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Article type : Original Scientific Paper

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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Keywords: hepatitis c, liver disease, cirrhosis, sofosbuvir, ledpasvir
Short title: 8 weeks vs.12 weeks for HCV

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Abbreviations: HCV, hepatitis C virus; LDV, ledipasvir; SOF, sofosbuvir; SVR, sustained virological response; DAA, direct acting antivirals; RBV, ribavirin; AASLD, American association for study of liver disease; IDSA, Infectious disease society of America; EASL. European association for study of the liver; HIV,

human immunodeficiency virus; HBV, hepatitis B virus; AA, African Americans; VA, Veterans Affairs; IL, interleukin.

Disclosures: Dr. Curry reports receiving research support from Gilead Sciences Inc. and Conatus, and consulting, advisory board/data safety monitoring board membership from Gilead Sciences Inc., Bristol Myers Squibb, AbbVie and Trio Health. Dr. Tapper has no conflict of interest. Dr. Bacon reports receiving research support from Merck, Gilead Sciences Inc., Bristol Myers Squibb, and AbbVie and consulting, speakers bureau and advisory board/data safety monitoring board membership from Merck, Gilead Sciences Inc., Bristol Myers Squibb, ISIS Pharmaceuticals, AbbVie, Valeant Pharmaceuticals, Trio Health and Janssen Pharmaceuticals; Dr. Dieterich reports receiving grant support or consulting fees from Gilead Sciences, Bristol Myers Squibb, AbbVie, Merck, Trio Health and Janssen Pharmaceuticals; Dr. Flamm reports receiving grant support form Gilead Sciences Inc, AbbVie, Bristol Myers Squibb and Merck and consulting fees from Gilead Sciences Inc, AbbVie, Bristol Myers Squibb, Merck, Trio Health and Janssen ; Ms. Guest reports receiving grant support from Gilead Sciences and AbbVie and she is an employee of Trio Health; Dr. Kowdley reports receiving grant support from AbbVie, Evidera, Galectin, Gilead Sciences, Immuron, Intercept Pharmaceuticals, Merck, NGM Biopharma, Novartis, Tobira Therapeutics and serves as a consultant or advisor to AbbVie, Enanta, Gilead Sciences, Intercept Pharmaceuticals, Merck, Trio Health and Verlyx; Ms. Lee reports receiving grant support from Gilead Sciences and AbbVie and she is an employee of Trio Health; Mr Milligan reports receiving grant support from Gilead Sciences and AbbVie and she is an employee of Trio Health Dr Tsai reports receiving advisory and speakers bureau fees from Gilead Sciences, Bristol Myers Squibb, AbbVie, Merck, Intercept Pharmaceuticals, Janssen Pharmaceuticals, Bayer, Trio Health and Valeant/Salix Pharmaceuticals and grant support from Gilead Sciences, Bristol Myers Squibb, AbbVie, Merck, Intercept Pharmaceuticals, Janssen Pharmaceuticals and Bayer and receives grant support from Gilead Sciences Inc, Bristol Myers Squibb, AbbVie, Merck, Intercept

Pharmaceuticals, Janssen Pharmaceuticals and Bayer; Dr. Younossi, receiving consulting fees from Gilead Sciences, AbbVie, Intercept Pharmaceuticals, Bristol Myers Squibb, Trio Health and GlaxoSmithKlinePLC ; Dr. Afdhal reports receiving grant support from Gilead Sciences Inc, AbbVie, and Bristol Myers Squibb and consulting/advisory board fees from Merck, Gilead Sciences Inc, Echosens, GlaxoSmithKline PLC, Ligand Pharmaceuticals, Inc, Janssen Pharmaceuticals Inc, Roivant Sciences Inc, Co-Crystal Pharma Inc, Trio Health and Shionogi, Inc and being employees of and having an equity interest in Springbank Pharmaceuticals, Allurion Technologies and Gilead Sciences Inc,.

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Funding source: Gilead Science Inc.

