

Goals and Benefits with HCV Treatment

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Module 4: [Evaluation and Preparation for Hepatitis C Treatment](#)

Lesson 1: [Goals and Benefits with HCV Treatment](#)

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Background

The goals for treating persons with chronic hepatitis C virus (HCV) are threefold: (1) eradicate HCV, (2) improve HCV-related health outcomes and survival in all populations, and (3) reduce transmission of HCV to others. For clinicians, the primary and immediate goal is to treat the individual with a regimen that has a very high likelihood of curing the individual of their HCV infection. 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, race, HIV status, or severity of hepatic fibrosis.[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.

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 least 12 weeks after completing HCV therapy ([Figure 1](#)).[\[8\]](#) In the current era, most expert guidelines recommend measuring an HCV RNA level 12 weeks after therapy to evaluate for SVR; individuals with an undetectable HCV RNA level at 12-week posttreatment, also known as an SVR12, are considered to have achieved a virologic cure.[\[7\]](#) Among persons who achieve an SVR12 with direct-acting antiviral (DAA) HCV therapy, greater than 99% go on to achieve a durable response and ongoing absence of detectable viremia.[\[9,10\]](#) Trial outcomes with SVR time frames of shorter duration (SVR8 and SVR4) have been presented in an effort to expedite conclusions from these trials, but SVR4 and SVR8 are not the standard time frame used in clinical practice to determine cure.

Durability of SVR

Long-term follow-up of persons who achieve an SVR12 or SVR24 has shown that nearly 100% remain HCV RNA negative years after therapy.[\[13,14,15\]](#) Several large studies have shown a minimal relapse rate, between 0 to 1% at 5 years.[\[16,17\]](#) Thus, an undetectable HCV RNA 12 or 24 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.[\[17,19\]](#)

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.[20,21,22,23] The following studies highlight data related to the impact of HCV eradication on hepatic fibrosis.

- In a pooled analysis of adults who had paired liver biopsies before and 1 month to 6 years after treatment with interferon-based therapies, individuals who achieved an SVR were twice as likely to have lower necroinflammatory scores after treatment, compared to those with virologic relapse (67% versus 32%) and some patients with an SVR had complete regression of liver fibrosis.[23]
- In a meta-analysis, investigators evaluated the impact of HCV treatment on liver stiffness, as measured by vibration-controlled transient elastography.[20] Individuals who achieved an SVR12 had a significantly greater decrease in liver stiffness at the end of treatment and after treatment than patients who failed to achieve an SVR12 (Figure 2).[20] 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).[20]
- In a recent study, investigators performed liver stiffness measurements in 70 patients treated with DAA therapy, among whom 95.7% achieved an SVR.[21] Treatment of HCV with DAA therapy resulted in a significant decrease in liver stiffness at the end of treatment and at 12 months posttreatment when compared with baseline measurements (Figure 3).[21]
- 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

Considering that achievement of SVR reduces liver fibrosis, one might expect that successful treatment of HCV would lead to a reduced risk of HCC. The following provides a summary of the impact of HCV DAA-based therapy on HCC occurrence and reoccurrence.

- Multiple large, controlled studies have clearly 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.[26,28,29]
- Although HCV eradication with HCV therapy reduces the risk of HCC occurrence, the risk of developing HCC remains substantial for persons who, prior to treatment, had advanced fibrosis or cirrhosis.[29] Accordingly, individuals who met HCC surveillance criteria prior to HCV treatment should continue to receive HCC surveillance every 6 months after achieving an SVR with HCV treatment.[8,29,30]
- It is important to note posttreatment transient elastography often overestimates the regression in fibrosis, probably because of reduced hepatic inflammation and congestion. Thus, persons with F3-4 fibrosis prior to HCV treatment should continue to have regular hepatocellular carcinoma surveillance, even if testing shows a reduction in liver stiffness or improvement in other non-invasive fibrosis measures.
- 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; most studies report no difference in the risk of recurrent HCC among DAA-treated and untreated persons. As such, DAA-treated individuals with a history of HCC require close ongoing HCC surveillance.[30,31,32,33,34]

Impact of HCV Treatment on Survival

In persons with chronic HCV infection, treatment with achievement of SVR12 or SVR24 has been shown to markedly reduce the risk of death, including liver-related and non-liver-related deaths.[[6,16,47,48](#)] Recently, multiple studies have shown major survival benefit in persons with chronic HCV who achieve SVR with DAA therapy.[[49,50](#)] The following summarizes key data related to the impact of DAA therapy on survival after achieving an SVR.

