LEARNING OBJECTIVES
Upon completion of this activity, participants should be better able to:

- Identify patients who are candidates for specific hepatitis C virus (HCV) therapeutic protocols based on prior treatment history and complicating comorbidities
- Describe currently available and emerging treatment options for HCV infection
- Initiate practice-based strategies to improve treatment adherence to HCV therapy

INTRODUCTION
Hepatitis C virus (HCV) infection, the most common blood-borne infection in the United States, currently affects approximately 3 million Americans; however, one-half of those infected do not know they are infected. If untreated, HCV infection can progress to cirrhosis, hepatocellular carcinoma (HCC), and the need for liver transplantation. HCV infection was associated with at least 50% of the almost 19,000 US deaths from HCC in 2010.

Despite the availability of effective treatments, most individuals infected with HCV do not receive treatment. According to results from a recent study, only 16% of people diagnosed with HCV infection have been prescribed treatment, and only 9% achieved a sustained virologic response (SVR) (Figure 1).

These sobering statistics may soon change in light of a profound shift in the management of HCV infection. Clinicians who manage HCV infection now commonly invoke the word “cure,” a reality for many patients due to the emergence of a number of all-oral, direct-acting antivirals (DAAs), with a remarkable level of therapeutic efficacy, tolerability, and convenience. All-oral treatments that achieve an almost 100% cure rate after 12 weeks of therapy—compared with the previous 24- to 48- week treatment protocols—
have changed the HCV paradigm, giving patients who are infected who had resisted being tested a reason to be tested and receive treatment.

**NATURAL HISTORY OF HCV INFECTION**

HCV is transmitted through contact with the blood of an infected individual. Acute HCV infections are diagnosed infrequently because most individuals infected with acute HCV remain asymptomatic; approximately 30% to 40% experience mild to moderate nonspecific symptoms, such as fever, nausea, abdominal pain, fatigue, or jaundice. Acute HCV infections resolve spontaneously in about 25% to 45% of exposed individuals for reasons that are not completely understood, but host immune and genetic factors are thought to play a role. The remaining 75% to 85% of patients with acute HCV infection go on to develop chronic HCV infection, usually within 6 months, which leads to most HCV-related morbidity and mortality. Over 30 years of chronic HCV infection, the risk of developing cirrhosis is 15% to 35%, and 1% to 3% of these cases progress to HCC each year.

Although the overall prevalence of HCV infection is decreasing, the prevalence of cirrhosis is currently increasing and expected to peak between 2010 and 2030, some 30 years after the peak of acute infections. Because many patients are unaware of their infection and not undergoing treatment, HCV infections ultimately place a tremendous burden on the healthcare system.

Optimal outcomes for individuals with HCV infection are achieved with fulfillment of key steps along a treatment continuum, referred to as the cascade of care. These include diagnosis and awareness of HCV infection and care seeking, HCV RNA testing and liver fibrosis staging once in care, and receiving and adhering to therapy. Recommended screenings, vaccinations, and guideline-driven care should be given throughout the treatment continuum.

**HCV SCREENING**

The current HCV testing recommendations are detailed in Table 1.
HEPATITIS C VIRUS INFECTION

HCV infection among persons born between 1945 and 1965 to be 3.25%—5 times higher than the prevalence in other adults.²,¹⁶ Therefore, the CDC revised their recommendations in 2012 to include one-time screening of the vast majority (75%) of Americans infected with HCV—those born between 1945 and 1965 (the baby boomer birth cohort).²,¹⁶ This, along with the more traditional targeted screening of individuals with risk factors, should result in a significant reduction in the number of individuals infected with HCV who do not realize that they are infected and therefore do not seek treatment.¹⁷ Identifying patients with undiagnosed HCV infection—and doing so in the early stages of infection—has been a significant obstacle in reducing the morbidity and mortality associated with HCV infection.

