Hepatitis C in a New Era: A Review of Current Therapies

Troy Kish, PharmD, BCPS; Andrew Aziz, PharmD; and Monica Sorio, PharmD

INTRODUCTION
The prevalence of chronic hepatitis C virus (HCV) infection has been estimated at between 1.2% and 1.7% in the adult global population, suggesting that 62 million to 89 million people are affected by the disease. The Centers for Disease Control and Prevention (CDC) currently estimates the number of chronically infected people in the U.S. to be 2.7 million to 3.9 million. In 2014, the cause of death for 19,659 U.S. residents was attributed in whole or in part to HCV. Total health care costs associated with HCV disease and its complications, excluding treatment expenses, were estimated to be $6.5 billion in 2011, with a projected increase to $9.1 billion by 2024. Treatment costs associated with HCV therapy have increased rapidly from $77 million in 2009 to $18.4 billion in 2015, with the approval of direct-acting antivirals (DAAs) driving those expenses.

The past several years have seen a radical shift in how HCV is treated and in the number of patients who are successfully cured of the disease. This article aims to summarize newly available treatment regimens, their indications, studies supporting their efficacy and safety, and special considerations for each regimen, such as coinfection with human immunodeficiency virus (HIV), compensated or decompensated cirrhosis, and chronic renal disease. A brief discussion of treatment costs will also be provided.

PATHOPHYSIOLOGY
HCV is a single-strand, positive-sense RNA virus with a life cycle that begins when a viral capsid binds to the hepatocyte, where it undergoes endocytosis and, subsequently, the viral RNA begins translation and protein production. Using the host’s ribosome, HCV creates a single polyprotein, which is then cleaved into structural and nonstructural (NS) components. Structural components include the new viral core and viral envelope proteins E1 and E2. Proteins that are not incorporated into new viruses but support virus replication are p7 and NS2. The remaining proteins NS3/4A, NS4B, NS5A, and NS5B form the replicase complex responsible for viral production. Once the new viruses are formed, they are packaged into envelopes to be released and further propagate the disease.

Acute HCV infections typically present with general nonspecific symptoms, such as malaise, right upper quadrant pain, and nausea, similar in general to other acute viral hepatitis presentations. Patients are often not even aware of the acute infection, and many never seek treatment. Those exposed to HCV have an estimated 75% to 85% likelihood of developing chronic infection, while the remainder experience spontaneous clearance of the virus. Of the chronically infected population, an estimated 5% to 20% develop cirrhosis over a prolonged period, often more than 20 years. Those with cirrhosis face a 25% risk of progressing to end-stage liver disease (ESLD) or hepatocellular carcinoma (HCC). The development of ESLD brings about several complications, such as hepatic encephalopathy, ascites, esophageal varices, spontaneous bacterial peritonitis, and, ultimately, the need for a liver transplant. According to the United Network for Organ Sharing, more than 7,000 liver transplants were performed in the United States in 2015.

Cirrhosis from HCV is cited as the primary reason patients require an organ transplant.

HCV is a diverse virus with at least seven well-characterized genotypes (GTs), defined as GTs 1–7, identified worldwide. These genotypes can differ by more than 50% in their nucleotide sequences, leading to varying responses to treatment strategies. Within these genotypes, there may be further division into subtypes, which is best demonstrated in HCV GT 1a and GT 1b. The geographic distribution of genotypes varies by region. GT 1 is the most observed genotype worldwide (accounting for 46% of cases) and the most common genotype in North America; GT 3 represents 30% of observed cases and is more prevalent in South Asia; GT 2 and GT 6 are most commonly found in East Asia; GT 4 is found predominantly in North Africa and the Middle East; and GT 5 accounts for less than 1% of cases, mostly in South Africa.

SCREENING AND DIAGNOSIS
The CDC recommends that any person born between 1945 and 1965 receive a one-time screening test for HCV. In addition, individuals not born in that period but with other risk factors — such as a history of injection or intranasal drug use, long-term hemodialysis, birth to an HCV-infected mother, receipt of a blood transfusion or organ transplant before July 1992, use of coagulation products prior to 1987, or incarceration — should receive a one-time screening test. Those with ongoing risk factors, such as injection drug users or men with HIV who have unprotected sex with men, should be screened at least annually.

The recommended screening test is either an enzyme immunoassay or enhanced chemiluminescence immunoassay for antibodies to HCV (anti-HCV), which can be done with a rapid screening test from fingerstick capillary blood or venous whole blood (OraQuick HCV, OraSure Technologies, Inc.) or from a regular blood sample. A positive antibody test should be followed up with a qualitative or quantitative polymerase

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Disclosures: The authors report no commercial or financial interests in regard to this article.
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The newer DAA drugs target various points of the HCV viral replication cycle. These medications affect key structures or the replication process either by directly binding to components of the replicase complex or by initiating RNA chain termination. Medications that target the NS3/4A protease contain the suffix “-previr,” medications that inhibit the NS5B polymerase have the suffix “-buvir,” and NS5A inhibitors end in “-avir.”

The HCV treatment guidance from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) recommends that all patients with chronic HCV infection should be treated except for those with short life expectancies (less than 12 months) that cannot be remediated by treating HCV or by performing a liver transplant. Barriers to universal treatment include appropriate screening to identify infected patients and treatment costs. While prioritization of patients is no longer explicitly stated, practitioners should consider several factors when selecting whom to treat and when.

Those who may experience the most immediate benefit from curing HCV are patients who have advanced cirrhosis (F3 or F4) or who have undergone liver transplantation. Patients with HIV or hepatitis B (HBV) coinfection may experience faster progression of fibrosis and may also benefit from HCV cure. It is important to screen patients for pre-existing HBV, as treating HCV in coinfected patients has led to instances of HBV virus reactivation; this has become a boxed warning on existing DAA medications. Patients with HCV-associated renal diseases, such as cryoglobulinemia or glomerular disease, type-2 diabetes, or severe fatigue, may see an improvement in these conditions with HCV resolution; however, data are lacking on non-IFN-based treatment regimens to support this. Finally, another benefit of treatment is a reduction in transmission by targeting patients such as injection drug users, incarcerated individuals, or those who engage in high-risk activities; this may reduce the disease burden in the population.

With GT 1 being the most common in the United States, there are a few general principles to keep in mind. GT 1 infections, historically one of the most difficult types of HCV to treat, can now potentially be addressed by up to six DAA options, all highly efficacious. GT 1 infections are one of the few that should be subtyped, based on the genetically fundamental differences in DAA agents and the genetic potential for resistance. People with GT 1 that cannot be subtyped should be treated for GT 1a infection. Another important factor in determining treatment for patients with GT 1a infections is identification of resistance-associated variants (RAVs). About 10% to 15% of GT 1-infected patients without prior exposure to NS5A inhibitors will still have detectable NS5A RAVs.

The following section will discuss the DAA treatment options available and the major clinical trials that support their use in different genotypes and patient populations. Tables 4, 5, and 6 are provided to summarize recommended regimens according to genotype or comorbid patient conditions.

