

Treatment of Hepatitis C in Patients with Cirrhosis

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Module 6: [Treatment of Special Populations and Special Situations](#)

Lesson 4: [Treatment of Hepatitis C in Patients with Cirrhosis](#)

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Background

Introduction: Patients with chronic hepatitis C infection and cirrhosis have an increased risk of developing severe liver-related complications, including hepatic decompensation, hepatocellular cancer, and death. Since nearly all patients with hepatocellular carcinoma have cirrhosis prior to developing hepatocellular carcinoma, the treatment of hepatitis C in patients with hepatocellular carcinoma is included in this overall discussion of treatment of hepatitis C in patients with cirrhosis. Multiple studies have shown that successful treatment of hepatitis C in patients with compensated cirrhosis will decrease subsequent cirrhosis-related complications. Accordingly, any patient with chronic hepatitis C infection who is diagnosed with compensated cirrhosis should be considered at a high priority for hepatitis C treatment. For HCV-infected patients with decompensated cirrhosis or hepatocellular cancer, treatment of HCV may provide benefit, but the treatment plans and goals may need modifying if the patient is planning to undergo liver transplantation.

Distinguishing Compensated and Decompensated Cirrhosis: One important step in treating hepatitis C in patients with cirrhosis is to determine whether the cirrhosis is compensated or decompensated. The treatment approach and goals are divergent based on the classification of compensated versus decompensated cirrhosis. In general, patients with compensated cirrhosis only have mild hepatic impairment (Child-Turcotte-Pugh class A) ([Figure 1](#)) and do not have jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy. In contrast, the patient should be considered to have decompensated cirrhosis if they have moderate or severe liver disease (Child-Turcotte-Pugh class B or C); patients with decompensated cirrhosis have experienced one or more of the following: ascites, jaundice, variceal hemorrhage, or hepatic encephalopathy. Patients who have become asymptomatic and completely stabilized after experiencing one feature of hepatic decompensation should be evaluated on a case-by-case basis to determine whether they could be considered for treatment similar to patients with compensated cirrhosis.

Impact of Hepatitis C Treatment in Patients with Cirrhosis: Multiple studies have shown that patients with hepatitis C and cirrhosis have significant improvement in inflammatory grade and have reversal of fibrosis following hepatitis C therapy, particularly when an SVR is attained. In one very extensive study, Poynard and coworkers pooled data involving 3010 hepatitis C treatment-naïve patients who received standard interferon (with or without ribavirin) or peginterferon (with or without ribavirin). Overall, 590 (20%) of the 3010 patients had improvement in fibrosis, but among the 153 patients with cirrhosis, 75 (49%) had reversal of cirrhosis. In a separate study, among cirrhotic patients treated with standard interferon who achieved an SVR, 108 (53%) of 183 had improvement in fibrosis, whereas only 19% of patients those who did not achieve an SVR had improvement in fibrosis. The long-term impact of newer direct-acting antiviral agents on fibrosis has not been adequately studied, but achievement of SVR with these regimens would presumably translate into a similar benefit as SVR seen with older regimens. In a separate study, van der Meer and coworkers followed 530 patients with advanced fibrosis or cirrhosis in Europe and Canada; all patients had interferon-based treatment for hepatitis C and SVR was clearly associated with lower all-

cause mortality ([Figure 2](#)). Further, a meta-analysis performed by Singal et al. analyzed 26 studies and concluded that achieving an SVR was associated with substantially lower liver-related morbidity and mortality.

Impact of Hepatitis C Treatment on Risk of Hepatocellular Cancer: Several studies have shown that treatment of hepatitis C in patients with cirrhosis with achievement of SVR lowers the subsequent risk of developing hepatocellular cancer. In the large study conducted by van der Meer that examined 530 patients with chronic hepatitis C infection and advanced fibrosis, after 10 years of follow-up, the cumulative occurrence of hepatocellular cancer was 5.1% in patients who achieved an SVR compared with 21.8% in those who did not achieve an SVR. In addition, Shiratori and colleagues found that interferon therapy for 271 cirrhotic patients with chronic hepatitis C reduced the incidence of hepatocellular carcinoma, especially for those who achieved SVR with therapy ([Figure 3](#)).

Safety Concerns: Experience with peginterferon (or interferon) plus ribavirin in the treatment of patients with compensated cirrhosis has shown a higher rate of treatment-related adverse effects than with patients who do not have cirrhosis. With the use of peginterferon-based therapies, treatment of decompensated cirrhosis has been problematic due to potential severe treatment-related adverse effects, such as development of anemia, neutropenia, thrombocytopenia, severe infections, bleeding, renal insufficiency, and hepatic decompensation. Among these potential serious adverse effects, the development of hepatic decompensation is the most important and is associated with a high mortality.

Treatment of HCV in Patients with Compensated Cirrhosis

Goals of Hepatitis C Therapy in Patients with Compensated Cirrhosis: The most important immediate goal of treatment is to achieve an SVR, since subsequent liver benefit is closely linked to obtaining an SVR. The next intermediate-term priority with therapy is to decrease the patient's risk of developing hepatic decompensation. The long-term goals are to diminish the risk of developing hepatitis C-related hepatocellular cancer and death. During treatment, it is important to avoid therapy-induced hepatic decompensation; this should become easier to achieve in the future with increasing availability and use of interferon-free all-oral regimens.

Response to Therapy: The impact of cirrhosis on the response to therapy has changed over time with evolving treatment regimens. The following summary illustrates a significant improvement in SVR rates among patients with cirrhosis with regimens that include new direct-acting agents.

