Goals and Benefits of HCV Treatment

This is a PDF version of the following document:
Module 4: Treatment of Hepatitis C Infection
Lesson 1: Goals and Benefits of HCV Treatment

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Background

The goals for treating persons with chronic hepatitis C virus (HCV) are fourfold: (1) cure HCV, (2) improve HCV-related health outcomes and survival, (3) reduce transmission of HCV to others, and (4) eliminate HCV as a public health threat. With the current armamentarium of highly effective and safe direct-acting antiviral (DAA) medications, cure of chronic HCV is expected in more than 95% of persons receiving HCV treatment, regardless of HCV genotype, baseline HCV RNA levels, severity of hepatic fibrosis, or other patient-related factors.[1,2] The health outcome benefits following successful treatment of persons with chronic HCV infection are multiple and include reduced prevalence of hepatic fibrosis, lower risk of developing hepatic failure, decreased occurrence of hepatocellular carcinoma (HCC), improved survival, and amelioration of some extrahepatic HCV-related manifestations.[3,4,5,6] With widespread treatment of HCV, the number of persons capable of transmitting HCV would decline dramatically, which could have a major impact on HCV incidence and the overall HCV epidemic. Both the reduction in HCV incidence and the improvement in individual health outcomes are critical benchmarks for meeting the World Health Organization goal of HCV elimination by 2030, which is defined by a 90% reduction in new infections and a 65% reduction in mortality when compared to 2015.

Virologic Cure and Sustained Virologic Response

HCV Eradication and Sustained Virologic Response (SVR)

The gold standard for determining cure of HCV is the demonstration of sustained undetectable HCV RNA levels after treatment.[7] A sustained virologic response (SVR) is an undetectable HCV RNA level using a sensitive assay (typically with a lower limit of 25 IU/mL) at a defined interval after completing HCV therapy (Figure 1).[8] Although an SVR 12 weeks following treatment completion (SVR12) has been the gold standard for assessing cure, recent studies have shown a very high concordance (98% to >99%) between SVR12 and SVR4, particularly among patients without cirrhosis.[9,10] While most expert guidelines recommend SVR12 as the gold standard for assessing cure, the AASLD-IDSA HCV Guidance offers SVR4 as an acceptable option for patients without cirrhosis or prior treatment experience.[8]

Durability of SVR

Long-term follow-up of persons who achieve an SVR has shown that nearly 100% remain HCV RNA-negative years after therapy, unless they are reinfected with HCV.[11,12,13] Several large studies have shown a negligible relapse rate, between 0 and 1% at 4 or 5 years, with either interferon-based or DAA-based therapy.[14,15,16] Thus, an undetectable HCV RNA 4 or 12 weeks after antiviral therapy can be considered a virologic cure. It is important to note that persons cured of HCV can become reinfected with HCV.[15,17]

Impact of HCV Treatment on Clinical Outcomes

Impact of HCV Treatment on Hepatic Fibrosis

Individuals who achieve an SVR are more likely to have an improvement in liver inflammation and fibrosis than those who do not achieve an SVR.[18,19,20,21] The following studies highlight data related to the impact of HCV eradication on hepatic fibrosis. Although elastography can provide insights into longitudinal changes in liver fibrosis, it is important to note repeat elastography is not typically performed after HCV treatment, and it can overestimate fibrosis regression early after treatment, as rapid improvements in liver stiffness likely reflect reduced hepatic inflammation and congestion.[22]

- In a large longitudinal cohort of individuals treated with DAAs at the Egyptian Liver Research Institute and Hospital, individuals were followed for an average of 7 years after treatment.[23] Among 2,365 patients who underwent both a baseline and end-of-follow-up FibroScan, 11.9% had ≥2 stage improvement in fibrosis, 17.8% showed a 1-stage improvement, 50.5% remained unchanged, and 19.8% had fibrosis progression. When stratified by baseline fibrosis staged, fibrosis reversal (≥2 stage improvement) occurred in 48.6% of those with F3 and 27.3% of those with F4 at baseline, while fibrosis regression (1-stage improvement) occurred in 24.8% of those with F3 and 20.2% of those with F4 at baseline.[23]
- In a meta-analysis, investigators evaluated the impact of HCV treatment on liver stiffness, as measured by vibration-controlled transient elastography.[18] Individuals who achieved an SVR12 had a significantly greater decrease in liver stiffness at the end of treatment (and after treatment) compared to patients who did not achieve an SVR12 (Figure 2).[18] In addition, the decline in liver stiffness among those who achieved an SVR12 was greater with DAA treatment than with interferon-based therapy (decrease of 5.1 kPa versus decrease of 2.8 kPa).[18]
- In one study, investigators performed liver stiffness measurements in 70 patients treated with DAA therapy, among whom 95.7% achieved an SVR.[19] Treatment of HCV with DAA therapy resulted in a significant decrease in liver stiffness at the end of treatment and at 12 months post-treatment when compared with baseline measurements (Figure 3).[19]
- In a multi-center, prospective cohort study that enrolled 71 Danish adults with advanced fibrosis, investigators found that liver stiffness decreased by an average of 20% at the end of sofosbuvir-based direct-acting antiviral therapy, and by an additional 15% 1 year after treatment, a finding that was suggestive of fibrosis regression.[24]

