



Effectiveness of 8- or 12-weeks of ledipasvir and sofosbuvir in real-world treatment-naïve, genotype 1 hepatitis C infected patients

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Summary

Background: Treatment of genotype 1 hepatitis C virus (HCV) infection with combination direct acting anti-virals is associated with very high rates of sustained virological response (SVR). Daily combination of ledipasvir and sofosbuvir for 12 weeks is approved for the treatment of genotype 1 HCV patients, though noncirrhotic patients who are naïve to treatment with a baseline HCV RNA <6 million IU/mL can be treated for 8 weeks. This guidance stemmed from a post hoc analysis of the ION 3 clinical trial, which demonstrated similar SVR for patients treated with ledipasvir and sofosbuvir with or without ribavirin for 8 or 12 weeks.

Aim: To compare the SVR for 8 weeks vs 12 weeks of ledipasvir and sofosbuvir in HCV infected patients in a real-world setting.

Methods: We performed an observational real-world cohort study of treatment success following 8 or 12 weeks of ledipasvir and sofosbuvir for treatment-naïve genotype 1 HCV patients.

Results: A total of 826 patients were treated for either 8 (n=252) or 12 weeks (n=574) with ledipasvir and sofosbuvir and achieved SVR rate of 95.3% and there was no statistical difference in SVR rates in the two groups irrespective of any clinical or virological variables.

Conclusions: In treatment-naïve HCV genotype 1 patients, SVR was 95% in those treated for either 8 weeks or 12 weeks with ledipasvir and sofosbuvir. 8 week ledipasvir and sofosbuvir can reduce costs without compromising outcomes for those patients who qualify for such regimen.

1 | INTRODUCTION

1.1 | Background

There is an estimated 80-185 million people infected with Hepatitis C virus (HCV) worldwide.^{1,2} Despite the reduction in new infections in recent years, morbidity and mortality related to chronic infection are likely to increase.³ Since 2011, there has been the development of several new regimens of direct acting anti-virals associated with significant improvements in efficacy and tolerability in treatment of HCV. Eradication of HCV is associated with decreased overall morbidity and mortality as well as increased quality of life and reduced healthcare utilisation.^{4,5} Based on the prevalence of infection and availability of highly effective direct acting antivirals, treatment is now recommended for all patients with chronic HCV infection.

However, due to the high wholesale cost of direct acting antiviral treatment regimens, one of the commonly cited barriers to treatment is the cost of therapy.⁶ Despite this high cost, treatment of naïve genotype 1 HCV patients is considered to be a cost-effective strategy when compared with other accepted medical practices.⁷⁻⁹ Ledipasvir and sofosbuvir fixed dose combination (LDV/SOF) is approved by the Food and Drug Administration for the treatment of genotype 1 HCV infection in treatment-naïve patients with and without cirrhosis based on two registration trials called ION-1 and ION-3.^{10,11} The ION-3 study of treatment-naïve noncirrhotic patients investigated LDV/SOF with or without ribavirin for 8 or 12 weeks and LDV/SOF for 12 weeks. Treatment-naïve noncirrhotic patients infected with genotype 1 who received LDV/SOF for 8 weeks achieved an SVR rate of 94%. This SVR was not inferior to a 12-week regimen of LDV/SOF in an intent-to-treat analysis. Relapse rates were found to be higher in the cohort of patients randomised to 8 weeks of treatment regardless of ribavirin. However, in a post hoc analysis of the ribavirin-free treatment arms, patients with baseline HCV RNA levels <6 million IU/mL were found to have similarly high SVR rates and low relapse rates regardless of 8- or 12-week treatment durations. While this analysis was not controlled, the Food and Drug Administration included consideration of 8 weeks of LDV/SOF in genotype 1 treatment-naïve patients without cirrhosis who have a pre-treatment viral load of <6 million IU/mL.¹² Despite the approval of the Food and Drug Administration, the American Association for Study of Liver Disease/Infectious Diseases Society of America guidelines for the treatment of HCV state that shortening of therapy for less than 12 weeks is not recommended in African-American patients, patients with Human Immunodeficiency Virus infection and patients with known interleukin-28B polymorphism CT or TT.¹³ Guidelines from the European Association for the Study of the Liver state that treatment may be shortened to 8 weeks in treatment-naïve patients without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 Log) IU/mL, however, caution should be exercised especially in patients with F3 fibrosis, pending confirmation of these results in real-life studies.¹⁴ Last, the English National Health Service guidance recommends 8 weeks of LDV/SOF for noncirrhotic treatment-naïve genotype 1 HCV infected

patients regardless of HCV viral load.¹⁵ Several heterogeneous real-world cohort studies have reported excellent SVR rates for patients treated for 8 weeks with LDV/SOF±ribavirin.¹⁶⁻²³

The importance of these recommendations for the possible shortening of duration cannot be underestimated as it is likely that there is a significant population of patients who meet these criteria who could benefit from a shortened, and thus less costly, course of treatment. However, the baseline HCV viral load cut off of 6 million IU/mL has been called into question, as the post hoc analysis was underpowered and may reflect a statistical artefact.²⁴

1.2 | Aim

We chose to evaluate SVR rates following LDV/SOF without ribavirin for genotype 1, treatment-naïve patients in a real-world cohort of patients who have been treated for 8 or 12 weeks.