POPULATIONS AT RISK OF HCV INFECTION

Percutaneous exposure is the primary route of HCV transmission, and 60% of acute HCV infections in the United States occur through injection drug use.⁷ Exposures from needle stick or sharps injuries due to inadequate infection control procedures are other sources of transmission. Persons who received a blood transfusion or solid organ transplant before 1992 (the year when screening of the blood supply became standard protocol) or clotting factor concentrates produced before 1987 are at increased risk, as are persons receiving hemodialysis or who have received a tattoo in an unregulated setting.⁷,⁸

HCV can also be transmitted through mucosal exposures, including sharing of contaminated devices during intranasal drug use.⁷,⁸ Sexual transmission of HCV occurs rarely among healthy, monogamous couples, but the risk is significantly higher in the context of human

---

Table 1. HCV Testing Recommendations⁷

<table>
<thead>
<tr>
<th>Birth cohort testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended once for persons born between 1945 and 1965</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factor screening and testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing should be performed for all persons with behaviors, exposures, or medical conditions associated with an increased risk of HCV infection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk behaviors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection drug use, current or ever; intranasal illicit drug use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term hemodialysis; getting a tattoo in an unregulated setting; healthcare workers after needle sticks, sharps, or mucosal exposures to HCV-infected blood; children born to HCV-infected women; certain prior transfusion or organ transplant recipients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other medical conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection; unexplained liver disease and chronic hepatitis, including elevated ALT levels</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; HIV = human immunodeficiency virus.
HEPATITIS C VIRUS INFECTION

immunodeficiency virus (HIV) coinflection, and men who have sex with men are at particularly high risk. Studies suggest that the risk of transmission from an infected mother to her infant is 4%, increasing to 25% if the mother is coinfected with HIV.

HCV infection is a significant concern in detained populations. About 29% of individuals who have been incarcerated in North America have been infected with HCV.

Risk factors such as intranasal drug use, a single injection drug use long ago, invasive medical procedures, or occupational exposures may be overlooked by both clinicians and patients. Nearly half of HCV-infected persons report no known risk factors.

SYMPTOMS OF HCV INFECTION

Patients describe fatigue as the most concerning and frequent symptom of their chronic HCV infection; fatigue is reported by up to 60% of patients, the majority of them women. Fatigue persisting for years or decades can affect quality of life and functioning, requiring far more effort to participate in routine activities and maintain social roles. Fatigue is often associated with depression and insomnia.

Many of the symptoms of HCV infection, such as fatigue, abdominal pain, and depression, are not unique to HCV, and it can be difficult to distinguish whether these symptoms are due to HCV infection or other causes. It is also important to note that many patients are asymptomatic, even with chronic infection.

IDENTIFYING HCV INFECTION

Diagnosis of HCV infection is a multistep process beginning with testing for anti-HCV antibodies. A positive antibody test indicates either active HCV infection, a past infection that resolved, or a false-positive result. Following a positive antibody test, quantitative HCV RNA testing is required to confirm a current HCV infection. HCV RNA testing should be performed on any person testing positive for HCV antibodies, and any amount of detected HCV RNA is diagnostic for chronic infection. Quantitation of HCV RNA before initiation of antiviral therapy also aids in documenting baseline viral load.

HCV genotyping is performed once chronic HCV infection has been confirmed to determine the optimal type and duration of antiviral therapy. Concurrently, patients are evaluated for conditions that accelerate liver fibrosis, including alcohol use, HIV, or hepatitis B virus (HBV) infection, as these factors influence HCV treatment selection and timing. There are 6 major HCV genotypes, including multiple subtypes, with genotype 1 predominating in the United States (75%), followed by genotypes 2 and 3 (16% and 8%).

ASSESSMENT OF LIVER FIBROSIS

Assessment of liver fibrosis (Table 2) helps determine the severity of HCV-associated liver disease, the urgency of treatment, and the treatment duration and follow-up monitoring. Fibrosis assessment by liver biopsy or noninvasive testing is currently recommended. Liver biopsy is considered the diagnostic standard for staging of fibrosis, but it is an expensive and invasive procedure, with associated morbidity risks. As a result, there are many available alternative, less invasive approaches to assessing liver fibrosis.
Alternatives include serum tests, which evaluate proprietary blood marker panels to estimate the extent of fibrosis. However, false-positive results due to treatment- or disease-induced variation in markers are a concern with current serum tests. Simple calculations, like fibrosis-4 and aspartate aminotransferase (AST)-to-platelet ratio index, can also be performed on routine laboratory panels (complete blood count [CBC], extended chemistry) and aid in initial fibrosis assessment.

Ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are attractive alternatives to liver biopsy because they are non-invasive and precise in detection of structural changes and can detect occult portal hypertension or nodular liver, which are consistent with advanced disease. Other features such as splenomegaly, ascites, or gastric varices can be visualized with CT or MRI. Transient elastography, a newer modality for measuring liver stiffness, was approved in the United States in 2013. Transient elastography allows rapid, noninvasive fibrosis staging at the point of care.