**LEDPASVIR/SOFOSBUVIR**

The approval of the combination of ledipasvir 90 mg and sofosbuvir 400 mg (LVD/SOF) (Harvoni, Gilead Sciences) as a single-tablet formulation in October 2014 ushered in a new era for HCV treatment. Sofosbuvir is a potent pan-genotypic NS5B

### Table 1 Levels of Fibrosis by META VIR Score

<table>
<thead>
<tr>
<th>META VIR Score</th>
<th>Pathophysiological Changes</th>
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<tbody>
<tr>
<td>F0</td>
<td>No fibrosis present—normal liver</td>
</tr>
<tr>
<td>F1</td>
<td>Mild fibrosis</td>
</tr>
<tr>
<td>F2</td>
<td>Moderate fibrosis</td>
</tr>
<tr>
<td>F3</td>
<td>Severe fibrosis</td>
</tr>
<tr>
<td>F4</td>
<td>Cirrhosis</td>
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</table>

### Table 2 Child–Turcotte–Pugh (CTP) Score for Categorization of Cirrhosis Compensation

<table>
<thead>
<tr>
<th>CTP class A (5–6 points)</th>
<th>Least severe disease</th>
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<tr>
<td>CTP class B (7–9 points)</td>
<td>Moderately severe disease</td>
</tr>
<tr>
<td>CTP class C (&gt; 10 points)</td>
<td>Severe disease/decompensated</td>
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Components of CTP include serum bilirubin, prothrombin time or international normalized ratio, serum albumin, presence of hepatic encephalopathy, and presence of ascites.

TREATMENT OVERVIEW

Historically, HCV was treated with pegylated-interferon (PEG-IFN) alpha plus ribavirin (RBV) given for 24 weeks or 48 weeks. This combination produced mediocre sustained virological response (SVR) rates of 40% to 50% and was accompanied by a number of intolerable adverse effects, such as hemolytic anemia, flu-like symptoms, and psychiatric disturbances. A treatment breakthrough came in 2011 with the approval of two oral DAs, boceprevir (Victrelis, Merck Sharp & Dohme) and telaprevir (Incivek, Vertex Pharmaceuticals). These agents were used in combination with PEG-IFN plus RBV for patients with GT 1 and increased SVR rates to as much as 70%; however, these medications came with cumbersome dosing regimens, strict dietary requirements, and unfavorable adverse effect profiles. A paradigm shift occurred in late 2013 with the approval of simeprevir (Olysio, Janssen) and sofosbuvir (Sovaldi, Gilead Sciences) within weeks of one another. These agents were the first oral once-daily treatments that were well tolerated and were able to produce SVR rates greater than 90% either together in combination or with PEG-IFN plus RBV in select genotypes. Following the approval of additional DAA medications, treatments that do not use IFN became available for all HCV genotypes. Several well-tolerated, all-oral regimens are now approved to treat patients with various HCV genotypes, stages of liver disease, and comorbidities.

The newer DAA drugs target various points of the HCV viral replication cycle. These medications affect key structures or the replication process either by directly binding to components of the replicase complex or by initiating RNA chain termination. Medications that target the NS3/4A protease contain the suffix “-previr,” medications that inhibit the NS5B polymerase have the suffix “-buvir,” and NS5A inhibitors end in “-avir.”

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**LEDPASVIR/SOFOSBUVIR**

The approval of the combination of ledipasvir 90 mg and sofosbuvir 400 mg (LVD/SOF) (Harvoni, Gilead Sciences) as a single-tablet formulation in October 2014 ushered in a new era for HCV treatment. Sofosbuvir is a potent pan-genotypic NS5B
RNA polymerase inhibitor with a high barrier to resistance that was approved separately by the Food and Drug Administration (FDA) as Sovaldi in December 2013. This nucleotide prodrug is hepatically converted to its active form, uridine analogue triphosphate, which incorporates into HCV RNA and halts viral replication. Sofosbuvir is a P-glycoprotein (P-gp) substrate, so caution should be taken with P-gp inducers, such as rifampin or St. John’s wort. Sofosbuvir and its metabolites are renally eliminated, and its metabolites are seen to accumulate in the setting of impaired renal function. Safety, efficacy, and dosing adjustments in patients with severe renal impairment or end-stage renal disease have not been established, so its use is not recommended when a patient’s creatinine clearance (CrCl) is less than 30 mL/min. The FDA released a warning in 2015 regarding the coadministration of amiodarone and sofosbuvir-containing regimens following reports of serious symptomatic bradycardia and consequent deaths. Although the drug-interaction mechanism is unclear, the combination should be avoided; cardiac monitoring is recommended if alternative options are not available.10,12 Ledipasvir, which acts as a direct inhibitor on the active site of the NS5A protein, is available only in combination with sofosbuvir in the single-tablet regimen. This therapy is extremely well tolerated, with fatigue (13%), headache (14%), and nausea (7%) being among the most common adverse effects in patients treated for 12 weeks. The frequency of adverse effects increases in patients treated with concurrent RBV or those with decompensated cirrhosis, but these are likely to be attributed to the RBV and the patient’s underlying disease more than the LVD/SOF. The use of LVD/SOF should be avoided in patients who are taking medications that suppress gastric acid, such as proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs), because this may reduce concentrations of LVD. If concomitant therapy is necessary, administering LVD/SOF at the same time as acid suppression therapy under fasting conditions is recommended. Doses of PPIs should not exceed 20 mg of omeprazole or equivalent, and H2RAs should not exceed 40 mg of famotidine twice daily or equivalent.13

**Genotype 1**

A daily regimen of LVD/SOF alone for 12 weeks is recommended in GT 1a or GT 1b treatment-naive patients with or without compensated cirrhosis. This is based on the ION-1 study, which examined 12 weeks versus 24 weeks of LVD/SOF with or without RBV in 865 treatment-naive patients with and without compensated cirrhosis (16% of patients in the analysis had compensated cirrhosis). A majority of patients (67%) in the trial had GT 1a infection. In all four treatment arms, rates of SVR at 12 weeks post-treatment (SVR12) ranged from 95% to 99% (95% confidence interval [CI], 94–100%), with no statistically significant differences based on length of treatment, use of RBV, or GT 1 subtype.14

The ION-3 trial compared eight weeks of LVD/SOF, 12 weeks of LVD/SOF, and eight weeks of LVD/SOF plus RBV in 647 GT 1 patients without cirrhosis. SVR12 rates were 93% to 95% across all three treatment arms (95% CI, 89–100%). However, the eight-week treatment arms had a higher rate of relapse compared with the 12-week arm (5% [11 of 215] versus less than 1% [three of 216], respectively). Post hoc analyses of the two RBV-free arms assessed baseline predictors of relapse and identified lower relapse rates in patients who had baseline HCV RNA levels below 6 million IU/mL; these relapse rates were no different than those in the 12-week treatment arm (2% [two of 123] versus 2% [two of 131], respectively).15 GT 1a and GT 1b treatment-naive patients without cirrhosis are a rare subgroup of patients in whom pretreatment viral load is clinically relevant in determining treatment options. For those who qualify, eight weeks of treatment may be an effective and cost-saving alternative to the traditional 12 weeks of treatment, though this practice is currently not recommended for African-Americans, patients coinfected with HIV, or those with IL28B polymorphisms CT or TT. Additional outcomes data for patients treated with a shortened course of LVD/SOF are needed to improve the strength of this recommendation.16

