Background

The goals for treatment of 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 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 the overall HCV epidemic.
Virologic Cure 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) after at least 12 weeks of 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 are considered to have achieved an SVR12 and virologic cure. \[^{7}\] Among persons who achieve an SVR12 with direct-acting antiviral (DAA) therapy, more than 99% go on to achieve an SVR24. \[^{9,10}\] 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 SVR.

**Durability of SVR**

Long-term follow-up of patients who achieve an SVR24 has shown that nearly 100% remain HCV RNA negative years after therapy. \[^{11,12,13}\] Several large studies have shown a minimal relapse rate, between 0 to 1% at 5 years. \[^{14,15}\] 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. \[^{15,16}\]
Impact of HCV Treatment on Clinical Outcomes

Impact of HCV Treatment on Hepatic Fibrosis

Patients who achieve an SVR are more likely to have an improvement in liver inflammation and fibrosis than those who do not achieve an SVR.\cite{17,18,19,20} The following studies highlight data related to the impact of HCV eradication on hepatic fibrosis.

- In a pooled analysis of patients who had paired liver biopsies before and 1 months 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.\cite{20}
- In a meta-analysis, investigators evaluated the impact of HCV treatment on liver stiffness, as measured by vibration-controlled transient elastography.\cite{17} 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).\cite{17} 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 2.8kPa).\cite{17}
- In a recent study, investigators performed liver stiffness measurements in 70 patients treated with DAA therapy, among whom 95.7\% achieved an SVR.\cite{18} 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).\cite{18}
- Several studies have confirmed the long-term histologic benefit with successful interferon-based therapy.\cite{11,21,22}
- Vibration-controlled transient elastography often overestimates the regression in fibrosis, probably because of reduced hepatic inflammation and congestion. Patients with F3-4 fibrosis prior to HCV treatment should continue to have regular hepatocellular carcinoma surveillance, even if testing shows a reduction in hepatic fibrosis.

Impact of HCV Treatment on Hepatocellular Carcinoma

Since treatment of HCV with achievement of SVR reduces liver fibrosis, then it would be expected that successful treatment of HCV would reduce the risk of HCC occurrence. In 2016, however, a report from Barcelona involving a small cohort of patients noted a high recurrence rate of HCC in persons who achieved an SVR with DAA therapy.\cite{23} This report raised concern that DAA therapy may possibly increase the occurrence and recurrence of HCC. In addition, several small single-center, uncontrolled reports noted an increase in a new diagnosis of HCC after DAA therapy, but these results involved single centers, were uncontrolled, and had skewed patient populations with more advanced liver disease.\cite{24} Subsequently, multiple large, controlled studies have clearly shown a major reduction in the risk of HCC occurrence after achievement of SVR with HCV therapy; in these studies, control groups consisted of patients who did not achieve an SVR.\cite{4,25,26,27} Several of the more recent studies exclusively involved persons treated with DAA therapy.\cite{24,26,28} Treatment of HCV in persons with advanced fibrosis should not be withheld due to a fear of increasing the risk of developing HCC. It is important to note that although HCV eradication with HCV therapy reduces the risk of HCC occurrence, the risk of developing HCC remains substantial for patients with pretreatment advanced fibrosis or cirrhosis.\cite{28} Accordingly, individuals who meet HCC surveillance criteria prior to HCV treatment should continue to receive HCC surveillance every 6 months after achieving an SVR with HCV treatment.\cite{8,28} In addition, in patients with a prior history of HCC, successful treatment with DAA therapy does not appear to reduce the risk of HCC recurrence and therefore these patients need close surveillance. Nevertheless, patients with a history of HCC should receive HCV DAA treatment due to multiple treatment-related benefits.

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.\cite{6,14,29,30} Multiple studies have now documented strong survival benefit with successful treatment of chronic HCV using interferon-based regimens.\cite{6,29,31,32,33,34} More recently, data from multiple studies have shown major survival benefit in persons with chronic HCV who achieve SVR with DAA therapy.\cite{35,36} The following summarizes several key studies showing survival benefit with successful HCV treatment.