Impact of HCV Treatment on Hepatocellular Carcinoma

- Multiple observational studies have shown a reduction in the risk of HCC occurrence after achievement of SVR with HCV therapy; in these studies, control groups consisted of persons with HCV who were treated but did not achieve an SVR.[4,25,26,27] Several of the more recent studies exclusively involved persons treated with DAA therapy who were followed longitudinally.[26,28,29]
- Although HCV eradication with HCV therapy can reduce the long-term risk of HCC, the risk of developing HCC remains substantial for persons who, prior to treatment, had cirrhosis.[29] Accordingly, individuals who meet HCC surveillance criteria prior to HCV treatment should continue to receive HCC surveillance every 6 months, even after achieving an SVR with HCV treatment.[8,29,30]
- Among persons with a history of successfully treated HCC, there are conflicting data regarding the impact of DAA therapy on the risk of HCC recurrence, with most studies reporting a reduced risk of recurrent HCC among DAA-treated and untreated persons.[31] As such, DAA-treated individuals with a history of HCC require close ongoing HCC surveillance.[30,32,33,34,35]

Impact of HCV Treatment on Extrahepatic Manifestations

Infection with HCV can cause a myriad of extrahepatic complications, including cryoglobulinemia, membranoproliferative glomerulonephritis, dermatologic disorders, insulin resistance and diabetes mellitus,

and B-cell non-Hodgkin's lymphoma.[36,37,38] There is evidence that the risk of HCV-related extrahepatic manifestations is lower after HCV clearance with DAA therapy.[39,40] Notably, in a retrospective cohort study that involved 160,875 United States veterans with chronic HCV, patients who achieved an SVR12 with interferon-based therapy had substantial reductions in HCV-related extrahepatic manifestations when compared with individuals who did not achieve an SVR with HCV treatment or were not treated at all (Figure 4).[41] In some patients, successful treatment of HCV is associated with improvement or remission of these underlying conditions.[42,43] In addition, achieving an SVR has been shown to reduce the chance of impaired fasting glucose and diabetes development by 50%, an effect that is independent of other established risk factors for diabetes, such as age and body mass index. A recent meta-analysis of 48 studies showed that an SVR reduced extrahepatic mortality by 56%, improved response to malignant B-cell lymphoproliferative therapy, and vastly improved the chances of a complete resolution of cryoglobulinemic vasculitis.[3]

Impact of HCV Treatment on Quality of Life

A subset of patients with chronic HCV can experience symptoms of functional impairment that include fatigue or reduced mental stamina.[37] Studies on the impact of SVR with HCV therapy have consistently demonstrated significant improvements in health-related quality of life. Patients who achieve SVR often report reduced fatigue, improved physical functioning, and enhanced mental health compared to those who do not achieve SVR or remain untreated.[44,45,46,47] This improvement in patient-reported outcomes has been observed in advanced HCV disease as well as in people with HCV and HIV coinfection. Furthermore, achieving an SVR with HCV treatment can improve work productivity. These results underscore the anticipated economic benefits of successful HCV treatment, with decreased work-related limitations and increased workforce participation.[48] Most of the data on the relationship between HCV treatment and quality of life have been generated from clinical trial participants. Published reports of patient experiences with SVR across a broad sociodemographic and community spectrum remain limited at this time.

Impact of HCV Treatment on Survival

In persons with chronic HCV infection, treatment with achievement of an SVR has been shown to markedly reduce the risk of death, including liver-related and non-liver-related deaths.[6,14,49,50] Studies have shown survival benefit in persons with chronic HCV (with or without advanced liver disease) who achieve SVR with DAA therapy.[51,52] The following summarizes key data related to the impact of HCV treatment on survival after achieving an SVR.