2 | PATIENT AND METHODS

2.1 | Study design/setting

The study cohort comprises treatment-naïve, genotype 1 patients treated in community and academic practices affiliated with the Trio Health's Innovation Platform. Patients received LDV/SOF for either 8 or 12 weeks at the discretion of their treating physician. Data were collected through Trio Health's Innovation Platform, a unique platform that has the ability to collect and aggregate real-time data for disease management. Baseline information as well as outcomes data were collected through both the specialty pharmacies and clinicians in academic and community practices that work with Trio Health and were entered into the portal via a combination of nightly file feeds and manual user entry. In addition to data collection, the portal also scrubbed and mapped data, applied proprietary logic to identify errors, and prompted specialty pharmacies and clinicians to input data to ensure all data were complete and accurate. For this study, de-identified data were collected from this process, which was approved as an Institutional Review Board exemption under category 45 CFR 46.

This retrospective review of a prospectively defined cohort is based on data from treatment-naïve patients who were treated for 8 or 12 weeks with LDV/SOF between October 2014 and March 2015. Patients were recruited in real-world community and academic practices affiliated with Trio Healthcare. All patients were treatment naïve and received LDV/SOF without ribavirin for 8 or 12 weeks. The primary endpoint was SVR12, defined by a negative hepatitis C viral load by polymerase chain reaction assessed at 12 weeks following the completion of therapy. Treatment start and end dates were defined by pharmacy dispensing records. Additional clinical characteristics were recorded, including age, gender, ethnicity, physician-reported fibrosis burden, transplant status, comorbidities (human immunodeficiency virus [HIV], hepatitis B [HBV], diabetes), treatment duration and physician practice type. Collected laboratory values include HCV genotype, initial viral load, alanine and aspartate

aminotransferase (ALT, AST), haemoglobin, and platelet count. Assessment of HCV RNA was performed as per standard clinic practice by the treating physician and reported in standardised international units. Fibrosis stage was determined by liver biopsy, serum biomarkers and vibration controlled elastography assessment by FibroScan as per the usual practice and was reported by the treating physician. Fibrosis staging was not performed in 12.6% of the patients enrolled.

2.2 | Statistical analysis

Associations between each individual potential predictor variable and the SVR modelled both as a “per protocol” and “intention to treat” were assessed. Predictor variables were entered into univariable ordinal regression models with fibrosis stage as the ordinal outcome. Predictor variables with two-tailed $P \leq .25$ were entered into multivariable logistic regression models. Manual backward stepwise elimination was used to generate the best-fitting multivariable logistic model. Forced adjustments for severe fibrosis and thrombocytopenia were subsequently performed for each variable in logistic regression analyses. These analyses were repeated for the overall cohort in addition to subgroup analyses for patients treated for 8 and 12 weeks.

3 | RESULTS

3.1 | Treatment cohort

A total of 826 patients received LDV/SOF treatment for either 8 or 12 weeks. Two hundred and fifty two patients were treated for 8 weeks and 574 were treated for 12 weeks (Figure 1). Fifty-one per cent of patients were male, 52% were Caucasian and 17% of patients were African American. All patients were treatment-naïve. The majority (63%) of patients were treated in community practices and there was no difference in the duration of therapy between community and academic practices. Baseline characteristics of the cohort are presented in Table 1. Patients receiving 12 weeks of treatment were significantly older, more likely to be male gender, have more advanced fibrosis, have lower platelet counts, and have higher viral loads.

There were 587 who were deemed not to have liver cirrhosis by liver biopsy, FibroScan or serum fibrosis markers, and had a platelet count of $>100\ 000/\mu\text{L}$ and an AST to platelet index (APRI) of <1.0 . Two hundred and thirty-nine patients did not have formal staging of liver fibrosis or had a platelet count of $<100\ 000/\mu\text{L}$ or an APRI of >1.0 . Sustained virological response rates were assessed for the entire cohort of patients ($n=826$) and for those formally deemed not to have liver cirrhosis.