Patients who failed specific types of treatment, namely regimens containing an NS3 protease inhibitor (telaprevir, boceprevir, or simeprevir) and a DAA (simeprevir or sofosbuvir), were studied separately from other treatment-experienced patients without cirrhosis. The ION-2 study evaluated treatment-experienced patients with GT 1a or GT 1b who received 12 weeks versus 24 weeks of LVD/SOF with or without RBV. Among the 440 patients, 209 (47.5%) had previously failed IFN plus RBV and 231 (52.5%) had failed a protease-inhibitor–containing regimen. Compensated cirrhosis was seen in 20% of the patients enrolled, and 79% had GT 1a infection. For patients with cirrhosis, SVR12 rates were significantly lower in the 12-week treatment group, both with and without use of RBV (86% [19 of 22] and 82% [18 of 22], respectively), versus the 24-week treatment group (99% [86 of 87] and 99% [88 of 89]; 95% CI, 95–100% for both).16 In GT 1a or GT 1b treatment-experienced patients with compensated cirrhosis, 24 weeks of LVD/SOF alone is recommended.10 It is important to note that the addition of RBV was not shown to significantly alter outcomes in the ION-2 study. Rather, guidance recommendations are based on other subsequent studies.

The SIRIUS study compared 12 weeks of LVD/SOF plus RBV to 24 weeks of LVD/SOF alone in 155 patients with GT 1 who had previously failed PEG-IFN/RBV plus telaprevir or boceprevir. Rates of SVR12 in both groups were 96% (74 of 77; 95% CI, 89–99%) and 97% (75 of 77; 95% CI, 89–99%), respectively.17 Another study by Wyles et al. enrolled 51 patients with GT 1, with or without compensated cirrhosis, who had failed an SOF-containing regimen, to be retreated with LVD/SOF plus RBV for 12 weeks. Participants achieved a 98% (50 of 51) SVR12 rate, and the one patient who failed treatment was actually infected with HCV GT 3 but erroneously enrolled into the intention-to-treat cohort.18 Furthermore, a meta-analysis by Reddy et al. looked at data from patients with GT 1 and compensated cirrhosis. Of the 513 patients, 47% had previously failed a DAA-containing regimen. SVR12 was achieved in 95% to 98% of these patients when they were retreated with 12 to 24 weeks of LVD/SOF, with or without RBV (95% CI, 94–98%).19 These studies provided evidence for a shorter, more cost-effective alternative to 24 weeks of LVD/SOF for patients who can tolerate RBV.

To date, there are no data from randomized controlled trials demonstrating significant differences in treatment responses to LVD/SOF among the GT 1 subtypes. Therefore, guideline
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Genotype 4

A daily regimen of LVD/SOF alone for 12 weeks is recommended in GT 4 patients with or without compensated cirrhosis. This is based on the SOLAR trial, which enrolled 21 patients with HCV GT 4, of whom 13 (68%) were treatment-naïve and eight (32%) were treatment-experienced with PEG-IFN/RBV. Of the 21 patients, 20 (95%) achieved SVR12 (95% CI, 75–100%); the one treatment failure was a treatment-naïve patient who withdrew consent at week 7 due to non-compliance. Another study by Abergel et al. examined 44 patients with HCV GT 4 treated with LVD/SOF alone for 12 weeks; 22 patients were treatment-naïve and 22 were treatment-experienced with PEG-IFN/RBV. Forty-one of 44 patients (93%) achieved SVR12 (95% CI, 81–99%): 21 of 22 in the treatment-naïve group and 20 of 22 in the treatment-experienced group. There is less evidence for the use of LVD/SOF in patients with GT 4 and compensated cirrhosis. The SYNERGY study enrolled only seven patients with compensated cirrhosis, and the study by Abergel et al. enrolled 10; however, all of these patients achieved SVR12. For treatment-experienced patients, the recommendation is to treat with a daily regimen of LVD/SOF plus RBV for 12 weeks. An alternative regimen of LVD/SOF alone for 24 weeks is also suggested, though there is very little data to support this recommendation.

Genotypes 5 or 6

A daily regimen of LVD/SOF alone for 12 weeks is recommended in GT 5 or GT 6 patients with or without compensated cirrhosis. A study by Abergel et al. examined 41 patients with HCV GT 5. Of these patients, nine (22%) had compensated cirrhosis and 20 were treatment-experienced. Patients received LVD/SOF for 12 weeks; 39 of 41 (95%) achieved SVR12 (95% CI, 75–100%). Of the two treatment failures, neither patient was treatment-experienced, and one had compensated cirrhosis. A study by Gane et al. examined patients with both GT 3 and GT 6. For patients with GT 6, treatment with LVD/SOF for 12 weeks achieved SVR12 in 24 of 25 patients. The only treatment failure was due to the patient’s withdrawal from the trial at week 8. Of the 25 patients, two were treatment-experienced and two had cirrhosis. While this study observed patients with GT 3, there is no indication for the use of LVD/SOF in HCV GT 3, primarily due to the existing literature on numerous preferred regimens. There is also no recommendation to add RBV or extended treatment duration in treatment-experienced patients.

Decompensated Cirrhosis

Recommendations for the treatment of patients with decompensated cirrhosis are identical for both GT 1 and GT 4 infections. In patients who have not failed an SOF-based regimen, a daily regimen of LVD/SOF plus initial low-dose RBV (600 mg a day, then increased as tolerated) for 12 weeks is recommended. For patients who cannot tolerate or are otherwise ineligible for RBV, a daily regimen of LVD/SOF for 24 weeks is also recommended. This is based on the SOLAR-1 study, which examined 108 patients with GT 1 and GT 4 infection and decompensated cirrhosis. Patients were randomized to 12 weeks or 24 weeks of LVD/SOF plus RBV. The SVR12 rate in Child–Turcotte–Pugh (CTP) class B patients was 87% (26 of 30) for 12 weeks and 89% (24 of 27) for 24 weeks of treatment, while SVR12 rates in CTP class C patients were 86% (19 of 22) for 12 weeks and 87% (20 of 23) for 24 weeks of treatment.

The SOLAR-2 study was an expansion of the SOLAR-1 study that enrolled 329 patients with identical inclusion criteria and treatment interventions. Among patients with GT 1 HCV and CTP class B cirrhosis, SVR12 was achieved by 87% (23 of 26; 90% CI, 70–96%) with 12 weeks of treatment and 96% (23 of 24; 90% CI, 81–100%) with 24 weeks of treatment. The SVR12 rate in GT 1 HCV patients with class C cirrhosis was 90% (20 of 22; 90% CI, 66–96%) with 12 weeks of treatment and 78% (14 of 18; 90% CI, 60–91%) with 24 weeks of treatment. Among all patients with GT 4, SVR12 was achieved by 78% (14 of 18; 90% CI, 56–92%) with 12 weeks of treatment and 94% (16 of 17; 90% CI, 75–100%) with 24 weeks treatment.

For patients who have failed prior SOF-based regimens, a daily regimen of LVD/SOF plus initial low-dose RBV (600 mg a day, then increased as tolerated) for 24 weeks is recommended. There are no data on the use of this regimen in patients with compensated cirrhosis. However, LVD/SOF for 24 weeks was studied as a treatment option for patients with GT 1 infection and compensated cirrhosis who had failed a prior course of SOF-based therapy. A total of 41 patients entered this study, and SVR12 was achieved in 71% (29 of 41) of patients.