- In a meta-analysis of 35 studies that included 33,360 persons with chronic HCV infection, investigators showed a clear benefit in 5-year overall survival in persons who achieved an SVR with treatment compared with those who had not achieved an SVR.[53] All the studies analyzed involved interferon-based therapies, and some included individuals with cirrhosis or persons with HIV coinfection (Figure 5).[53]
- In an observational cohort analysis of 103,346 persons with chronic HCV (genotype 1, 2, or 3) in the Veterans Affairs Hepatitis C Clinical Case Registry, investigators examined the impact of achieving SVR with DAA treatment on mortality.[51] Among the 40,664 persons treated with a DAA regimen, 39,374 (96.8%) achieved an SVR. The mortality rate in persons who achieved an SVR was significantly lower than in those who did not achieve an SVR with treatment, after adjusting for baseline demographics, clinical characteristics, and comorbidity (Figure 6).[51] The reduction in mortality was 69.3% among those who achieved an SVR compared to persons who did not receive HCV treatment.[51]
- Two separate cohort studies of persons with HCV and successfully treated HCC have found a significantly lower overall risk of death among persons who receive DAA therapy when compared to those who do not, suggesting that selected patients with a history of HCC should receive HCV DAA treatment due to multiple treatment-related benefits, including overall improved survival.[54,55]
- Several studies evaluating contemporary trends have suggested a signal of benefit since the introduction of DAA therapy with decreased hospitalization, longer survival, and reduced liver transplantation rates in patients with advanced HCV liver disease.[56,57,58]

Population-Level Benefits of HCV Elimination

In addition to the benefits that HCV treatment provides to the individual, it has health and economic benefits at the population level. Modeling studies have shown that treatment of HCV in persons at high risk of transmitting HCV to others, particularly people who inject drugs (PWID), can lead to substantial reductions in HCV incidence and prevalence.[59,60,61,62] This strategy, which is known as treatment as prevention, has also been shown to facilitate real-world HCV microelimination efforts among key populations, including incarcerated individuals and persons with HIV.[63,64,65,66,67] In addition to preventing person-to-person transmission of HCV and facilitating population-level microelimination, HCV treatment has also been shown to be cost-effective at a population level, with substantial cost savings incurred by avoiding the costly long-term outcomes of HCV, including cirrhosis, end-stage liver disease, and hepatocellular carcinoma.[68,69,70,71] In one recent United States-based costing analysis, authors estimated that between 2013 and 2022, treatment of HCV with DAAs provided a $15 million net economic benefit to Medicaid, with $43 million in cumulative net savings to Medicaid estimated by the end of 2026.[72]

Summary Points

- There are multiple goals with HCV antiviral therapy, including (1) cure HCV, (2) improve HCV-related health outcomes and survival in all populations, (3) reduce transmission of HCV to others, and (4) eliminate HCV as a public health threat.
- An SVR is defined as an undetectable HCV RNA level at 4 or 12 weeks after stopping HCV treatment.
- An SVR is durable and indicates HCV cure.;
- Achieving an SVR following HCV treatment results in improvement of hepatic fibrosis, decreased development of HCC, improvement in survival, and reduction in extrahepatic manifestations associated with chronic HCV.
- HCV treatment is cost-effective at a population level, with substantial cost savings incurred by avoiding the costly long-term outcomes of HCV, including cirrhosis, end-stage liver disease, and hepatocellular carcinoma.

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Figures

Figure 1 (Image Series) - Sustained Virologic Response 12 (SVR 12) (Image Series) - Figure 1 (Image Series) - Sustained Virologic Response 12 (SVR 12)
Image 1A: SVR 12 After 8-Week HCV Treatment Course

This graphic shows an example of an SVR12 in a person who received 8 weeks of HCV DAA therapy. The SVR12 is shown by the undetectable HCV RNA 12 weeks after treatment was stopped.