- **Ledipasvir-Sofosbuvir:** The ION-1 trial enrolled treatment-naive patients and subjects who received 12 or 24 weeks of therapy with ledipasvir-sofosbuvir achieved SRV12 rates greater than 95%; up to 20% of the subjects enrolled could have cirrhosis (compensated). The SVR12 rates were similar regardless of whether the patient had cirrhosis or whether they received 12 or 24 weeks of therapy ([Figure 4](#)). In the ION-2 trial, which enrolled treatment-experienced patients, those with cirrhosis had lower SVR12 rates if they received 12 weeks (86%) versus 24 weeks (100%) of therapy ([Figure 5](#)). In both the ION-1 and ION-2 studies, the addition of ribavirin did not significantly improve the SVR12 rates. In the SIRIUS trial, 155 treatment-experienced patients with HCV genotype 1 and compensated cirrhosis were randomized to receive a 12-week course of ledipasvir-sofosbuvir plus ribavirin or a 24-week course of ledipasvir-sofosbuvir; the SVR12 rate was 96% for patients in the 12-week ledipasvir-sofosbuvir plus ribavirin group and 97% in the 24-week ledipasvir-sofosbuvir group ([Figure 6](#)). Reddy and coworkers performed a post-hoc analysis of 7 clinical trials in which 513 patients with compensated cirrhosis received ledipasvir-sofosbuvir, with or without ribavirin; the analysis showed that a 12-week course of ledipasvir-sofosbuvir was effective in treatment-naive patients, but treatment-experienced patients had lower response rates with 12 versus 24 weeks; ribavirin did not significantly improve SVR rates in this study.
- **Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir plus Ribavirin:** In the TURQUOISE II trial, the combination of ombitasvir-paritaprevir-ritonavir and dasabuvir plus ribavirin was given for 12 or 24 weeks to 380 patients with Child-Turcotte-Pugh class A cirrhosis. The study included HCV treatment-naive and treatment-experienced patients. Among the patients who received 12 weeks of therapy 191 (92%) of 208 achieved an SVR12; for those who received 24 weeks, SVR12 was achieved in 165 (95.9%) of 172 patients ([Figure 7](#)). Only 2% of patients discontinued therapy due to adverse effects.
- **Peginterferon plus Ribavirin:** In several trials, investigators showed that treatment of patients with advanced fibrosis or cirrhosis (compensated) with peginterferon and ribavirin could achieve SVR, but the rates were at least 5 to 15% lower in patients with cirrhosis than in those without cirrhosis. These studies also showed higher rates of treatment-related complications, particularly hematologic adverse effects, in patients with cirrhosis than in those without cirrhosis. Many of these patients had baseline cytopenias that may have become severe as a result of treatment with peginterferon and ribavirin.
- **Peginterferon plus Ribavirin plus First-Generation Protease Inhibitor:** Available data from the phase 3 SPRINT-2 trial showed that patients with advanced fibrosis (Metavir F3 or F4) who received a regimen consisting of boceprevir plus peginterferon plus ribavirin had significantly lower SVR rates than those with Metavir F0-F2. A meta-analysis of 5 studies involving boceprevir plus peginterferon plus ribavirin in patients with cirrhosis reported lower SVR rates than in patients without cirrhosis, but rates were particularly good in patients who had undetectable HCV RNA levels at week 8 of therapy. Similarly, in the phase 3 ADVANCE, OPTIMIZE, and PROVE3 studies, patients who received telaprevir plus peginterferon plus ribavirin regimen clearly had a lower SVR rate if they had advanced fibrosis or cirrhosis than

patients without fibrosis. In the French Compassionate Use of Protease Inhibitors in Viral C Cirrhosis study (CUPIC), 674 patients with genotype 1 hepatitis C and cirrhosis were treated with a triple therapy regimen that included telaprevir or boceprevir; overall 40% of patients had a serious adverse event but SVR rates were relatively high.

- **Simeprevir plus Sofosbuvir:** In the COSMOS study, the Cohort 2 patients with chronic HCV genotype 1 and advanced fibrosis (Metavir F3 or F4) received a 12- or 24-week treatment course with simeprevir plus sofosbuvir, with or without ribavirin. For patients treated for 24 weeks, the SVR12 was 93% with ribavirin and 100% without ribavirin and for patients who received 12 weeks the SVR12 was 93%, with or without ribavirin ([Figure 8](#)). The phase 3 OPTIMIST-2 trial is in progress and is evaluating the effectiveness and safety of a 12-week course of simeprevir plus sofosbuvir in patients with genotype 1 infection and cirrhosis, including treatment-naïve and treatment-experienced patients.
- **Sofosbuvir-Based Regimens:** In the NEUTRINO trial, patients with GT 1,4,5, or 6 treated with sofosbuvir plus peginterferon plus ribavirin had high SVR rates, but the SVR rates were lower in those with cirrhosis (80%) than those without cirrhosis (92%). In the FISSION trial, patients with GT 2 or 3 had lower SVR rates when treated with sofosbuvir plus ribavirin if they had cirrhosis. Similarly, in the POSITRON trial, patients treated with sofosbuvir plus ribavirin had lower SVR rates if they had cirrhosis, but sub-analysis established the lower response was only with genotype 3. The VALENCE trial, which involved treatment of GT 2 or 3 patients with sofosbuvir and ribavirin showed that treatment-experienced patients had lower SVR rates if they had cirrhosis. In contrast, similar SVR rates were seen in treatment-naïve patients with or without cirrhosis. In the FUSION study, patients with cirrhosis treated with sofosbuvir plus ribavirin plus sofosbuvir had much better SVR rates with 16 weeks of therapy than with 12 weeks. In a phase 2 trial, 47 treatment-experienced genotype 2 or 3 patients, with or without cirrhosis, received a 12-week course of sofosbuvir plus peginterferon and ribavirin; the SVR 12 rates for the patients with cirrhosis was 93% with genotype 2 and 83% for genotype 3, which was similar to that observed in patients without cirrhosis.

Recommendation for Therapy: For patients with compensated cirrhosis (Child-Turcotte-Pugh Class A), including those with hepatocellular carcinoma, the AASLD/IDSA/IAS-USA guidance recommends using the same general treatment approach as used for patients without cirrhosis, with several key exceptions primarily related to duration of therapy or inclusion of ribavirin:

- **Treatment-naïve genotype 1a:** The duration of therapy should be extended from 12 weeks to 24 weeks in patients with compensated cirrhosis who receive either (a) daclatasvir plus sofosbuvir, with or without ribavirin, (b) ombitasvir-paritaprevir-ritonavir plus dasabuvir plus ribavirin or (c) sofosbuvir plus simeprevir, with or without ribavirin.
- **Treatment-naïve genotype 1b:** The duration of therapy should be extended from 12 weeks to 24 weeks in patients with cirrhosis who receive a) daclatasvir plus sofosbuvir, with or without ribavirin, or (b) sofosbuvir plus simeprevir.
- **Treatment-experienced genotype 1a (prior failure with peginterferon plus ribavirin):** The 12-week ledipasvir-sofosbuvir regimen should be modified in patients with compensated cirrhosis by either extending the duration of therapy to 24 weeks or by adding ribavirin to the 12-week course. The regimen ombitasvir-paritaprevir-ritonavir plus dasabuvir should include ribavirin and should be extended to 24 weeks. Use of sofosbuvir plus simeprevir (with or without ribavirin) should be extended to 24 weeks.
- **Treatment-experienced genotype 1b (prior failure with peginterferon plus ribavirin):** The 12-week ledipasvir-sofosbuvir regimen should be modified in patients with compensated cirrhosis by either extending the duration of therapy to 24 weeks or by adding ribavirin to the 12-week regimen; the extension to 24 weeks is preferred. Use of sofosbuvir plus simeprevir (with or without ribavirin) should be extended to 24 weeks.
- **Treatment-experienced genotype 1a or 1b (prior failure with sofosbuvir-containing regimen):** In patients with cirrhosis, the 12-week ledipasvir-sofosbuvir regimen should be extended to 24 weeks.
- **Treatment-experienced genotype 1a or 1b (prior failure with peginterferon,**

ribavirin, and a protease inhibitor): The 12-week ledipasvir-sofosbuvir and ribavirin regimen recommended in this setting for patients without cirrhosis should be modified in patients with compensated cirrhosis by either extending the duration of therapy to 24 weeks or by adding ribavirin to the 12-week regimen; the former strategy (extending to 24 weeks) is preferred.

- **Treatment-naive genotype 2:** The 12-week course of sofosbuvir plus ribavirin should be extended to 16 weeks in patients with cirrhosis. The 12-week course of daclatasvir plus sofosbuvir should be extended from 12 to 24 weeks in patients with cirrhosis.
- **Treatment-naive genotype 3:** The 12-week course of daclatasvir plus sofosbuvir should be extended from 12 to 24 weeks in patients with cirrhosis, and ribavirin should be added.
- **Treatment-experienced genotype 3:** The 12-week course of daclatasvir plus sofosbuvir should be extended from 12 to 24 weeks in patients with cirrhosis, and ribavirin should be added.