Cirrhosis in the Patient With HCV Infection
Cirrhosis, the end-stage condition resulting from chronic liver injury, is characterized by extensive fibrosis that distorts the normal liver architecture by the destruction of normal liver tissue, which is replaced by less functional nodular tissue. Many patients are unaware that they have HCV infection until symptoms of end-stage liver disease occur. Because appropriate treatment of HCV infection depends on whether the patient has cirrhosis, clinicians must be able to recognize its clinical manifestations in patients with HCV infection.

Symptoms and signs that raise the suspicion of cirrhosis are often apparent during a routine history and physical examination. These include distended abdominal veins, gynecomastia, jaundice, loss of body hair, fluid-filled abdomen, palmar erythema (specifically, reddening at the thenar and hypothenar eminences that does not affect the center of the palm), spider angiomata, and white nails (Terry nails).

Cirrhosis–Related Complications
Patients with cirrhosis have increased risk of serious complications and should be screened regularly for signs of decompensation, including ascites, encephalopathy, gastroesophageal varices, hepatorenal syndrome, and/or spontaneous bacterial peritonitis. Decompensated cirrhosis is associated with poor long-term outcomes, and patients with any of these complications should be evaluated in a transplant setting, if possible.

Additional monitoring is required for patients with advanced liver disease. Baseline endoscopy to detect esophageal varices is recommended for all patients with cirrhosis, followed by surveillance endoscopy at defined intervals depending on baseline findings. For patients with advanced fibrosis (F3 or F4), HCC surveillance by ultrasound every 6 months is recommended.
GOALS OF HCV TREATMENT
Significant decreases in HCV prevalence and incidence are possible as more persons are success-
fully treated. The goal of HCV treatment is to achieve an SVR, defined as absence of detectable
virus 12 weeks after finishing treatment (SVR12).7 Achievement of SVR is equivalent to a cure
in HCV, and patients with SVR experience improvement in fibrosis, portal hypertension, and
liver inflammation. In patients with advanced fibrosis, SVR from antiviral therapy leads to sig-
nificant reductions in liver failure, HCC, liver transplantation, and mortality.32-35

RECOMMENDED HCV TREATMENTS
Regimens for HCV Genotype 1
Currently, 4 antiviral regimens of comparable efficacy are recommended for treatment of HCV
genotype 17: (1) the nonstructural (NS)3/4A protease inhibitor simeprevir and the HCV
nucleotide analog NS5B polymerase inhibitor sofosbuvir, administered as separate pills once per
day36,37; (2) the HCV NS5A inhibitor ombitasvir, the HCV NS3/4A protease inhibitor pari-
taprevir, and the cytochrome P450 3A inhibitor ritonavir administered as a 3-drug combination
pill twice daily in addition to twice-daily dasabuvir, an HCV non-nucleoside NS5B polymerase
inhibitor (with or without ribavirin [RBV])38; (3) a fixed-dose combination of sofosbuvir and
the HCV NS5A inhibitor ledipasvir once daily39; and (4) the NS5A replication complex inhibitor
daclatasvir combined with sofosbuvir, administered as separate pills once daily. Daclatasvir in
combination with sofosbuvir is currently FDA-approved for treatment of HCV genotype 3 but
is a recommended initial therapy for HCV genotype 1 based on promising phase 3 data.40 Inform-
ation on dose and duration for recommended HCV regimens is summarized in Table 3.7,34-44

Genotype 1a vs Genotype 1b
Administration of the ombitasvir/paritaprevir/ritonavir plus dasabuvir regimen differs depend-
ing on HCV subtype.7 The addition of RBV for 24 weeks (for patients with cirrhosis) or 12
weeks (for patients without cirrhosis) is recommended for patients with HCV genotype 1a.
For patients with HCV genotype 1b and cirrhosis, 12 weeks of added RBV is recommended.

Data from the TURQUOISE-II trial41 in patients with HCV genotype 1 and cirrhosis
who have not received treatment highlight the importance of subgenotype in treatment selec-
tion. Patients were given ombitasvir/paritaprevir/ritonavir and dasabuvir plus RBV for 12 or
24 weeks. Among patients with genotype 1a, fewer achieved SVR with 12 weeks of treatment
(88.6%) than with 24 weeks (94.2%). By contrast, patients with genotype 1b infection had
similar SVR rates regardless of treatment duration (98.5% vs 100%, respectively).

