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I. Introduction

Hepatitis C virus (HCV) infection is a major public health problem that carries a significant burden of disease in the United States and worldwide.\cite{1-3} HCV infection is the most common chronic blood-borne infection in the United States. Nearly all healthcare workers, regardless of practice setting, will encounter patients at risk for or who have known HCV infection.

Public health goals related to HCV infection in the United States include identifying persons infected with HCV early in the course of their disease, linking and referring them to care and treatment, and improving their access to and quality of care and treatment. This manual is intended for use as a quick reference for all clinicians on the evaluation, diagnosis, treatment, and management of chronic HCV infection. The reader is referred to the American Association for the Study of Liver Diseases (AASLD) Practice Guideline. Diagnosis, Management, and Treatment of Hepatitis C: An Update\cite{3} for preferred approaches to the diagnostic, therapeutic and preventive aspects of care. A summary of the guideline recommendations is provided in Appendix A.
**Facts and Figures**[1-6]

**Facts**
Worldwide, HCV infection accounts for approximately 15% of acute viral hepatitis, 60%-70% of chronic hepatitis, and up to 50% of cirrhosis, end-stage liver disease, and liver cancer.

Approximately 75% of 80% patients with acute HCV infection develop chronic HCV infection. Most people with chronic HCV infection are unaware of their condition.

In the United States, HCV infection is the leading cause of hepatocellular carcinoma and the leading indication for liver transplantation.

**Figures**

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 - 210 million</td>
<td>Estimated number of people worldwide who are chronically infected with HCV</td>
</tr>
<tr>
<td>3 - 4 million</td>
<td>Estimated number of people worldwide who are infected with HCV each year</td>
</tr>
<tr>
<td>3.2 million</td>
<td>Estimated number of noninstitutionalized civilian Americans who have chronic HCV infection</td>
</tr>
<tr>
<td>156,725</td>
<td>The number of veterans with HCV infection who, in 2009 were receiving care from the Veterans Health Administration, the largest single provider of medical care to individuals with HCV infection</td>
</tr>
<tr>
<td>35,000 - 185,000</td>
<td>Estimated number of Americans who are infected with HCV each year</td>
</tr>
<tr>
<td>17,000</td>
<td>Estimated new cases of HCV infection in 2007</td>
</tr>
<tr>
<td>10,000 - 12,000</td>
<td>Estimated number of HCV-related deaths in the United States annually 50 – 60 Age group (years) of the largest cohort of Americans with chronic HCV infection</td>
</tr>
<tr>
<td>75% - 80%</td>
<td>Percentage of people infected with HCV who will develop chronic infection</td>
</tr>
<tr>
<td>5% - 20%</td>
<td>Percentage of people infected with HCV who will develop cirrhosis over a period of 20-30 years</td>
</tr>
<tr>
<td>1% - 5%</td>
<td>Percentage of people infected with HCV who will die from liver cancer or cirrhosis</td>
</tr>
<tr>
<td>1.8%</td>
<td>Approximate risk for HCV infection after a needle stick or sharps exposure to HCV-positive blood</td>
</tr>
<tr>
<td>$279 million</td>
<td>The amount of money spent on peginterferon alfa, based on a 1-month supply per patient, in 2002-2007.</td>
</tr>
</tbody>
</table>
II. HCV Infection

The Virus
The HCV is a small (40 to 60 nm in diameter) enveloped, single-stranded RNA virus of the family Flaviviridae and genus Hepacivirus. HCV is able to rapidly mutate; thus, changes in the envelope proteins may help it evade the immune system.

HCV Genotypes
At least 6 major genotypes and more than 50 subtypes of HCV have been identified worldwide. These genotypes have significant geographic distribution:

- The most common genotypes in the United States are 1a and 1b (approximately 75% of cases), but genotypes 2a and 2b are also relatively common (10%-20% of cases).[7]
- HCV genotype 3a is particularly prevalent in intravenous-drug abusers in Europe and the United States.
- Identification of the HCV genotype is helpful in defining the epidemiology of HCV infection. Genotype does not affect severity of disease, but it can affect response to treatment. Genotypes 2 and 3 are more likely to respond to treatment with IFN-based therapies; genotype 1 typically requires longer-term treatment and is less likely to respond to available therapies.[8]

Genotyping is discussed in the section Diagnosis and Evaluation.

Epidemiology and Natural History of HCV
HCV infection is classified as acute or chronic.[9]

- Acute HCV infection is defined as infection occurring in the first 6 months after viral infection. Acute HCV infection is asymptomatic in 50%-90% of cases. In addition, infection is not spontaneously eradicated in 50%-90% of cases. Spontaneous eradication depends on the route of transmission, the presence of symptomatic hepatitis, and the age at which infection occurs.
- Chronic HCV infection is infection persisting for more than 6 months. Chronic HCV infection is often asymptomatic and is frequently discovered incidentally.
- At least 20% of patients with chronic HCV infection develop cirrhosis, which generally takes at least 10-20 years to develop.
- A small percentage of patients who develop hepatocellular carcinoma, which takes 20–40 years to develop; men, alcoholics, patients with cirrhosis, people over the age of 40 years, and those infected for 20–40 years are at higher risk for developing HCV-related hepatocellular carcinoma.
HCV is a blood-borne virus, spread primarily through blood-to-blood contact. Prior to the 1990s, the principal routes of HCV infection were blood transfusion, unsafe injection practices, and intravenous drug use. These modes of transmission account for approximately 70% of cases in industrialized countries. Screening of blood products for HCV has virtually eradicated transfusion-transmitted HCV infection. Currently, new HCV infections are primarily due to intravenous or nasal drug use and unsafe medical or surgical procedures.

**Risk Factors and Indications for Routine Screening**

As part of a comprehensive health evaluation, all persons should be screened for behaviors that place them at high risk for HCV infection, including those who:

- Have injected illicit drugs, including those who have injected drugs only once and do not consider themselves to be drug users
- Have conditions or a history of conditions associated with a high prevalence of HCV infection:
  - HIV infection
  - Hemophilia and received blood clotting factor concentrates before 1987
  - History of long-term hemodialysis
  - Unexplained abnormal transaminase levels
- Had a blood transfusion or organ transplant before July 1992, including:
  - Those notified that they had received blood from a donor who later tested positive for HCV infection
- Had known exposure to HCV-positive blood:
  - Needle stick injury
  - Mucosal exposure (i.e., intranasal cocaine, sexual promiscuity, body piercing, body tattoo)
- Were born to an HCV-infected mother (to avoid detecting maternal antibody, these children should not be tested before age 18 months)
- Have current HCV-infected sexual partner

Sporadic transmission from unknown sources, such as cuts or wounds, or medical procedures, such as unsafe injection practices, is responsible for approximately 10% of acute HCV infection and 30% of chronic HCV infection.
**HIV Coinfection**
The introduction of effective combined antiretroviral therapy has transformed HIV infection from a deadly disease to a chronic illness. However, the reduction in AIDS-related mortality has been paralleled by an increase in liver-related morbidity and mortality due to chronic HCV coinfection. In fact, liver disease is the second leading cause of death in people with AIDS, and 66% of these deaths are due to HCV-related liver disease.\(^9\)

**Screening for HCV Infection**
HIV-infected patients suspected of having acute or chronic HCV infection should first be tested for antibodies to HCV (anti-HCV). In addition, HCV RNA testing should be performed in the following groups:

- Those with a positive anti-HCV test;
- Those for whom antiviral treatment is being considered, using a highly-sensitive quantitative HCV RNA assay; or
- Those with unexplained liver disease whose anti-HCV test is negative and who are immunocompromised or suspected of having acute HCV infection.\(^3\)

**Avoiding Secondary Transmission**
HCV-infected individuals should receive the following advice and counseling to raise awareness about and prevent secondary transmission of HCV infection:

- Avoid activities that could result in percutaneous or mucus membrane exposure of others to their blood (eg, sharing a toothbrush, dental equipment, or shaving equipment)
- Cover any bleeding wound
- Stop using illicit drugs
- If using illicit drugs, do not reuse or share syringes, needles, or other supplies (eg, cotton or alcohol swabs) and paraphernalia for illicit drug use, and dispose of syringes and needles after 1 use in a puncture-proof container
- Do not donate blood, organs, tissues, or semen
- Practice safe sex
When HCV infection is detected, patients should be referred to a specialist for evaluation and diagnosis. A sample patient referral checklist is provided in Appendix B.