Treatment of HCV in Patients Awaiting Liver Transplantation

Goals of Hepatitis C Therapy in Patients Awaiting Liver Transplantation: All patients with detectable HCV RNA levels at the time of liver transplantation will infect the transplanted liver with hepatitis C virus. Further, the course of liver disease progression is accelerated in patients who have post-transplantation hepatitis C (when compared with patients who undergo liver transplant for other reasons). Accordingly, the immediate treatment goal in patients awaiting liver transplantation is to suppress hepatitis C RNA to an undetectable level, ideally for at least 30 days prior to transplant. The intermediate goal is to prevent the transplanted liver from becoming infected with hepatitis C virus. Suppression of hepatitis C RNA levels for at least 30 days prior to transplant markedly reduces the risk of the transplanted liver becoming infected with hepatitis C. The long-term goal is to have a successful liver transplantation, a more likely goal to achieve if the transplanted liver does not get infected with hepatitis C.

Treatment Data: The impact of cirrhosis on the response to therapy has changed over time with evolving treatment regimens. The following summary illustrates a significant improvement in SVR rates among patients with cirrhosis with regimens that include new direct-acting agents.

- **Peginterferon plus Ribavirin:** In a multicenter trial in the United States, Everson and coworkers randomized pre-transplant patients with hepatitis C to receive peginterferon plus ribavirin versus control. Their findings suggested peginterferon and ribavirin prevented post-transplant recurrence of HCV in selected patients, with greatest efficacy seen in those who received at least 16 weeks of therapy.
- **Peginterferon plus Ribavirin plus First-Generation Protease Inhibitor:** No major studies have been published that have examined the impact of these regimens on post-transplantation graft infection when given to pre-transplant patients.
- **Sofosbuvir plus Ribavirin:** In an open label, phase 2 trial (Study 2025), Curry et al. reported on 61 patients with chronic HCV awaiting liver transplantation who received sofosbuvir 400 mg once daily plus weight-based ribavirin 1000 to 1200 mg once daily for up to 48 weeks; the treatment was discontinued on the day of transplantation. Patients enrolled in the study had hepatocellular carcinoma, but well-compensated liver disease (Child-Turcotte-Pugh score of 7 or less). Overall, 72% of the patients had GT1 infection. Among the patients who underwent transplantation, 43 (93%) of 46 had undetectable HCV RNA level at the time of transplantation and 30 (70%) of the 43 patients with an undetectable HCV RNA prior to transplant remained undetectable 12 weeks post-transplantation ([Figure 9](#)). Patients with longer periods of undetectable HCV RNA prior to transplantation had better post-transplantation SVR rates, with only one HCV recurrence among patients with undetectable HCV RNA levels for 30 days or more.

Recommendation for Therapy: Many patients awaiting liver transplantation have decompensated cirrhosis (see the recommendations in the section below on Guidance for the Treatment of Patients with Decompensated Cirrhosis). The European Association for the Study of Liver Disease (EASL) recommendations state that treatment of hepatitis C in patients awaiting liver transplantation is indicated because treatment prevents graft infection (if HCV RNA has been undetectable for at least 30 days prior to transplantation). These guidelines recommend that patients with Child-Turcotte-Pugh class A preferably receive sofosbuvir plus weight-based ribavirin until liver transplantation; transplantation with Child-Turcotte-Pugh class A is an uncommon scenario, but could occur in a patient with hepatocellular carcinoma requiring transplantation. For patients with decompensated cirrhosis awaiting transplantation, the EASL guidelines recommend using sofosbuvir plus ribavirin until transplant, but with close monitoring at a center that has experience managing these patients.

Treatment of HCV in Patients with Decompensated Cirrhosis

Goals of Hepatitis C Therapy in Patients with Decompensated Cirrhosis: Patients are considered to have decompensated cirrhosis if they develop any of the following complications: jaundice, variceal bleeding, ascites or encephalopathy. The treatment of patients with decompensated cirrhosis (Child-Turcotte-Pugh class B or C) is extremely complex since most of these patients will require liver transplantation for long-term survival. The immediate treatment goal for patients with decompensated cirrhosis differs based on whether the patient is a candidate for liver transplantation. For patients who are not a candidate for transplantation, the short-term goal of therapy is to achieve an SVR, with the hope that some degree of liver fibrosis will reverse as a result of therapy and the patient could stabilize or improve their clinical condition. For HCV-infected patients who are candidates for liver transplantation, the short-term or intermediate goal of HCV therapy is to completely suppress HCV RNA prior to and at the time of the liver transplantation. The rationale for this goal is that patients with detectable HCV at the time of liver transplantation will uniformly infect their new liver with HCV, which significantly reduces the life of the liver graft. Pre-transplantation treatment of HCV should be part of a larger plan to prevent reinfection of the new liver with HCV and thus improve post-transplantation outcomes.

Response to Therapy: Limited data exist for hepatitis C treatment in patients with decompensated cirrhosis, primarily because of concerns related to treatment-related toxicity.

- **Daclatasvir-Based Regimens:** In unpublished trials, daclatasvir has been used with sofosbuvir and low initial dose ribavirin to successfully treat patients with genotype 1 HCV and advanced cirrhosis; the SVR rates have been higher with genotype 1b than 1a. Similarly, SRV12 rates were higher with Child-Turcotte-Pugh class B than with class C.
- **Interferon:** In an early trial reported by Crippin and coworkers, investigators attempted to treat 15 patients with decompensated cirrhosis with low-dose interferon with or without ribavirin, but none achieved an SVR and most of the patients had serious adverse events. In a second study conducted by Thomas and colleagues, 20 patients received 5 million units of interferon daily while awaiting liver transplantation; the treatment duration was for a mean of 14 months and 4 of the patients had no recurrence of HCV post transplantation. Forns and coworkers treated 30 patients, including 13 with decompensated cirrhosis, with interferon plus ribavirin for 12 weeks and 20% achieved an SVR. In a large trial conducted by Everson and colleagues, 119 patients with advanced liver disease (most with decompensated cirrhosis) received low-dose accelerating regimens of interferon (5 patients received peginterferon plus ribavirin); the overall SVR rate was 24%, including 13% with genotype 1 and 50% with genotype 2 or 3.
- **Peginterferon plus Ribavirin:** In a relatively large trial conducted by Iacobellis and colleagues, 66 patients with decompensated cirrhosis received peginterferon plus ribavirin for 6 months and 20% of the patients achieved an SVR, including 7% with genotype 1 and 44% with genotype 2 or 3.
- **Peginterferon plus Ribavirin plus First Generation Protease Inhibitor:** In one study, investigators examine the risks and benefits of treatment with peginterferon alfa and ribavirin plus either boceprevir or telaprevir in patients with cirrhosis, including patients with compensated and decompensated cirrhosis. In this setting, patients with decompensated cirrhosis has a significantly lower SVR12 rate (35%) than patients with compensated cirrhosis (54%). In addition, patients with decompensated cirrhosis had higher rates of adverse effects than those with compensated cirrhosis.
- **Sofosbuvir-Based Regimens:** In an open-label, nonrandomized, phase 2 trial, Afdhal and coworkers treated 50 patients with cirrhosis, portal hypertension and documented gastrointestinal varices with sofosbuvir 400 mg once daily plus weight-based ribavirin 1000 to 1200 mg once daily for 48 weeks; in the study, 25 of the patients were observed during the first 24 weeks of the study and then received therapy. Preliminary results at 24 weeks showed patients tolerated this regimen well and virologic suppression was achieved in 7 (100%) of 7 patients with Child-Turcotte-Pugh class A and in 14 (93%) of 15 patients with

Child-Turcotte-Pugh class B. Although the number of patients were small and only preliminary results are available, treatment with sofosbuvir plus ribavirin, when compared with the observation group, was associated with decreases in necroinflammation, improvement with albumin and platelet count, and resolution of ascites and encephalopathy.