Abstract

Background: Treatment of genotype 1 hepatitis C virus (HCV) infection with combination direct acting antivirals is associated with very high rates of sustained virologic response (SVR). Daily combination of ledipasvir and sofosbuvir for 12 weeks is approved for the treatment of genotype 1 HCV patients, though non-cirrhotic 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: The aim of this study is to compare the SVR for 8 weeks verses 12 weeks of ledipasvir and sofosbuvir in HCV infected patients in the 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: 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.

Introduction

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 antivirals 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 utilization[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 non-cirrhotic patients investigated LDV/SOF with or without ribavirin for 8 or 12 weeks and LDV/SOF for 12 weeks. Treatment-naïve non-cirrhotic 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 randomized 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 pretreatment 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]. Lastly the English National Health Service guidance recommends 8 weeks of LDV/SOF for non-cirrhotic 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 artifact [24].

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.

Patient and Methods

Study design/Setting: The study cohort comprises treatment-naive, 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 the purpose of 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 was 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), hemoglobin, and platelet count. Assessment of HCV RNA was performed as per standard clinic practice by the treating physician and reported in standardized 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,

Statistical analysis

Associations between each individual potential predictor variable and the SVR modeled 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-values ≤ 0.25 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.

Results

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 percent 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/μ□ 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 /μL 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.

Virological outcomes

SVR12 was achieved in 787/826 (95.3%) of patients in the entire cohort. Twenty- two patients were lost to follow up, 7 patients discontinued therapy and there were 2 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 9 relapses in total, with 3 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 & Table 2). Five hundred and seventy-seven patients met the HCV viral load of < 6 million IU/ml to receive 8 weeks of LDV/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 n94.9%.

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 verses 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 study. SVR was achieved in 96% of African American patients treated with LDV/SOF. There were 9 relapses in the entire cohort and 6 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=0.29). 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% verses 95%; p=0.28), 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.

Discussion

The efficacy and better tolerability of all oral antiviral 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] [27, 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 non-cirrhotic 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 than12 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 antiviral therapy.

In this real-world experience of HCV treatment in genotype1 treatment-naïve patients, high SVR rates, comparable to what 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 centers included some patients who did not have a formal assessment of liver fibrosis and had platelet counts of < 100,000/μL 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 is similar to that recently published by Ioannou and colleagues who analyzed the real world effectiveness of DAA treatment in the Veterans Affairs National Health Care System. Twenty-seven percent 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 non-cirrhotic 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 non-randomized design that precludes rigid comparisons of the treatment duration. Additionally, treatment duration was at the discretion of the treating 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 antiviral therapy. Additionally were do not have data on concomitant use of medications such as acid-reducing medications for this study. 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/μL. In order to more stringently evaluate the efficacy of LDV/SOF for 8 verses 12 weeks in true non-cirrhotic patients, we further analyzed the SVR rates in a cohort with formal assessment of liver fibrosis, platelet count of > 100,000/μL 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 anlaysis, 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 verses 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 [32, 33].

Despite these limitations, our study has comparable rates of SVR to that observed in registration trials for LDV/SOV [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 non cirrhotic treatment naïve patients with HCV RNA< 6million IU/ml [31, 34]. The generalizability of the clinical data from ION-3 has also been demonstrated by multiple other, real-world studies comparing 8 verses 12 weeks of LDV/SOF multiple geographies and patient care settings including patients with HIV disease [17, 19, 20, 22, 35-37].

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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Figure legends

Figure 1: Distribution of all patients who were treated with LDV/SOF for 8 weeks 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.

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

verses 1b for patients treated for 8 weeks (blue) and 12 weeks (purple) (b); SVR rates patients with known fibrosis scores receiving 8 weeks (blue) verses 12 weeks (purple) (c).

Figure 3: Overall SVR rates for patients without cirrhosis treated with LDV/SOF for 8 weeks and 12 weeks (a); SVR rates for patients without cirrhosis with known genotype 1a vereses 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).

