Learning Objectives

1. Recognize and screen patients with high risk behaviors and those in disease prevalent birth cohorts
2. Decrease time of initiation of treatment and improve long-term treatment rates
3. Explain the reported safety and efficacy of currently available treatments for HCV in patients co-infected with HIV
4. List HCV drug combinations to avoid based on potential for drug-drug interactions
5. Discuss clinical trial data and emerging therapies and agents
6. Select appropriate new therapies and agents for optimal treatment of their patients
7. Discuss with patients chronic and acute HCV infection’s natural history, impacts, and treatment

Content Highlights

This icon depicts a key point identified in a section.

This icon depicts faculty commentary provide by:
Jonathan S. Appelbaum, MD, FACP, AAHIVS
Education Director and Professor of Internal Medicine
Interim Chair, Department of Clinical Sciences
Florida State University College of Medicine
Tallahassee, FL
INTRODUCTION

The treatment of HCV has undergone a dramatic evolution in the last several years. Whereas traditional interferon-based therapy for HCV was limited by poor efficacy and a heavy burden of side effects, interferon-free antiviral regimens are now available, offering new options for patients and altering the approach to this serious disease. The rapid pace of drug research, development, and approval requires frequent updates to treatment guidelines and leaves many clinicians wondering when, in whom, and how to manage chronic HCV infection.

In this CME program, we will discuss the latest findings in HCV through a review of salient presentations at the 2016 Digestive Disease Week meeting and the latest society recommendations for the appropriate use of antiviral therapy in patients with chronic HCV infection.

OVERVIEW

Worldwide, an estimated 180 million people have chronic HCV infection. Although the prevalence of HCV in the US remains uncertain, recent estimates suggest that about 3.5 million Americans are currently infected. The risks of chronic HCV infection are substantial. Over a median of 20 years, approximately one third of patients with chronic HCV develop cirrhosis, which can further progress to liver failure and hepatocellular carcinoma (HCC). The persistence of chronic HCV infection also increases risk for transmission, such as through sharing needles during injection drug use.

Until recently, conventional therapy for HCV was limited to interferon-based regimens (i.e., peginterferon plus ribavirin, with or without other agents). These regimens were associated with long treatment duration, poor response rates, and high rates of toxicity. In the last several years, the introduction of direct-acting antivirals (DAAs) has revolutionized the treatment of HCV. The first generation of DAA agents—boceprevir and telaprevir—demonstrated high rates of sustained virologic response (SVR) in clinical trials, but still required peginterferon plus ribavirin for full effectiveness. However, the newer, more recently approved DAA agents are associated with high SVR rates across most HCV genotypes and patient populations, and are effective in shorter treatment courses and without interferon. Now, multiple DAA regimens are available and recommended for use in chronic HCV, with rates of SVR approaching 100% in most patient types.

In May, 2016, the Digestive Disease Week (DDW) meeting convened experts in the management of HCV and other diseases. Among the many presentations were several that described the extent and impact of the epidemic of HCV, the safety and efficacy of current treatments across populations, and novel DAA agents and regimens in late stages of development. Here, we review salient emerging information on the burden and management of HCV for primary care clinicians.

Question 1
In recent years, the rate of new HCV infections in the US has continued many years of reductions. True or false?

A. True
B. False

IMPACTS AND DYNAMICS OF THE HCV EPIDEMIC

Norah Terrault, MD, presented an overview of the current state of HCV at DDW 2016, including the impacts and dynamics of the HCV epidemic. Among the data cited by Dr. Terrault was evidence describing a steady increase in age-adjusted death rates due to chronic HCV. One study estimated that deaths due to HCV in the US increased to more than 15,000 per year in 2007, exceeding deaths due to HIV infection, which were less than 13,000 per year. Furthermore, government data indicate that after years of declining infection rates, the rate of new HCV infections in the US increased by 2.5-fold from 2010 to 2013. The greatest increases were found among people aged 20-39 years, with the highest rate of infection among people aged 20-29. The increase in infection rate appears to be greatest in young people from non-urban areas in the eastern half the US. In one study, 75% of young people with new HCV infection reported injection drug use, and 75% of these people had previously abused prescription opioids.