- **Ledipasvir-Sofosbuvir plus Ribavirin:** In Cohort A of the phase 2, SOLAR-1 study, investigators prospectively enrolled 108 patients with hepatitis C genotype 1 or 4 infection and decompensated liver disease (Child-Turcotte-Pugh class B or C). A total of 108 patients were randomized to receive either a 12-week or 24-week course of ledipasvir-sofosbuvir plus ribavirin; the ribavirin dose started at 600 mg per day and then titrated up as tolerated. Overall 65% of patients were HCV treatment experienced. Patients receiving the 12-week regimen had an SVR12 rate of 87%, which was similar to the SVR12 rate of 89% in the 24-week regimen; these data excluded 6 patients who underwent liver transplantation ([Figure 10](#)). The results were similar in the Child-Turcotte-Pugh class B and C groups. Overall, the regimen of ledipasvir-sofosbuvir plus ribavirin was safe and well tolerated.
- **Simeprevir-Based Regimens:** In a multicenter cohort study, investigators at the University of California at San Francisco and Kaiser Permanente reported on their experience treating 160 patients with genotype 1 HCV-infection and cirrhosis, including patients with Child-Turcotte-Pugh class B or C liver disease. All patients in the analysis received a 12-week course of simeprevir plus sofosbuvir, with or without ribavirin. Overall 85% of patients achieved an SVR12; the SVR12 rates were higher in the Child-Turcotte-Pugh class A (91%) than the Child-Turcotte-Pugh class B/C (73%). There were significantly more treatment-related complications in the Child-Turcotte-Pugh class B/C than the Child-Turcotte-Pugh class class A.

Guidance for the Treatment of Patients with Decompensated Cirrhosis. The AASLD/IDSA addresses the this group of patients in the section [Unique Patient Populations: Patients with Decompensated Cirrhosis](#); for a summary of treatment recommendations for patients with decompensated cirrhosis see the [Summary Box](#). For patients with decompensated cirrhosis (moderate-to severe hepatitis impairment; Child-Turcotte-Pugh class B or C) very little data exist to guide therapy. The key recommendation from the AASLD/IDSA guidance is that general management and treatment of all patients with decompensated cirrhosis should be performed by a medical practitioner highly experienced in managing HCV-infected persons with decompensated cirrhosis. Accordingly, referral of these patients to an expert, ideally at a transplant center, is strongly recommended. Patients with decompensated cirrhosis include patients who may or may not be a candidate for liver transplantation and may include patients with hepatocellular carcinoma.

Summary Points

- Treatment of hepatitis C in patients with compensated cirrhosis (Child-Turcotte-Pugh class A) is a high priority because of the risk of developing severe liver-related complications.
- For patients with hepatitis C-related cirrhosis, treatment of hepatitis C is associated with significant reversal in hepatic fibrosis and reduced risk of developing hepatocellular carcinoma, especially when the patient achieves an SVR with therapy.
- For patients with hepatitis C and compensated cirrhosis, the regimen choice and duration is generally the same as the approach in patients without cirrhosis, except that in some circumstances for patients with cirrhosis the regimen duration may need to be extended and the addition of ribavirin may be indicated.
- With use of new hepatitis C therapies, patients with hepatitis C and cirrhosis can have similar SVR12 rates as those without cirrhosis, especially with adjustments in therapy duration when indicated.
- Treatment of hepatitis C in patients with liver transplantation is recommended since all patients with detectable HCV RNA levels at the time of liver transplantation will infect the transplanted liver and post-transplantation hepatitis C infection is associated with an accelerated course of liver disease.
- Treatment of hepatitis C in patients with decompensated cirrhosis is extremely challenging and sparse data exists in this patient population. Treatment of hepatitis C in these patients should be performed only by highly experienced hepatitis C medical providers.

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Figures

Figure 1 Child-Turcotte-Pugh Classification for Severity of Cirrhosis

The Child-Turcotte-Pugh (CTP) classification system utilizes two clinical parameters (encephalopathy and ascites) and three laboratory values (bilirubin, albumin, and prothrombin time). Patients are classified as class A, B, or C based on their total points.

Source: Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60:646-9.

| Child-Turcotte-Pugh Classification for Severity of Cirrhosis | | | |
|--|----------------|---|---------------------------------|
| | Points* | | |
| | 1 | 2 | 3 |
| Encephalopathy | None | Grade 1-2 (or precipitant induced) | Grade 3-4 (or chronic) |
| Ascites | None | Mild to moderate (diuretic responsive) | Severe (diuretic refractory) |
| Bilirubin (mg/dL) | < 2 | 2-3 | >3 |
| Albumin (g/dL) | > 3.5 | 2.8-3.5 | <2.8 |
| INR | <1.7 | 1.7-2.3 | >2.3 |
| *Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points) | | | |
| Class A = 5 to 6 points (least severe liver disease) | | | |
| Class B = 7 to 9 points (moderately severe liver disease) | | | |
| Class C = 10 to 15 points (most severe liver disease) | | | |

Figure 2 Clinical Events Related to Hepatitis C Treatment Response

Abbreviations: HCC = hepatocellular cancer

In this international, multicenter study, 530 patients with chronic hepatitis C and advanced fibrosis or cirrhosis were followed after receiving interferon-based therapy. Patients who achieved SVR had substantially lower hepatic-related complications and lower mortality.

Source: 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;308:2584-93.