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)	0.05
Male n (%)	114 (45.2)	310 (54.0)	0.02
Race n (%)			
Black	37 (15.9)	106 (19.8)	
Hispanic/Latin	14 (6.0)	31 (5.8)	0.07
White	145 (62.2)	282 (52.7)	
Genotype 1a n (%)	172 (69.4)	380 (66.9)	0.86
Initial Viral Load IU/ML Median (10^6) (IQR)	1.33 (0.39-2.33)	2.56 (0/89-6.23)	0.0001
Academic Practice n (%)	83 (32.9)	219 (38.2)	0.16
Advanced Fibrosis n (%)	32 (12.7)	142 (24.7)	0.0001
Platelets< 100K/ml n (%)	2 (0.79)	21 (3.7)	0.02
Post Transplant N (%)	1 (0.4)	4 (0.7)	0.60
Diabetes	24 (9.8)	75 (13.3)	0.04

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

Table 2: Characteristics of all relapses

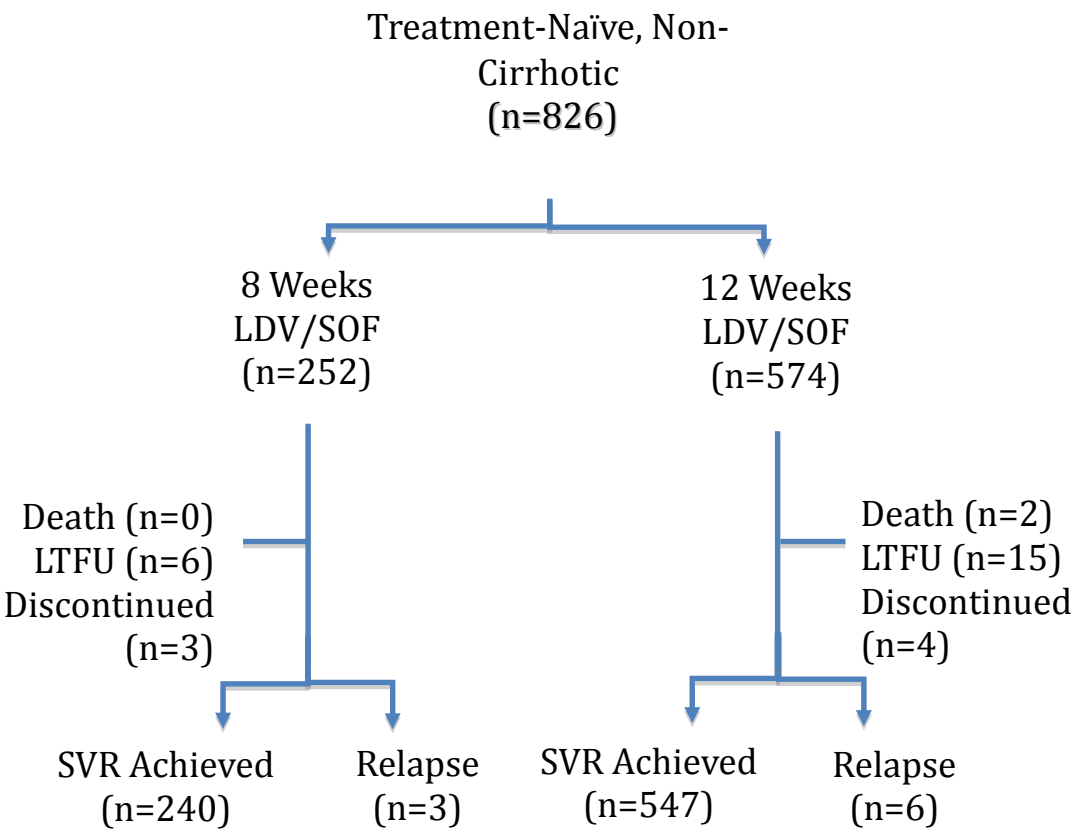
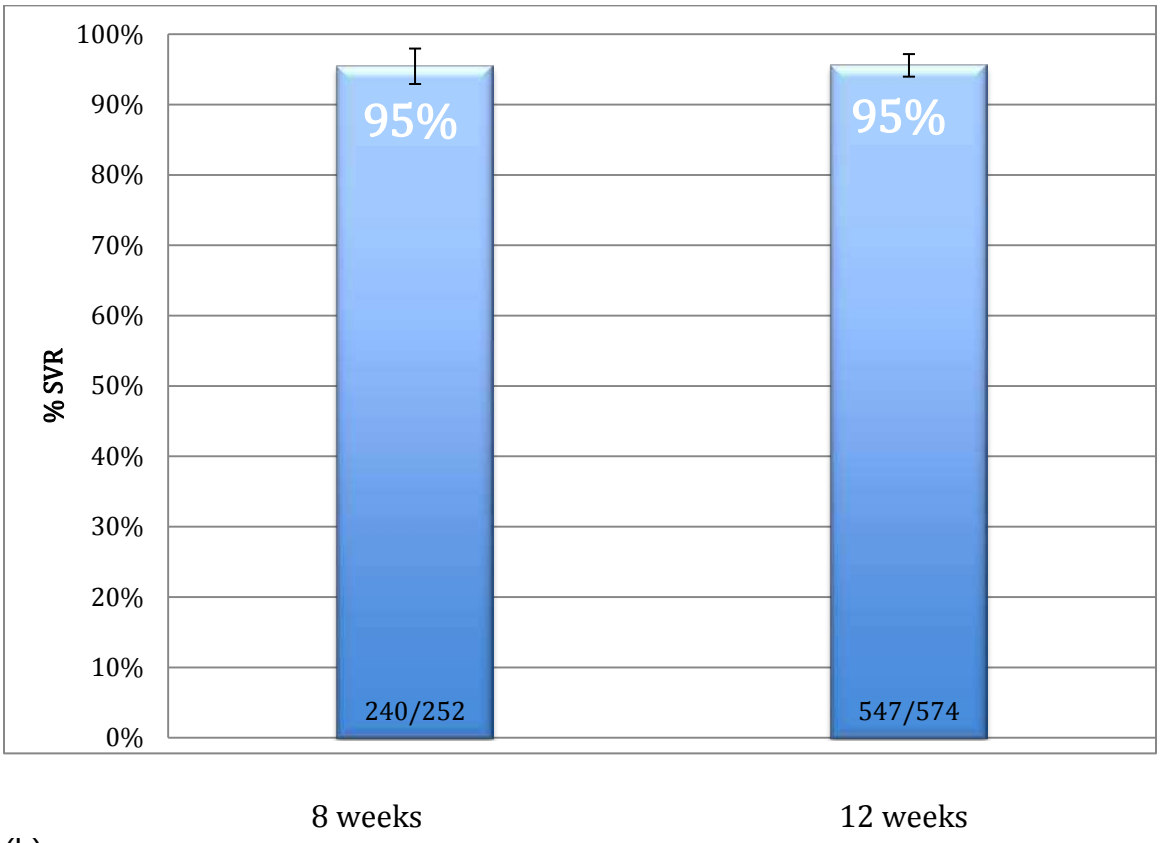