Patients Coinfected With HIV

Data from the ION-4 study examined 12-week courses of LVD/SOF in GT 1 and GT 4 treatment-naïve and -experienced patients, with and without compensated cirrhosis, who were coinfected with HIV. A total of 335 patients were enrolled, 98% of whom had GT 1 infection. Patients had to have stable HIV disease, defined as an RNA viral load of less than 50 copies/mL and a CD4 lymphocyte count of at least 100 cells/mm3. The allowed antiretroviral therapy (ART) regimens consisted of tenofovir/emtricitabine plus either efavirenz, rilpivirine, or raltegravir. Overall, 96% (321 of 335; 95% CI, 93–98%) of patients achieved SVR12. The results were similar regardless of prior treatment history or cirrhosis status.

Of the many potential drug–drug interactions that exist between LVD/SOF and ART, very few have been determined to be of clinical significance. Pharmacokinetic studies have shown that LVD increases levels of tenofovir disoproxil fumarate (TDF), which may potentiate the risk of renal toxicity. This is due to LVD’s inhibitory effect on the P-gp system, which increases the plasma concentration of other P-gp substrates. In November 2016, the FDA approved tenofovir alafenamide (TAF) (Vemlidy, Gilead Sciences), which has a different pharmacokinetic profile than TDF, and an interaction has not been noted. This formulation of tenofovir can also be found in combination tablet regimens for the treatment of HIV. Other ART drugs that interact with LVD via the P-gp system include rilpivirine, abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, and rilpivirine. The area under the curve (AUC) for LVD was increased by 96% when it was coadministered with rilpivirine-boosted atazanavir; however, this interaction does not
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require a dose adjustment. Furthermore, the increase in tenofovir levels was greatest when it was taken concomitantly with LVD and ritonavir. As a result, all patients on ritonavir-based ART regimens were excluded from LVD/SOF clinical trials.29

**PARITAPREVIR/RITONAVIR/OMBITASVIR PLUS DASABUVIR**

The combination of paritaprevir 150 mg, ritonavir 100 mg, and ombitasvir 25 mg forms the backbone of three regimens: Vieckira, Vieckira XR, and Technivie (Abbvie, Inc). Vieckira consists of those three drugs and dosages plus dasabuvir 250 mg (PrOD). Vieckira’s dosing is two tablets of combined ombitasvir, paritaprevir, and ritonavir taken once daily plus one tablet of dasabuvir taken twice daily. Vieckira XR simplifies this by combining all four medications into a single tablet (dasabuvir 200 mg, ombitasvir 8.33 mg, paritaprevir 50 mg, and ritonavir 33.3 mg), but requires the patient to take three tablets once daily.20 Technivie consists only of paritaprevir 150 mg, ritonavir 100 mg, and ombitasvir 25 mg (PrO) and is used exclusively for treatment of GT 4 patients.21 Ombitasvir is an N5A inhibitor with pangenotypic antiviral activity, paritaprevir is an inhibitor of the NS3/4A serine protease, and dasabuvir is a nonnucleoside NS5B polymerase inhibitor. Ritonavir is a potent inhibitor of cytochrome P450 (CYP) 3A4 enzymes used as a pharmacoenhancer for paritaprevir, but it does not have any intrinsic antiviral activity.30

**Genotype 1**

For treatment-naive noncirrhotic patients with GT 1a infection, the recommended treatment is a regimen of PrO once daily plus dasabuvir 250 mg twice daily plus weight-based RBV for 12 weeks.10 This recommendation is based on data from two clinical trials, the first of which, SAPPHIRE-I, enrolled 631 treatment-naive noncirrhotic patients with GT 1a and GT 1b infections. Patients were randomized to either PrOD plus RBV for 12 weeks or placebo. The overall SVR12 rates were 96% (455 of 473), including 95% (307 of 322) for GT 1a and 98% (148 of 151) for GT 1b (95% CI, 95–98%).32 The second trial, PEARL-IV, examined the efficacy of 12 weeks of PrOD with or without RBV in 305 treatment-naive patients with GT 1a infection. The SVR12 rate was 97% (97 of 100) in the RBV group versus 90% (185 of 200) in the RBV-free group. Compared with the RBV group, the RBV-free group also demonstrated significantly increased rates of in-treatment virological failure and post-treatment relapse (2.0% versus 7.8%, respectively). This trial confirmed the need for RBV in combination with PrOD for treatment of GT 1a infections.33

For treatment-naive or -experienced patients with GT 1a infection and compensated cirrhosis, an alternative would be a daily regimen of PrOD plus RBV for 24 weeks, though this regimen is not preferred given the long duration of RBV therapy.10 The combination was initially granted FDA labeling based on the TURQUOISE-II trial, which enrolled 380 treatment-naive and IFN/RBV-experienced patients with CTP class A cirrhosis and GT 1a or GT 1b HCV infection. Patients were randomized to 12 weeks or 24 weeks of PrOD plus RBV. Overall, SVR12 rates were high in both the 24-week (96%; 165 of 172) and 12-week (92%; 191 of 208) groups (97.5% CI, 92.6–99.3% and 87.6–96.1%, respectively). For patients with GT 1a infection, the difference was more apparent, as the SVR12 rate in the 12-week group was less than that of the 24-week group: 89% (124 of 140) versus 95% (59 of 62), respectively. This was mostly due to the GT 1a treatment-experienced cohort, where null responders to IFN/RBV had an SVR12 rate of 87% in the 12-week group versus 95% in the 24-week group.34 Regardless, the recommendation to extend treatment duration to 24 weeks was extrapolated to both treatment-naive and IFN/RBV-experienced patients with GT 1a infection and compensated cirrhosis.

In October 2015, the FDA released a warning regarding the use of PrOD/PrO-containing regimens in patients with cirrhosis. Post-marketing analysis demonstrated that patients on these regimens were at increased risk for rapid-onset liver injury and, in some cases, hepatic decompensation, including patients with CTP class A compensated cirrhosis. This risk was especially high during the first four weeks of treatment, leading to a change in labeling and a contraindication for PrOD/PrO in patients with decompensated cirrhosis. Of note, the risk of liver injury was significantly higher in patients with GT 1a infections than those with GT 1b infections.35

The SAPPHIRE-II trial enrolled 297 noncirrhotic patients with GT 1a or GT 1b infection who were treatment-experienced with IFN/RBV to receive PrOD plus RBV for 12 weeks. The overall SVR12 rate was 96% (286 of 297), with 166 of 173 patients with GT 1a and 119 of 123 patients with GT 1b achieving SVR12 (95% CI, 94.2–98.4%).36