- In a retrospective cohort study, investigators examined the impact of HCV treatment during the years 1990 and 2003 in 5 hepatology units in Europe and Canada.[[51](#)] Individuals with advanced fibrosis who underwent antiviral therapy and achieved an SVR had reduced overall mortality, liver-related death, liver failure, and hepatocellular carcinoma compared with those who did not achieve an SVR ([Figure 4](#)).[[51](#)]
- 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 when compared with those who had not achieved an SVR; all the studies analyzed all involved interferon-based therapies, and some included individuals with cirrhosis or persons with HIV coinfection ([Figure 5](#)).[[52](#)]
- 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.[[49](#)] 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](#)).[[49](#)] The reduction in mortality was 69.3% among those who achieved an SVR compared to persons who did not receive HCV treatment.[[49](#)]
- Recent 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 patients with a history of HCC should receive HCV DAA treatment due to multiple treatment-related benefits, including overall improved survival.[[53,54](#)]
- A few studies evaluating contemporary trends have suggested an early signal of benefit since the introduction of DAA therapy with decreased mortality and liver transplantation rates in patients with advanced HCV liver disease.[[56,57](#)]

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.[[35,36,37](#)] There is growing evidence that most HCV-related extrahepatic manifestations improve after eradication of HCV, particularly in females.[[38,39](#)] Most notably, 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 7](#)).[[40](#)] In some patients, successful treatment of hepatitis C is associated with improvement or remission of these underlying conditions.[[41,42](#)] 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](#)]

Viral Factors that May Impact Response to Therapy

HCV Genotype

Hepatitis C is classified into 6 major genotypes, numbered 1 through 6. In the prior interferon era of treatment, genotype was the strongest predictor of obtaining an SVR.[1] In the current direct-acting antiviral (DAA) era, particularly with the approval of pangenotypic regimens, the role of HCV genotype in predicting treatment response has decreased significantly given the high efficacy of different DAA combinations across all genotypes and the introduction of pangenotypic agents. Overall, with a preferred regimen, the SVR12 rate is greater than 95%, regardless of HCV genotype.[2]

HCV RNA Level

In the registration clinical trials of peginterferon and ribavirin, a baseline HCV RNA level over 2 million IU/mL was associated with a 9% lower chance of cure.[3] Subsequent studies found that patients with high HCV RNA levels and genotype 1 infection had a 16 to 27% lower chance of achieving an SVR depending on the cutoff used.[4] In the current DAA era, the baseline HCV RNA usually has little impact on the likelihood of achieving an SVR. One exception to this is when considering whether to use 8 or 12 weeks of ledipasvir-sofosbuvir in treatment-naïve persons. A post hoc analysis from the ION-3 trial in treatment-naïve patients without cirrhosis noted that participants with a baseline HCV RNA level less than 6 million IU/mL had similar relapse rates using 8 or 12 weeks of therapy.[5] Subsequent studies have also shown comparable SVR rates for treatment-naïve individuals without cirrhosis who received either 8 or 12 weeks of ledipasvir-sofosbuvir (if the baseline HCV RNA level was less than 6 million IU/mL).[6] Baseline HCV RNA levels have not been associated with likelihood of SVR with the more recently approved pangenotypic DAA regimens.

Host Factors that May Impact Response to Therapy

Race

Several clinical trials involving DAA therapy did not demonstrate significant differences in SVR by race, although these trials may not have been sufficiently powered to detect a difference if one existed.[] Several observational studies of DAA effectiveness in the United States Veterans Administration have suggested a slightly reduced likelihood of SVR among Black individuals after adjusting for baseline characteristics.[] The largest of these observational studies analyzed 2014-2015 DAA HCV treatment data by race and found similar overall SVR rates ([Figure 8](#)), but after adjusting for baseline characteristics, the odds of achieving an SVR were slightly lower in Black or Hispanic individuals, when compared with White persons ([Figure 9](#)).[] It is important to note that the absolute difference in SVR rates were small (1 to 4 percentage points) and these findings have not been reproduced in settings outside the Veterans Administration. One analysis using nationwide observational data from the Veterans Administration facilities found that among persons with chronic HCV, Black individuals were less likely to receive DAA therapy than White persons.[] Overall, when taken together, these data show that SVR12 rates with DAA therapy are excellent across all racial groups, and that while subtle differences might exist, they do not in any way preclude the use of these DAA in Black or Hispanic persons.[]

Age

In multiple studies with interferon-based therapy, increasing age was significantly associated with poor tolerance and a lower chance of cure.[] In contrast, HCV treatment with DAA therapy in the elderly is well tolerated and SVR rates are similar to those seen in younger patients.[] The excellent response in elderly patients has included data in septuagenarians and octogenarians.[] In a retrospective analysis of 17,487 patients with chronic HCV infection in the Department of Veterans Affairs healthcare system, age did not significantly impact the SVR rates, even when analyzed using multivariate models ([Figure 10](#)).[]