3.2 | Virological outcomes

SVR12 was achieved in 787/826 (95.3%) of patients in the entire cohort. Twenty-one patients were lost to follow-up, seven patients

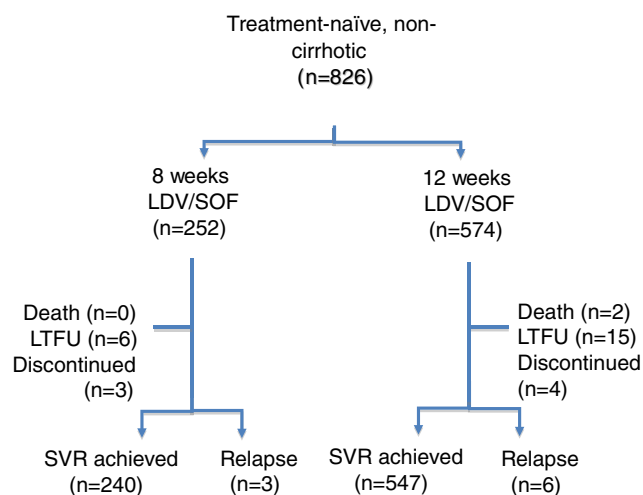


FIGURE 1 Distribution of all patients who were treated with LDV/SOF for 8 and 12 weeks. The number of patient achieving SVR and those experiencing relapse are shown for 8 and 12 weeks of treatment. The numbers of patient who died, discontinued therapy or who were lost to follow-up (LTFU) are displayed for both treatment durations

TABLE 1 Baseline characteristics of patients

	8 weeks (n=252)	12 weeks (n=574)	P value
Age >65 years, n (%)	65 (25.8)	188 (32.8)	.05
Male, n (%)	114 (45.2)	310 (54.0)	.02
Race, n (%)			
Black	37 (15.9)	106 (19.8)	.07
Hispanic/Latin	14 (6.0)	31 (5.8)	
White	145 (62.2)	282 (52.7)	
Genotype 1a, n (%)	172 (69.4)	380 (66.9)	.86
Initial viral load, IU/mL median (10^6) (IQR)	1.33 (0.39-2.33)	2.56 (0/89-6.23)	.0001
Academic practice, n (%)	83 (32.9)	219 (38.2)	.16
Advanced fibrosis, n (%)	32 (12.7)	142 (24.7)	.0001
Platelets <100 K/mL, n (%)	2 (0.79)	21 (3.7)	.02
Post-transplant, N (%)	1 (0.4)	4 (0.7)	.60
Diabetes	24 (9.8)	75 (13.3)	.04

discontinued therapy and there were two deaths during treatment. None of the treatment discontinuations were related to study medications. Patients lost to follow-up or those that discontinued treatment are considered treatment failures in the intent-to-treat analysis. Intent-to-treat SVR12 was 95.2% for patients treated for 8 weeks and 95.3% for patients treated for 12 weeks. There was no difference in SVR by viral subtype regardless of duration of treatment (Figure 2). There were nine relapses in total, with three patients treated for 8 weeks for a relapse rate of 1.2%. Six patients in the 12-weeks treatment group relapsed for a relapse rate of 1.1% (Figure 1 and Table 2). Five hundred and seventy-seven patients met the HCV viral load of <6 million IU/mL to receive 8 weeks of LDV/