Patients With Cirrhosis vs No Cirrhosis
Treatment duration may depend on the presence or absence of cirrhosis. Among patients with
HCV genotype 1 infection without cirrhosis, greater than 90% experience SVR with 12 weeks
of treatment. Treatment of HCV in the presence of cirrhosis is more complicated, particularly
in patients who have had prior treatment, and often requires longer treatment durations and
the addition of RBV.

In the ION-1 study,39 patients with cirrhosis who were treatment-naïve were given ledipasvir
### Table 3. Novel Treatments for HCV Infection

#### Genotype 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Duration (weeks)</th>
<th>SVR12 Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cirrhosis</td>
<td>Cirrhosis</td>
<td>No Cirrhosis</td>
</tr>
<tr>
<td>Daily simeprevir + sofosbuvir (150 mg/400 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-naïve or treatment-experienced</td>
<td>12</td>
<td>24</td>
</tr>
</tbody>
</table>

**Daily ombitasvir/paritaprevir/ritonavir (25 mg/150 mg/100 mg) + twice-daily dasabuvir (250 mg)**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Preferred Regimen</th>
<th>Alternative Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>+ RBV for 12</td>
<td>95.3; 97</td>
</tr>
<tr>
<td>1b</td>
<td>12</td>
<td>98; 99</td>
</tr>
</tbody>
</table>

**Daily ledipasvir/sofosbuvir (90 mg/400 mg)**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Preferred Regimen</th>
<th>Alternative Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Daily daclatasvir (60 mg) and sofosbuvir (400 mg) for 12 weeks for treatment-naïve patients who cannot tolerate RBV</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Daily sofosbuvir (400 mg) + RBV for 12 weeks (no cirrhosis) or 16 weeks (cirrhosis)</td>
<td></td>
</tr>
</tbody>
</table>

**Daily daclatasvir/sofosbuvir (60 mg/400 mg)**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Preferred Regimen</th>
<th>Alternative Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Daily daclatasvir (60 mg) + sofosbuvir for 12 weeks (no cirrhosis) or 24 weeks ± RBV (with cirrhosis)</td>
<td>Daily sofosbuvir (400 mg) + RBV + weekly pegIFN for 12 weeks (IFN-eligible)</td>
</tr>
<tr>
<td>3</td>
<td>Daily sofosbuvir (400 mg) + RBV + weekly pegIFN for 12 weeks (IFN-eligible)</td>
<td></td>
</tr>
</tbody>
</table>

**Genotypes 2-6**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Preferred Regimen</th>
<th>Alternative Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Daily fixed-dose ledipasvir/sofosbuvir (90 mg/400 mg) for 12 weeks</td>
<td>Daily sofosbuvir (400 mg) + RBV + IFN for 12 weeks</td>
</tr>
<tr>
<td>4</td>
<td>Daily fixed-dose ombitasvir/paritaprevir/ritonavir (25 mg/150 mg/100 mg) + RBV for 12 weeks</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Daily sofosbuvir (400 mg) + RBV for 24 weeks</td>
<td></td>
</tr>
</tbody>
</table>

**5**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Preferred Regimen</th>
<th>Alternative Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Daily fixed-dose ledipasvir/sofosbuvir (90 mg/400 mg) for 12 weeks</td>
<td>Daily sofosbuvir (400 mg) + RBV + weekly pegIFN for 12 weeks</td>
</tr>
</tbody>
</table>

**6**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Preferred Regimen</th>
<th>Alternative Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Daily fixed-dose ledipasvir/sofosbuvir (90 mg/400 mg) for 12 weeks</td>
<td>Daily sofosbuvir (400 mg) + RBV + weekly pegIFN for 12 weeks</td>
</tr>
</tbody>
</table>

---

*aRecommended in guidelines but not FDA-approved for genotype 1; †This study was conducted in patients coinfected with HIV.*
and sofosbuvir with or without RBV for either 12 or 24 weeks. SVR rates of greater than 97% were observed across all treatment arms and durations. Based on these results, patients with cirrhosis who are treatment-naïve can be administered a shorter, RBV-free regimen of 12 weeks of ledipasvir/sofosbuvir.