**Diagnosis**

Chronic HCV infection is diagnosed when anti-HCV is present in the serum and serum transaminase levels remain elevated for more than 6 months. Testing for HCV RNA by polymerase chain reaction (PCR) confirms the diagnosis and documents viremia; the viral genome will be detectable in serum by PCR in almost all patients.

The differential diagnosis of chronic HCV infection includes assessment for the following conditions:
- Autoimmune hepatitis
- Chronic hepatitis B virus and D virus infections
- Alcoholic hepatitis
- Nonalcoholic steatohepatitis (fatty liver)
- Sclerosing cholangitis
- Primary biliary cirrhosis
- Wilson disease
- Alpha-1-antitrypsin-deficiency
- Drug-induced liver disease

Laboratory tests used in the diagnosis and differential diagnosis of HCV infection are defined in Table 1.
Table 1. Biochemical Indicators of HCV Infection

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Effect of Chronic HCV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminotransferases or transaminases</td>
<td>ALT and AST levels increase up to 20 times (but usually less than 5 times) the upper limit of normal. Up to 40% of people with chronic HCV infection have normal ALT levels, even when tested on multiple occasions. ALT levels are usually higher than AST levels, but this may be reversed in patients with cirrhosis.</td>
</tr>
<tr>
<td>Alkaline phosphatase Gamma glutamyl transpeptidase</td>
<td>Alkaline phosphatase and gamma glutamyl transpeptidase levels are usually normal. If elevated, they may indicate cirrhosis.</td>
</tr>
<tr>
<td>Lactate dehydrogenase Creatine kinase</td>
<td>Lactate dehydrogenase and creatine kinase levels are usually normal.</td>
</tr>
<tr>
<td>Albumin Bilirubin Prothrombin timed Iron Ferritin</td>
<td>Albumin and bilirubin levels, and prothrombin time are normal until late-stage disease. Iron and ferritin levels may be slightly elevated.</td>
</tr>
<tr>
<td>Platelet count White blood cell count Serum globulins</td>
<td>Low platelet and white blood cell counts and raised levels of serum globulins (including immunoglobulins and rheumatoid factor) are frequent in patients with severe fibrosis or cirrhosis, providing clues to the presence of advanced disease.</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase

**Serologic Tests**

Serologic tests for making the diagnosis of HCV infection include enzyme immunoassay (EIA), recombinant immunoblot assay (RIBA), and direct HCV RNA assays as defined in Table 2. In addition, a reference for interpretation of HCV test results is found in Appendix C. Persons suspected of having HCV infection should be screened initially for the presence of anti–HCV by EIA. Active HCV infection should be confirmed by testing for HCV RNA using a PCR or transcription-mediated amplification assay.
Table 2. Serologic Tests for Diagnosing HCV Infection

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIA</td>
<td>The currently available third-generation tests (EIA-3) have a specificity and sensitivity of &gt; 99%.</td>
</tr>
<tr>
<td>RIBA</td>
<td>RIBA is a blood test that detects antibodies to HCV. RIBA is more specific than some HCV screening tests (eg, EIA) and is sometimes used to confirm the results of these tests.</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>Detection of HCV RNA in blood is the currently accepted “gold standard” for the diagnosis of active HCV infection. Two types of PCR HCV RNA tests are used: qualitative* and quantitative.</td>
</tr>
</tbody>
</table>

Qualitative tests (PCR and TMA assays) detect low levels of HCV RNA in the serum, and results are reported as positive or negative, not numerically. A single negative qualitative test does not exclude viremia because viral load is variable. Testing for HCV RNA is useful when amino transferase levels are normal or slightly elevated, when the anti-HCV is negative in someone with suspected HCV, when the cause of liver disease is unknown, and in persons who are immunosuppressed.

Quantitative tests measure the amount of virus present in serum (viral load). Viral load can be assessed using quantitative PCR or branched-DNA tests. Serum levels of HCV RNA can vary by up to 10-fold over time; these assays are not well standardized and results on the same specimen will vary at different laboratories, but they can provide insight into the nature of HCV infection. Most patients with chronic HCV infection have HCV RNA levels of 100,000 – 10,000,000 copies/mL or 50,000 – 5,000,000 IU/mL.

*Qualitative testing is rarely indicated because quantitative assays are so sensitive.

anti-HCV = antibodies to HCV virus; EIA = enzyme immunoassay; PCR = polymerase chain reaction; RIBA = recombinant immunoblot assay; RNA = ribonucleic acid; TMA = transcription-mediated amplification
Genotyping
HCV genotyping should be performed for all HCV-infected persons before initiating IFN-based treatment, to plan for dosing and duration of treatment and to estimate the likelihood of response. Patients with HCV genotypes 2 and 3 are 2-3 times more likely to respond to IFN-based treatment than are patients with genotype 1. Furthermore, for patients needing combination therapy, the recommended dose and duration of treatment depend on the HCV genotype. HCV genotypes do not change during the course of HCV infection, so once identified, genotypes do not need to be tested again.

Liver Biopsy
Currently available noninvasive tests may be useful in defining the presence or absence of advanced fibrosis in persons with chronic HCV infection, but they should not replace the liver biopsy in routine clinical practice. Liver biopsy is helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage: ruling out other causes of liver disease, such as alcoholic liver injury, nonalcoholic fatty liver disease, and iron overload; and helping the clinician to decide whether to begin treatment and monitor the response to treatment.

A liver biopsy should be considered for patients with chronic HCV infection if the patient and healthcare provider wish information regarding stage of fibrosis for prognostic purposes or to make decisions regarding treatment.

Chronic HCV infection causes the following changes in liver tissue:

• Piecemeal necrosis: necrosis and inflammation at the edge of the portal areas
• Hepatocellular necrosis: focal inflammation in the liver parenchyma
• Portal inflammation: inflammatory cells in the portal areas
• Fibrosis
  – Early stage: confined to the portal tracts
  – Intermediate stage: expansion of the portal tracts and bridging between portal areas or from portal areas to the central area
  – Late stage: frank cirrhosis characterized by architectural disruption of the liver with fibrosis and regeneration.