Figure 2:

(a)



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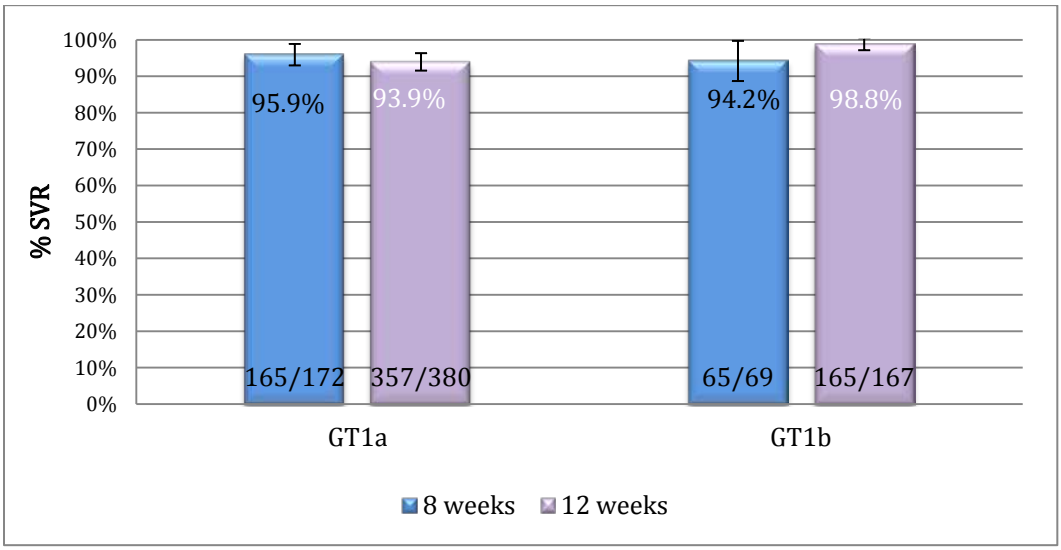