Clinical Events According to Hepatitis C Treatment Response

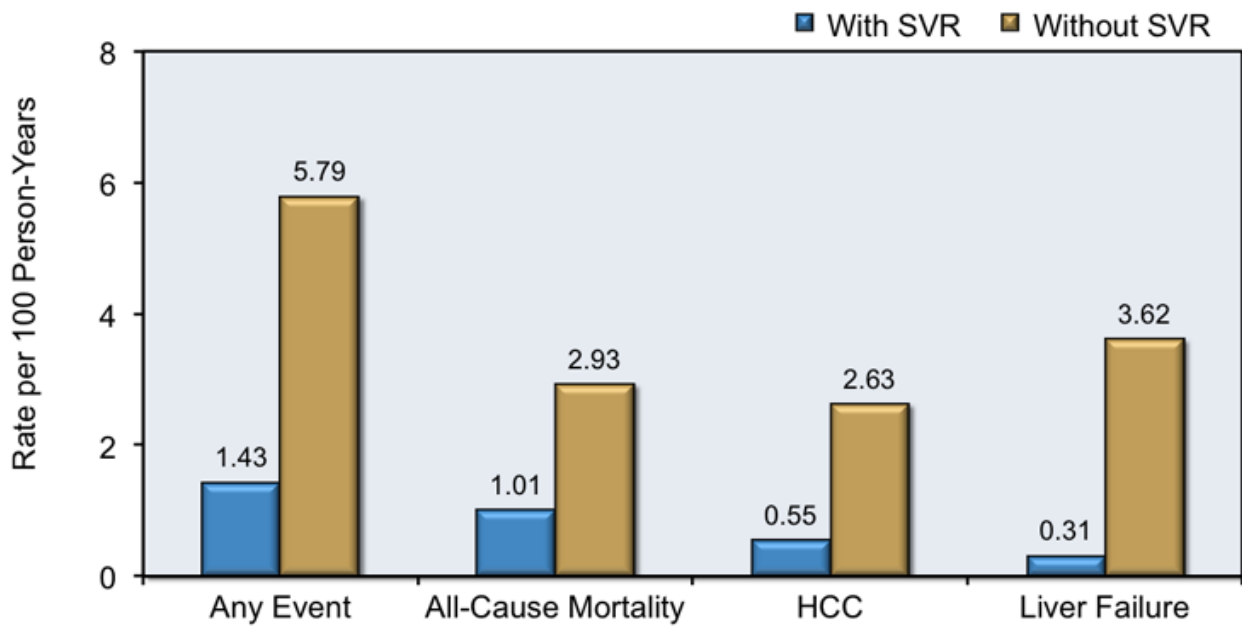


Figure 3 Incidence of HCC Related to Hepatitis C Treatment in Cirrhotic Patients

This study evaluated 345 patients with chronic hepatitis C and cirrhosis. Of the total 345 patients, 271 received treatment with an interferon-based regimen. Treated patients had lower subsequent risk of developing HCC, particularly those who achieved SVR.

Source: Shiratori Y, Ito Y, Yokosuka O, et al. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. *Ann Intern Med.* 2005;142:105-14.

Incidence of HCC Related to Interferon-Based Treatment for Cirrhotic HCV

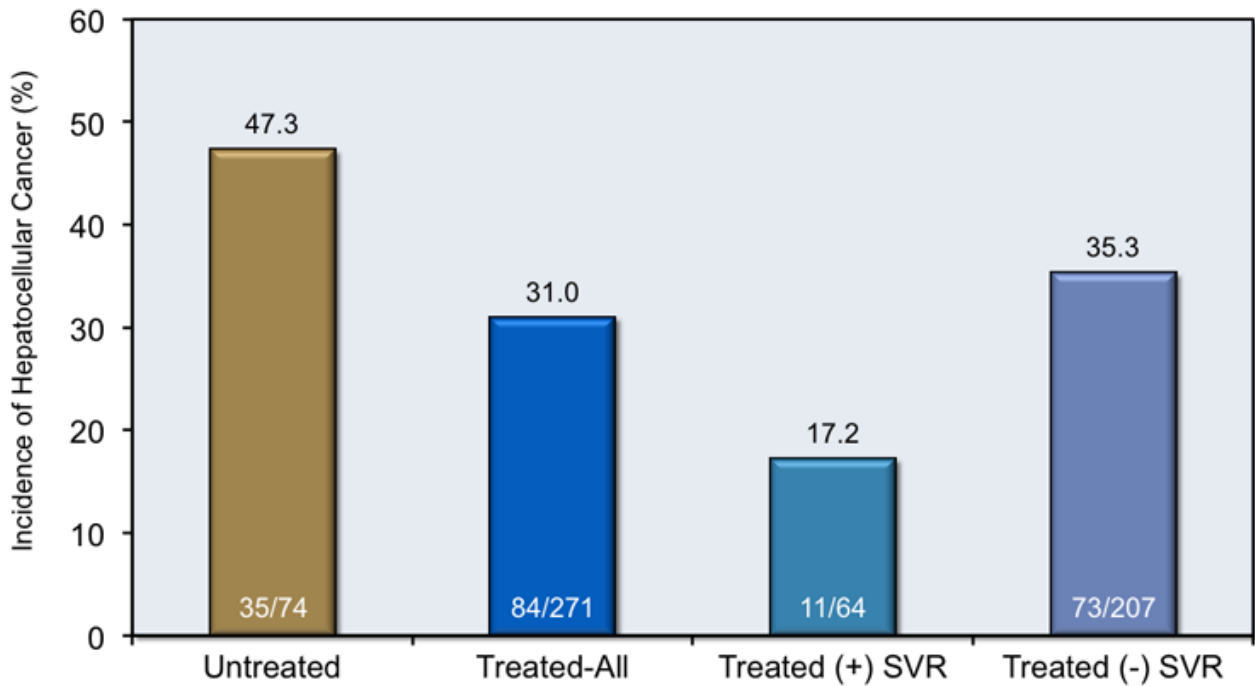


Figure 4 ION-1: Ledipasvir-Sofosbuvir in Treatment-Naive Patients with or without Cirrhosis

In the ION-1 trial, treatment-naive patients received 12 or 24 weeks of ledipasvir-sofosbuvir and all of these treatment arms had very high SVR rates, regardless of the duration of therapy or the presence of cirrhosis. The addition of ribavirin to the regimen did not improve SVR rates (data not shown).

Source: Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370:1889-98.

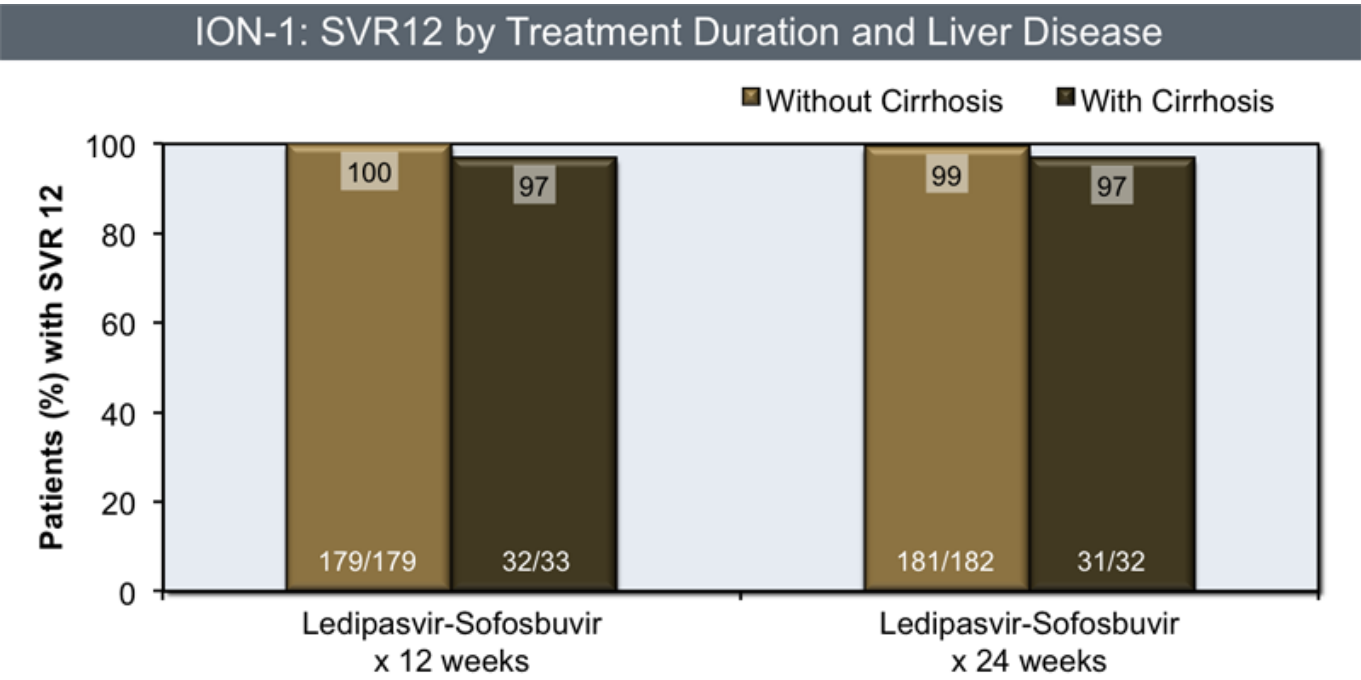


Figure 5 ION-2: Ledipasvir-Sofosbuvir in Treatment-Experienced Patients with or without Cirrhosis