Source: illustration by David H. Spach, MD

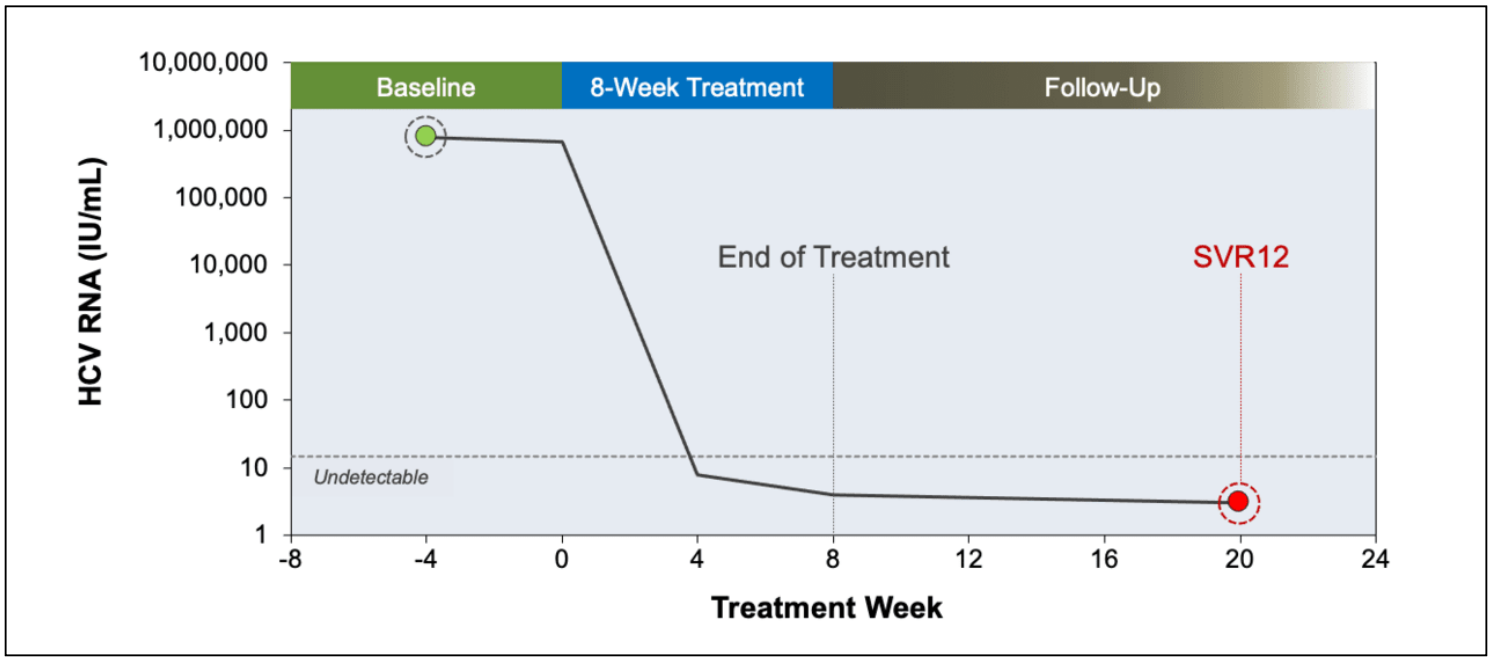


Figure 1 (Image Series) - Sustained Virologic Response 12 (SVR 12)
Image 1B: SVR 12 After 12-Week HCV Treatment Course

This graphic shows an example of an SVR12 in a person who received 12 weeks of HCV DAA therapy. The SVR12 is shown by the undetectable HCV RNA 12 weeks after treatment was stopped.