Degree of Hepatic Fibrosis

Advanced fibrosis is typically defined as F3 (pre-cirrhosis or bridging fibrosis) and F4 (cirrhosis) on liver biopsy. In earlier DAA trials, lower SVR rates were observed among persons with compensated cirrhosis.[] In subsequent trials, newer medication, longer duration of treatment, and modified therapy (with the addition of ribavirin) have all contributed to improved responses in patients with compensated cirrhosis.[] The one exception to this has been treatment of persons with genotype 3 HCV and cirrhosis, a group that has emerged as the hardest to treat in the DAA era. Nevertheless, two regimens—glecaprevir-pibrentasvir and sofosbuvir-velpatasvir have been shown to achieve high SVR rates in persons with genotype 3 HCV and compensated cirrhosis.[] Similarly, when using currently recommended DAA regimens for persons with compensated cirrhosis, studies show SVR12 rates are greater than 90% across all genotypes.[] Individuals with decompensated cirrhosis (Child-Turcotte-Pugh class B or C) treated with 12 weeks of ledipasvir-sofosbuvir have lower SVR rates (86 to 87%) compared with SVR rates of 95% or greater in similarly treated persons without cirrhosis.[] In a similar study, SVR12 rates of 94% were observed in persons with decompensated cirrhosis when treated with a 12-week regimen of sofosbuvir-velpatasvir plus ribavirin.[]

Prior Treatment

Type of Treatment Response with Prior Failure

Prior treatment failure with interferon-based therapy does not significantly impact treatment response to DAA therapy. In general, when using DAA therapy for persons previously treated with an interferon-based regimen, more than 95% should achieve an SVR with retreatment. In contrast, prior treatment failure with a regimen that consisted of or included DAA therapy can impact retreatment response rates, especially if certain HCV resistance-associated substitutions developed during treatment.[] Nevertheless, with the multiple DAA options now available, most persons with prior DAA treatment failure have very good options available.[] The addition of ribavirin or extension of therapy duration may be required with some regimens to overcome the treatment refractory aspect of persons who previously experienced treatment failure.[]

Summary Points

- There are multiple goals with antiviral therapy for hepatitis C, including (1) eradicate HCV, (2) improve HCV-related health outcomes and survival in all populations, and (3) reduce transmission of HCV to others.
- A sustained virologic response is defined as an undetectable HCV RNA level 12 weeks after stopping antivirals; this is referred to as the SVR12, and the SVR12 has a high correlation with SVR24. 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.
- In the DAA treatment era, HCV genotype has a reduced role in predicting treatment response given the availability of a variety of DAA combinations with high efficacy across genotypes.
- Older patients, including those 70 years of age and older have comparable responses to DAA therapy when compared with younger patients.
- With newer DAA therapies, individuals with more advanced fibrosis and compensated cirrhosis typically have HCV treatment SVR rates greater than 95% with 12-week treatment regimens. Persons with decompensated cirrhosis are more difficult to treat and often have reduced response rates.

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Figures

Figure 1 Sustained Virologic Response 12 (SVR 12)