For treatment-naive or -experienced patients with GT 1b, the recommended treatment is a daily regimen of PrOD for 12 weeks, regardless of cirrhosis status.10 This was determined by the PEARL-II and PEARL-III trials. The PEARL-II trial examined 179 IFN/RBV-experienced patients without cirrhosis and with GT 1b infection. Treatment with PrOD with or without RBV resulted in high SVR12 rates in both groups: 100% (91 of 91) with RBV and 97% (85 of 88) without RBV.37 The PEARL-III trial randomized 419 treatment-naive, noncirrhotic patients with GT 1b to PrOD with or without RBV for 12 weeks. The SVR12 rate was high for both treatment groups: 99% (209 of 210) with RBV and 99% (207 of 209) without RBV.38 The need for RBV in GT 1b infections was further diminished by the TURQUOISE-III trial, which observed 60 treatment-naïve, noncirrhotic patients with GT 1b to PrOD with or without RBV for 12 weeks. The SVR12 rate was high for both treatment groups: 99% (209 of 210) with RBV and 99% (207 of 209) without RBV.39 The use of PrOD with or without RBV in patients with advanced renal failure was evaluated in the RUBY-I trial. Patients with GT 1a and GT 1b infection and stage 4 or 5 chronic kidney disease (CKD) (defined by an estimated glomerular filtration rate of less than 30 mL/min/1.73 m2), without cirrhosis or anemia, were treated for 12 weeks. Twenty patients were enrolled, and SVR12 rates were 85% (11 of 13) in those with RBV and 100% (seven of seven) without RBV.40

**HIV Coinfection**

Standard fixed-dose regimens of PrOD have been deemed safe and effective for patients with GT 1 HCV and HIV infection.
Hepatitis C in a New Era: A Review of Current Therapies

Data from TURQUOISE-I compared 12- and 24-week regimens of PrOD plus RBV in coinfected patients who were required to have a CD4 count of at least 200 cells/mm³ (or at least 14%) and an HIV RNA level of less than 40 copies/mL while receiving atazanavir- or raltegravir-based HIV ART. Regarding HCV status, patients were treatment-naïve or had failed IFN/RBV; they were noncirrhotic or had compensated cirrhosis. Rates of SVR₁₂ were 94% for patients in the 12-week group (95% CI, 79–89%) and 91% in the 24-week group (95% CI, 76–97%). While the efficacy of this regimen has been demonstrated, there are numerous drug–drug interactions between PrOD and HIV medications that make this option unfavorable in the treatment of coinfected patients.

Genotype 4

For any cohort of patients with GT 4 infection, regardless of treatment history or cirrhosis status, the recommended treatment is a daily regimen of PrO plus RBV for 12 weeks. This is based on data from several clinical trials, the first of which was PEARL-I. This trial enrolled 86 treatment-naïve patients with GT 4 infection without cirrhosis. Patients were randomized to PrO with or without RBV for 12 weeks. The rates of SVR₁₂ were higher in the RBV group (100%, 42 of 42) than in the non-RBV group (91%, 40 of 44) (95% CI, 91.6–100% and 78.3–97.5%, respectively). The AGATE-I trial randomized 120 patients with GT 4 infection without cirrhosis who were treatment-naïve and IFN/RBV-experienced to PrO plus RBV for 12 weeks or 16 weeks. SVR₁₂ rates were high in both groups: 96% (57 of 59) for the 12-week group and 98% (60 of 61) for the 16-week group. The AGATE-II trial randomized 160 patients with GT 4 infection with and without cirrhosis who were treatment-naïve and IFN/RBV-experienced. The 100 noncirrhotic patients were treated with PrO plus RBV for 12 weeks, while the 60 cirrhotic patients were randomly assigned to 12 weeks or 24 weeks of PrO plus RBV. For noncirrhotic patients, the SVR₁₂ rate was 94%. For cirrhotic patients, SVR₁₂ rates were high in both groups: 97% (30 of 31) for the 12-week group and 93% (27 of 29) for the 24-week group. These trials demonstrated that, for GT 4 infections, combination with RBV improves SVR₁₂ rates, but extending the length of treatment beyond 12 weeks had no significant impact on SVR₁₂ rates, regardless of treatment history or cirrhosis status. Again, due to the increased risk of liver failure, this combination is to be used with caution in patients with compensated cirrhosis and is contraindicated in patients with decompensated cirrhosis.

SIMEPREVIR PLUS SOFOSBUVIR

The combination of simeprevir 150 mg and sofosbuvir 400 mg (SMV/SOF) is an oral, once-daily, two-medication regimen containing an NS3/4A and NS5B polymerase inhibitor combination that was used off-label for GT 1 HCV infection until it received FDA approval in November 2014. Each component was separately approved in 2013 with adjunct PEG-INF and/or RBV, but these combinations have proven inferior to the oral DAA combination of SMV/SOF in terms of efficacy, tolerability, adherence, pill burden, serious adverse events, treatment duration, and monitoring parameters. Simeprevir is a reversible NS3/4A protease inhibitor mainly metabolized via CYP3A4 and excreted via the biliary route. Coadministration with moderate or strong CYP3A inhibitors and HIV medications such as protease inhibitors or pharmacokinetic enhancers such as ritonavir can increase simeprevir plasma concentrations. Likewise, CYP3A inducers can reduce simeprevir plasma concentrations, leading to suboptimal efficacy. Monitoring of liver enzymes and serum bilirubin is recommended. The use of SMV is not recommended in patients with moderate or severe hepatic impairment because cases of hepatic decompensation and failure have been reported, and significant increases of simeprevir plasma concentrations have been seen. Simeprevir is also not recommended in the presence of baseline GT 1a NS3A polymorphism Q80K or in patients who previously failed a regimen with simeprevir. The Q80K mutation is associated with reduced SVR₁₂, and all patients with GT 1a infection should be screened before initiating a simeprevir-containing regimen.

The SMV/SOF combination is generally well tolerated, with headache (14–20%), fatigue (12–20%), and nausea (11–15%) being the most commonly reported adverse events in clinical trials. Some patients may experience photosensitivity (5%), while 1% may experience a grade 3 rash when using SMV; appropriate monitoring should be conducted.

An open-label, randomized phase 2 trial investigated the efficacy of SMV/SOF once daily with or without RBV for 12 weeks or 24 weeks in treatment-naïve and PEG-IFN/RBV-experienced patients with GT 1 HCV infection. Two cohorts were established: Cohort 1 consisted of previous nonresponders to PEG-IFN/RBV with stage F0–F2 fibrosis, and cohort 2 included treatment-naïve or PEG-IFN/RBV nonresponders with stage F3–F4 fibrosis. Overall, SVR₁₂ was achieved in 92% of patients (154 of 167), including 90% (72 of 80) of F0–F2 patients and 94% (82 of 87) of F3–F4 patients. Patients who received 24 weeks of treatment in cohort 2 all achieved SVR₁₂, suggesting duration extension may be useful in patients with a history of relapse and/or advanced fibrosis. Otherwise, SVR₁₂ rates were similar regardless of therapy duration, adjunct RBV, treatment status, baseline polymorphism, or degree of fibrosis. The authors concluded that SMV/SOF for 12 weeks is an effective, IFN-free, oral regimen for GT 1 infection.

Kwo and colleagues facilitated the phase 3 OPTIMIST-1 trial, which evaluated eight-week and 12-week regimens of SMV/SOF in GT 1-infected treatment-naïve and -experienced patients without cirrhosis. Rates of SVR₁₂ in the 12-week arm were 97% (150 of 155; 95% CI, 94–100%), superior to a historical control rate and higher in comparison to the eight-week arm (83% [128 of 155]; 95% CI, 76–89%). Consistently high SVR (95% or greater) was observed in the 12-week arm regardless of treatment experience status, genotype subtype, or baseline mutation. In the eight-week arm, patients with a baseline NS3 Q80K mutation had lower responses to therapy versus patients with the baseline mutation in the 12-week arm (73% versus 96%, respectively). This study further supports the efficacy of 12 weeks of SMV/SOF in GT 1-infected noncirrhotic patients.