Patients Who Have Previously Received Treatment
Prior treatment experience is another driver of treatment duration. In patients with HCV genotype 1 without cirrhosis who have failed a prior pegylated interferon (pegIFN)/RBV regimen, DAA regimens are given for 12 weeks.7 For patients with compensated cirrhosis, treatment may be extended to 24 weeks and RBV may be added, depending on the regimen. For patients who have failed sofosbuvir/RBV with or without pegIFN, ledipasvir/sofosbuvir/RBV is recommended for 12 weeks or 24 weeks, depending on absence or presence of cirrhosis. Patients with HCV genotype 1 without cirrhosis who have undergone prior treatment with an NS3 protease inhibitor/pegIFN/RBV regimen or with simeprevir/sofosbuvir and no prior NS5A inhibitors can be retreated with daclatasvir/sofosbuvir or with ledipasvir/sofosbuvir for 12 weeks or for 24 weeks if they have cirrhosis. Patients without cirrhosis who have failed simeprevir/sofosbuvir should be treated with ledipasvir/sofosbuvir/RBV for 12 weeks, and if they have cirrhosis, treated with ledipasvir/sofosbuvir for 24 weeks, with limited data supporting the addition of RBV.

Treatment for Other HCV Genotypes
HCV genotype 2 infections are treated with sofosbuvir plus RBV for 12 weeks, extending to 16 weeks for patients with cirrhosis.7 In July 2015, the Food and Drug Administration (FDA) approved the HCV NS5A inhibitor daclatasvir for the treatment of chronic genotype 3 HCV infection, in combination with sofosbuvir. An alternative regimen is sofosbuvir plus pegIFN and RBV for 12 weeks. HCV genotype 4 infections are treated with ledipasvir/sofosbuvir for 12 weeks, ombitasvir/paritaprevir/ritonavir plus RBV for 12 weeks, or sofosbuvir plus RBV for 24 weeks. Sofosbuvir/RBV/IFN for 12 weeks is an alternative regimen. HCV genotypes

<table>
<thead>
<tr>
<th>Highest Priority for Treatment Owing to Highest Risk for Severe Complications</th>
<th>High Priority for Treatment Owing to High Risk for Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced fibrosis (F3) or compensated cirrhosis (F4)</td>
<td>Fibrosis (F2)</td>
</tr>
<tr>
<td>Organ transplant</td>
<td>HIV-1 coinfection</td>
</tr>
<tr>
<td>Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis)</td>
<td>HBV coinfection</td>
</tr>
<tr>
<td>Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis</td>
<td>Other comorbid liver disease</td>
</tr>
<tr>
<td></td>
<td>Debilitating fatigue</td>
</tr>
<tr>
<td></td>
<td>Type 2 diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Porphyria cutanea tarda</td>
</tr>
</tbody>
</table>

Table 4. Treatment Prioritization in HCV7
5 and 6 infections are rare in the United States, and data are limited to guide clinicians in treatment selection. Ledipasvir plus sofosbuvir is the currently recommended regimen for genotypes 5 and 6 (Table 3).7,36-44

**Treatment Prioritization**

The highest priority for treatment is given to patients with advanced fibrosis (F3 or F4).7 Other conditions are prioritized by risk for producing severe complications (Table 4).7

**Considerations for Patients With Renal Impairment**

Many patients with HCV infection have comorbid renal disease, and the presence of HCV infection has been associated with an increased risk of end-stage renal disease and rapid decline in kidney function.45 Newer regimens are safe for most patients with renal impairment, including those with estimated glomerular filtration rates (eGFRs) as low as 30 mL/min.7 Early data from ongoing trials show safety and efficacy in patients with eGFR below 30 mL/min, suggesting that these drugs will be useful across the spectrum of renal impairment.46,47 Dose adjustment recommendations for patients with renal impairment are summarized in Table 5.7

**ADVERSE EVENTS OF TREATMENT**

Whereas interferon (IFN)-based regimens are marked by high toxicity, new agents for HCV

<table>
<thead>
<tr>
<th>Table 5. Dose Adjustment Recommendations for Patients With Renal Impairment7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Degree of Renal Impairment</strong></td>
</tr>
</tbody>
</table>
| Mild to moderate (CrCl 30 mL/min-80 mL/min) | No dosage adjustment is required when using:  
  - Daclatasvir  
  - Sofosbuvir  
  - Simeprevir  
  - Fixed-dose ledipasvir/sofosbuvir (90 mg/400 mg)  
  - Fixed-dose ombitasvir/paritaprevir/ritonavir (25 mg/150 mg/100 mg) plus twice-daily dasabuvir (250 mg) |
| Severe (CrCl <30 mL/min) | No dosage adjustment is required when using:  
  - Daclatasvir  
  - Consider fixed-dose paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) if:  
  - No cirrhosis  
  - Treatment need is urgent  
  - Renal transplant not possible  
  - Patient has appropriate genotype  
  Treatment can be considered after consultation, because safety and efficacy data are not available for all regimens for patients with severe renal impairment |