A classification commonly used to stage fibrosis is a 0-4-point scale:

• Stage F0: no fibrosis
• Stage F1: enlargement of the portal areas
• Stage F2: fibrosis extending out from the portal areas with rare bridges between portal areas
• Stage F3: many bridges of fibrosis that link up portal and central areas of the liver
• Stage F4: cirrhosis
V. Treatment of Chronic HCV Infection*

The goal of HCV treatment is to eradicate the virus and prevent the development of cirrhosis and its complications. Thus, for patients in whom liver histology is available, treatment is indicated in those with bridging fibrosis or compensated cirrhosis, provided they have no contraindications (Table 3) to treatment.\[3\]

General Indications and Contraindications

Table 3. Selection of Patients for Treatment of Chronic HCV Infection: Indications and Contraindications\[3\]

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age 18 years or older, and</td>
<td>• Major uncontrolled depressive illness</td>
</tr>
<tr>
<td>• HCV RNA positive in serum, and</td>
<td>• Solid organ transplant (renal, heart, or lung)</td>
</tr>
<tr>
<td>• Liver biopsy showing chronic hepatitis with significant fibrosis (bridging fibrosis or higher), and</td>
<td>• Autoimmune hepatitis or other autoimmune condition known to be exacerbated by peginterferon-ribavirin</td>
</tr>
<tr>
<td>• Compensated liver disease (total serum bilirubin &lt;1.5 g/dL; INR 1.5; serum albumin &gt; 3.4 mg/dL, platelet count 75,000/mm³ and no evidence of hepatic decompensation (hepatic encephalopathy or ascites), and</td>
<td>• Untreated thyroid disease</td>
</tr>
<tr>
<td>• Acceptable hematological and biochemical indices (hemoglobin 13 g/dL for men and 12 g/dL for women; neutrophil count 1500 /mm³ and serum creatinine &gt;1.5 mg/dL, and</td>
<td>• Pregnant or unwilling to comply with adequate contraception</td>
</tr>
<tr>
<td>• Willing to be treated and to adhere to treatment requirements, and</td>
<td>• Severe concurrent medical disease such as severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>• No contraindications</td>
<td>• Known hypersensitivity to drugs used to treat HCV</td>
</tr>
</tbody>
</table>

HCV = hepatitis C virus; RNA = ribonucleic acid
**Historic Standard of Care: Peginterferon-Ribavirin**

Treatment of chronic HCV is based on the HCV genotype. Response-guided treatment is based on the quantitative HCV RNA (viral load) prior to and at various predetermined time points during treatment.

The combination of peginterferon-ribavirin (Rebetol® and Copegus®), a nucleoside guanosine analogue, given for 24-48 weeks is the standard of care for chronic HCV infection.[11-13] Therapeutic use of peginterferon alfa, a natural human antiviral protein, augments normal antiviral processes. Peginterferon alfa acts through a single receptor and signals the well-characterized JAK-STAT (Janus kinase/signal transducers and activators of transcription) pathway to up- or down-regulate hundreds of genes that function in immune response pathways. Two peginterferon alfa molecules are available for use in combination with ribavirin (peginterferon alfa-2a [PEGASYS®] and peginterferon alfa-2b [PegIntron®]). HCV RNA should be tested using a highly sensitive quantitative assay at the initiation of or shortly before treatment again and at week 12 of treatment.[3]

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**Treatment of Patients With Genotype 1 or Genotype 4 HCV Infection**

Treatment with peginterferon-ribavirin should be planned for 48 weeks. When using peginterferon alfa-2a, the dose is 180 μg per week subcutaneously combined with ribavirin at doses of 1000 mg for patients ≤ 75 kg and 1200 mg for those > 75 kg. When using peginterferon alfa-2b, the dose is 1.5 μg/kg per week subcutaneously together with ribavirin at doses of 800 mg for patients < 65 kg, 1000 mg for those > 65-85 kg, 1200 mg for those > 85-105 kg, and 1400 mg for those > 105 kg.

Treatment may be discontinued in patients who do not achieve an early virologic response ([EVR], ≥ 2 log10 IU/mL reduction in HCV RNA at week 12 of treatment).

Patients who do not achieve a complete EVR (undetectable HCV RNA at week 12 of treatment) should be retested at week 24, and if the HCV RNA test remains positive, treatment should be discontinued.

For patients with genotype 1 infection who have delayed viral clearance (HCV RNA test becomes negative between weeks 12 and 24), consideration should be given to extending treatment to 72 weeks.

Patients with genotype 1 infection whose treatment continues through 48-72 weeks and whose measurement of HCV RNA with a highly sensitive assay is negative at the end of treatment should be retested for HCV RNA 24 weeks later to evaluate for a sustained virologic response ([SVR], HCV RNA negative 24 weeks after cessation of treatment).

---

**Treatment of Patients With Genotype 2 or Genotype 3 HCV Infection**

Treatment with peginterferon alfa at the doses described above plus ribavirin should be administered for 24 weeks, using a ribavirin dose of 800 mg.

Patients whose treatment continues through 24 weeks and are HCV RNA-negative using a highly-sensitive assay should be retested for HCV RNA 24 weeks later to evaluate for an SVR.

Patients with HCV-related cirrhosis who achieve an SVR, regardless of viral genotype, should still be monitored for hepatocellular carcinoma at 6 to 12-month intervals.
Retreatment for Failed Response

Retreatment with peginterferon-ribavirin in patients whose prior full course of peginterferon-ribavirin treatment did not achieve an SVR is not recommended, even if a different type of peginterferon alfa is administered.

Retreatment with peginterferon-ribavirin can be considered for patients who do not respond or experience relapses and have previously been treated with nonpegylated-interferon alfa with or without ribavirin, or with peginterferon alfa monotherapy, particularly if these patients have bridging fibrosis or cirrhosis.

Maintenance treatment is not recommended for patients with bridging fibrosis or cirrhosis who did not respond to a prior course of peginterferon-ribavirin.

Host Genetics and Viral Response

Individuals who have had HCV contact and infection show 3 different phenotypes following antiviral treatment: spontaneous viral clearance, chronic HCV infection, and SVR. Many factors, including genetics, influence the evolution of these phenotypes. The variability in response to treatment (Table 4), especially between patients of different racial groups, suggests that human genetic variability might explain differences in treatment response.

Genome-wide association studies have demonstrated an association between host polymorphisms located upstream of the IL-28B (IFN lambda 3) gene and SVR to treatment with a combination of peginterferon-ribavirin. These polymorphisms are also associated with spontaneous clearance of acute HCV infection, particularly in asymptomatic patients. The distribution of IL-28B polymorphisms varies among populations worldwide and helps to explain heterogeneity in response to interferon-based treatments in different ethnic or racial groups. IL-28B genotype is a stronger predictor of SVR than other well-documented factors such as viral genotype, viral load, or presence of fibrosis, but it does not affect type, dose, or duration of treatment; thus, determination of the IL-28B genotype is not required prior to beginning treatment. Treating physicians must decide whether to obtain IL-28B genotype for their HCV-infected patients and how that information, if obtained, will be incorporated into decisions regarding treatment.
Table 4. Virologic Response to Treatment of HCV Infection\textsuperscript{[3]}