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

Source: illustration by David H. Spach, MD

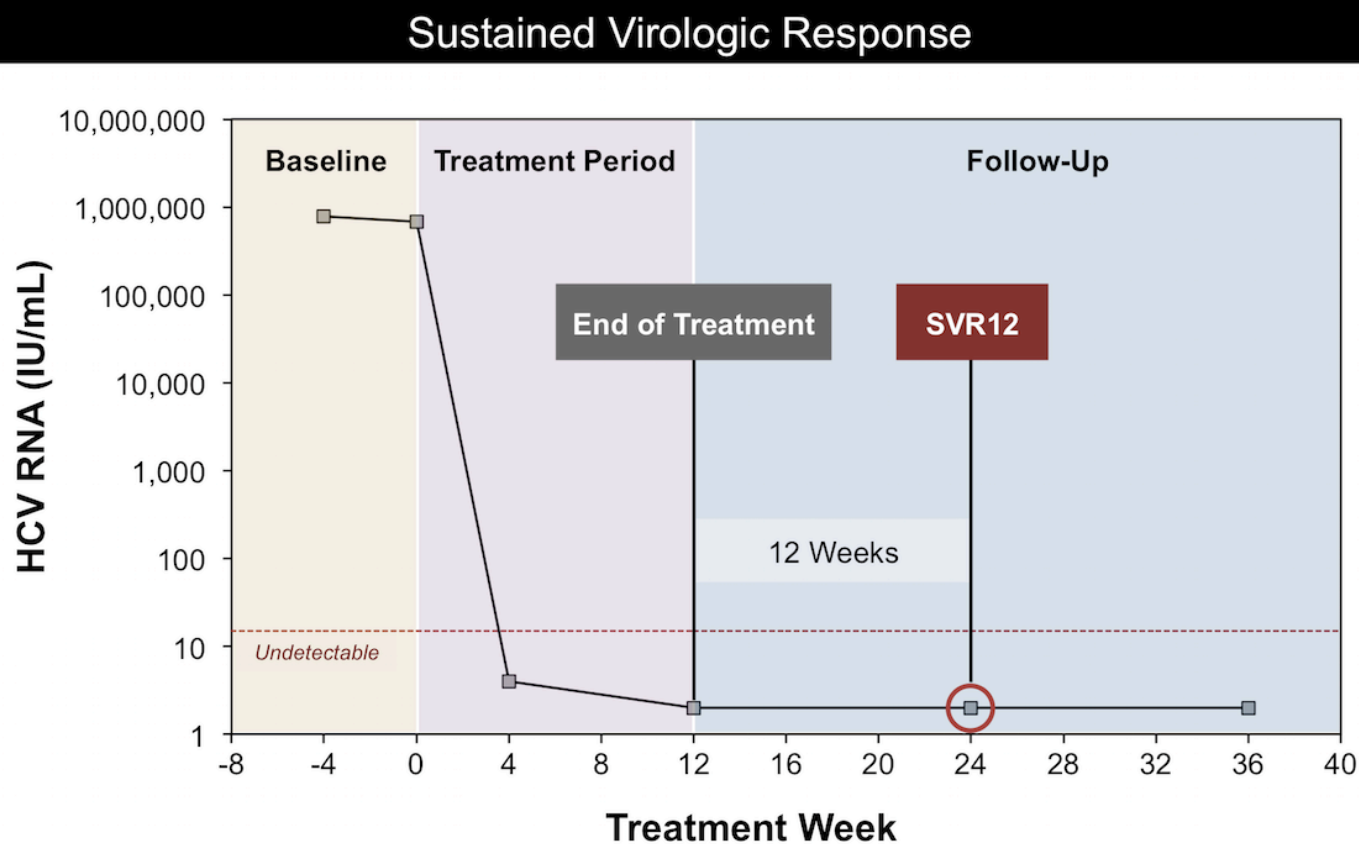


Figure 2 Liver Stiffness in Persons With or Without SVR12

In this review and meta-analysis, investigators compared liver stiffness measured by vibration-controlled transient elastography (VCTE) before and after treatment. This graph compares liver stiffness before and after treatment in adults who attained SVR12 with those who do not achieve SVR12. The decline in liver stiffness among persons who achieved an SVR12 was greater when treated with direct-acting antiviral therapy than with interferon-based therapy (decrease of 5.1 kPa versus decrease of 2.8kPa).

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.

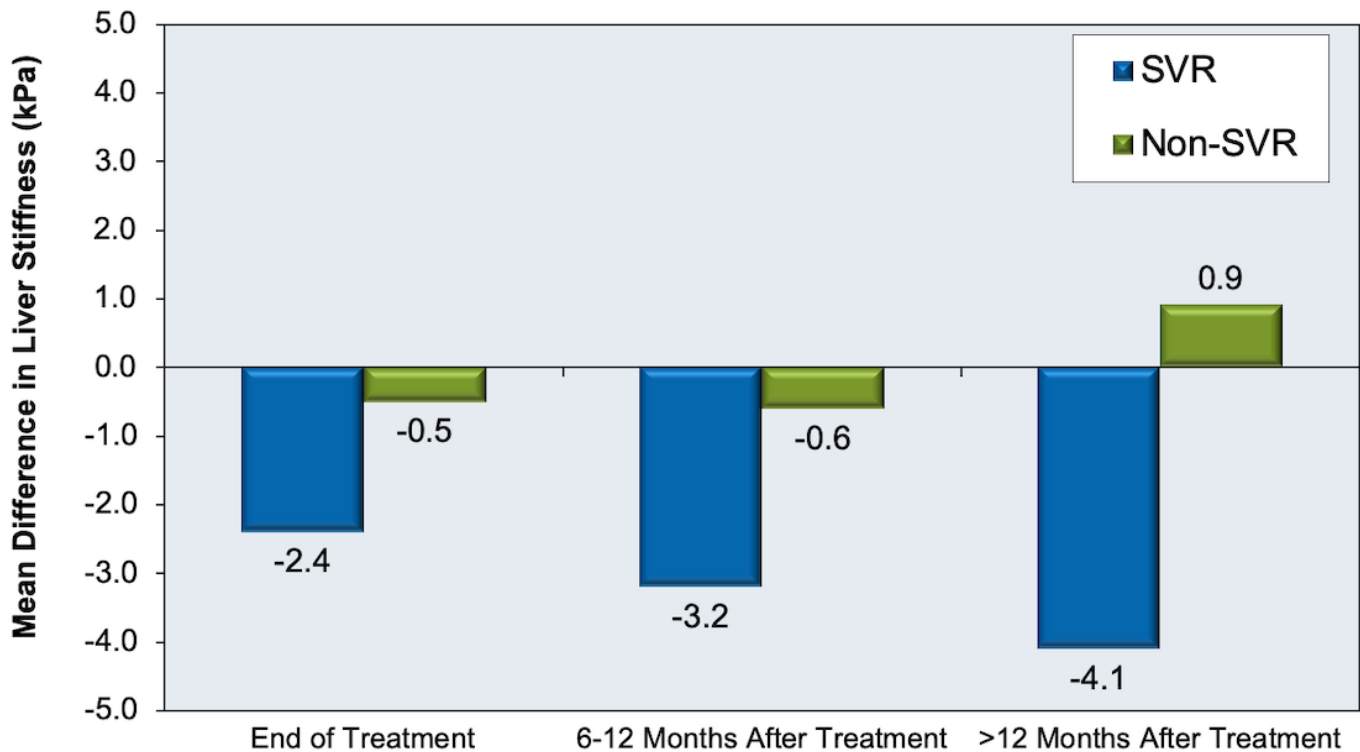


Figure 3 Liver Stiffness Treatments in Persons Treated with Direct-Acting Antiviral Therapy