Source: illustration by David H. Spach, MD

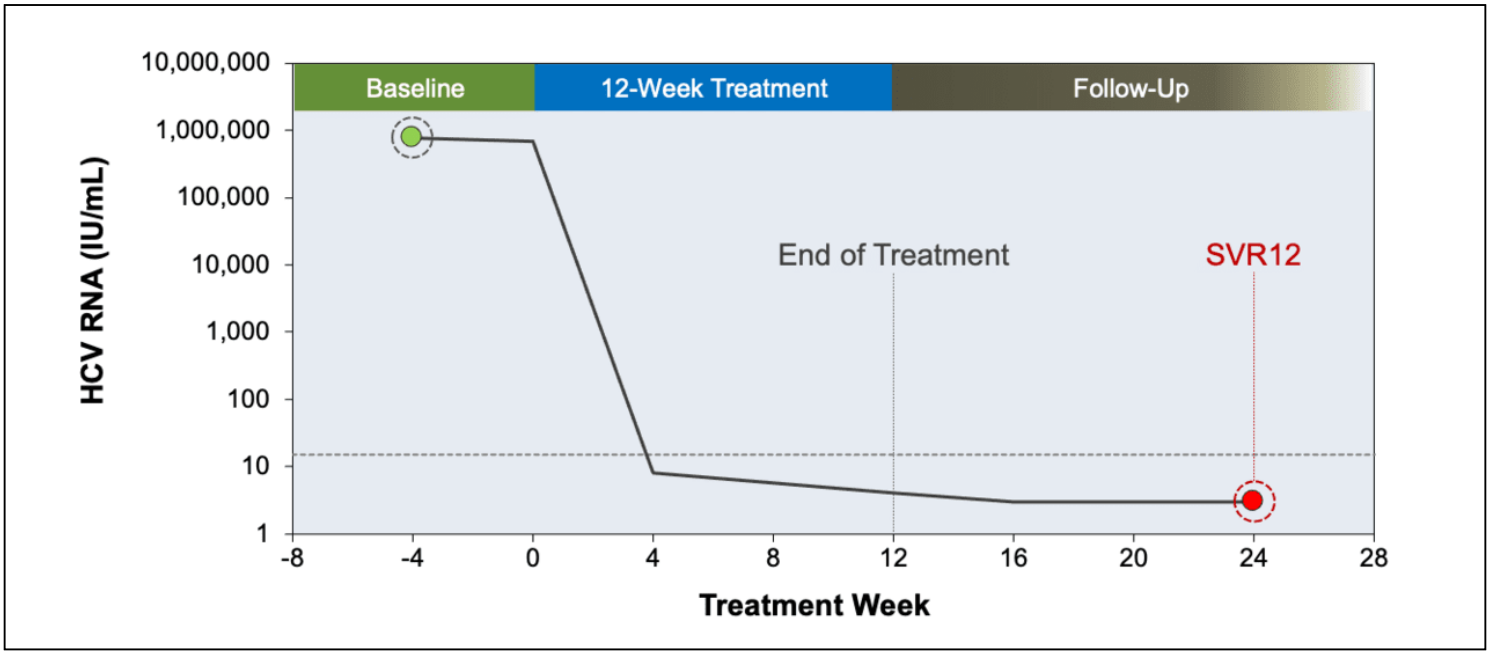


Figure 2 Liver Stiffness in Persons With or Without SVR12

This graph compares liver stiffness before and after treatment in adults who attained SVR12 versus those who did not achieve SVR12.

Source: Singh S, Facciorusso A, Loomba R, Falck-Ytter YT. Magnitude and Kinetics of Decrease in Liver Stiffness After Antiviral Therapy in Patients With Chronic Hepatitis C: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2018;16:27-38.e4.