The OPTIMIST-2 trial analyzed the safety and efficacy of 12 weeks of treatment in compensated cirrhotic patients. SVR₁₂ was reached in 83% of patients (86 of 103; 95% CI, 76–91%), superior to a historical control rate. However, SVR rates were lower in patients with the baseline GT 1a Q80K mutation (74% versus 92%, respectively) or who had failed prior therapy (79% versus 88%, respectively). Based on these findings, SMV/SOF...
is considered a second-line, alternative regimen in cirrhotic GT 1-infected treatment-naive patients in the absence of Q80K polymorphism.48

**DACLATASVIR AND SOFOSBUVIR**

Daclatasvir 60 mg (Daklinza, Bristol-Myers Squibb) and sofosbuvir 400 mg (DCV/SOF) is a two-tablet, once-daily oral NS5A inhibitor/NS5B RNA polymerase inhibitor regimen. Daclatasvir/sofosbuvir with or without RBV was initially approved only for HCV GT 3 infection in July 2015, but its indication was expanded in February 2016 to treat GT 1 and GT 3, including special populations with HIV coinfection or advanced cirrhosis, or after liver transplant.49 Daclatasvir exhibits its action by binding to the NS5A protein, consequently inhibiting RNA viral replication and viral assembly. In combination with sofosbuvir, headache (6–30%) and fatigue (14–17%) are the most commonly reported adverse effects. Daclatasvir is a substrate of CYP3A4 and requires dose adjustments when used in the presence of strong CYP inhibitors or moderate inducers; its use is contraindicated with strong inducers. For example, a decrease to 30 mg daily in the presence of a strong CYP3A4 inhibitor or increase to 90 mg daily with a moderate CYP3A4 inducer is recommended by the manufacturer. DCV/SOF should be considered for patients chronically receiving a PPI because concomitant use with omeprazole did not alter daclatasvir plasma concentrations.49

Sulkowski and colleagues conducted a phase 2a trial in which patients with GT 1, GT 2, or GT 3 HCV infection received DCV/SOF with or without RBV for 12 weeks if they were treatment-naive or 24 weeks if they had previous failure with telaprevir- or boceprevir-containing regimens. Among both treatment-naive and treatment-experienced GT 1 patients, 98% (164 of 167) achieved SVR12. Patients with GT 2 had SVR12 rates of 92% (24 of 26) versus 89% (16 of 18) for GT 3 patients. Overall, similar response rates were exhibited regardless of GT 1 subtype, duration of therapy, or add-on RBV.50

The ALLY-2 trial assessed DCV/SOF in GT 1, 2, 3, and 4 HIV-coinfected patients. Of the 203 patients, 85% (168 of 203) had GT 1 infection. Rates of SVR12 for patients with GT 1 infection were 96% (80 of 83) in the 12-week treatment-naive subgroup, 76% (31 of 41) in the eight-week treatment-naive subgroup, and 98% (43 of 44) in the 12-week treatment-experienced subgroup. Cure rates were 96% or greater for GT 1a and 1b patients treated for 12 weeks. Patients with GT 2 (n = 13), GT 3 (n = 10), and GT 4 (n = 3) who received 12 weeks of therapy demonstrated SVR12 rates of 100%; however, rates of SVR12 fell to 83% (five of six) and 67% (two of three) in GT 2 and GT 3, respectively, when patients were treated for eight weeks.51 In addition to the studies above, the ALLY-3 data further support the efficacy of DCV/SOF in GT 3 infection for 12 weeks with 89% of patients (135 of 152) achieving SVR12 (96% in noncirrhotic patients [115 of 120] and 63% in cirrhotic patients [20 of 32]).52

Poordad and colleagues included decompensated and three-month post-liver-transplant patients in their trial evaluating a 12-week course of DCV/SOF with RBV. The post-transplant cohort achieved 94% (50 of 53) SVR12, with high response in those who had GT 1 (95%) with no graft rejection or observed transplant medication drug interactions. In the advanced cirrhosis cohort, 50 of 60 patients (94%) achieved SVR12, but lower rates were seen in CTP class C (56%) in comparison with CTP class A or B.53

Daclatasvir 60 mg/sofosbuvir 400 mg for 12 weeks is a recommended regimen for GT 1 and GT 3 treatment-naive noncirrhotic patients, but is considered an alternative with or without RBV in those with compensated cirrhosis for 24 weeks. The ideal duration of therapy for cirrhotic patients is relatively unclear due to the small number of cirrhotic patients represented in the trials. Despite demonstrated efficacy in GT 2, DCV/SOF is not FDA-approved for this specific genotype, but can be considered in treatment-naive patients with or without cirrhosis. For patients with decompensated cirrhosis or after transplant, DCV/SOF may be considered in GT 1–4 with RBV for 12 weeks or for 24 weeks without RBV if ineligibile.10

**ELBASVIR/GRAZOPREVI**

The combination therapy of the NS5A inhibitor elbasvir 50 mg and the NS3/4A protease inhibitor grazoprevir 100 mg (EVR/GZR) (Zepatier, Merck Sharp & Dohme) as a single once-daily tablet was approved in early 2016 for the treatment of HCV GT 1 and GT 4. Both medications are eliminated primarily through liver metabolism via CYP3A, with less than 1% eliminated via renal excretion. Due to the dependence on the CYP3A pathway, use of EBR/GZR with strong inducers or inhibitors of this enzyme should be avoided.54 Prior to using this therapy in GT 1a patients, a screening test for NS5A polymorphisms at amino acid positions 28, 30, 31, or 93 must be completed because their presence will affect the recommended duration of therapy.49 The use of EBR/GZR is contraindicated in patients who have moderate-to-severe hepatic impairment (CPT class B or C), those taking medications that inhibit organic anion transporting polypeptides 1B1/1B3, and those taking strong inducers of CYP3A enzymes or efavirenz. Overall, the use of EBR/GZR is well tolerated across all patient populations regardless of comorbidities such as CKD or cirrhosis. In treatment-naive patients, the most common adverse effects were fatigue (11%) and headache (10%), but the frequency was similar to that observed in the placebo arm (10% and 9%, respectively). Patients with CKD experienced more nausea (11%) than non-CKD patients, but it was similar to the 8% receiving placebo. Late elevations in serum alanine aminotransferase greater than five times the upper level of normal (ULN) were noted in 1% of patients around treatment week 8, but these were generally asymptomatic and resolved upon completion of therapy. Patients who received RBV plus EBR/GZR experienced increased frequency of elevated bilirubin greater than 2.5 times the ULN (6% versus 1%), but this is largely attributed to RBV.54

A 12-week course of EBR/GZR was evaluated in both treatment-naive patients with compensated cirrhosis and non-cirrhotic patients with GT 1, GT 4, and GT 6 in the C-EDGE trial. Overall, 211 patients with GT 1a, 171 patients with GT 1b, 26 patients with GT 4, and 13 patients with GT 6 were enrolled. Two-thirds of the patients had fibrosis stage F0–F2, 12% had F3 fibrosis, and 22% had F4 fibrosis (cirrhotic). The overall SVR12 rate was 95% (299 of 316), with rates of 92% (144 of 157) for GT 1a, 99% (129 of 131) for GT 1b, 100% (18 of 18) for GT 4, and 80% (eight of 10) for GT 6. The reasons for failure were loss to follow-up or discontinuation in four patients, viro-
logical breakthrough in one patient, and virological relapse in 12 patients. Analysis of the association of SVR12 and presence of pre-existing RAVs in GT 1a and GT 1b patients showed that NS3/4A polymorphisms had no discernable affect on cure but NS5A mutations were associated with failure (SVR12 in 58% [11 of 19]).