Despite this disturbing recent increase in the prevalence of HCV among young Americans, baby-boomers still account for about three quarters of all chronic HCV infections. These adults, born between 1945 and 1965, constitute the “birth cohort” that is specified by current screening guidelines. While new infections occur...
predominantly in younger people, aging baby boomers account for most of the morbidity and mortality related to HCV. As people in this birth cohort age, a corresponding wave of advanced liver fibrosis is expected to rise, peaking between 2010 and 2030. Among people with chronic HCV, the prevalence of cirrhosis was about 5% in 1990 and 25% in 2010; it is predicted to reach 40% by 2020.

Treatment with DAA regimens can slow or reverse progression of liver disease in HCV-infected patients, highlighting the importance of identifying and treating chronic HCV infection. Nevertheless, despite the availability of accurate tests and effective treatments for HCV, most chronically infected people remain undiagnosed and untreated (Figure 1).14

Most individuals with HCV do not know they are infected, are not evaluated for treatment, and do not receive necessary care.15,16

KEY POINT
Jonathan S. Appelbaum, MD, FACP, AAHIVS
As a result of the large numbers of people who will need treatment for HCV, primary care physicians must participate in the screening and treatment of these patients. There simply are not enough gastroenterologists, hepatologists, or infections disease specialists to care for this volume of patients. Thankfully, the evaluation, treatment, and management of HCV infection has become much simpler since the emergence of DAA. However, the first step in breaking this cascade is to identify (screen) for HCV.

FIGURE 1. The cascade of care for HCV in the US14

The limited access to care and low cure rates described in the literature conflict with the increasing effectiveness of newer HCV treatments (Figure 2). Since the introduction of the first specific therapy for HCV—standard interferon, in 1991—SVR rates have climbed steadily with the approval of novel therapies, from ribavirin in 1998, to peginterferon in 2001, protease inhibitors in 2011, and the new DAAs in recent years. Today’s DAA regimens are associated with SVR rates of 90%-100% across genotypes and populations.8

FIGURE 2. Increasing rates of SVR with the emergence of novel therapies8

*IFN-based regimens used for up to 12 months; DAA used for 8-12 weeks
IFN: interferon, RBV: ribavirin, PEG-IFN: peginterferon, PI: protease inhibitor (i.e., boceprevir, telaprevir), DAA: direct-acting antiviral, SVR: sustained virologic response
Dr. Terrault concluded with a review of data describing the impact of achieving SVR on HCV-related morbidity and mortality. These data demonstrate significant reductions in risks for all-cause mortality, liver-related mortality, liver transplantation, liver failure, and HCC when SVR is achieved. In fact, one study demonstrated regression of liver fibrosis in 60% of patients who achieved SVR following DAA-based therapy for HCV. Finally, SVR is also associated with non-liver benefits, including lower rates of diabetes, renal disease, and lymphoma and improved quality of life.

**SCREENING FOR HCV: TESTING THE BIRTH COHORT**

The US Preventive Services Task Force (USPSTF) currently recommends screening for HCV in persons at high risk for infection and one-time of all adults born between 1945 and 1965. This recommendation is based on the finding that people in this birth cohort account for approximately three fourths of all chronic HCV infections in the US. As noted, routine screening is essential because most individuals with HCV do not know they are infected, are not evaluated for treatment, and do not receive necessary care. However, implementing these screening recommendations has proved difficult in many settings.

The USPSTF recommends screening for hepatitis C virus (HCV) infection in persons at high risk for infection. The USPSTF also recommends offering one-time screening for HCV infection to adults born between 1945 and 1965.