This study enrolled 70 persons who received direct-acting antiviral therapy for chronic HCV infection. This graphic shows liver stiffness measurement at baseline, end-of-treatment, and 12-month posttreatment. Overall, 48.6% of the participants had a 30% or greater improvement in the liver stiffness measurement (at end of follow-up compared with baseline).

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.

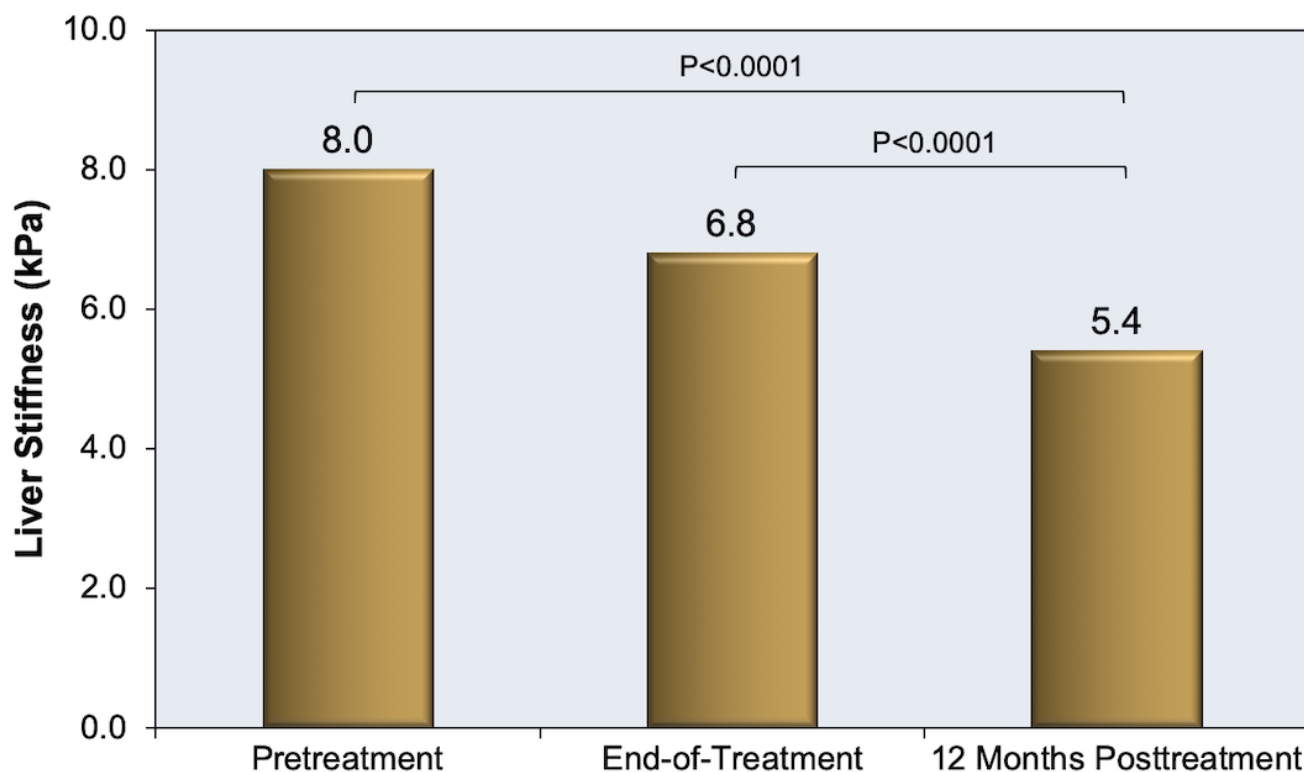


Figure 4 Clinical Outcome by Response to Treatment in Patients with Chronic Hepatitis C and Advanced Fibrosis

This retrospective study was performed in Europe and Canada and examined whether sustained virologic response following hepatitis C treatment correlated with clinical outcomes. The major finding was that treatment was associated with improved clinical outcomes, primarily because of lower rates of liver failure.

Source: Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med. 2007;147:677-84.