In the ION-2 trial, treatment-naive patients received 12 or 24 weeks of ledipasvir-sofosbuvir; patients with cirrhosis had better SVR12 rates if they received 24 weeks of therapy. The addition of ribavirin to the regimen did not significantly improve SVR rates (data not shown).

Source: Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014;370:1483-93.

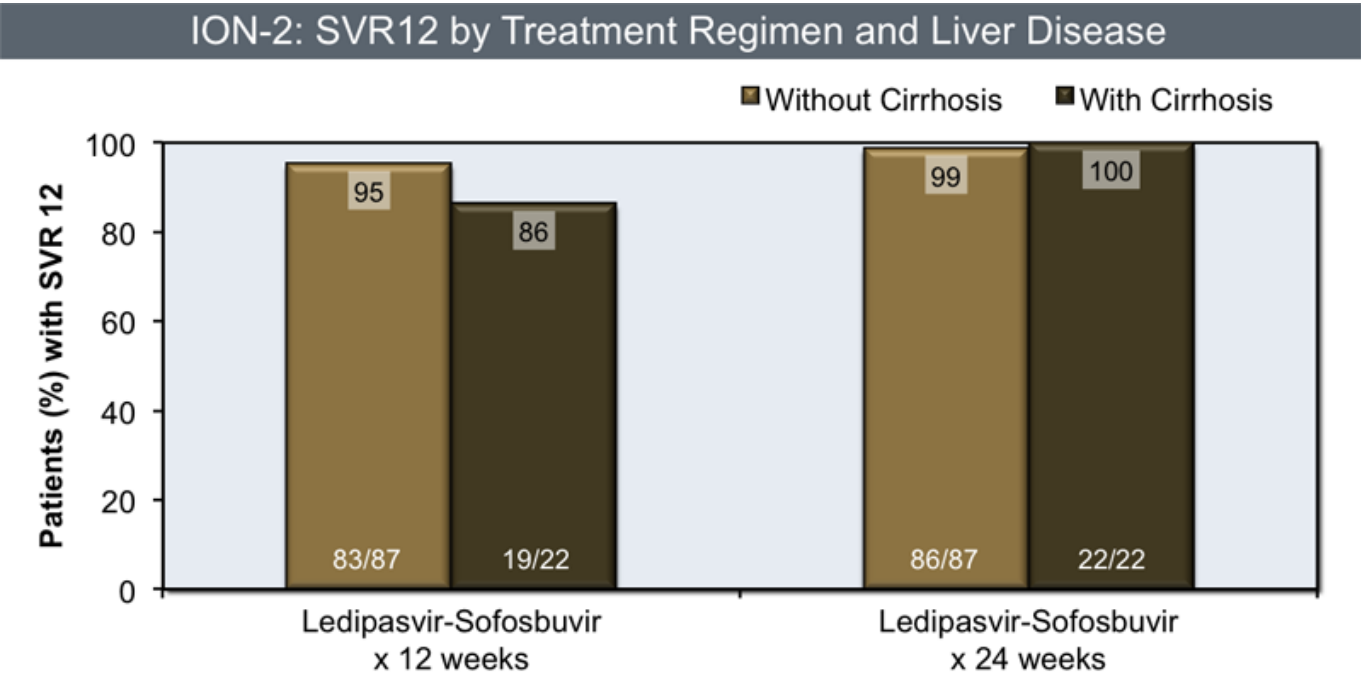


Figure 6 SIRIUS: Treatment of Patients with Cirrhosis using Ledipasvir-Sofosbuvir

Treatment-experienced patients with genotype 1 HCV and compensated cirrhosis received either a 12-week course of ledipasvir-sofosbuvir and ribavirin or a 24-week course of ledipasvir-sofosbuvir. The SVR12 rates were similar in the two groups.

Bourlière M, Bronowicki JP, de Ledinghen V, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). *Lancet Infect Dis.* 2015;15:397-404.

SIRIUS: SVR 12 by Treatment Duration and Regimen

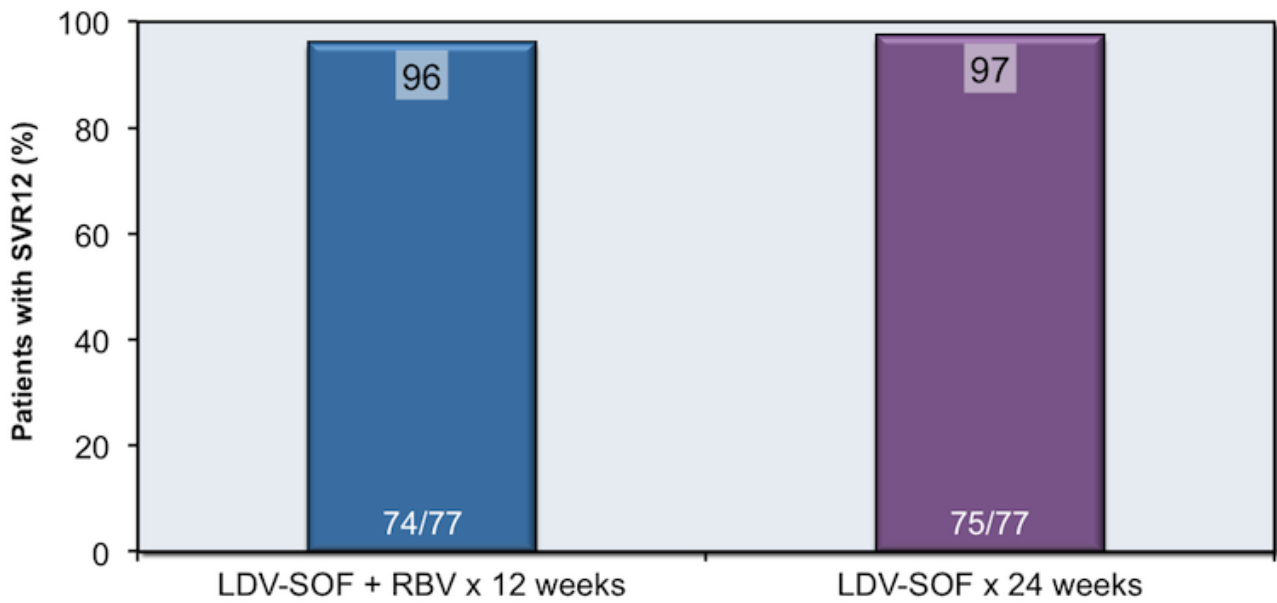


Figure 7 Treatment with Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir plus Ribavirin in Patients with Compensated Cirrhosis

This graph shows SVR12 rates with a 12- or 24-week course of Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir plus Ribavirin in Patients with Compensated Cirrhosis. Results are shown based on prior treatment and prior treatment response.