In a paper presented at the 2016 DDW, Patil and colleagues reported the impact of a quality improvement project on routine screening for HCV in patients from the birth cohort. Using a retrospective chart-review methodology, the team investigated the prevalence of screening for HCV among inpatients on the internal medicine service of a single hospital in New York City. Overall, they found that only 25.6% of eligible patients admitted during the study period were screened for HCV, 5.4% of whom tested positive. The team identified several intriguing barriers to routine screening of birth cohort patients. One third of the patients were not screened because of physician-related barriers, most (74.7%) because the resident circumvented the screening protocol; the remaining one quarter were not screened due to inaccurate recording of the patient’s date of birth. An additional 13% of patients declined screening. Less common barriers included altered mental status, inability to consent, and failure to send the order to test to the laboratory. The unfortunate central finding of this study is that nearly 75% of eligible inpatients were not screened for HCV as recommended, despite the implementation of quality improvement measures and clinician education.

In one study, nearly 75% of eligible inpatients were not screened for HCV as recommended, despite the implementation of quality improvement measures and clinician education.

**KEY POINT**

Jonathan S. Appelbaum, MD, FACP, AAHIVS

Primary care providers must incorporate HCV screening for appropriate populations into their normal preventive work flow. The use of reminders into EHR systems is one approach.

**KEY POINT**

Jonathan S. Appelbaum, MD, FACP, AAHIVS

As with HIV, there are very specific guidelines for the screening of HCV infection. Since the Baby Boomer generation has the highest prevalence of the disease, patients born between 1945 and 1965 should be screened once for HCV infection. Other populations at risk must also be screened, such as those infected with HIV and injection drug users.

**Improving Screening and Identification**

Community-based strategies have been proposed to improve the screening and identification of patients with risk for HCV. An example is routine testing for HCV at drug and alcohol rehabilitation centers. Ramers and colleagues presented the results of one such testing and linkage-to-care program at DDW 2016. In this program, teams consisting of counselors, phlebotomists, and care coordinators deployed to several Federally Qualified Health Centers and drug and alcohol rehabilitation centers...
in the San Diego area and performed point-of-care testing for HCV. Patients testing positive for chronic HCV were linked to treatment by an HCV care navigator. In all, 20% of screened participants tested positive for HCV antibodies (indicating exposure to HCV) and 14% were positive for HCV RNA (indicating chronic HCV), illustrating the high rates of HCV exposure and infection in at-risk populations.

Patients with active HCV infection were linked to care, including treatment with DAA. Cure rates, using a per-protocol analysis, approached 100% across genotypes and stages of liver disease. The lowest cure rate was 78% among cirrhotic patients with genotype 3 HCV; 100% cure rates were demonstrated among non-cirrhotic patients with genotype 1, 2, or 3 HCV. Despite the success of the program, the authors noted that the administrative burden and limited capacity of such approaches remain barriers to expanding access to HCV care and cure.

**Question 2**
Current evidence suggests that the mortality rate related to chronic HCV infection is…

A. Stable
B. Increasing
C. Decreasing
D. Insufficient information available

**Answer key on page 13**

**ENDING THE EPIDEMIC? CURE AS PREVENTION**

With the introduction of highly effective DAA regimens capable of curing HCV in nearly all infected patients, the elimination of HCV emerges as a real possibility. Camilla Graham, MD, in a presentation at DDW 2016, noted that broad use of DAA therapy in people with chronic HCV infection can prevent both the complications of HCV among those infected and the transmission of HCV to uninfected individuals. Dr. Graham continued by noting barriers to achieving this goal, such as the challenge of identifying and linking infected people to care and the cost and availability of current DAA regimens.23

Furthermore, as Dr. Graham pointed out, much remains unknown about the epidemic. In the US, for example, we do not know how exactly many people have HCV, how many acquire HCV each year, or how many die of HCV each year.23 Some of the challenges to improving our management of the epidemic include the definitions used by the CDC to identify new infections, which may be overly stringent, and the lack of screening and treatment in populations such as people born outside the birth cohort, incarcerated individuals, people who inject drugs (PWID), and those outside the health care system.23,24 For example, it was estimated that incarcerated individuals accounted for up to one third of all HCV antibody-positive cases in the US in 2006.25