- In a study that utilized the United States Veterans Affairs database, investigators compared 34,480 matched pairs of individuals with HCV infection and age-matched controls without HCV and demonstrated HCV infection increased the risk of death by approximately 37%, but treatment of chronic HCV at least 48 weeks with peginterferon and ribavirin was associated with a 60% reduction in mortality compared with untreated veterans (Figure 4).\cite{34}

- 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.\cite{37} Individuals with advanced fibrosis who underwent antiviral therapy and achieved an SVR had reduction in overall mortality, liver-related death, liver failure, and hepatocellular carcinoma when compared with those who did not achieve an SVR (Figure 5).\cite{37}

- 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; the studies analyzed all involved interferon-based therapies, but some included patients with cirrhosis and some included patients with HIV coinfection (Figure 6).\cite{38}

- 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.\cite{35} 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 and in those who were not treated (Figure 7).\cite{35} The reduction in mortality was 69.3% when comparing those who achieved an SVR with those who were not treated.\cite{35}

**Impact of HCV Treatment on Extrahepatic Manifestations**

Hepatitis C 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.\cite{39,40,41} There is growing evidence that most of HCV-related extrahepatic manifestations improve after eradication of HCV. 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 8).\cite{42} In some patients, successful treatment of hepatitis C is associated with improvement or remission of these underlying conditions.\cite{43,44} 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.\cite{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.[45,46,47] In the current direct-acting antiviral (DAA) era, 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 pan-genotypic agents. Overall, with a preferred regimen, the SVR12 rate is greater than 95%, regardless of HCV genotype.[48,49,50,51,52]

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.[45] 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.[53] 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 patients; 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.[54] 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).[55]
Host Factors that May Impact Response to Therapy

Race

African-American patients with hepatitis C have historically had poorer responses to interferon-based therapy, as shown in a comparative analysis of responses to treatment with peginterferon and ribavirin in persons with genotype 1 infection (SVR rate in African-Americans was 19% versus 52% in Caucasians).[56] Latinos with genotype 1 treated with peginterferon and ribavirin also have had reduced SVR rates compared with Caucasians (34% versus 49%).[57] 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.[58,59,60] Several observational studies of DAA effectiveness in the United States Veterans Administration have suggested a slightly reduced likelihood of SVR in black patients after adjusting for baseline characteristics.[61,62,63] The largest of these observational studies analyzed 2014-2015 DAA HCV treatment data by race and found similar overall SVR rates (Figure 9), but after adjusting for baseline characteristics the SVR rates were lower in blacks and Hispanics (Figure 10).[63] One analysis using observational nationwide data from the Veterans Administration facilities found that among persons with chronic HCV, blacks were less likely than whites to receive DAA therapy.[64] Overall, when taken together, these data show that SVR12 rates with DAA therapy are excellent across all racial groups, but subtle differences exist, with slightly lower SVR12 rates in blacks and Hispanics when compared with whites.[65]

IL28B Genotype

The large difference in response rates with interferon-based therapy between African-Americans and Caucasians is largely explained by genetic differences in the IL28B gene region on chromosome 19. This region encodes for the host production of interferon-lambda. The majority of African-Americans have the less favorable genotypes (CT or TT). In the interferon era, the CT or TT genotype was associated with a 40% lower SVR rate compared to patients with the CC allele.[66] Asians have the highest proportion of the CC genotype, which may explain their better response to interferon-based therapy. The IL28B genotype does not appear to influence treatment response to interferon-free DAA therapy.

Age

In multiple studies with interferon-based therapy, increasing age was significantly associated with poor tolerance and a lower chance of cure.[67,68] In contrast, HCV treatment with DAA therapy in the elderly is well tolerated and SVR rates are similar to those seen in younger patients.[67,69,70] The excellent response in elderly patients has included data in septuagenarians and octogenarians.[71] 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 11).[70]