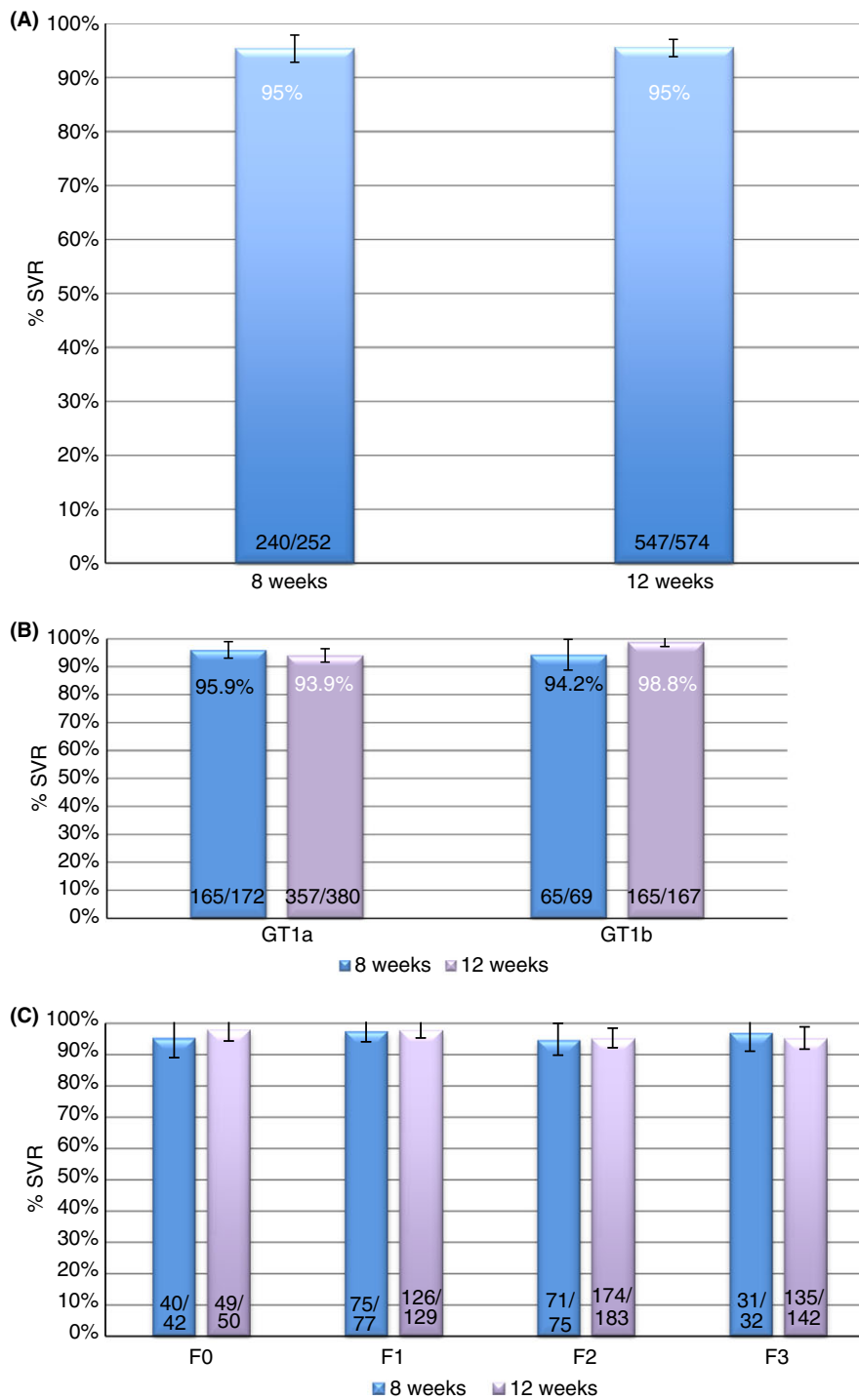


FIGURE 2 Overall SVR rates for all patients treated with LDV/SOF for 8 weeks (95%) and 12 weeks (95%) (A); SVR rates for patients with known genotype 1a vs 1b for patients treated for 8 weeks (blue) and 12 weeks (purple) (B); SVR rates patients with known fibrosis scores receiving 8 weeks (blue) vs 12 weeks (purple) (C)

SOF. Two hundred and fifty-one patients (38%) who were received 8 weeks of treatment achieved and SVR of 95.2%, while 416 (62%) patients with HCV RNA levels <6 million IU/mL and were eligible for 8 weeks but were treated for 12 weeks, had a similar SVR of 94.9%.

Excluding patients without a formal stage of liver fibrosis, a platelet count of <100 000/mL and an APRI of >1.0, the SVR rate was 97% and was not different in those treated for 8 weeks (97%) and

those treated for 12 weeks (97%). In this cohort, SVR was similar across all stage of liver fibrosis (F0-3) for 8 and 12 weeks (Figure 3). There was no difference in SVR noted in those who had diabetes mellitus vs those that did not with SVR rates of 95% seen in both cohorts. Per protocol analysis demonstrated that SVR rate in diabetics treated for 8 weeks was 96% and 98% in those treated for 12 weeks. There were 143 (17%) African Americans included in the

TABLE 2 Characteristics of all relapses

Practice type	Patient age	Patient gender	Patient ethnicity (group)	Genotype group	Actual regimen name	Duration	Baseline VL
Academic	64	F	Black	1A	LDV-SOF	8	805 000
Academic	67	M	White	1A	LDV-SOF	8	646 400
Community	78	F	Black	1A	LDV-SOF	8	1 973 539
Community	61	F	White	1A	LDV-SOF	12	3 020 000
Community	61	M	Black	1A	LDV-SOF	12	3 569 042
Community	60	F	White	1A	LDV-SOF	12	11 291 000
Community	58	M	Black	1UNKNOWN	LDV-SOF	12	2 245 736
Academic	46	M	Unknown	1A	LDV-SOF	12	2 456 117
Community	63	F	Black	1B	LDV-SOF	12	2 977 629

study. SVR was achieved in 96% of African American patients treated with LDV/SOF. There were nine relapses in the entire cohort and six relapses occurred in African American patients. While the SVR rate in the patients treated for 8 weeks (n=37) was numerically lower than those treated for 12 weeks (n=106), this did not reach statistical significance. (89% vs 94%; $P=.29$). Again while there was no statistically significant difference in SVR rate noted between African American patients treated for 8 weeks and those African American patients who eligible to received for 8 weeks but were treated for 12 weeks (89% vs 95%; $P=.28$), the result was numerically lower.