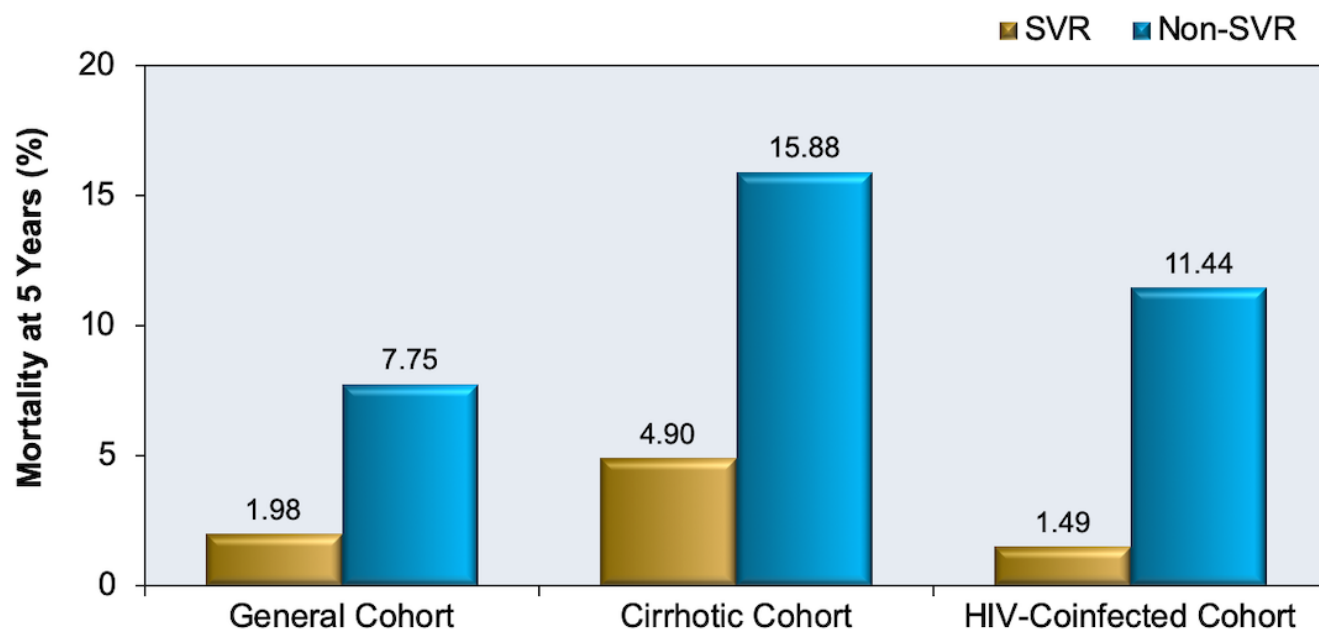
Clinical Outcomes by Response to Hepatitis C Treatment			
Outcome	Patients with SVR	Patients without SVR	Hazard Ratio
	Events per 10,000 Patient-Years		
Overall death	71	193	0.44
Liver-Related death	36	283	0.14
Non-liver-related Death	36	40	1.21
Liver failure	0	365	0.03
Hepatocellular carcinoma	107	277	0.46

Figure 5 5-Year Survival 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.

5-Year Mortality Rates for SVR versus Non-SVR Groups



Abbreviations: SVR= sustained virologic response

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 Jan 29. [Epub ahead of print]