Dr. Graham noted that the urgency to improve the detection and treatment of HCV is illustrated by the impact of chronic infection on mortality. HCV currently kills more people in the US than the next 60 notifiable infectious diseases combined, and those who die from HCV are 25 years younger on average than those who die without HCV.26,27 And the annual number of deaths associated with HCV in the US continues to increase, in contrast to declining death rates from other notifiable infectious conditions, such as tuberculosis.26
The Potential of Improving Treatment of HCV-Infected PWID

PWID are at high risk for HCV infection, reinfection, and transmission. In fact, the majority of new cases of HCV infection in high-income countries occur among PWID, and reinfection following cure can further complicate treatment by introducing viruses resistant to some agents and mixing viral genotypes. Clearly, reversing the epidemic of HCV in the US will require innovative approaches to diagnosing and treating PWID. However, increased treatment rates alone may not be sufficient to reduce the infection rate in this population, and additional harm-reduction strategies are needed.

Two interventions that might improve HCV treatment outcomes among PWID are opiate substitution therapy and high-coverage needle and syringe programs (i.e., needle exchange). In the absence of HCV treatment, these interventions alone may not substantially reduce the prevalence of HCV in PWID. But according to modeling studies, when combined with effective HCV therapy, these interventions can contribute to substantial reductions (e.g., >50% in 10 years) in the prevalence of chronic HCV in PWID, thereby addressing the epidemic at its core.

Another potential strategy is the “bring your friends” approach, in which an individual is treated for HCV and all his or her HCV-infected neighbors (i.e., members of the patient’s injection network) are treated as well. Compared to other treatment approaches, such as treating infected PWID at random, mathematical modeling suggests that the “bring your friends” strategy could substantially reduce the prevalence of HCV among PWID. The advantages of this strategy include the peer support of patients’ networks and reduced risk for reinfection by lowering the reservoir of HCV within a network.

GUIDELINE-BASED TREATMENT: EVOLVING STRATEGIES

With the continuing emergence of new DAA agents and regimens, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) provide frequent updates to their recommendations for the identification and treatment of HCV infection.

At the DDW 2016, Nancy Reau, MD, provided an update on current AASLD-IDSA guidelines, as well as data describing the burden of HCV disease. For example, Dr. Reau cited data from the prospective, community-based REVEAL-HCV study, which evaluated causes of death among people with and without HCV infection in seven townships in Taiwan. Most affected people in this population acquired HCV infection through iatrogenic means, and HCV treatment was rare, offering a window into the natural course of HCV infection. Over an average of 16.2 years of follow up, all-cause mortality was more than twice as high among patients with detectable HCV RNA (30.1%), compared to patients who were negative for anti-HCV antibodies (12.4%), and patients with anti-HCV antibodies but undetectable HCV RNA (12.8%), a statistically significant difference (P<0.001 both comparisons).

One interesting finding of this study was the significantly higher mortality rate associated with chronic HCV, both for hepatic and non-hepatic causes of death. A detectable HCV viral load was associated with significantly increased risk of death from circulatory diseases, kidney disease, esophageal cancer, and prostate cancer, illustrating the wide impacts of chronic HCV infection.

2016 AASLD-IDSA Recommendations

Screening for HCV

The latest HCV testing recommendations from the AASLD-IDSA mirror those of the USPSTF: one-time testing of people in the birth cohort and testing of all other people with risk factors for HCV infection (e.g., injection drug use, hemodialysis, incarceration, HIV infection). Implementing these recommendations is the first step toward reducing the burden of HCV on patients and society.

But once a diagnosis of chronic HCV infection is made, the question is when and whom to treat?

Question 3

Based on AASLD-IDSA recommendations, which of the following patients with chronic HCV infection should NOT be treated?