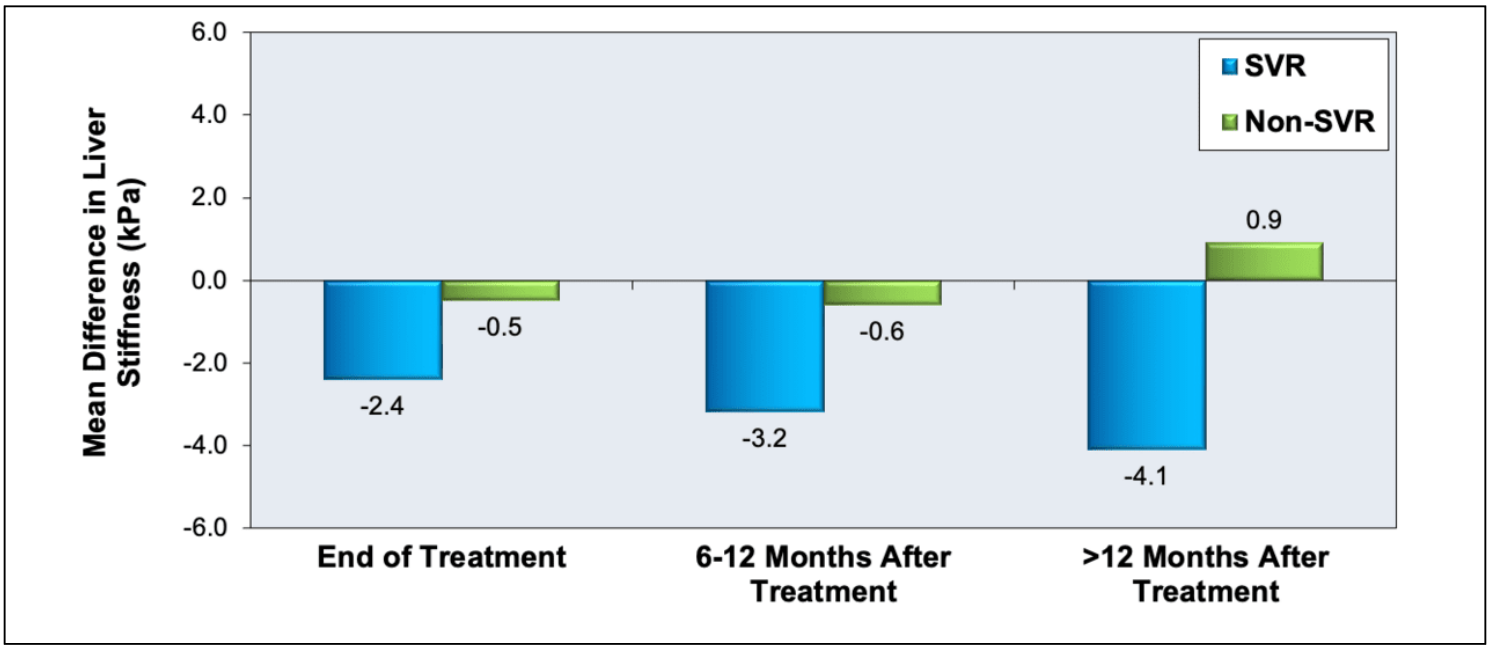


Figure 3 Median Liver Stiffness Treatments in Persons Treated with Direct-Acting Antiviral Therapy

Source: Chan J, Gogela N, Zheng H, et al. Direct-Acting Antiviral Therapy for Chronic HCV Infection Results in Liver Stiffness Regression Over 12 Months Post-treatment. Dig Dis Sci. 2018;63:486-92.