We examined the effect of baseline predictors on virological outcome and we were unable to identify any variable that was significantly associated with treatment failure in either per-protocol or intention-to-treat analyses in multivariable logistic regression models.

4 | DISCUSSION

The efficacy and better tolerability of all oral anti-viral regimens in patients with chronic HCV infection is well established with SVR rates 21-fold higher now than in the interferon era.²⁵ These improvements in SVR are noted across multiple patient populations leading to the widespread use of these agents even in patients with advanced disease.^{26–28} However, due to the high cost of these regimens and the implementation of a triage system by health care agencies to allocate treatment, there are still significant populations of patients who have not yet been treated and are at risk of disease progression. Socioeconomic reasons have now replaced medical contraindications as the primary reason for patients to be denied access to treatment.^{29,30} Shortening the duration of treatment could significantly reduce the costs of treatment and in many cases, can be cost-saving. Post hoc analysis of the ION-3 registration trial identified a cohort of treatment-naïve noncirrhotic patients with low viral load who are likely to have similar SVR rates to patients who received a 12-week treatment course of LDV/SOF. In view of this the Food and Drug Administration included the option for an 8-week duration of treatment for patients meeting these pretreatment criteria. International guidelines have suggested caution in the use of treatment

regimens of less than 12 weeks in this population pending the results of real-world studies addressing shorter durations of treatment. Reducing the duration of treatment for these patients could result in significant cost savings and possibly allow more patients to receive much needed anti-viral therapy.

In this real-world experience of HCV treatment in genotype1 treatment-naïve patients, high SVR rates, comparable to that was observed in registration trials, were achieved. There were no differences in SVR between the 8- and 12-week cohorts and no differences were observed in SVR across genotype subtype or fibrosis stage. This analysis of a real-world cohort of patients treated in community and academic medical centres included some patients who did not have a formal assessment of liver fibrosis and had platelet counts of <100 000/ μ L or an APRI of >1.0. When we excluded these patients from the SVR analysis, the SVR rates were 97%.

Five hundred and seventy-seven patients met the HCV viral load of <6 million IU/mL criteria to receive 8 weeks of LDV/SOF. Two hundred and fifty-one patients (38%) received 8 weeks of treatment and SVR was achieved in 95.2% while 416 (62%) patients with HCV RNA levels <6 million IU/mL were treated for 12 weeks and SVR was achieved in 94.9%. Shortening the course of treatment by 4 weeks for these 416 patients could possibly have resulted in significant cost savings across the entire cohort.

Our data are similar to that recently published by Ioannou and colleagues who analysed the real-world effectiveness of DAA treatment in the Veterans Affairs National Health Care System. Twenty-seven per cent of patients receiving LDV/SOF were treated for 8 weeks and achieved SVR rates of 94.3%.³¹ In a subgroup analysis of those treatment-naïve noncirrhotic patients with HCV RNA levels <6 million IU/mL, 48% were treated for 8 weeks and achieved SVR of 95%, similar to the SVR achieved by the 38% of patients in our study treated for 8 weeks.

Prior studies have shown higher rates of virological relapse in genotype 1a patients after 8 weeks of treatment. In this real-world cohort, very low and no difference was observed in relapse rates across genotype subtype and treatment duration.

Our study is limited by the retrospective nonrandomised design that precludes rigid comparisons of the treatment duration. In addition, treatment duration was at the discretion of the treating