A. 50-year-old man with compensated cirrhosis
B. 62-year-old man with end-stage renal disease
C. 38-year-old woman with current injection drug use
D. 78-year-old woman with lung cancer and life expectancy of 9 months

Answer key on page 13
Treatment Options and Recommendations
Without treatment, chronic HCV infection is associated with multiple risks, including liver fibrosis, cirrhosis, and HCC. Cure of HCV can substantially reduce the risk for serious liver disease and HCC, even in patients who have already progressed to cirrhosis. The new DAA agents and regimens, which are safer and more effective than traditional interferon-based therapy, should lower barriers to treatment and help minimize risks for HCV-related complications and mortality in treated patients.

Accordingly, current AASLD-IDSA guidelines recommend treatment for all patients with chronic HCV infection. The only patients for whom treatment may be inappropriate are those with short life expectancies (e.g., <1 year) that cannot be improved with HCV therapy, organ transplantation, or other directed therapy. The goal of HCV therapy is to achieve cure, defined as SVR, thereby reducing mortality and morbidity. Unfortunately, because of the expense of DAA regimens, many insurers currently restrict reimbursement to patients who have more advanced liver disease (e.g., advanced fibrosis [F3/F4] or cirrhosis [F4]).

Currently recommended agents for the treatment of chronic HCV infection, by mechanism of action

As noted by Dr. Reau in her presentation, certain factors must be considered when selecting therapy for individual patients. Important considerations include HCV genotype, stage of liver fibrosis, and prior HCV treatment experience. Each characteristic must be considered when selecting an appropriate HCV regimen. For current regimens, in other words, one size does not fit all.

Regimens recommended by guidelines are listed in Table 1. In addition to these recommended regimens, certain alternative regimens are cited by guidelines for some patients, according to genotype and cirrhosis status. In patients with cirrhosis, dose adjustments...
### TABLE 1. Recommended regimens for treatment-naïve patients with chronic HCV infection

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration (wks)</th>
<th>Genotypes</th>
<th>Comp. cirrhosis</th>
<th>Decomp. cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbasvir/grazoprevir</td>
<td>12</td>
<td>1a, 1b, 4</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>12</td>
<td>1a, 1b, 4, 5, 6</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir plus dasabuvir</td>
<td>12</td>
<td>1a, 1b, 4</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Simeprevir plus sofosbuvir</td>
<td>12</td>
<td>1a, 1b</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir</td>
<td>12</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Daclatasvir plus sofosbuvir</td>
<td>12</td>
<td>1a, 1b, 3</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### TABLE 2. Potential DDI between HCV agents and other commonly used medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daclatasvir</th>
<th>Ledipasvir</th>
<th>Paritaprevir/ritonavir/ombitasvir + dasabuvir</th>
<th>Simeprevir</th>
<th>Sofosbuvir</th>
<th>Elbasvir/grazoprevir</th>
<th>Velpatasvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid-reducing agents</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Alfuzosin/tamsulosin</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Buprenorphine/ naloxone</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Cisapride</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Digoxin</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Ergot derivatives</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Milk thistle</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Macrolide antimicrobials</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Other antiarrhythmics</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Phosphodiesterase 5 inhibitors</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Pimozide</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Rifamycin</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedatives</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Statins</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
</tbody>
</table>

✔ Check prescribing information for detailed DDI information. Not all DDI are class specific; see product prescribing information.
may be necessary for some agents, based on the stage of liver disease, and guidelines should be consulted. Patients with significant liver disease should be referred to a specialist for management, and those with the most severe disease should be evaluated for liver transplant.

Certain agents and regimens are no longer recommended by guidelines. Based on inferior outcomes and/or excessive risk for harm, regimens containing peginterferon and the use of sofosbuvir plus ribavirin are not recommended.34

One important consideration when using the DAA regimens noted in Table 1 is the potential for drug-drug interactions (DDI) with commonly used prescription and over-the-counter medications. The risk for DDI varies by DAA; salient potential DDI are listed in Table 2, for your reference. Potential DDI between HCV agents and antiretroviral therapy for HIV will be discussed in a moment.

EMERGING CLINICAL DATA

Data presented at the 2016 DDW further described the use of certain DAA regimens in patients with chronic HCV. Paul Pockros, MD, presented a review of current and emerging DAA regimens, including evaluations of sofosbuvir/velpatasvir and ombitasvir/paritaprevir/ritonavir plus dasabuvir.