The addition of weight-based RBV to EBR/GZR was evaluated in 79 GT 1 patients who had previously failed PEG-IFN and RBV combined with boceprevir, telaprevir, or simeprevir in the open-label C-SALVAGE study. At baseline, 62% of patients had GT 1b and 38% had GT 1a; 47% had a fibrosis score of F0–F2, and 43% had F4 fibrosis. The SVR12 rates were 96% (76 of 79), with three patients experiencing virological relapse. Evaluations for baseline RAVs found that 34 patients (43%) had NS5A mutations and eight (10%) had NS5A RAVs. Of the NS3A RAVs, only four were noted to result in a fivefold reduction in grazoprevir susceptibility. The rates of SVR12 were 93% (28 of 30) and 75% (three of four) for patients with RAVs that conferred a fivefold or less and a greater-than-fivefold decrease in susceptibility, respectively. Patients were followed for an additional 12 weeks to provide data on SVR12 rates. The follow-up analysis showed no additional patients experiencing disease relapse, confirming the durability of cure achieved with EBR/GZR plus RBV in this treatment-experienced group.

Investigators in the C-WORTHY group evaluated multiple treatment combinations involving varying doses of EBR (20 mg versus 50 mg), the addition of RBV, and durations of therapy ranging from eight to 18 weeks in treatment-naïve and pretreated GT 1 patients with or without cirrhosis or HIV coinfection. This review focuses only on EBR 50 mg, as that is the currently available formulation. Among mono-infected patients treated for 12 weeks, there appeared to be no advantage to adding RBV; cure rates were 93% (79 of 85; 95% CI, 85–97%) with RBV and 98% (43 of 44; 95% CI, 88–100%) without. This trend was reversed in the HIV-coinfected group, which saw SVR12 rates of 97% (28 of 29; 95% CI, 82–100%) with RBV and 87% (26 of 30; 95% CI, 69–96%) without. A notable decline in SVR12 rates was seen in the eight-week EBR/GZR plus RBV GT 1a-only treatment group, 80% of whom (24 of 30; 95% CI, 61–92%) achieved SVR12. The participants in the 12-week versus 18-week cohort were either treatment-naive cirrhotic or previous null responders to treatment with PEG-IFN and RBV at any stage of cirrhosis. Rates of SVR12 among treatment-naïve patients were similar regardless of receiving RBV or being treated for 12 versus 18 weeks. Treatment-naïve patients treated with the most basic regimen of EBR/GZR for 12 weeks achieved SVR12 rates of 97% (28 of 29; 95% CI, 82–100%). Those treated for 12 weeks with the addition of RBV reported 90% SVR12 (28 of 31; 95% CI, 74–98%), while patients treated for 18 weeks achieved 97% (31 of 32; 95% CI, 84–100%) with RBV and 94% (29 of 31; 95% CI, 79–99%) without RBV. The SVR12 rates were similar among all groups in the null-response cohort (32–33 patients per group) regardless of treatment duration or the addition of RBV, with ranges of 91% to 100% cure. Combining all groups for analysis, SVR12 rates for patients receiving RBV were 92% and 98% for 12 and 18 weeks, respectively, and 94% and 95% in patients not receiving RBV for 12 and 18 weeks, respectively. Rates of virological failure were similar in both the treatment-naïve (5%; six of 123) and previous null responders (3%; four of 130). Evaluating the effect of RAVs on cure, 32% of patients had baseline NS3 mutations and 92% achieved SVR12 (96% SVR12 in wild type), while 14% possessed baseline NS5A RAVs, of whom 82% achieved SVR12 (97% SVR12 in wild type).

EBR/GZR was evaluated in patients with GT 1 and stage 4 and stage 5 CKD, including patients receiving intermittent hemodialysis. Of the 122 evaluable patients, 115 (94%) achieved SVR12. Of the seven patients not achieving SVR, six discontinued the study for reasons other than virological failure, but the seventh experienced viral relapse and was noted to have an NS5A RAV at baseline. Thirty-six patients had NS3/4A RAVs at baseline and achieved cure, while 16 others with an NS5A RAV at baseline achieved SVR12. This trial concluded that EBR/GZR daily for 12 weeks was safe and effective in treating this population; however, it should be noted that only 6% (14) of the patients had stage F4 cirrhosis, making it difficult to extrapolate results to that group.

Finally, this combination was studied in a cohort of patients with GT 1, GT 4, and GT 6 who were coinfected with HIV in a nonrandomized, open-label trial. The patients either needed to be stable on ART containing TDF or abacavir with emtricitabine or lamivudine in addition to either raltegravir, dolutegravir, rilpivirine, or elvitegravir with a CD3 or CD4 T-cell count greater than 200 cells/mcL and an undetectable HIV RNA, defined as less than 20 copies/mL. Patients also could be ART-naïve if they had a CD4 cell count greater than 500 cells/mcL and a viral load of less than 50,000 copies/mL. The overall SVR12 rate was 96% (210 of 218; 95% CI, 92.9–98.4%) and was similar across GT 1a, GT 1b, and GT 4. In addition, high rates of SVR12 were seen in historically difficult populations, such as those with cirrhosis baseline HCV viral loads greater than 800,000 IU/mL. Of the eight patients who failed, one was lost to follow-up, two acquired reinfection with HCV, and five had virological breakthroughs. This trial demonstrated the efficacy and safety of this combination with select ART regimens.

Velpatasvir/Sofosbuvir

The combination of the NS5A inhibitor velpatasvir (100 mg) and the NS5B polymerase inhibitor sofosbuvir (400 mg) (VEL/SOF) (Epclusa, Gilead Sciences) was approved as a once-daily single-pill combination product on June 28, 2016. This therapy is the first indicated as a 12-week treatment for all HCV genotypes with or without compensated cirrhosis and for patients with decompensated cirrhosis when used with RBV. It has no specific contraindications aside from those given for RBV therapy.

As this combination includes SOF, it is not recommended for patients receiving amiodarone due to the risk of severe bradycardia. Administration of VEL/SOF with agents that increase gastric pH should be avoided due to reduced absorption of velpatasvir; however, if medically necessary, VEL/SOF should be administered with food four hours prior to acid suppression therapy. The adverse effects of VEL/SOF are generally mild and similar to those of placebo in patients without cirrhosis or with compensated cirrhosis. The most commonly noted reactions are headache (22%), fatigue (15%), nausea (9%), insomnia (5%), and asthenia (5%). Patients with decompensated cirrhosis experience fatigue (32%), anemia (26%), nausea (15%),
headache (11%), and diarrhea (10%) as their most common adverse effects; this increase may largely result from the addition of RBV. Uncommon but noteworthy increases in lipase (3–6% versus 1–3%) and creatine kinase (1–2% versus 0–1%) were seen compared with patients receiving placebo.