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 patients with compensated cirrhosis,[61,72] 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.[60,73,74,75] The one exception to this has been treatment of persons with genotype 3 HCV with cirrhosis, which has proven less than optimal with most DAA regimens. Two regimens—glecaprevir-pibrentasvir and sofosbuvir-velpatasvir have been shown to achieve high SVR rates in persons with genotype 3 HCV and compensated cirrhosis.[51,52] When using currently recommended DAA regimens for persons with compensated cirrhosis, the SVR12 rates are greater than 90%. This is true across all DAA regimens. Patients with decompensated cirrhosis (Child-Turcotte-Pugh class B or C) had SVR rates of 86 to 87% with 12 weeks of ledipasvir-sofosbuvir compared with SVR rates of greater than 95% in similarly treated patients without cirrhosis.[77] In a separate study, SVR12 rates of 94% were observed in patients with decompensated cirrhosis when treated with a 12
week regimen of sofosbuvir-velpatasvir plus ribavirin.[78]
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.\[79,80\] Nevertheless, with the multiple DAA options now available, most patients with prior DAA treatment failure have very good options available.\[81\]

The addition of ribavirin or extension of therapy duration is used with some regimens to overcome the negative impact that may occur as a result of prior treatment.\[81,82\]
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 eradication of HCV.
- Achieving an SVR following treatment of HCV 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.
- With DAA therapy, excellent SVR rates are observed across all racial groups, but subtle differences exist, with slightly lower SVR12 rates in blacks and Hispanics when compared with whites.
- 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 patients with more advanced fibrosis and compensated cirrhosis can have SVR rates greater than 95% with 12-week treatment regimens. Patients with decompensated cirrhosis are more difficult to treat and often have reduced response rates.
Citations


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References

[PubMed Abstract] -

[PubMed Abstract] -


Figures

Figure 1 Sustained Virologic Response 12 (SVR 12)

This graphic shows an example of an SVR12 in a patient 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
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 patients who attained SVR12 with those who do not achieve SVR12. The decline in liver stiffness among those who achieved an SVR12 was greater in those treated with direct-acting antiviral therapy than in those treated with interferon-based therapy (decrease of 5.1 kPa versus decrease of 2.8 kPa).

This study enrolled 70 patients 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 patients had a 30% or greater improvement in the liver stiffness measurement (at end of follow-up compared with baseline).

Investigators used a national sample of HCV-infected veterans and HCV-uninfected controls to examine the effect of HCV treatment on survival. This graphic illustrates that longer treatment duration with interferon-based therapy correlated with improved survival.

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.


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients with SVR</th>
<th>Patients without SVR</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events per 10,000 Patient-Years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Death</td>
<td>71</td>
<td>193</td>
<td>0.44</td>
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<tr>
<td>Liver-Related Death</td>
<td>36</td>
<td>283</td>
<td>0.14</td>
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<tr>
<td>Non-Liver-Related Death</td>
<td>36</td>
<td>40</td>
<td>1.21</td>
</tr>
<tr>
<td>Liver Failure</td>
<td>0</td>
<td>365</td>
<td>0.03</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>107</td>
<td>277</td>
<td>0.46</td>
</tr>
</tbody>
</table>
Figure 6 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, including a total of 33,360 patients. The 5-year mortality rates shown are based on whether the patient achieved an SVR.

Figure 7 Impact of SVR on Mortality Rates with DAA Therapy

**Figure 8 HCV Treatment and Outcome of Extrahepatic Manifestations**


<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No Treatment</th>
<th>Treatment without SVR</th>
<th>Treatment with SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed cryoglobulinemia</td>
<td>0.72</td>
<td>0.52</td>
<td>0.33</td>
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<td>Glomerulonephritis</td>
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<td>1.62</td>
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<tr>
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<td>0.75</td>
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<tr>
<td>Stroke</td>
<td>9.14</td>
<td>4.64</td>
<td>5.10</td>
</tr>
</tbody>
</table>
Figure 9 Sustained Virologic Response Rates (Unadjusted), by Race


Other = Asian, Pacific Islander, American Indian, Alaskan Native
Figure 10 Sustained Virologic Response Rates (Adjusted Odds Ratio), by Race


Other = Asian, Pacific Islander, American Indian, Alaskan Native
In this retrospective analysis of DAA treatment of HCV in the Department of Veterans Affairs healthcare 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.