Velpatasvir/sofosbuvir

One report evaluated results from the ASTRAL-2 and -3 clinical trials, which tested velpatasvir/sofosbuvir, without ribavirin, in subjects infected with HCV genotype 2 or 3.42 These open-label, multinational trials included subjects with no cirrhosis or compensated cirrhosis and both treatment-naive and –experienced patients. Patient-reported outcomes were assessed using instruments such as the SF-36 and other functional and productivity tools. A total of 818 subjects with patient-reported outcome data were enrolled and evaluated (25% cirrhotic, 78% treatment-naive, 33% genotype 2, 67% genotype 3). SVR-12 was achieved by 99.3% of patients with genotype 2 infection, and 95.3% of those with genotype 3 infection. Patient-reported outcomes also improved significantly, starting during early treatment. On multivariate analysis, both treatment with velpatasvir/sofosbuvir and SVR were independently associated with significant improvements in patient-reported outcomes.

Other results from the ASTRAL trial program included evaluation of velpatasvir/sofosbuvir plus ribavirin or sofosbuvir plus ribavirin in patients with cirrhosis.42 Subjects with all genotypes of HCV were included, although sofosbuvir plus ribavirin was used only in subjects with genotype 2 or 3 infections. In all, 488 subjects were treated with these ribavirin-containing regimens (39% cirrhotic, including 17% with decompensated cirrhosis). By the end of treatment, changes from baseline in patient-reported outcomes were similar among patients with and without cirrhosis. After treatment cessation, significant improvements from baseline in almost all patient-reported outcomes were demonstrated, regardless of the presence of cirrhosis. Whereas the presence of cirrhosis was associated with significant impairments in patient-reported measures at baseline, no negative association with cirrhosis was apparent with treatment.

Two studies evaluated the addition of a novel NS3/4A protease inhibitor (GS-9857 or voxilaprevir) to velpatasvir/sofosbuvir, with or without ribavirin, in treatment-experienced patients.42 Overall, the combination produced high SVR-12 rates (96%-100%) across all six genotypes, including among patients with prior DAA treatment experience and those with resistance-associated variants (RAVs) at baseline. These findings suggest that this novel combination has pan-genotypic efficacy, a high barrier to resistance, and utility in treatment-experienced patients.

Ombitasvir/paritaprevir/ritonavir

Two studies evaluated the use of ombitasvir/paritaprevir/ritonavir in combination with other agents. The first evaluated ombitasvir/paritaprevir/ritonavir plus dasabuvir and sofosbuvir in patients with HCV genotype 1 infection who had failed prior DAA therapy.42 One goal of this study was to identify a combination of agents currently available in the clinic to treat patients who have failed DAA therapy. This open-label phase 2 study enrolled subjects with genotype 1a (for whom ribavirin was added) and genotype 1b. Treatment duration was 12 weeks, except in patients with genotype 1a and cirrhosis, who were treated for 24 weeks. Across all groups, SVR ranged from 93% to 100%. There was only 1 virologic failure, a patient with
genotype 1a and no cirrhosis who had a relapse. The combination was well tolerated, and SVR was achieved regardless of the presence of multiple baseline RAVs.

**Question 4**
Which of the following agents is not yet approved for the treatment of HCV infection?

A. Daclatasvir  
B. Ledipasvir  
C. Pibrentasvir  
D. Simeprevir

A second study evaluated ombitasvir/paritaprevir/ritonavir plus ribavirin in patients with genotype 4 HCV and compensated cirrhosis. The multinational, open-label, phase 3 study randomized subjects to 12 or 16 weeks of treatment. Rates of SVR were high in both groups (97%-100%), and were not affected by the presence of baseline RAVs.

**Future HCV Regimens: A peek at the Pipeline**
Dr. Pockros also presented a review of agents and regimens in development for the treatment of HCV (Table 3).

