-516.