CrCl = creatinine clearance.
have very few adverse events (AEs) associated with them and considerably improved tolerability. Cognitive impairments in memory, concentration, and attention were well documented AEs of HCV infection exacerbated by treatment with RBV and pegIFN.48 Very few AEs leading to discontinuation have been reported with the all-oral antiviral regimens.36,38,39 The most common AEs with newer drugs are occasional and manageable fatigue, headache, nausea, pruritus, and insomnia (Table 6).36,38,39

There is increased potential for adverse interactions between DAA treatments for HCV infection and concomitant medications taken by patients for other conditions. Thus, evaluation for risk of drug-drug interactions is an important consideration in treatment choice. Common medications, including certain acid-reducing drugs, antimicrobials, herbal preparations, and medications for blood pressure and cholesterol, are known to interact with HCV drugs.7 Of note, proton pump inhibitors (PPIs) decrease the absorption of ledipasvir, and statins have been shown to interact with several classes of HCV DAA drugs.

### Table 6. Selected AEs With All-Oral, IFN-Free HCV Regimens3,36,38,39

<table>
<thead>
<tr>
<th>AE</th>
<th>2-Drug Combinations (%)</th>
<th>3-Drug Combination (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sofosbuvir + Ledipasvir</td>
<td>Simeprevir + Sofosbuvir</td>
</tr>
<tr>
<td>Any AE</td>
<td>79</td>
<td>66</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AE leading to death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Asthenia</td>
</tr>
<tr>
<td>Rash</td>
</tr>
</tbody>
</table>

*Only 12-week data are shown.*
PATIENT EDUCATION

Patient education plays a key role in HCV management, and patients must be counseled on ways to protect the liver from further damage. The greatest risk of further liver damage is from alcohol consumption, other viral infections, and medications. Because the safety of alcohol consumption in advanced liver disease remains unknown, patients with chronic HCV infection should be encouraged to decrease or discontinue alcohol use. Hepatitis A virus (HAV) and HBV vaccinations for susceptible individuals and HIV testing are also recommended. Newly prescribed medications, including over-the-counter (OTC) drugs and herbal supplements, should not be taken without first checking with a healthcare clinician, and acetaminophen should be limited to 2 g/day in patients with cirrhosis. Healthy weight management and physical activity are recommended for patients who are overweight or obese.

Patient education should include information about how to minimize the risk of viral transmission to others. Persons who have HCV infection should not share personal items that might come into contact with blood, such as razors, toothbrushes, dental appliances, or nail clippers, and they must cover any open wounds. Table 7 outlines key themes that clinicians can share with their patients to protect the liver from further harm and to minimize the risk of HCV transmission.

ADHERENCE

For patients with chronic HCV infection, adherence to both a medication regimen and an overarching medical plan that includes follow-up visits, additional screenings and vaccinations, and lifestyle modifications can be especially challenging.

<table>
<thead>
<tr>
<th>Table 7. Patient Counseling Messages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>To protect the liver from further harm</strong></td>
</tr>
<tr>
<td>• Reduce or discontinue alcohol use</td>
</tr>
<tr>
<td>• Obtain HAV and HBV vaccinations if susceptible</td>
</tr>
<tr>
<td>• Avoid new medicines, including OTC and herbal agents, until checking with a healthcare clinician</td>
</tr>
<tr>
<td>• Obtain HIV risk assessment and testing</td>
</tr>
<tr>
<td>• Cirrhosis</td>
</tr>
<tr>
<td>o Limit acetaminophen to 2 g/d</td>
</tr>
<tr>
<td>o EGD for variceal screening</td>
</tr>
<tr>
<td>o Imaging every 6 months for HCC screening</td>
</tr>
<tr>
<td><strong>For patients who are overweight or obese</strong></td>
</tr>
<tr>
<td>• Consider weight management or losing weight</td>
</tr>
<tr>
<td>• Follow a healthy diet</td>
</tr>
<tr>
<td>• Stay physically active</td>
</tr>
<tr>
<td><strong>To minimize risk of HCV transmission</strong></td>
</tr>
<tr>
<td>• Do not donate blood, tissue, or semen</td>
</tr>
<tr>
<td>• Do not share appliances that might come into contact with blood (razors, nail clippers, toothbrushes, dental appliances)</td>
</tr>
</tbody>
</table>