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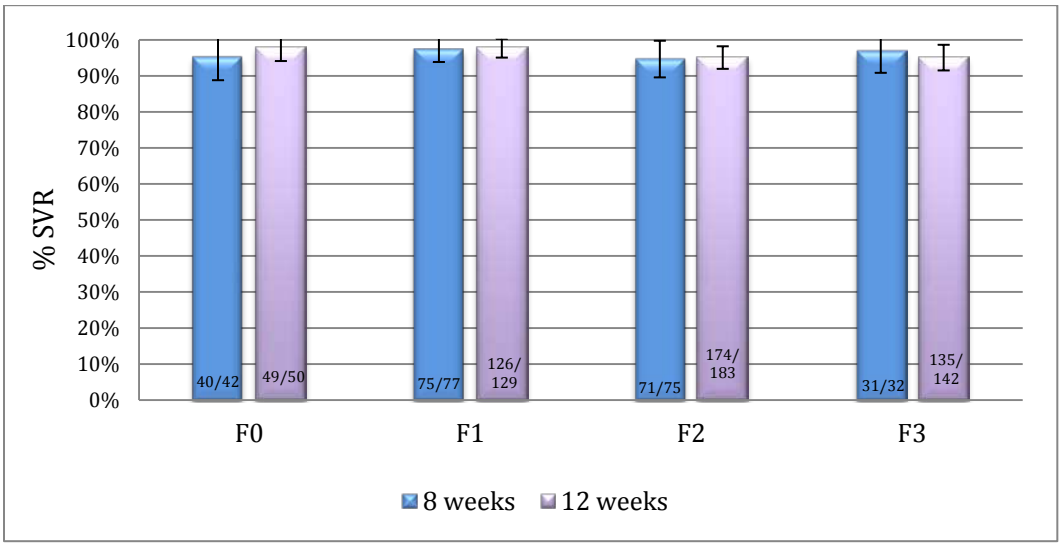