<table>
<thead>
<tr>
<th>Virologic Response</th>
<th>Definition</th>
<th>Clinical Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid virologic response</td>
<td>HCV RNA negative at treatment week 4 by a sensitive PCR-based quantitative assay</td>
<td>May allow shortening of treatment course for genotypes 2 and 3 and possibly genotype 1 with low viral load; predicts a higher likelihood of achieving viral cure</td>
</tr>
<tr>
<td>Early virologic response (EVR)</td>
<td>$\geq 2 \log_{10}$ IU/mL reduction* in HCV RNA level compared with baseline HCV RNA level (partial EVR) or HCV RNA negative at treatment week 12 (complete EVR)</td>
<td>Not reaching EVR predicts a lower likelihood of achieving viral cure</td>
</tr>
<tr>
<td>End-of-treatment response</td>
<td>HCV RNA negative by a sensitive test at the end of 24 or 48 weeks of treatment</td>
<td>Best predictor of a long-term response to treatment</td>
</tr>
<tr>
<td>Sustained virologic response (SVR)</td>
<td>HCV RNA negative at 24 weeks after cessation of treatment; also referred to as viral cure</td>
<td></td>
</tr>
<tr>
<td>Breakthrough</td>
<td>Reappearance of HCV RNA in serum while still on treatment</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>Reappearance of HCV RNA in serum after treatment is discontinued or appearance of HCV RNA in serum while still on treatment</td>
<td></td>
</tr>
<tr>
<td>Nonresponder</td>
<td>Failure to clear HCV RNA from serum after 24 weeks of treatment</td>
<td></td>
</tr>
<tr>
<td>Null responder</td>
<td>Failure to decrease HCV RNA by $&lt; 2 \log_{10}$ IU/mL after 24 weeks of treatment</td>
<td></td>
</tr>
<tr>
<td>Partial responder</td>
<td>$2 \log_{10}$ IU/mL decrease in HCV RNA but remains HCV RNA positive at week 24</td>
<td></td>
</tr>
</tbody>
</table>

*\textit{HCV = hepatitis C virus; RNA = ribonucleic acid; PCR = polymerase chain reaction}*

*\textit{Used} when recording changes in hepatitis C viral load; each $\log_{10}$ corresponds to a factor of 10. A 1 $\log_{10}$ reduction means that the starting (baseline) viral load dropped by 10 times; a 2 $\log_{10}$ reduction means that the starting (baseline) viral load dropped by 100 times.*

Treatment response is greatest in patients with HCV genotypes 2 and 3, in whom SVR rates of approximately 80% can be achieved with 24 weeks of therapy.\textsuperscript{[17]} Patients with HCV genotype 1 are the most difficult to treat; their SVR rates are approximately 40% after 48 weeks of therapy.\textsuperscript{[18]}

**Side Effects of Treatment**

Peginterferon alfa agents are given by subcutaneous injection. Side effects of treatment are numerous and common. The prescribing information for all of these agents includes a black box warning. Links to the prescribing information, including contraindications, warnings and precautions, adverse reactions, and drug interactions can be found in Appendix D.

*\textit{Note: Readers are referred to published clinical practice guidelines for evidence-based recommendations and treatment algorithms for patients with chronic HCV infection.} [3,11]*
VI. A New Standard of Care: HCV Direct-Acting Antivirals (DAAs)

DAAs
Advances made in the use of the combination of peginterferon-ribavirin have led to SVR rates of approximately 55%. However, with treatment failure occurring in nearly half of patients, underscoring the need for more effective therapies. A new standard of care for these patients with HCV is emerging with the advent of DAAs, which are NS3A/4B protease inhibitors that interfere with specific steps in the HCV lifecycle. The new standard of care for treatment-naive HCV genotype 1 patients is triple therapy with a DAA, a peginterferon alfa-2, and ribavirin because of the concern that use of a DAA alone may lead to the selection of resistant viruses. Two DAAs, boceprevir (VICTRELIS™) and telaprevir (INCIVEK™), were approved in 2011 for use in treatment-naive patients with HCV genotype 1. Key results from the phase 3 trials of these agents are provided in Appendix E.

Boceprevir
Boceprevir (Victrelis™), an oral HCV protease inhibitor, was approved for the treatment of chronic HCV infection on May 13, 2011. Boceprevir is highly effective in increasing the likelihood of SVR when used with standard combination therapy in patients with a HCV type 1 infection.[22,23] A link to the prescribing information, including contraindications, warnings and precautions, adverse reactions, and drug interactions can be found in Appendix D.

<table>
<thead>
<tr>
<th>Boceprevir Regimen for Treatment-Naive Persons With Chronic HCV Genotype 1 Infection[24]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lead in: peginterferon-ribavirin for 4 weeks</td>
</tr>
<tr>
<td>2. Follow with boceprevir 800 mg orally 3 times daily for 24 weeks</td>
</tr>
<tr>
<td>3. Check HCV RNA level at 8 weeks</td>
</tr>
<tr>
<td>- If viral suppression by 8 weeks, then total therapy is 28 weeks</td>
</tr>
<tr>
<td>- If no viral suppression at 8 weeks, then total therapy is 48 weeks, with peginterferon-ribavirin for final 20 weeks</td>
</tr>
</tbody>
</table>

**Summary**

Weeks 1-4: peginterferon-ribavirin

Weeks 5-28: peginterferon-ribavirin + boceprevir

Weeks 29-48: peginterferon-ribavirin
Telaprevir

Telaprevir (Incivek™), an oral HCV protease inhibitor, was approved for the treatment of chronic HCV infection on May 23, 2011. Telaprevir is highly effective in increasing the chances of SVR across all IL28B genotypes of HCV when used with standard combination therapy in patients with a HCV type 1 infection.[25] Telaprevir appears effective given either with peginterferon alfa-2a or -2b. A link to the prescribing information, including contraindications, warnings and precautions, adverse reactions, and drug interactions can be found in Appendix E.

<table>
<thead>
<tr>
<th>Telaprevir Regimen for Treatment-Naive Persons With Chronic HCV Genotype 1 Infection[25]</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-week regimen if RVR by 4 weeks and viral suppression before 24 weeks:</td>
</tr>
<tr>
<td>1. Peginterferon-ribavirin + telaprevir 750 mg oral every 8 hours for 12 weeks</td>
</tr>
<tr>
<td>2. Peginterferon-ribavirin for 12 weeks</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
</tr>
<tr>
<td>Weeks 1-12: peginterferon-ribavirin + telaprevir</td>
</tr>
<tr>
<td>Weeks 13-24: peginterferon-ribavirin</td>
</tr>
<tr>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>48-week regimen if detectable HCV RNA at 8 weeks and viral suppression before 24 weeks:</td>
</tr>
<tr>
<td>1. Peginterferon-ribavirin + telaprevir 750 mg oral every 8 hours for 12 weeks</td>
</tr>
<tr>
<td>2. Peginterferon-ribavirin for 36 weeks</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
</tr>
<tr>
<td>Weeks 1-12: peginterferon-ribavirin + telaprevir</td>
</tr>
<tr>
<td>Weeks 13-48: peginterferon-ribavirin</td>
</tr>
</tbody>
</table>

A glossary of terms is provided in Appendix F.
VII. References

13. Craxi A. EASL clinical practice guidelines: management of hepatitis C virus infection. J Hepatology. 2011. [This article is temporarily withdrawn at the request of the editor and author.]
VIII. APPENDICES

Appendix A: Summary of AASLD Practice Guideline Recommendations for Diagnosis, Management, and Treatment of Hepatitis C

Appendix B: Checklist for Referring a Patient With Chronic HCV Infection for Specialist Care

Appendix C: Reference for Interpretation of HCV Test Results

Appendix D: Professional and Community Resources

Appendix E: Summary of Key Results From Phase 3 Clinical Trials of Boceprevir and Telaprevir for HCV Infection

Appendix F: Glossary of Terms
Appendix A: Summary of AASLD Practice Guideline Recommendations for Diagnosis, Management, and Treatment of Hepatitis C


Testing and Counseling
As part of a comprehensive health evaluation, all persons should be screened for behaviors that place them at high risk for hepatitis C virus (HCV) infection.