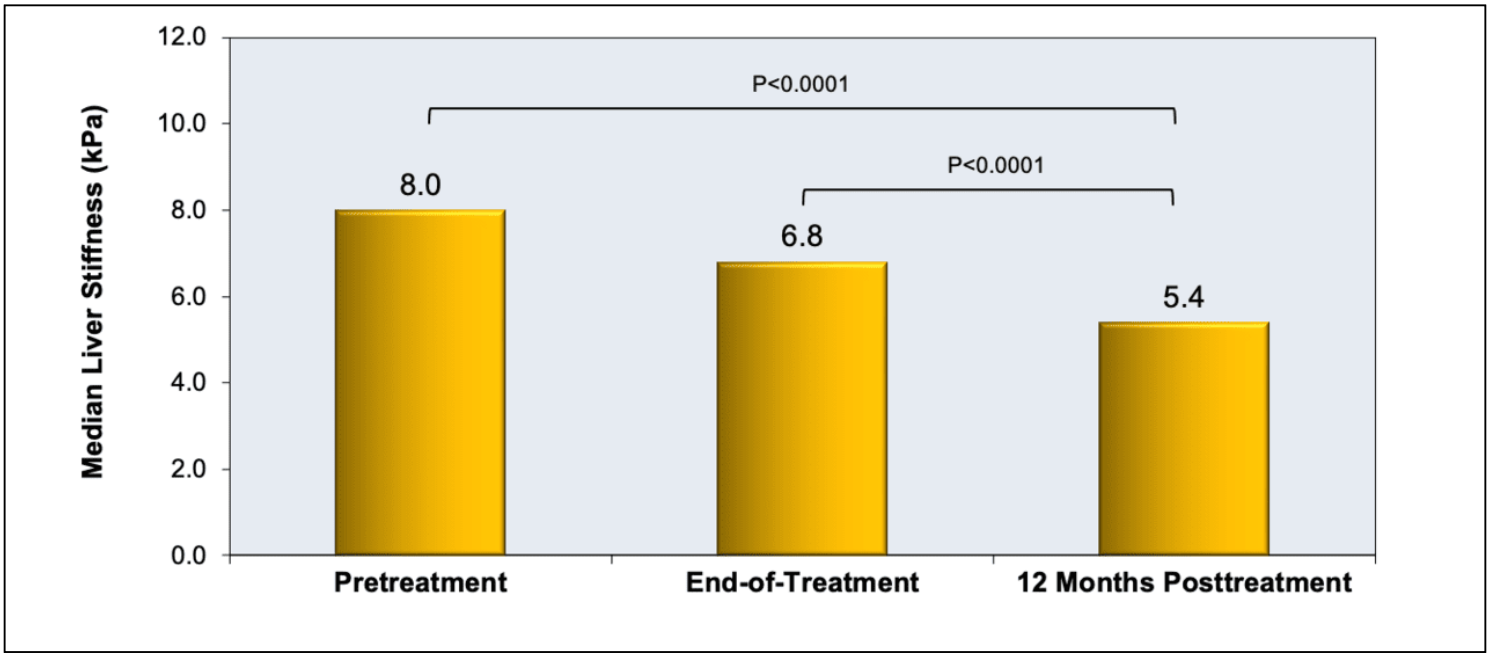


Figure 4 HCV Treatment and Outcome of Extrahepatic Manifestations

Source: Mahale P, Engels EA, Li R, et al. The effect of sustained virological response on the risk of extrahepatic manifestations of hepatitis C virus infection. Gut. 2018;67:553-61.

Impact of SVR on HCV-Related Extrahepatic Conditions

Outcomes	No Treatment	Treatment without SVR	Treatment with SVR
	Events per 1,000 Patient-Years		
Mixed cryoglobulinemia	0.72	0.52	0.33
Glomerulonephritis	2.83	1.62	1.09
Porphyria cutanea tarda	0.52	0.37	0.16
Lichen planus	0.68	0.71	0.56
Non-Hodgkin's lymphoma	0.91	0.55	0.43
Diabetes mellitus	21.6	17.0	13.9
Coronary heart disease	1.01	0.58	0.75
Stroke	9.14	4.64	5.10

Figure 5 5-Year Mortality Rate Following HCV Treatment Based on SVR Response

This graphic is based on data from 31 studies published from 2000 to 2014 that included 33,360 participants. The 5-year mortality rates shown are based on whether the patient achieved an SVR.

Source: Simmons B, Saleem J, Heath K, Cooke GS, Hill A. Long-Term Treatment Outcomes of Patients Infected With Hepatitis C Virus: A Systematic Review and Meta-analysis of the Survival Benefit of Achieving a Sustained Virological Response. Clin Infect Dis. 2015;61:730-40.