EGD = esophagogastroduodenoscopy.
Treatment-related factors that historically have increased the risk of nonadherence include low tolerability, inadequate management of AEs, greater frequency of treatment, higher pill burden, and longer treatment duration. However, in this new era of all-oral DAAs, those reasons for nonadherence may soon dissipate, given their safety profile and ease of use. A recent analysis of adherence in 3 phase 3 clinical trials reported medication adherence rates of more than 98.5% across all treatment groups receiving oral ombitasvir/paritaprevir/ritonavir plus dasabuvir and RBV or placebo. Adherence rates for the once-daily and twice-daily components of this regimen were equally high, pointing to adherence benefits of simpler, all-oral regimens.

Patient-related barriers to treatment initiation, including medical or psychiatric comorbidities, lack of acceptance of treatment (eg, asymptomatic nature of disease, competing priorities, and AEs), and lack of access to treatment (eg, cost and distance to specialist), substance use, lack of social support, and the presence of cirrhosis also can negatively affect patient adherence. However, clinicians can support patients and improve adherence by accounting for these factors in selecting treatment that best fits the patient’s personal situation. Patient counseling regarding treatment, adherence, and lifestyle modifications is critical to the management of chronic HCV.

**COST OF TREATMENT**

HCV infection treatment eligibility has increased due to broadening of insurance coverage and the availability of IFN- and RBV-free regimens with minimal contraindications. With improved tolerability of the newer regimens, more patients will seek treatment for HCV infection. Unfortunately, many patients with HCV infection are uninsured or underinsured, and the costs of HCV treatment with newer oral regimens is currently very high, exceeding $80,000 for a 12-week

---

**Table 8. Resources for Patients With HCV**

| Nonprofit organizations | • NeedyMeds.org  
| • Partnership for Prescription Assistance (www.pparx.org)  
| • Patient Access Network Foundation (www.panfoundation.org)  
| • Patient Advocate Foundation Co-Pay Relief (www.copays.org) |

| Pharmaceutical industry programs | • Clinical trials  
| • Patient assistance programs  
| o AbbVie (https://www.viekira.com/proceed-support)  
| o Bristol-Myers Squibb (http://www.bmspaf.org/pages/contact-us.aspx)  
| o Gilead (https://harvoni.com/support-and-savings/support-registration)  
| o Janssen (http://www.olicsio.com/hcp/affordability) |

| Government organizations | • Local health department programs  
| • CDC: Hepatitis C Information for Health Professionals (http://www.cdc.gov/hepatitis/hcv/)  
However, treatment assistance programs, which can provide medications free of charge, are available through nonprofit organizations and the pharmaceutical industry (Table 8).

**MONITORING FOR PATIENTS WHO ACHIEVE SVR**

Members of the healthcare team should work collaboratively to help patients who achieve SVR avoid reinfection and subsequent liver damage by providing the necessary support to help them stay on treatment and continuing to perform routine screening, as needed. For patients without advanced fibrosis, follow-up is the same as for patients never infected with HCV. Patients with advanced fibrosis should undergo ultrasound surveillance for HCC every 6 months. Patients with cirrhosis should continue endoscopy screening for varices, with rescreening interval determined by the baseline findings. Assessment for HCV reinfection is recommended only for patients with ongoing risk of HCV infection. Patients who achieve SVR but have a nonviral risk of liver disease, such as fatty liver, alcohol use, or iron overload, should be monitored for progression of fibrosis.

**SUMMARY**

Radical improvements in HCV therapy herald an era in which it may be possible to cure almost everyone with HCV infection. With the introduction of all-oral, IFN-free antiviral regimens, it is now possible to offer highly tolerable and effective treatments for chronic HCV infection. Identification of patients with HCV infection is still a major barrier to treatment, and clinicians should screen not only adults at increased risk but also those adults born between 1945 and 1965. Patient counseling is critical to the successful management of chronic HCV, and members of the healthcare team should work collaboratively to provide education regarding necessary lifestyle modifications, follow-up screening, vaccinations, treatment adherence, and ways to minimize HCV transmission.