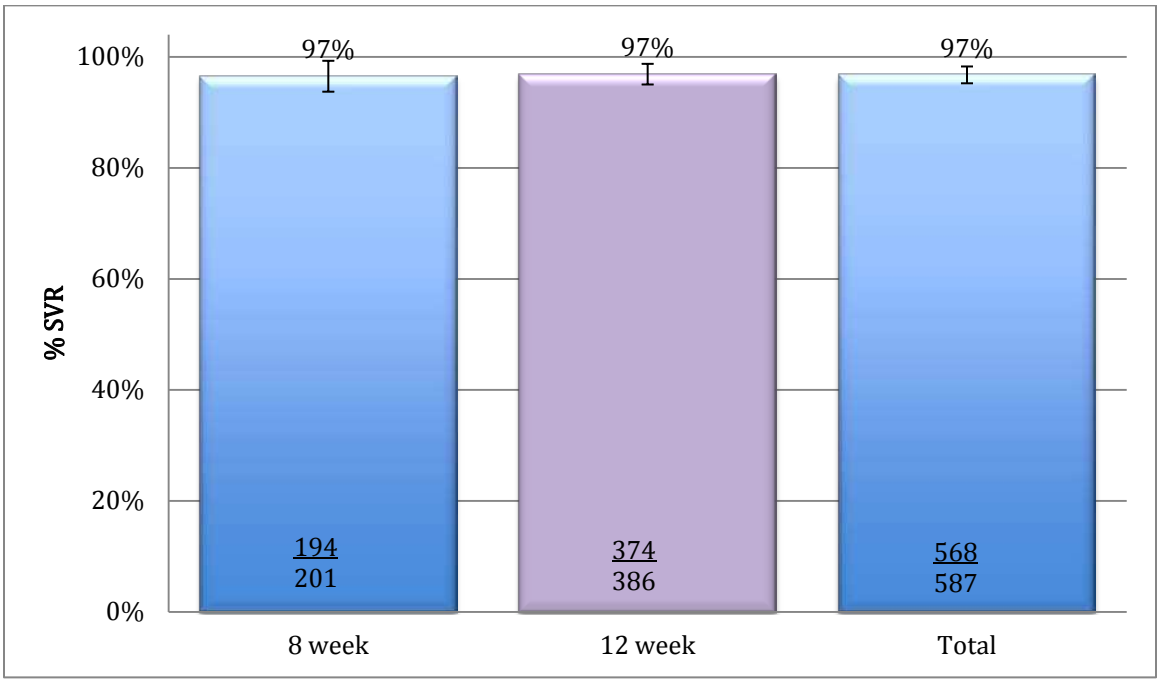
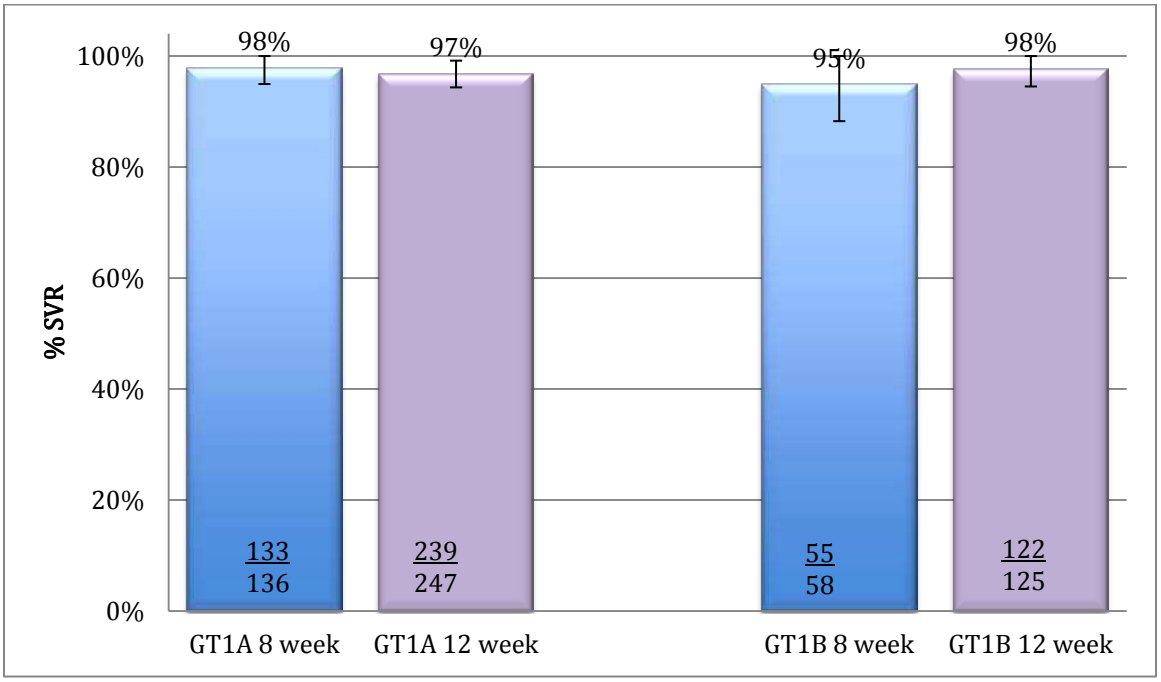


Figure 3:

(a)



(b)



(c)