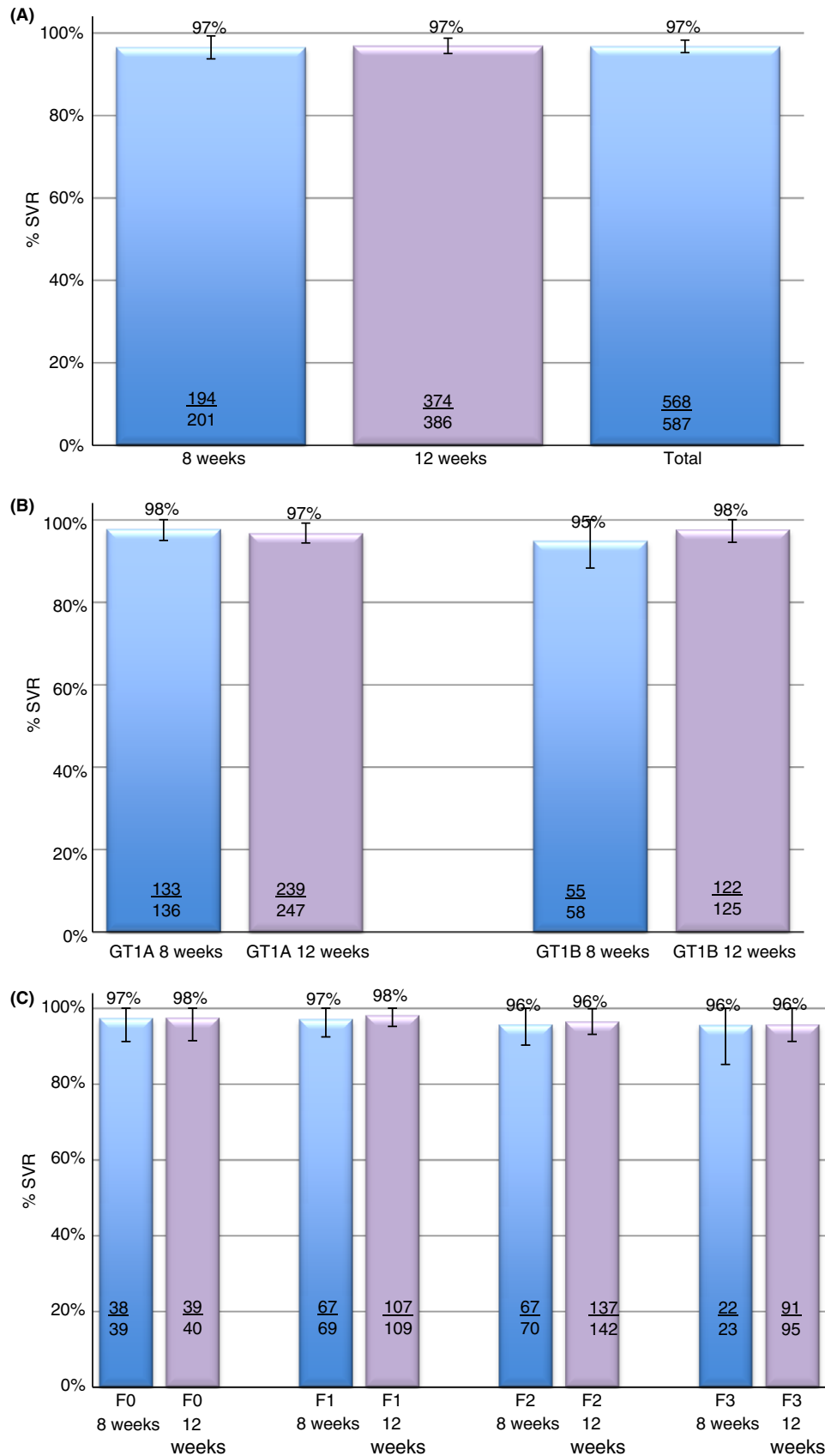


FIGURE 3 Overall SVR rates for patients without cirrhosis treated with LDV/SOF for 8 and 12 weeks (A); SVR rates for patients without cirrhosis with known genotype 1a versus 1b receiving 8 weeks (blue) and 12 weeks (purple) (B); and SVR rates for patient with known fibrosis scores receiving 8 weeks (blue) and 12 weeks (purple) (C)

physician and as such there were significantly more patients older than 65 years, of male gender, diabetics and more advanced fibrosis patients in the cohort treated for 12 weeks. Details such as IL28B polymorphism were not available, however this assay is rarely used in the current era of direct acting anti-viral therapy. Additionally we do not have data on concomitant use of medications such as acid-reducing medications for this study, though this is unlikely to have changed the results.³² Our entire cohort included some patients who did not have a formal assessment of liver fibrosis as well as patients who had platelet count of $<100\ 000/\mu\text{L}$. To more stringently evaluate the efficacy of LDV/SOF for 8 vs 12 weeks in true non-cirrhotic patients, we further analysed the SVR rates in a cohort with formal assessment of liver fibrosis, platelet count of $>100\ 000/\mu\text{L}$ and an APRI of >1.0 and showed excellent SVR rates of 97% in the 8 and 12 weeks cohorts (Figure 3).