Persons who are at risk should be tested for the presence of HCV infection.

Persons infected with HCV should be counseled on how to avoid transmitting HCV to others.

Laboratory Testing
Patients suspected of having acute or chronic HCV infection should first be tested for antibodies to HCV (anti-HCV).

HCV RNA testing should be performed in:
- Patients with a positive anti-HCV test;
- Patients for whom antiviral treatment is being considered, using a sensitive quantitative assay; or
- Patients with unexplained liver disease whose anti-HCV test is negative and who are immunocompromised or suspected of having acute HCV infection.

HCV genotyping should be performed in all HCV-infected persons prior to interferon-based treatment in order to plan for the dose and duration of therapy and to estimate the likelihood of response.

Liver Biopsy
A liver biopsy should be considered in patients with chronic HCV infection if the patient and health care provider wish information regarding stage of fibrosis for prognostic purposes or to make decisions regarding treatment.

Currently available noninvasive tests may be useful in defining the presence or absence of advanced fibrosis in persons with chronic HCV infection, but should not replace the liver biopsy in routine clinical practice.

Initial Treatment
Treatment decisions should be individualized and based on the severity of liver disease, the potential for serious side effects, the likelihood of treatment response, the presence of comorbid conditions, and the patient’s readiness for treatment.

For patients in whom liver histology is available, treatment is indicated in those with bridging fibrosis or compensated cirrhosis, provided that they have no contraindications to therapy.

The optimal therapy for chronic HCV infection is the combination of a peginterferon-ribavirin.

HCV RNA should be tested by a highly sensitive quantitative assay at the initiation of or shortly before treatment and again at week 12 of therapy.
Genotypes 1 or Genotype 4 HCV Infection
Treatment with peginterferon-ribavirin should be planned for 48 weeks. When using peginterferon alfa-2a, the dose is 180 μg per week subcutaneously combined with ribavirin at doses of 1000 mg for patients ≤ 75 kg and 1200 mg for those > 75 kg. When using peginterferon alfa-2b, the dosage is 1.5 μg/kg per week subcutaneously together with ribavirin at doses of 800 mg for patients < 65 kg, 1000 mg for those > 65-85 kg, 1200 mg for those > 85-105 kg, and 1400 mg for those > 105 kg.

Treatment may be discontinued in patients who do not achieve an early virologic response ([EVR], ≥ 2 log_{10} IU/mL reduction in HCV RNA at week 12 of treatment).

Patients who do not achieve a complete EVR (undetectable HCV RNA at week 12 of treatment) should be retested at week 24, and if the HCV RNA test remains positive, treatment should be discontinued.

For patients with genotype 1 infection who have delayed viral clearance (HCV RNA test becomes negative between weeks 12 - 24), consideration should be given to extending therapy to 72 weeks.

Patients with genotype 1 infection whose treatment continues through 48 - 72 weeks and who are then HCV RNA-negative using a highly sensitive assay should be retested for HCV RNA 24 weeks later to evaluate for a sustained virologic response ([SVR], HCV RNA negative 24 weeks after cessation of treatment).

Genotype 2 or Genotype 3 HCV Infection
Treatment with peginterferon-ribavirin should be administered for 24 weeks, using a ribavirin dose of 800 mg.

Patients whose treatment continues through 24 weeks and who are then HCV RNA-negative using highly sensitive assay should be retested for HCV RNA 24 weeks later to evaluate for an SVR.

Patients with HCV-related cirrhosis who achieve an SVR, regardless of the genotype, should continue to be monitored at 6 - 12 month intervals for the development of hepatocellular carcinoma.

Retreatment for Failed Response
Retreatment with peginterferon-ribavirin in patients who did not achieve an SVR after a prior full course of peginterferon-ribavirin is not recommended, even if a different type of peginterferon alfa is administered.

Retreatment with peginterferon-ribavirin can be considered for patients who do not respond to treatment or patients who relapse after previous treatment with nonpegylated interferon alfa with or without ribavirin, or with peginterferon alfa monotherapy, particularly if they have bridging fibrosis or cirrhosis.

Maintenance therapy is not recommended for patients with bridging fibrosis or cirrhosis who have not responded to a prior course of peginterferon-ribavirin.

Special Patient Groups
Regardless of the serum alanine aminotransferase level, the decision to initiate therapy with peginterferon-ribavirin should be individualized and based on the severity of liver disease by liver biopsy, the potential for serious side effects, the likelihood of response, and the presence of comorbid conditions.

The treatment regimen for HCV-infected persons with normal transaminase levels should be the same as that used for persons with elevated serum aminotransferase levels.
Children
The diagnosis and testing of children suspected of being infected with HCV should proceed as for adults.

Routine testing for anti-HCV at birth of children born to HCV-infected mothers is not recommended because of the high rate of positive anti-HCV tests due to passive transfer from the mother. Testing for anti-HCV may be performed at 18 months of age or older.

Testing for HCV RNA may be considered at 1-2 months of age in infants born to HCV-infected mothers if early diagnosis is desired.

Children aged 2-17 years who are infected with HCV should be considered appropriate candidates for treatment using the same criteria as those used for adults (see Table 3).

Children should be treated with peginterferon alfa-2b, 60 μg/m² weekly in combination with ribavirin, 15 mg/kg daily for a duration of 48 weeks.

HIV-Infected Persons
Anti-HCV testing should be performed in all HIV-infected persons.

HCV RNA testing should be performed to confirm HCV infection in HIV-infected persons who are positive for anti-HCV, as well as in those who are anti-HCV negative and have evidence of unexplained liver disease.

HCV should be treated in the HIV/HCV coinfected patient in whom the likelihood of serious liver disease and a treatment response are judged to outweigh the risk for morbidity from the adverse effects of therapy.

Initial treatment of HCV in most HIV-infected patients should be peginterferon–ribavirin for 48 weeks at doses recommended for HCV mono-infected patients described above.

When possible, patients receiving zidovudine and especially didanosine should be switched to an equivalent antiretroviral agent before beginning therapy with ribavirin.

HIV-infected patients with decompensated liver disease (Child-Turcotte-Pugh [CTP] Class B or C) should not be treated with peginterferon–ribavirin and may be candidates for liver transplantation.

Persons With Chronic Kidney Disease, End-Stage Renal Disease, and Kidney Transplantation
All persons with chronic kidney disease awaiting renal replacement therapy (hemodialysis or kidney transplantation) should be screened for HCV in order to plan for management and treatment.

The decision to perform a liver biopsy in patients with kidney disease should be individualized and based upon the clinical assessment for the need for therapy and the need to establish the severity of the liver disease.

Persons with chronic HCV infection and mild kidney disease (glomerular filtration rate > 60 mL/min) can be treated with the same combination antiviral therapy as that used in persons without kidney disease.

Persons with chronic HCV infection and severe kidney disease who are not undergoing hemodialysis can be treated with reduced doses of both peginterferon alfa (peginterferon alfa-2a, 135 μg/week; peginterferon alfa-2b, 1 μg/kg/week) and ribavirin (200–800 mg/day) with careful monitoring for adverse effects.