**TABLE 3. Selected DAA in development for HCV**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-493 (glecaprevir)</td>
<td>NS3/4A</td>
</tr>
<tr>
<td>ABT-550 (pibrentasvir)</td>
<td>NS5A</td>
</tr>
<tr>
<td>AL-335</td>
<td>NS5</td>
</tr>
<tr>
<td>MK-3682</td>
<td>NS5B</td>
</tr>
<tr>
<td>MK-8408 (ruzasvir)</td>
<td>NS5A</td>
</tr>
<tr>
<td>Odalasvir</td>
<td>NS5A</td>
</tr>
</tbody>
</table>

Several studies have evaluated the safety and efficacy of a novel combination of the NS3/4A protease inhibitor ABT-493 (glecaprevir) and the NS5A inhibitor ABT-550 (pibrentasvir) in patients with chronic HCV infection. Both DAA have pan-genotypic efficacy and high barriers to resistance. In one study, non-cirrhotic patients with genotype 1 or 2 infection were treated for 8 weeks using this novel combination. At study end, the team reported SVR-12 rates of 97%-98%, with no virologic failures, regardless of prior treatment history or the presence of baseline RAVs.

A similar study evaluated the combination of ABT-493 and ABT-550 in non-cirrhotic, treatment-naïve patients with genotype 3 infection. An 8-week course of treatment achieved SVR-12 of 97%, with no virologic failures, regardless of the presence of baseline RAVs. Based on these and other results, the combination of ABT-493 and ABT-550 is currently being evaluated in phase 3 trials for use as a pan-genotypic ribavirin-free regimen in multiple populations, including patients with HIV/HCV coinfection, prior DAA failure, cirrhosis, and renal impairment.

Other short-duration regimens in development include a three-drug regimen with the NS5B inhibitor MK-3682, grazoprevir, and the NS5A inhibitor MK-8408 (ruzasvir); a combination of the nucleotide polymerase inhibitor AL-335 and the NS5A inhibitor odalasvir, with or without simeprevir; and a 6-week course of sofosbuvir/ledipasvir for patients with genotype 1 HCV.

In conclusion, Dr. Pockros noted that shorter duration regimens with single, fixed-dose double- or triple-agent combinations should be available for all genotypes by 2017.

**MANAGING HCV IN SPECIAL POPULATIONS**

Certain patient populations require special consideration when selecting treatment. The most salient special populations are those with decompensated cirrhosis (described briefly in Table 1), renal impairment, post-liver-transplant HCV, or HIV/HCV coinfection. Patients with HIV are especially at high risk for HCV infection and represent a challenge to clinical management.
Furthermore, recommendations regarding the management of these patients have evolved substantially in recent years. Coinfection with HIV can increase risk for complication and mortality in patients with HCV, and vice versa. For example, complications associated with viral hepatitis are the leading cause of death in patients coinfected with HIV/HCV in the US, outpacing AIDS-related complications.43,44

Current guidelines from the US Department of Health and Human Services (DHHS) recommend immediate initiation of antiretroviral therapy (ART) for all HIV-infected patients, including those with HCV coinfection, to reduce risk for disease progression and transmission.45 If concomitant HCV therapy is planned, consideration should be given to selecting an ART regimen with lower risk for DDI and overlapping toxicities in conjunction with HCV therapy.45

Current guidelines recommend immediate initiation of antiretroviral therapy for all HIV-infected patients, including those with HCV coinfection. If concomitant HCV therapy is planned, consideration should be given to selecting an antiviral regimen with lower risk for drug-drug interactions and overlapping toxicities.

KEY POINT
Jonathan S. Appelbaum, MD, FACP, AAHIVS

Simultaneous treatment of HIV-HCV coinfection is desirable, and most of the currently preferred HIV regimens are compatible with HCV treatment. The good news is that the dismal cure rates we saw with peginterferon/ribavirin in the past are no longer the norm. In fact, patients coinfected with HIV-HCV who are treated for both infections according to current guidelines have similar HCV cure rates to mono-infected patients.