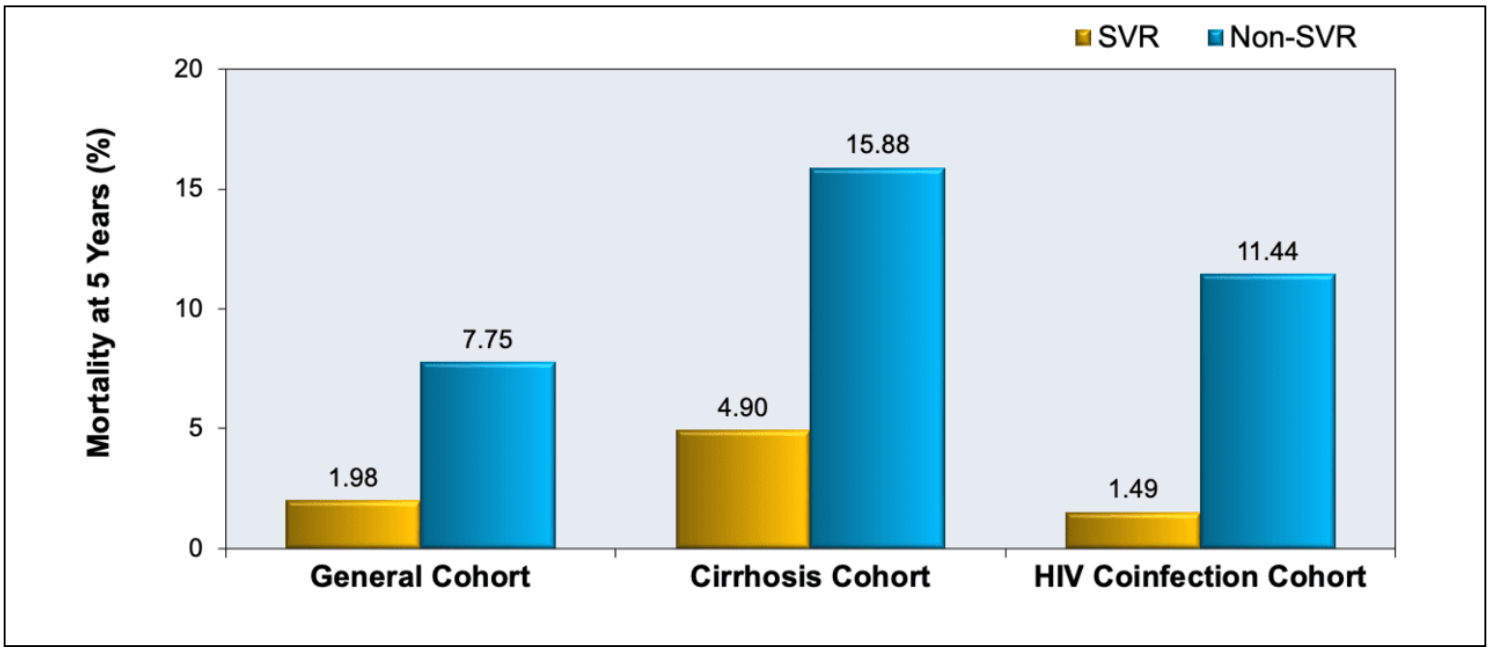
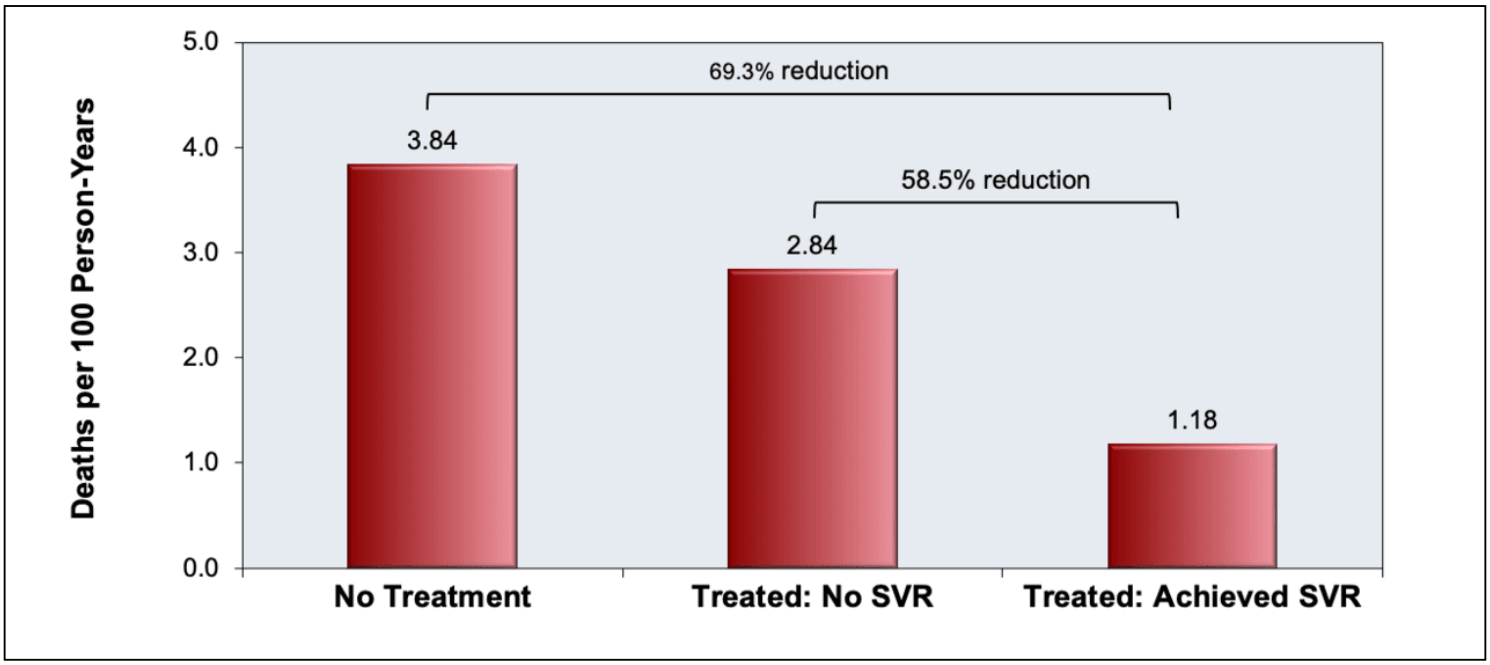


Figure 6 Impact of SVR on Mortality Rates with DAA Therapy

Source: Backus LI, Belperio PS, Shahoumian TA, Mole LA. Direct-acting antiviral sustained virologic response: Impact on mortality in patients without advanced liver disease. Hepatology. 2018;68:827-38.