Treatment of HCV in patients on dialysis may be considered with either standard interferon (peginterferon alfa-2a) at a dose of 3 mU thrice weekly or reduced-dose peginterferon alfa-2a, 135 ug/week or 2b 1 ug/kg/week. Ribavirin can be used in combination with peginterferon alfa in a markedly reduced daily dose with careful monitoring for anemia and other adverse effects.
Treatment is not recommended for patients with chronic HCV infection who have undergone kidney transplantation, unless they develop fibrosing cholestatic hepatitis.

Patients with cryoglobulinemia, mild-to-moderate proteinuria, and slowly progressive kidney disease can be treated with either standard-dose or reduced-dose peginterferon-ribavirin.

Patients with cryoglobulinemia and marked proteinuria with evidence of progressive kidney disease or an acute flare of cryoglobulinemia can be treated with rituximab, cyclophosphamide plus methylprednisolone, or plasma exchange followed by peginterferon alfa-based treatment once the acute flare process has subsided.

**Black Persons**

Black persons infected with HCV who are appropriate treatment candidates should be treated with the current optimal regimen consisting of peginterferon-ribavirin.

African Americans with baseline neutropenia (absolute neutrophil count < 1500 mm$^3$) should not be excluded from HCV treatment.

**Persons With Cirrhosis**

Patients with HCV-related compensated cirrhosis (CTP class A), can be treated with the standard regimen of peginterferon-ribavirin, but will require close monitoring for adverse events.

Patients with HCV-related decompensated cirrhosis should be referred for consideration of liver transplantation.

Interferon alfa-based therapy may be initiated at a lower dose in patients with decompensated cirrhosis (CTP class B and C), preferably in patients who have already been accepted as candidates for liver transplantation and as long as treatment is administered by experienced clinicians with vigilant monitoring for adverse events.

Growth factors can be used for treatment-associated anemia and leukopenia to improve quality of life and may limit the need for antiviral dose reductions in patients with decompensated cirrhosis.

**Solid Organ Transplant Recipients**

Treatment of HCV-related disease following liver transplantation should be initiated in appropriate candidates after demonstration of recurrent histologic disease but should be undertaken with caution and under the supervision of a physician experienced in transplantation.

Peginterferon alfa, either with or without ribavirin, should be the preferred regimen when treating patients with HCV after liver transplantation.

Interferon alfa-based therapy should not be used in recipients of heart, lung, or kidney grafts, except for patients who develop fibrosing cholestatic hepatitis.
Appendix B: Checklist for Referring a Patient With Chronic HCV Infection for Specialist Care

Date: 

Referring Physician
Name: 
Address: 
Phone #: 
Fax #: 

Patient Information
Name: 
Date of birth: 
Address: 
Phone #: 

Reason for referral: 

Laboratory results (performed within the last 6 months) attached:
☐ HCV RNA PCR
☐ HCV genotype, viral load
☐ Alpha-fetoprotein
☐ HBV serology
☐ HAV IgM
☐ Anti-HIV
☐ Comprehensive metabolic panel
☐ ALT, AST, GGT, bilirubin (direct and indirect)
☐ Iron studies
☐ Total protein, albumin, globulin
☐ Complete blood count
☐ Prothrombin time
☐ Thyroid function tests
☐ ANA, AMA

☐ Other: 

Medical history: 

Family history: 

Current medications: 

Signature: 

AMA = antimitochondrial antibody; ALT = alanine aminotransferase; ANA = antinuclear antibody; AST = aspartate aminotransferase; GGT = gamma-glutamyl transpeptidase; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; PCR = polymerase chain reaction
## Appendix C: Reference for Interpretation of HCV Test Results

<table>
<thead>
<tr>
<th>If Your HCV Result Is:</th>
<th>Interpretation</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-HCV Screening Test</strong>*</td>
<td><strong>Anti-HCV Supplementation Test</strong></td>
<td><strong>Anti-HCV</strong></td>
</tr>
<tr>
<td>Negative</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td>Positive</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>Positive</td>
<td>Not done</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive ratio§</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Not needed</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Not done</td>
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<tr>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive/ Not done</td>
<td>Positive</td>
</tr>
<tr>
<td>Positive</td>
<td>Indeterminate</td>
<td>Not done</td>
</tr>
<tr>
<td>Positive</td>
<td>Indeterminate</td>
<td>Positive</td>
</tr>
<tr>
<td>Positive</td>
<td>Indeterminate</td>
<td>negative</td>
</tr>
</tbody>
</table>

* Anti-HCV = antibodies to HCV virus; RIBA = recombinant immunoblot assay; RNA = ribonucleic acid; s/co = signal-to-cutoff ratio

* EIA (enzyme immunoassay) or CIA (enhanced chemiluminescence immunoassay).
† RIBA (recombinant immunoblot assay), a more specific anti-HCV assay.
• Single negative HCV RNA result cannot determine infection status, as persons might have intermittent viremia.
§ Samples with high signal-to-cut-off ratios usually (>95%) confirm positive, but supplemental serologic testing was not performed. Fewer than 5/100 tests may represent false positives; more specific testing should be requested, if indicated.[1]
Appendix D. Professional and Community Resources

Practice Guidelines and Position Statements

American Gastroenterological Association. GI Locator Service.
https://secure.gastro.org/GILocator/locator.asp

American Gastroenterological Association Medical Position Statement on the Management of Hepatitis C
http://www.gastrojournal.org/article/S0016-5085(05)02271-7/fulltext

Diagnosis, Management, and Treatment of Hepatitis C: An Update

EASL Clinical Practice Guidelines: Management of Hepatitis C Virus Infection
http://www.easl.eu/assets/application/files/d0df9f948c85a72_file.pdf

Sexually Transmitted Diseases Treatment Guidelines, 2010, Hepatitis C

Professional Resources

American Association for the Study of Liver Diseases
http://www.aasld.org/Pages/Default.aspx

Combating the Silent Epidemic of Viral Hepatitis
Action Plan for the Prevention, Care & Treatment of Viral Hepatitis

Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C

Infectious Diseases Society of America
http://www.idsociety.org

Medscape Hepatitis C Resource Center

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Chronic Hepatitis C: Current Disease Management

Prescribing information for peginterferon alfa-2a (Pegasys®):

Prescribing information for peginterferon alfa-2b (PegIntron):

Prescribing information for ribavirin (Rebetol):

Prescribing information for ribavirin (Copegus):
Prescribing information for boceprevir (Victrelis):

Prescribing information for telaprevir (Incivik):

United States Department of Veterans Affairs: Hepatitis C for Healthcare Providers
Hepatitis C for Healthcare Providers

Viral Hepatitis Action Coalition
http://viralhepatitisaction.org/

World Health Organization: Hepatitis C
Hepatitis C

Community Resources

American College of Gastroenterology
ACG Hepatitis C Treatment Resource Kit
http://www.acg.gi.org/patients/hepatitisc.asp

American Liver Foundation
http://www.liverfoundation.org/

Centers for Disease Control and Prevention
Hepatitis C Information for the Public, Patient Education Materials
http://www.cdc.gov/hepatitis/C/PatientEduC.htm

Hepatitis C Guide
WebMD
http://www.webmd.com/hepatitis/hepc-guide/hepatitis-c-resources

Hepatitis Education Project
http://www.hepeducation.org/

Hepatitis Foundation International
http://www.hepfi.org/

HCV Advocate
http://www.hcvadvocate.org/

National Institute of Allergy and Infectious Diseases
Hepatitis C

United States Department of Veterans Affairs
Hepatitis C for the Public
## Appendix E: Summary of Key Results From Phase 3 Clinical Trials* of Boceprevir and Telaprevir for Chronic HCV Genotype 1 Infection In Adults