The case in favor of treating HCV in coinfected patients has gathered strength with the newly approved, highly effective DAA regimens. Whereas cure rates were relatively low with conventional interferon-based therapy, especially in certain populations (including HIV coinfected and/or African American patients46), cure rates with currently available DAA regimens typically exceed 90% in clinical trials that included coinfected patients.45

Question 5
All of the following regimens are recommended for the treatment of HCV in HIV coinfected patients, EXCEPT:

A. Ledipasvir/sofosbuvir
B. Sofosbuvir plus simeprevir
C. Peginterferon plus ribavirin and simeprevir
D. Paritaprevir/ritonavir/ombitasvir plus dasabuvir

Answer key on page 13

Considerations in Treating HIV/HCV Coinfection

The 2016 AASLD-IDSA guidelines recommend specific DAA regimens based on HCV genotype; these recommendations are the same for monoinfected and HIV-coinfected patients, although potential DDI with ART must be considered (Table 4).34 Guidelines also recommend against the interruption of ART to treat HCV and against the use of HCV treatment courses shorter than 12 weeks.34

SUMMARY

The introduction of highly effective DAA therapy has revolutionized the treatment of chronic HCV infection, with cure rates exceeding 90% in most trials and patient populations. Guidelines now recommend HCV therapy for patients with chronic HCV infection and more than 1 year of life expectancy, as well as those with reduced life expectancy due to liver disease complications. However, the cost of the new DAA regimens may limit reimbursement to patients with more advanced liver disease (F3/F4 fibrosis or cirrhosis). Furthermore, there are numerous potential DDI between the new DAA and antiretroviral drugs and other common medications (e.g., statins, acid-suppressing drugs). And new agents are continually developed and approved for use. Clinicians who manage patients with HCV must be familiar with the indications for HCV therapy and the appropriate use of new DAA regimens.
### TABLE 4. Recommendations for HCV regimens in HIV/HCV coinfected patients

<table>
<thead>
<tr>
<th>HCV agent or regimen</th>
<th>ARV agents</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir</td>
<td>Okay with most ARV</td>
<td>Dose adjustment with atazanavir/ritonavir or efavirenz or etravirine</td>
</tr>
<tr>
<td>Elbasvir/grazoprevir or Simeprevir</td>
<td>Abacavir, Emtricitabine, Enfuvirtide, Lamivudine, Raltegravir, Dolutegravir, Rilpivirine, Tenofovir</td>
<td>Cobicistat, Efavirenz, Etravirine, Nevirapine, Protease inhibitors</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir</td>
<td>Efavirenz, Etravirine, Nevirapine, Tipranavir</td>
<td>Avoid TDF if CrCl &lt;60 mL/min</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>Okay with most ARV</td>
<td>Avoid TDF if CrCl &lt;60 mL/min, Avoid ritonavir or cobicistat</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir plus dasabuvir</td>
<td>Atazanavir, Dolutegravir, Emtricitabine, Enfuvirtide, Lamivudine, Raltegravir, Tenofovir</td>
<td>Do not use in coinfected patients not taking ARV</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Didanosine, Stavudine, Zidovudine</td>
<td></td>
</tr>
</tbody>
</table>

ARV: antiretroviral therapy for HIV-1 infection, CrCl: creatinine clearance, DDI: drug-drug interactions, TDF: tenofovir disoproxil fumarate

**Answer Key**

*Below are the answers to questions dispersed through the eMonograph*

**Q1** A. True

**Q2** B. Increasing

**Q3** D. 78-year-old woman with lung cancer and life expectancy of 9 months

**Q4** C. Pibrentasvir

**Q5** C. Peginterferon plus ribavirin and simeprevir
References


18. Crissien AM, Minteer WB, Pan JJ, Frenette CT, Pockros PJ. Regression of advanced fibrosis or cirrhosis measured by elastography in patients with chronic hepatitis C who achieve sustained virologic response after treatment for HCV. *AASLD Annual Meeting*, November 13-17, 2015; San Francisco, CA.