Source: Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med. 2014;370:1973-82.

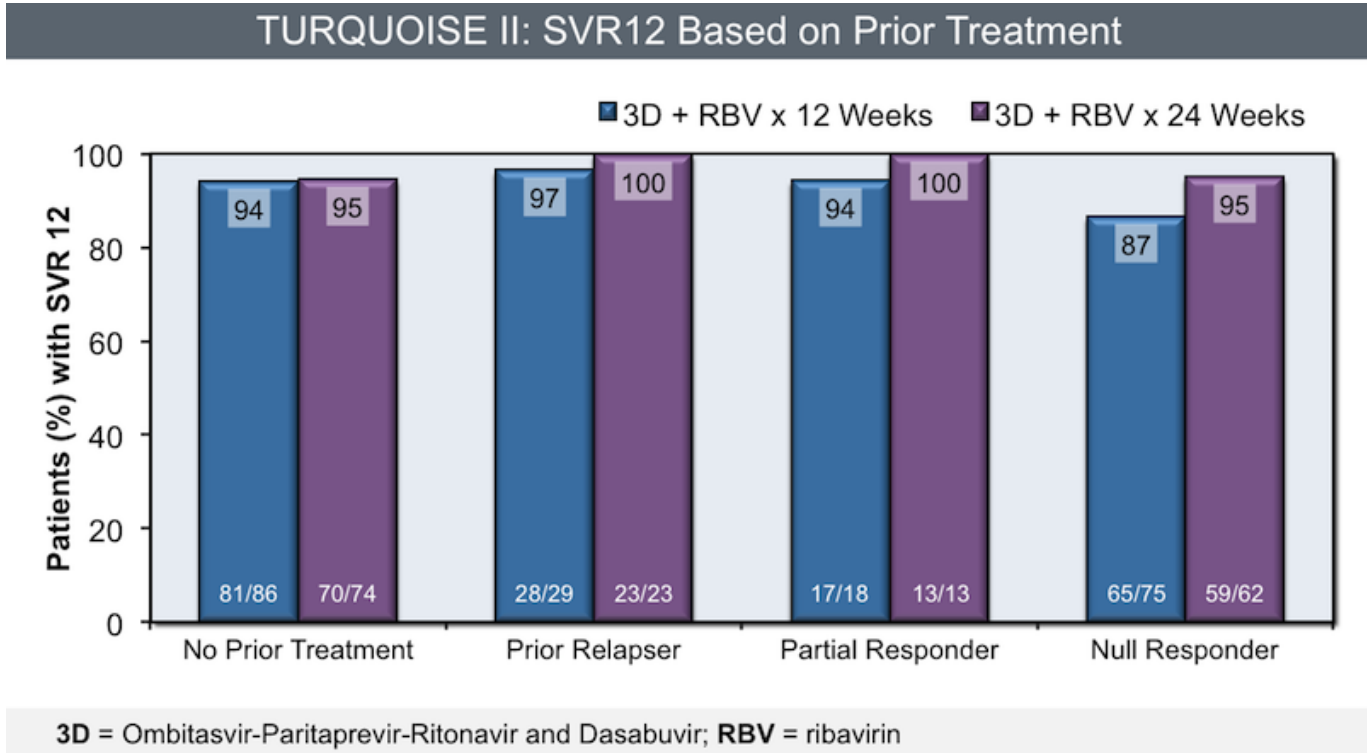


Figure 8 COSMOS: Treatment of Patients with F3-F4 Fibrosis using Sofosbuvir and Simeprevir

Patients with genotype 1 HCV in Cohort 2 (F3 or F4 fibrosis) of the COSMOS trial received treatment with a 12- or 24-week course of sofosbuvir and simeprevir, with or without ribavirin.

Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naïve patients: the COSMOS randomised study. *Lancet*. 2014;384:1756-65.

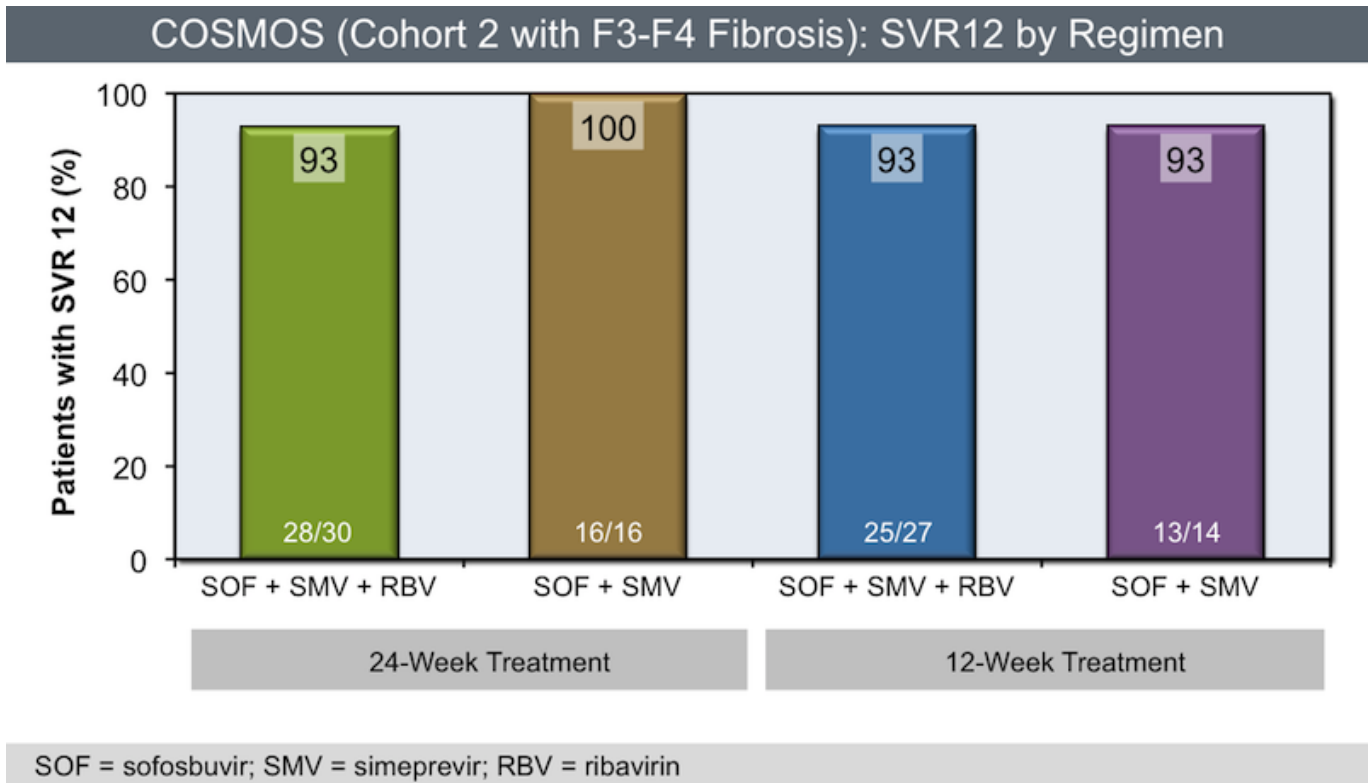


Figure 9 Treatment with Sofosbuvir and Ribavirin Prior to Liver Transplantation

Patients with hepatitis C and hepatocellular carcinoma received sofosbuvir plus ribavirin for up to 48 weeks prior to liver transplantation. Sofosbuvir plus ribavirin prevented hepatitis C recurrence in most of the treated patients, with the best success rates observed in those who had undetectable HCV RNA levels for at least 30 days prior to liver transplant.