**CASE: A 54-Year-Old African American Man With Elevated Liver Enzymes**

**PRESENTATION**

George presents to a new primary care clinic for follow-up after an initial laboratory screening reveals elevated liver enzymes. He denies a history of gastrointestinal bleeding, frequent nose bleeds, rapid weight gain with increased abdominal girth, insomnia, or difficulty concentrating. He states that he feels well, other than having mild fatigue. He does not smoke but drinks 4 to 5 glasses of beer per week and denies any history of illicit drug use. At age 28, he underwent surgery for inguinal hernia repair, and he received a tattoo in his 20s. His family history is negative for liver disease, and he has no prior history of jaundice or known elevation of liver enzymes. He is taking...
HEPATITIS C VIRUS INFECTION

a PPI for gastroesophageal reflux disease and had severe symptoms during a prior attempt at discontinuation.

Initial Physical Findings
- Head, eyes, ears, nose, and throat: sclera anicteric, conjunctiva pink, neck without adenopathy or thyromegaly
- Abdomen: soft, nontender, without palpable mass or fullness; normal bowel sounds; liver span of 7 to 8 cm in the midclavicular line; liver and spleen not palpable
- Extremities: no clubbing or cyanosis; trace pedal edema bilaterally
- Skin: mild palmar erythema; few spider angiomata on trunk

Laboratory Findings
- CBC: within normal limits
- HIV test: negative
- Comprehensive metabolic panel: within normal limits, except elevated AST (72 IU/L) and alanine aminotransferase (56 IU/L)
- Decreased platelet count: 155 x 10^9/L
- HCV antibody test: positive

Clinical Decision Point
What would be an appropriate next step in George’s care?
A. Order cytomegalovirus DNA test
B. Order Epstein-Barr virus DNA test
C. Order HBV DNA test
D. Order HCV RNA test
E. Order HIV RNA test

COMMENT
A positive HCV antibody test could suggest active HCV infection and is an indication to perform a quantitative HCV RNA test. Testing for HCV genotype and for current or prior infection with HAV, HBV, and HIV are typically performed concurrently to assist in determining the optimal treatment and duration, should a diagnosis of HCV be made. Correct answer: D

CASE (cont’d)
George’s test results are as follows:
- HCV RNA: 1 million copies
- HCV genotype: 1a
- HAV antibody: negative
- HBV surface antigen and surface and core antibodies: negative
- Ultrasound: nodular liver contour with increased echogenicity without any focal lesions; mild splenomegaly; no ascites
- Transient elastography: 15 kPa
HEPATITIS C VIRUS INFECTION

Based on these results and the presence of palmar erythema and spider angiomata, the clinician informs George that he has HCV infection and cirrhosis.

Clinical Decision Point

Which treatment(s) would be appropriate for George?
A. Ledipasvir/sofosbuvir for 8 weeks
B. Ledipasvir/sofosbuvir for 24 weeks
C. Ombitasvir/paritaprevir/ritonavir, dasabuvir plus RBV for 24 weeks
D. Simeprevir/sofosbuvir for 24 weeks

COMMENT

Ledipasvir/sofosbuvir is not a reasonable choice for a patient requiring a full-dose PPI. Ombitasvir/paritaprevir/ritonavir, dasabuvir plus RBV is an option for George because he has HCV genotype 1a and cirrhosis, for which 24 weeks is the correct duration of treatment. Simeprevir/sofosbuvir can also be given to patients with cirrhosis for 24 weeks. Correct answers: C and D

CASE CONCLUSION

The clinician discusses the importance of abstaining from alcohol, obtaining HAV and HBV vaccinations, seeking advice before taking OTC medications, and treatment adherence with George and provides education on minimizing the risk of transmission to others. George begins treatment and achieves an SVR. The clinician recommends follow-up ultrasonography every 6 months to screen for HCC and a baseline esophagogastroduodenoscopy to screen for esophageal varices.

REFERENCES


37. Lawitz E, Matusow G, DeJesus E, et al. A phase 3, open-label, single-arm study to evaluate the efficacy and safety of 12 weeks of simeprevir (SMV) plus sofosbuvir (SOF) in treatment-naive or -experienced patients with chronic HCV genotype 1 infection and cirrhosis: OPTIMIST-2. Presented at: 50th Annual Meeting of the European Association for the Study of the Liver (EASL); April 22-26, 2015; Vienna, Austria. Abstract S264.


47. Nazario HE, Ndungu M, Modi A. Safety and efficacy of sofosbuvir + simeprevir without ribavirin in hepatitis C genotype 1-infected patients with end-stage renal disease or GFR <30 mL/min. Presented at: 50th Annual Meeting of the European Association for the Study of the Liver (EASL); April 22-26, 2015; Vienna, Austria. Abstract PO802.