Further limitations include the small numbers of patients for subgroup analysis, thus limiting the power of this study to determine significant differences in SVR by treatment duration in these subgroups. The overall SVR rate for African Americans treated with LDV/SOF was 96%. The numbers of African American patients treated for 8 weeks in this study is small and though the SVR rates are not significantly different for 8 weeks and 12 weeks of treatment, there is a numerically lower SVR rate and relapse is more commonly seen in African American patients in this study (Table 2). The small numbers of African American patients in this study limits any definitive conclusions regarding 8 vs 12 weeks in this population. As with other studies of African American patients, which demonstrate similar SVR rates for 8 and 12 weeks we suggest that caution be used in shortening treatment in this population because of a higher relapse rate.^{33,34}

Despite these limitations, our study has comparable rates of SVR to that observed in registration trials for LDV/SOF.¹⁰ Our study also supports the real-world effectiveness study by Ioannou and colleagues for the VA cooperative and supports the VA treatment guidelines and the English National Health Service guidance on shortening duration of treatment in noncirrhotic treatment-naïve patients with HCV RNA <6 million IU/mL.^{31,35} The generalisability of the clinical data from ION-3 has also been demonstrated by multiple other, real-world studies comparing 8 vs 12 weeks of LDV/SOF multiple geographies and patient care settings including patients with HIV disease.^{17,19,20,22,36–38}

In conclusion, our study supports the FDA recommendation that clinicians should consider 8 weeks of LDV/SOF for initial treatment of HCV genotype 1, treatment-naïve, non-cirrhotic patients.

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REFERENCES

1. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology*. 2013;57:1333-1342.

2. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol.* 2014;61(Suppl 1):S45-S57.
3. Razavi H, Waked I, Sarrazin C, et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. *J Viral Hepat.* 2014;21(Suppl 1):34-59.
4. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA.* 2012;308:2584-2593.
5. Younossi ZM, Stepanova M, Sulkowski M, Naggie S, Henry L, Hunt S. Sofosbuvir and ledipasvir improve patient-reported outcomes in patients co-infected with hepatitis C and human immunodeficiency virus. *J Viral Hepat.* 2016;23:857-865.
6. Iyengar S, Tay-Teo K, Vogler S, et al. Prices, costs, and affordability of new medicines for hepatitis C in 30 countries: an economic analysis. *PLoS Med.* 2016;13:e1002032.
7. Chhatwal J, He T, Lopez-Olivo MA. Systematic review of modelling approaches for the cost effectiveness of hepatitis C treatment with direct-acting antivirals. *Pharmacoeconomics.* 2016;34:551-567.
8. Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Ann Intern Med.* 2015;162:397-406.
9. Younossi ZM, Park H, Saab S, Ahmed A, Dieterich D, Gordon SC. Cost-effectiveness of all-oral ledipasvir/sofosbuvir regimens in patients with chronic hepatitis C virus genotype 1 infection. *Aliment Pharmacol Ther.* 2015;41:544-563.
10. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med.* 2014;370:1879-1888.
11. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med.* 2014;370:1889-1898.
12. US Food Drug Administration. Centre for drug evaluation and research. Sofosbuvir and ledipasvir fixed-dose combination, in 2014: NDA 205834. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205834Orig1s000MedR.pdf. Accessed January 2017.
13. AASLD-IDS. Initial treatment of HCV infection. <http://www.hcvguidelines.org/full-report/initial-treatment-hcv-infection> Accessed July 2016.
14. European Association for Study of Liver. EASL recommendation on treatment of hepatitis C 2015. *J Hepatol.* 2015;63:199-236.
15. UK National Institute for Health Care and Excellence. Appraisal consultation document. Ledipasvir-sofosbuvir for treating chronic hepatitis C, 2015. <https://www.nice.org.uk/guidance/ta363>. Accessed January 2017.
16. Marshall VJ, Rife K, Hirsch A, et al. Real life treatment outcomes with 8 week course treatment for hepatitis C without cirrhosis confirmed by transient elastography. *Hepatology.* 2015;62(Suppl 1):779A.
17. Roytman M, Tang AL, Wu C, et al. Real Life Experience with Sofosbuvir and Ledipasvir fixed dose regimen in the multicentric cohort of patients with chronic hepatitis C. *Hepatology.* 2015;62(Suppl 1):761A.
18. Buggisch B, Boker K, Gunther R, et al. Ledipasvir/Sofosbuvir (LDV/SOF) for 8 weeks in genotype 1 (GT1) treatment-naive non cirrhotic patients with HCV viralload < 6 millions IU/ML (6M): a comparative analysis of the phase-3 ION-3 data and real world effectiveness. *J Hepatol.* 2016;64:S810.
19. Crespo J, Fernandez I, Cabezas J, et al. Effectiveness and safety of sofosbuvir / Ledipasvir treatment for monoinfected genotype 1 HCV patients in real life clinical practice: results from the Spanish Hepa-C cohort. *J Hepatol.* 2016;64:S217.
20. Lai JB, Witt MA, Witt DJ. Real World Effectiveness of 8, 12 and 24 weeks of Ledipasvir(LDV)/Sofosbuvir(SOF)- based therapy for hepatitis C (HCV) genotype 1: analysis in a large integrated health care system. *J Hepatol.* 2016;64:S778.
21. Latt NL, Gevorkyan R, Yanny BT, Sahota A. Ledipasvir / Sofosbuvir for 8 weeks in non cirrhotic treatment naive patients with genotype 1 hepatitis C infection: real life experience in a community setting. *J Hepatol.* 2016;64:S802.
22. Qureshi K, Andres J, Regester J, et al. Real-Life outcomes of 8 weeks regimen of sofosbuvir and ledipasvir without ribavirin in non cirrhotic treatment naive hepatitis C genotype 1 patients with less than 6 millions IU/ML viral load. *J Hepatol.* 2016;64:S786.
23. Terrault NA, Zeuzem S, Di Bisceglie AM, et al. Effectiveness of ledipasvir-sofosbuvir combination in patients with hepatitis C Virus Infection and Factors Associated With Sustained Virologic Response. *Gastroenterology.* 2016;151:1131-1140 e5.
24. O'Brien TR, Feld JJ, Kottlil S, Pfeiffer RM. No scientific basis to restrict 8 weeks of treatment with ledipasvir/sofosbuvir to patients with hepatitis C virus RNA <6,000,000 IU/mL. *Hepatology.* 2016;63:28-30.
25. Moon AM, Green PK, Berry K, Iannou GN. Transformation of hepatitis C antiviral treatment in a national healthcare system following the introduction of direct antiviral agents. *Aliment Pharmacol Ther.* 2017;45:1201-1212.
26. Guarino M, Morisco F, Valvano MR, et al. Systematic review: interferon-free regimens for patients with HCV-related Child C cirrhosis. *Aliment Pharmacol Ther.* 2017;45:1193-1200.
27. Pillai AA, Maheshwari R, Vora R, et al. Treatment of HCV infection in liver transplant recipients with ledipasvir and sofosbuvir without ribavirin. *Aliment Pharmacol Ther.* 2017;45:1427-1432.
28. Reddy KR, Kim JK, Kuo A, et al. All-oral direct-acting antiviral therapy in HCV-advanced liver disease is effective in real-world practice: observations through HCV-TARGET database. *Aliment Pharmacol Ther.* 2017;45:115-126.
29. Dieterich D, Bacon BR, Curry MP, et al. Access to therapy in the era of all DAA regimens: real world experiences from the TRIO Network. *Gastroenterology.* 2016;150:S1040.
30. Younossi ZM, Bacon BR, Dieterich DT, et al. Disparate access to treatment regimens in chronic hepatitis C patients: data from the TRIO network. *J Viral Hepat.* 2016;23:447-454.
31. Ioannou GN, Beste LA, Chang MF, et al. Effectiveness of Sofosbuvir, Ledipasvir/Sofosbuvir, or Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir Regimens for Treatment of Patients With Hepatitis C in the Veterans Affairs National Health Care System. *Gastroenterology.* 2016; 151:457-471.
32. Tapper EB, Bacon BR, Curry MP, et al. Evaluation of proton pump inhibitor use on treatment outcomes with ledipasvir and sofosbuvir in a real-world cohort study. *Hepatology.* 2016;64:1893-1899.
33. Wilder JM, Jeffers LJ, Ravendhran N, et al. Safety and efficacy of ledipasvir-sofosbuvir in black patients with hepatitis C virus infection: a retrospective analysis of phase 3 data. *Hepatology.* 2016;63:437-444.
34. Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Real-world effectiveness of ledipasvir/sofosbuvir in 4,365 treatment-naive, genotype 1 hepatitis C-infected patients. *Hepatology.* 2016; 64:405-414.
35. Chronic hepatitis C virus (HCV) infection: treatment considerations from the Department of Veterans Affairs National Hepatitis C Resource Center Program and national Viral Hepatitis Program. <http://www.hepatitis.va.gov/provider/index.asp> Accessed March 2017.
36. Terrault NA, Zeuzem S, Di Bisceglie AM, et al. Treatment Outcomes with 8, 12 and 24 week regimens of Ledipasvir/Sofosbuvir for the treatment of hepatitis C infection: analysis of a multicenter prospective, observational study. *Hepatology.* 2015;62(Suppl 1):256A.

37. Lai JB, Witt MA, Pauly MP, et al. Eight- or 12-week treatment of hepatitis C with ledipasvir/sofosbuvir: real-world experience in a large integrated health system. *Drugs*. 2017;77:313-318.
38. Ingiliz P, Christensen S, Kimhofer T, et al. Sofosbuvir and ledipasvir for 8 weeks for the treatment of chronic hepatitis C virus (HCV) infection in HCV-monoinfected and HIV-HCV-coinfected individuals: results from the German hepatitis C cohort (GECCO-01). *Clin Infect Dis*. 2016;63:1320-1324.

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