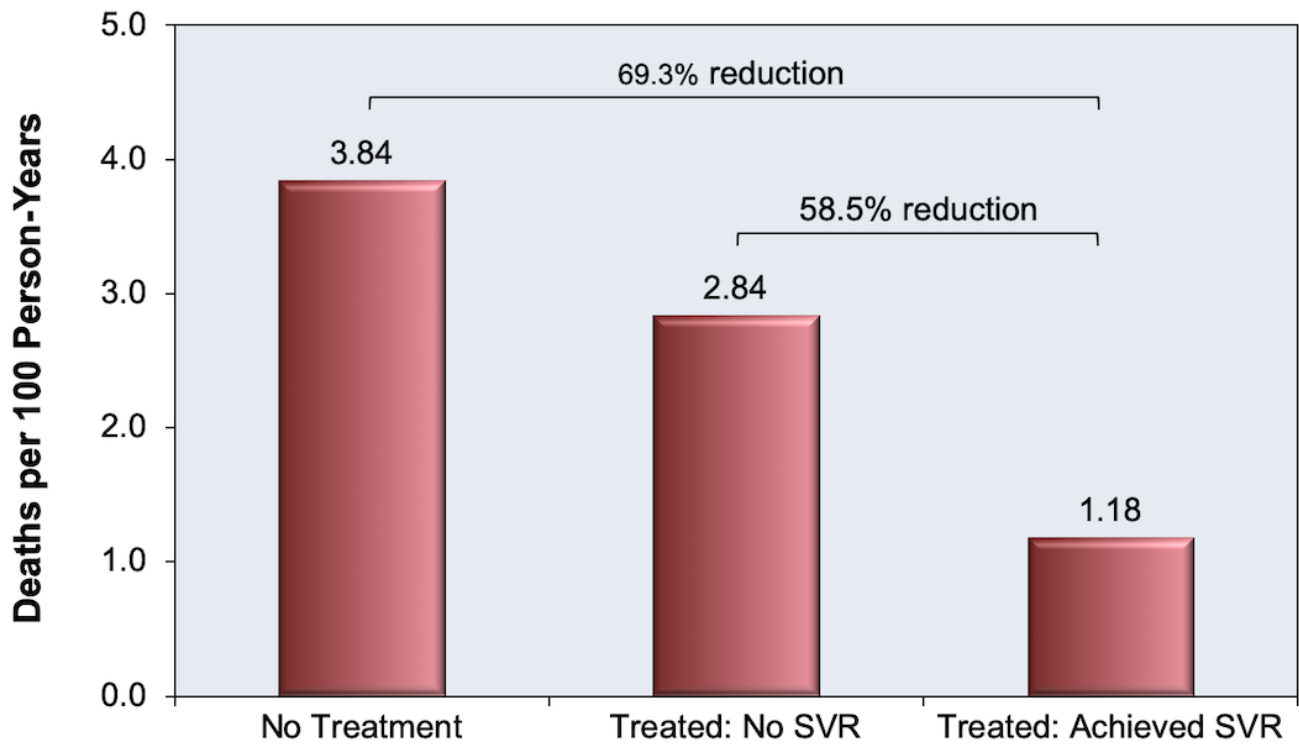


Figure 7 HCV Treatment and Outcome of Extrahepatic Manifestations

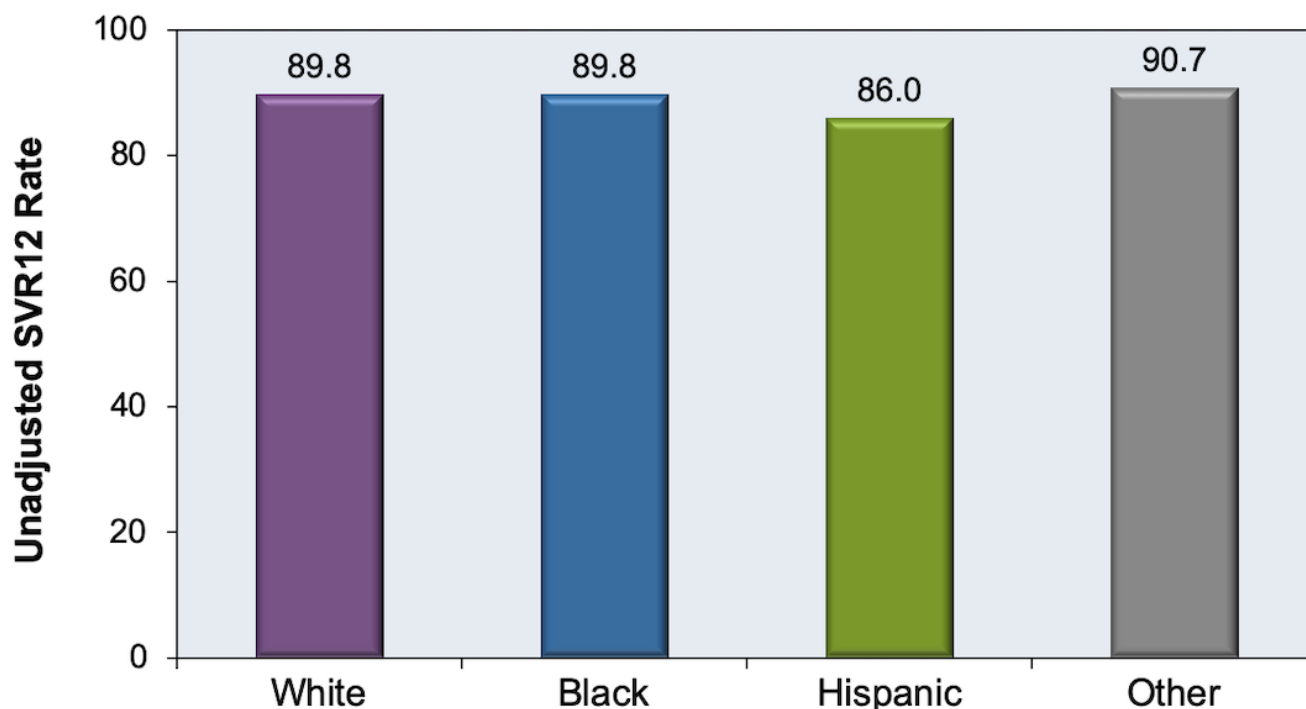
Source: Mahale P, Engels EA, Li R, et al. The effect of sustained virological response on the risk of extrahepatic manifestations of hepatitis C virus infection. Gut. 2018;67:553-61.