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Study Design</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPOND-2**</td>
<td>Compared 2 treatment regimens containing boceprevir in combination with open-label peginterferon alfa-2b-ribavirin to treatment peginterferon-ribavirin plus placebo in previously-treated adults (Nonresponders or relapsers) with chronic HCV genotype 1 infection</td>
<td>SVR** rate was significantly higher in the 2 boceprevir groups (59%, 66%) vs 21% in the control group (P &lt; .001)</td>
<td>More serious adverse events, discontinuations, and dose modifications due to adverse events in the boceprevir groups vs the control group</td>
</tr>
<tr>
<td></td>
<td>Primary endpoint was sustained virologic response (SVR), defined as undetectable plasma HCV RNA at week 24 of follow-up</td>
<td>Patients with undetectable HCV RNA at week 8, had SVR rates of 86% and 88% after 32 and 44 weeks of triple therapy, respectively</td>
<td>Most frequent adverse events in all treatment groups were flulike symptoms that are typically associated with combined peginterferon-ribavirin therapy</td>
</tr>
<tr>
<td></td>
<td>Failure to achieve an undetectable HCV RNA level at week 12 triggered the stopping rule: discontinuation of all treatment and advancement to follow-up</td>
<td></td>
<td>Dysgeusia, rash, and dry skin were more frequent in the boceprevir groups vs the control group</td>
</tr>
<tr>
<td></td>
<td>In all 3 arms, peginterferon alfa-2b-ribavirin were administered for 4 weeks (the lead-in period); subsequently:</td>
<td></td>
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<tr>
<td></td>
<td>- Arm 1: received placebo plus peginterferon-ribavirin for 44 weeks (control group)</td>
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<tr>
<td></td>
<td>- Arm 2: received boceprevir plus peginterferon and ribavirin for 32 weeks; patients with a detectable HCV RNA level at week 8 received placebo plus peginterferon-ribavirin for an additional 12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Arm 3: received boceprevir plus peginterferon-ribavirin for 44 weeks</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Drug Doses</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>- Peginterferon alfa-2b: 1.5 μg/kg subcutaneous once weekly</td>
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<td></td>
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<tr>
<td></td>
<td>- Ribavirin: divided daily dose of 600-1400 mg/day based on body weight</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>- Boceprevir 800 mg 3 times daily (4 capsules of 200 mg each) orally</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical Trial | Study Design | Results | Safety
---|---|---|---
SPRINT-2[^1] | • Compared peginterferon alfa-2b-ribavirin with 2 treatment regimens in which boceprevir was added after a lead-in period of treatment with peginterferon-ribavirin alone | • Addition of boceprevir to standard therapy with peginterferon-ribavirin vs standard therapy alone, significantly increased the SVR rates; SVR rates were similar with 24 weeks and 44 weeks in boceprevir arms | • Adverse events occurred in > 98% of the study patients; serious adverse events occurred in 9%, 11%, and 12% of patients in arms 1, 2, and 3, respectively
• Self-identified blacks (n=159) and nonblacks (n=938) were enrolled separately into 2 cohorts and analyzed separately | • Nonblack cohort: the SVR rate was 40% in arm 1, 67% in arm 2 (P < .001), and 68% in arm 3 (P < .001) | • Fatigue, headache, and nausea were the most frequent clinical adverse events in all treatment arms
• Primary endpoint was sustained virologic response (SVR), defined as undetectable plasma HCV RNA at week 24 of follow-up | • Black cohort: the SVR rate was 23% in arm 1, 42% in arm 2 (P = .04, and 53% in arm 3 (P = .004) | • Anemia and dysgeusia were more frequent in boceprevir vs placebo arms (P < .001)
• In all 3 arms, peginterferon alfa-2b-ribavirin were administered for 4 weeks (the lead-in period) | Overall: the SVR rate was 38% in arm 1, 63% in arm 2 (P < .001), and 66% in arm 3 (P < .001) | • Use of erythropoietin use higher in boceprevir vs placebo arms (P < .001)
  • Arm 1: received placebo plus peginterferon-ribavirin for 44 weeks (control group) | | |
  • Arm 2: received boceprevir plus peginterferon-ribavirin for 24 weeks; those with a detectable HCV RNA level between weeks 8 and 24 received placebo plus peginterferon-ribavirin for an additional 20 weeks | | |
  • Arm 3: received boceprevir plus peginterferon-ribavirin for 44 weeks | | |
• Drug Doses | | |
  • Peginterferon alfa-2b: 1.5 μg/kg subcutaneous once weekly | | |
  • Ribavirin: divided daily dose of 600-1400 mg/day based on body weight | | |
  • Boceprevir 800 mg 3 times daily (4 capsules of 200 mg each) orally | | |
<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Study Design</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
</table>
| ADVANCE[^1]   | • Compared 2 regimens of telaprevir of different durations, combined with peginterferon alfa-2a-ribavirin, with a regimen of peginterferon alfa-2a-ribavirin alone  
  • Arm 1: received telaprevir combined with peginterferon alfa-2a-ribavirin for 12 weeks (T12PR group), followed by peginterferon-ribavirin alone for 12 weeks if HCV RNA was undetectable at weeks 4 and 12 or for 36 weeks if HCV RNA was detectable at either time point  
  • Arm 2: received telaprevir with peginterferon-ribavirin for 8 weeks and placebo with peginterferon-ribavirin for 4 weeks (T8PR group), followed by 12 or 36 weeks of peginterferon-ribavirin on the basis of the same HCV RNA criteria  
  • Arm 3: received placebo plus peginterferon-ribavirin for 12 weeks, followed by 36 weeks of peginterferon-ribavirin (PR group)  
  • Drug Doses  
    - Telaprevir: 750 mg q8h orally  
    - Peginterferon alfa-2b: 180 μg/week  
    - Ribavirin: 1000-1200 mg/day, based on body weight | • SVR rates were significantly higher in the T12PR and T8PR groups (75% and 69%, respectively) vs the PR group (44%, \( P < .001 \)); 58% of the patients in the telaprevir groups were eligible to receive a total of 24 weeks of treatment | • Rates of gastrointestinal disorders (nausea and diarrhea), pruritus, rash, and anemia were ≥ 10 percentage points higher in the T12PR and T8PR groups vs the PR group  
  • Rates of rash events and grade 3 rash*** events were 61% and 6%, respectively, in the T12PR group; 58% and 4%, respectively, in the T8PR group; and 48% and 1%, respectively, in the PR group during the overall treatment phase  
  • Rates of patients with hemoglobin levels < 10 g/dL and < 8.5 g/dL were 36% and 9%, respectively, in the T12PR group; 40% and 9%, respectively, in the T8PR group; and 14% and 2%, respectively, in the PR group  
  • Anemia and rash were the most frequently reported adverse events that led to the discontinuation of telaprevir-based regimens  
  • All treatment was discontinued due to adverse events in 10% of the patients in the T12PR group, 10% in the T8PR group, and 7% in the PR group  
  • All treatment was discontinued due to adverse events in 7%, 8%, and 4% of the patients in the same 3 groups, respectively, during the telaprevir (or placebo) phase of the study |
<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Study Design</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
</table>
| REALIZE<sup>[4]</sup> | • Evaluated the addition of telaprevir to standard therapy (peginterferon alfa-2a-ribavirin) in patients who had no response or a partial response to previous therapy, or who had a relapse after an initial response  
• Arm 1: received peginterferon alfa-2a-ribavirin for 48 weeks (control group)  
• Arm 2: received telaprevir plus peginterferon alfa-2a-ribavirin for 12 weeks, followed by peginterferon alfa-2a-ribavirin for 36 weeks  
• Arm 3: received peginterferon alfa-2a-ribavirin for 4 weeks, followed by telaprevir-peginterferon alfa-2a-ribavirin for 12 weeks, followed by peginterferon alfa-2a-ribavirin for 32 weeks (lead-in group)  
• Drug Doses  
  − Telaprevir: 750 mg q8h orally  
  − Peginterferon alfa-2b: 180 μg/week  
  − Ribavirin: 1000-1200 mg/day, based on body weight | SVR rates were significantly higher in the 2 telaprevir groups vs the control group (P < .001 for all comparisons) among patients who had:  
• A previous relapse (83% in the T12PR48 group, 88% in the lead-in T12PR48 group, and 24% in the PR48 group);  
• A partial response (59% in the T12PR48 group, 54% in the lead-in T12PR48 group, and 15% in the PR48 group); or  
• No previous response (29% in the T12PR48 group, 33% in the lead-in T12PR48 group, and 5%, in the PR48 group) | • Fatigue, pruritus, nausea, influenza-like illness, anemia, diarrhea, an rash were the most frequent adverse events (occurring in > 25% of patients) in the 2 telaprevir groups vs the control group  
• Serious adverse events (12%) and adverse events leading to permanent discontinuation of a study drug (13%) were more frequent in the 2 telaprevir groups vs the control group (5% and 3%, respectively)  
• Grade 3 adverse events (mainly anemia, neutropenia, and leukopenia) were more frequent in the 2 telaprevir groups (37%) vs the control group (22%)  
• The rate of grade 3 rash and grade 3 pruritus were 3% and 1% in the 2 telaprevir groups, respectively vs no patients in the control group  
• Rash as an adverse event of special interest occurred in 5% of patients in the 2 telaprevir groups vs no patients in the control group  
• In the 2 telaprevir groups, 4% of patients discontinued telaprevir and 1% of patients discontinued all drugs because of rash vs no patients in the control group |