Source: Curry MP, Forns X, Chung RT, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. *Gastroenterology*. 2015;148:100-107.

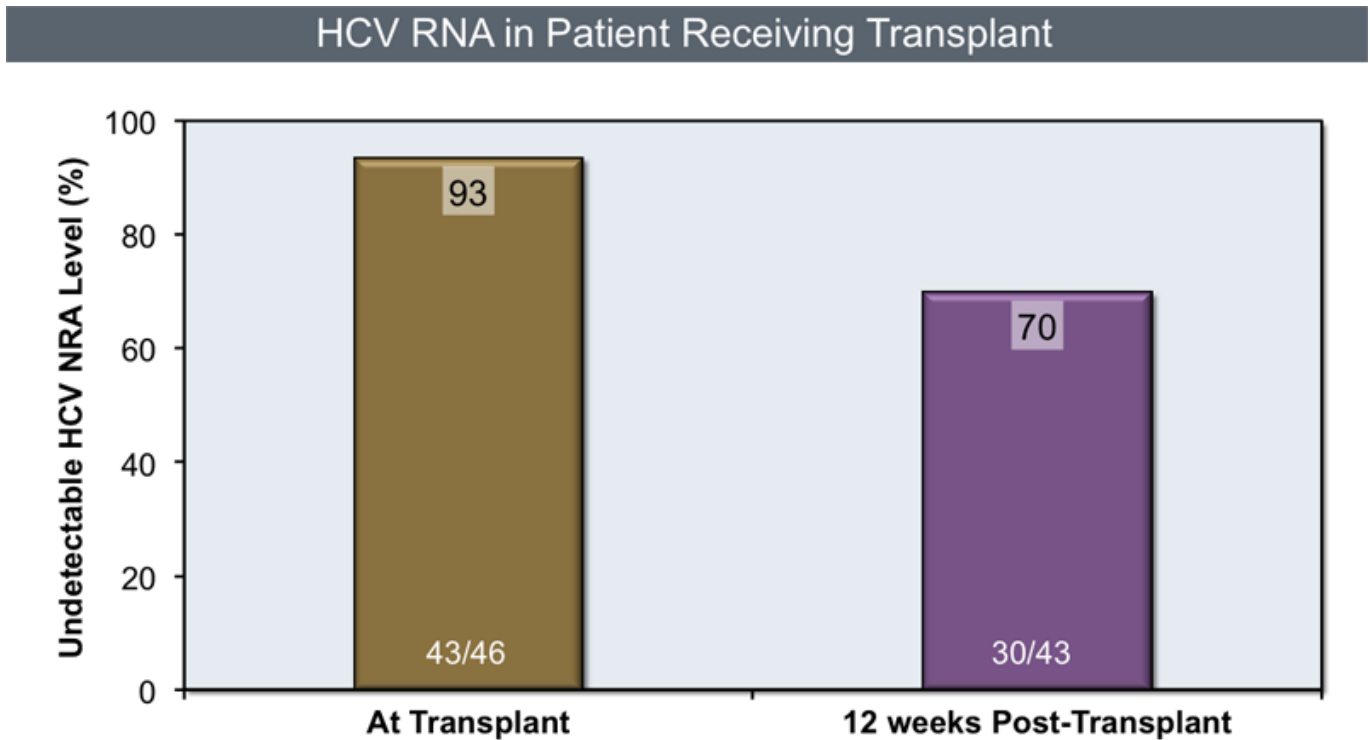
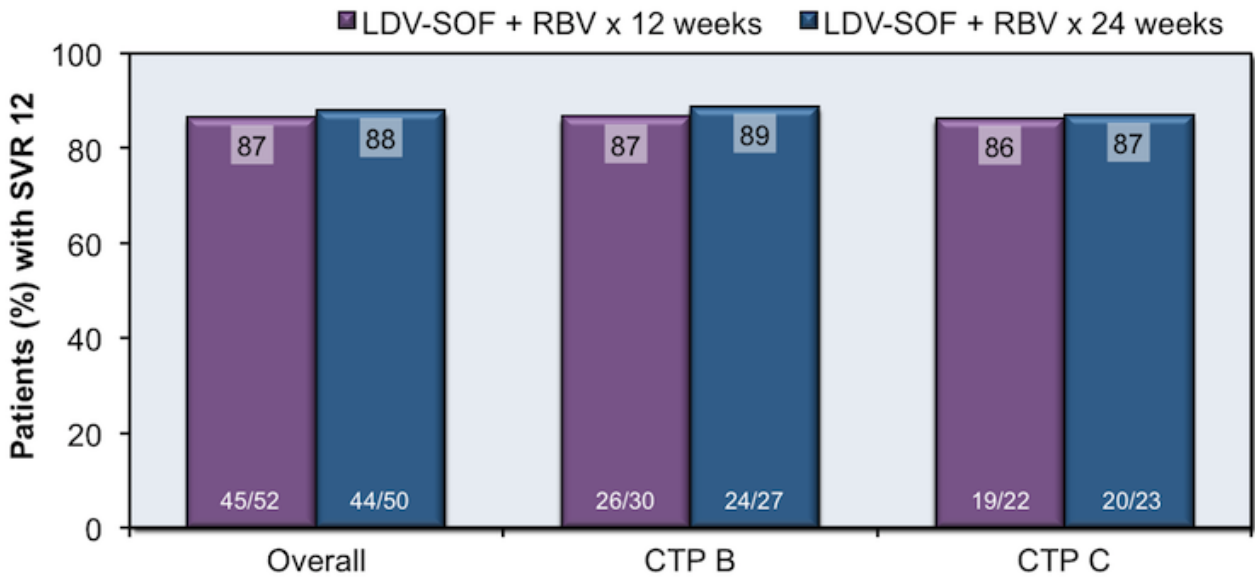


Figure 10 SOLAR-1: Treatment of Patients with Advanced Liver Disease using Ledipasvir-Sofosbuvir

In Cohort A of this trial, patients with advanced liver disease (Child-Turcotte-Pugh B or C) received either a 12- or 24-week course of ledipasvir-sofosbuvir and ribavirin.

Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. *Gastroenterology*. 2015;149:649-59.

SOLAR-1 Cohort A (Pre-Transplantation): SVR12 Results



Abbreviations: CTP=Child-Turcotte-Pugh

6 subjects excluded because received transplant while on study: (2 CTP B/24 week; 1 CTP 2/12 week; 3 CTP C/24 week)