Clinical Outcomes by HCV Treatment and Response			
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 8 Sustained Virologic Response Rates (Unadjusted), by Race

This graphic shows unadjusted sustained virologic response rates with DAA therapy among persons who are White, Black, Hispanic, and persons of another race.

Source: Su F, Green PK, Berry K, Ioannou GN. The association between race/ethnicity and the effectiveness of direct antiviral agents for hepatitis C virus infection. Hepatology. 2017;65:426-38.

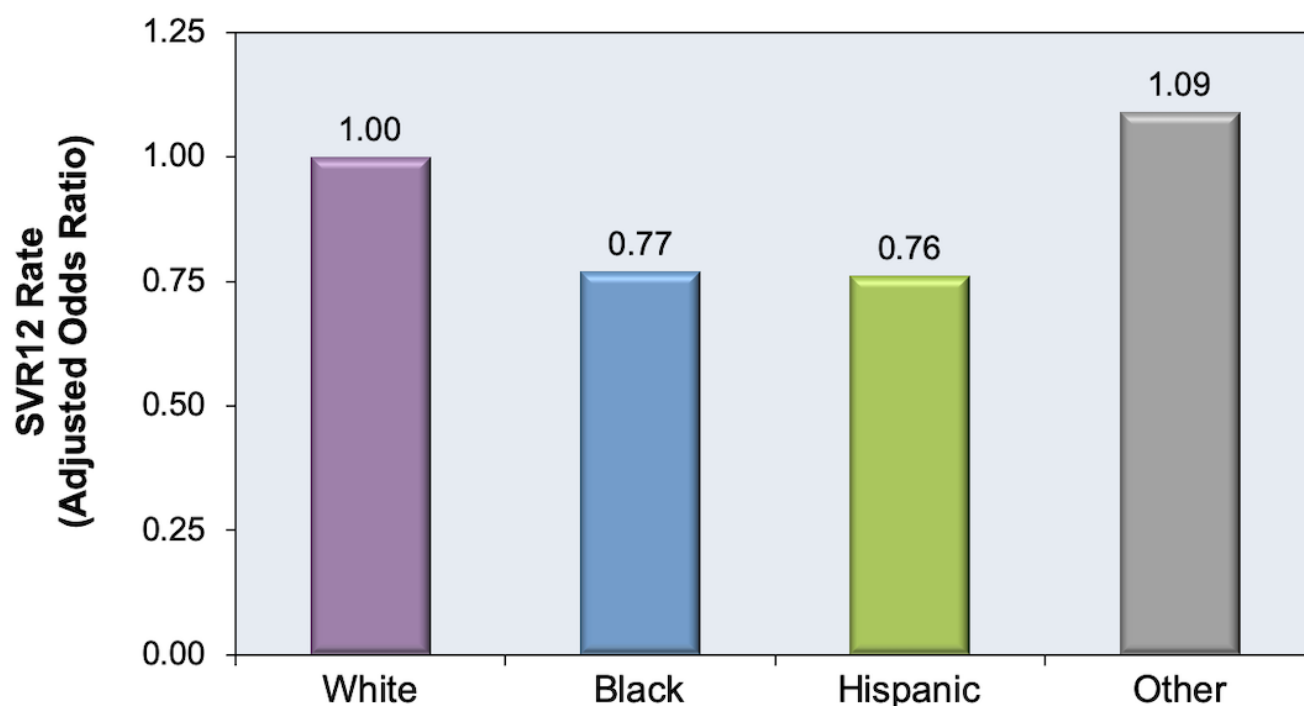


Other = Asian, Pacific Islander, American Indian, Alaskan Native

Figure 9 Sustained Virologic Response Rates (Adjusted Odds Ratio), by Race

This graphic shows adjusted odds ratio sustained virologic response rates with DAA therapy among persons who are White, Black, Hispanic, and persons of another race. This model includes the following baseline characteristics: age, genotype/subgenotype, regimen, gender, HCV viral load, platelet count, serum bilirubin level, serum albumin level, alcohol use disorder, diabetes, cirrhosis, decompensated cirrhosis, HCC, liver transplantation, and prior treatment.

Source: Su F, Green PK, Berry K, Ioannou GN. The association between race/ethnicity and the effectiveness of direct antiviral agents for hepatitis C virus infection. *Hepatology*. 2017;65:426-38.



Other = Asian, Pacific Islander, American Indian, Alaskan Native

Figure 10 Sustained Virologic Response, by Age Group

In this retrospective analysis of DAA treatment of HCV in the Department of Veterans Affairs health care system, investigators analyzed treatment response based on age. As shown in this graph, excellent SVR rates occurred across all age groups, including those 75 years of age and older.

Source: Su F, Beste LA, Green PK, Berry K, Ioannou GN. Direct-acting antivirals are effective for chronic hepatitis C treatment in elderly patients: a real-world study of 17 487 patients. *Eur J Gastroenterol Hepatol.* 2017;29:686-93.