**International, multicenter, randomized, double-blind, placebo-controlled**  
**Undetectable plasma HCV RNA at week 24 of follow-up**  
**Severe, involving > 50% of body surface or rash with the appearance of major systemic signs or symptoms**  
**Severe adverse event**  
**Severe adverse event**  
**A grade 3 skin event, any skin event resulting in permanent discontinuation of any or all study drugs, or any skin event defined as a serious adverse event**

**References**  
Appendix F: Glossary of Terms

**Acute Hepatitis C Virus (HCV) Infection**
A short-term illness that usually occurs within the first 6 months after someone is exposed to HCV.

**Boceprevir**
An oral inhibitor of the viral protease NS3/4A approved for the treatment of chronic HCV infection; the NS3 protease, a multifunctional enzyme, is one of 6 nonstructural proteins needed for viral replication and maturation.

**Breakthrough (of HCV viral load)**
After dropping to undetectable levels, HCV RNA becomes detectable again in the blood during treatment.

**Chronic HCV Infection**
An HCV infection lasting longer than 6 months. Approximately 75%-85% of people who become infected with HCV develop chronic infection, a silent disease that damages the liver over the course of decades. It is a leading cause of liver failure, liver cancer, and the leading indication for liver transplantation.

**Direct-acting Antiviral Agent (DAA)**
Several DAAAs in different pharmacological classes (nucleos(t)ide analogues, various families of non-nucleoside polymerase inhibitors, and protease inhibitors) are currently under development for the treatment of chronic HCV infection. DAAs target specific enzymes within HCV that are necessary for viral replication and are known as specifically-targeted antiviral therapy for hepatitis C, or STAT-C compounds. The enzymes targeted for antiviral therapy include the proteases and polymerases.

**Early Virologic Response (EVR)**
Occurs when HCV RNA cannot be detected in a patient’s blood or decreases by > 2 log10 IU/mL (100 times) from the starting level by week 12. Not reaching EVR predicts a lower likelihood of achieving cure.

**Genotype**
The genetic make-up of an organism or a virus. HCV has 6 genotypes and many subtypes. A person’s HCV genotype may be important in determining the severity of the disease and predicting response to treatment.

**HCV**
HCV is a small (55-65 nm), enveloped, positive-sense single-stranded RNA virus of the family Flaviviridae. Hepatitis C virus is the cause of HCV infection in humans.

**HCV Antibody (Anti-HCV)**
The antibody specific to HCV. The presence of anti-HCV in the blood indicates that a person was infected with HCV; however, it does not indicate whether the infection is new (acute), long-term (chronic), or no longer present.

**HCV RNA**
Genetic material found in people with hepatitis C. HCV RNA in the blood indicates a patient is currently infected with HCV.

**Interferon**
Naturally occurring protein made by the immune system in response to viral infection and inflammatory diseases. Interferon alfa, a synthetic form, is given by injection to treat HCV infection, usually in combination with the drug ribavirin.

**Null Response**
Failure to clear HCV RNA from serum after 24 weeks of treatment.

**Partial Response**
2 log10 IU/mL (100 times) decrease in HCV RNA but HCV RNA positive at week 24 of treatment.
**Peginterferon alfa**
A synthetic version of interferon alfa that is often used in combination with the drug ribavirin to treat HCV infection. The half-life of interferon alfa is longer than standard interferon alfa.

**Polymerase Inhibitor**
Compounds that inhibit the polymerase enzyme, which is necessary for HCV replication.

**Protease**
An enzyme that cuts proteins into smaller pieces. The HCV protease plays an essential role in the replication of HCV.

**Protease Inhibitor**
A class of compounds that inhibits the HCV protease enzyme, a protein necessary for making new viruses. Specifically, protease inhibitors prevent HCV protease from cutting a large protein (polyprotein) into smaller pieces that are used to build new viruses.

**Rapid Virologic Response (RVR)**
HCV RNA is negative (undetectable) at week 4 of treatment. Reaching rapid virologic response predicts a higher likelihood of sustained virologic response (viral cure) and can allow shortening of treatment course for HCV genotype 2 or 3.

**Relapse**
After dropping to undetectable levels, HCV RNA is detected again in blood after treatment ends.

**Ribavirin**
An antiviral medication called a nucleoside analogue. Ribavirin is usually used in combination with a peginterferon, and is not generally effective in the treatment of HCV when used as monotherapy.

**Specifically-targeted Antiviral Therapy for Hepatitis C (STAT-C) Compounds**
DAAs target specific enzymes within HCV that are necessary for viral replication. The enzymes targeted for antiviral therapy include the proteases and polymerases.

**Subtype**
Closely related isolates within each of the major genotypes.

**Sustained Virologic Response**
Undetectable plasma HCV RNA at 24 weeks after end of antiviral treatment.

**Telaprevir**
An oral inhibitor of the viral protease NS3/4A approved for the treatment of chronic HCV infection. The NS3 protease, a multifunctional enzyme, is one of 6 nonstructural proteins needed for viral replication and maturation.

**Treatment Failure**
Failure to clear HCV RNA from serum after 24 weeks of treatment.

**Treatment Naïve Patient**
A patient with HCV infection who has not received any antiviral treatment.

**Viral Load**
The amount of HCV RNA in the blood.