The efficacy of VEL/SOF was demonstrated in patients with GT 1, GT 2, GT 4, and GT 6 compared with placebo in a large, multicenter, double-blind trial. Patients with GT 5 were enrolled but not randomized due to the low prevalence of this genotype. Overall, 624 patients were enrolled in the treatment groups and 116 in the placebo group. The majority were white (79%) and male (60%); 19% had cirrhosis, and 32% had previously received unsuccessful treatment. The SVR_{12} rates were: GT 1a, 98% (206 of 210; 95% CI, 95 to greater than 99%); GT 1b, 99% (117 of 118; 95% CI, 95–100%); GT 2, 100% (104 of 104; 95% CI, 97–100%); GT 4, 100% (116 of 116; 95% CI, 97–100%); GT 5, 97% (34 of 35; 95% CI, 91–100%); and GT 6, 100% (41 of 41; 95% CI, 91–100%).

Separate clinical trials were required to demonstrate the efficacy of VEL/SOF in patients with GT 2 (n = 266) and GT 3 (n = 552) without cirrhosis or with compensated cirrhosis. The majority of patients enrolled were white men, and approximately 14% and 23% of GT 2 and GT 3 patients, respectively, had compensated cirrhosis. Similar rates of patients in both groups were previous null responders to prior HCV treatments. Patients with GT 2 were randomized to receive VEL/SOF or SOF/RBV for 12 weeks; of the 266 patients treated, about 14% had cirrhosis and about 14% had failed previous HCV treatment. Rates of SVR_{12} were 99% (133 of 134; 95% CI, 96–100%) for VEL/SOF compared with 94% (124 of 132; 95% CI, 88–97%) for SOF/RBV. No VEL/SOF patients experienced virological failure, but six (5%) SOF/RBV patients experienced relapse. In baseline resistance testing, 66% of patients had NSSA RAVs, and 10% had NS5B RAVs; however, all patients achieved SVR_{12}, indicating that these RAVs had no impact on treatment efficacy. Patients with GT 3 received VEL/SOF for 12 weeks or SOF/RBV for 24 weeks; 95% (264 of 277; 95% CI, 92–98%) in the VEL/SOF arm achieved SVR_{12} compared with 80% (221 of 275; 95% CI, 75–85%) in the SOF/RBV arm. Rates of virological failure were 4% (n = 11) for those receiving VEL/SOF and 14% (n = 38) for those receiving SOF/RBV. Eighty-eight percent (38 of 43) of patients with baseline NS5A RAVs and 97% of patients without baseline RAVs achieved SVR_{12}.

The ASTRAL-4 trial was a multicenter, open-label study evaluating the efficacy of VEL/SOF in patients with decompensated cirrhosis. Patients with any genotype and CPT class B were eligible to undergo treatment with VEL/SOF for 12 weeks or VEL/SOF with RBV for 12 or 24 weeks. Of the 267 patients undergoing treatment, the majority were white men, with 76% to 79% in each group having GT 1. Overall rates of SVR_{12} were 83% (75 of 90), 94% (82 of 87), and 86% (77 of 90) for those receiving VEL/SOF for 12 weeks, VEL/SOF plus RBV for 12 weeks, and VEL/SOF for 24 weeks, respectively. Twenty-two patients experienced virological failure, 11 in the 12-week VEL/SOF group, three in the VEL/SOF plus RBV arm, and eight in the 24-week VEL/SOF arm. Among observed patients, CPT scores improved in 47% (117 of 250), remained unchanged in 42% (106 of 250), and worsened in 11% (27 of 250). RAVs for NS5A were seen in 72 patients (28%); however, 89% of them achieved SVR_{12}, similar to the 92% in patients with no baseline resistance.

VEL/SOF for 12 weeks was studied in HIV/HCV coinfected patients with GT 1–6. Patients had to be stable on ART for eight weeks with a viral load of 50 copies/mL or less and a CD4 cell count of at least 100 cells/mm³. Participants could be receiving a non-nucleoside reverse transcriptase inhibitor, protease inhibitor, or integrase inhibitor in combination with either TDF/emtricitabine or abacavir/lamivudine. Of the 106 participants, 86% were men and 45% were African-American. Patients’ genotypes included GT 1a (n = 65); GT 1b (n = 12); GT 2 (n = 11); GT 3 (n = 12), and GT 4 (n = 4). The overall SVR_{12} rate was 95% (99 of 104) with no appreciable difference in rates for different genotypes, cirrhosis status, prior HCV treatment experience, or presence of baseline NSSA mutations. This data supports the use of VEL/SOF in the treatment of HIV/HCV coinfected patients.

**COSTS AND OTHER CONSIDERATIONS**

Much of the discussion about HCV treatment has focused on the costs of therapy given the large up-front prices. Based on average wholesale prices (AWPs), the cost of 12 weeks of treatment can range from approximately $65,000 to $113,000. The AWPs for a single day’s therapy and a full 12-week course of treatment are provided in Table 3. If the patient requires a regimen that also necessitates the use of RBV, additional drug acquisition costs need to be considered; however, as a variety of dosage formulations and manufacturers is available, this product is not included in the pricing table. It is important to consider additional monitoring costs or medical costs that

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**Table 3 Associated Treatment Costs Based on Average Wholesale Price (AWP)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Cost*</th>
<th>12-Week Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir (Daklinza, Bristol-Myers Squibb), all doses</td>
<td>$900</td>
<td>$75,600</td>
</tr>
<tr>
<td>Dasabuvir/ombitasvir/paritaprevir/ritonavir (Viekira Pak and Viekira XR, AbbVie)</td>
<td>$1,910</td>
<td>$99,980</td>
</tr>
<tr>
<td>Elbasvir/grazoprevir (Zepatier, Merck Sharp &amp; Dohme)</td>
<td>$780</td>
<td>$65,520</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir (Harvoni, Gilead Sciences)</td>
<td>$1,350</td>
<td>$113,400</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir (Technivie, AbbVie)</td>
<td>$1,095</td>
<td>$91,983</td>
</tr>
<tr>
<td>Simeprevir (Olysio, Janssen)</td>
<td>$948</td>
<td>$79,632</td>
</tr>
<tr>
<td>Sofosbuvir (Sovaldi, Gilead Sciences)</td>
<td>$1,200</td>
<td>$100,800</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir (Epclusa, Gilead Sciences)</td>
<td>$1,068</td>
<td>$89,712</td>
</tr>
</tbody>
</table>

* Discounts and negotiations may lower costs for institutions and payers.
Hepatitis C in a New Era: A Review of Current Therapies

Table 4  Genotype 1 Approved Regimens: Treatment-Naïve and Noncirrhotic Patients

<table>
<thead>
<tr>
<th>Medications</th>
<th>Dosing</th>
<th>Duration</th>
<th>Contraindications or Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir/ledipasvir*</td>
<td>400/90 mg once daily</td>
<td>12 weeks</td>
<td>Sofosbuvir: Avoid use with amiodarone, rosuvastatin, known CYP 450 inducers; ledipasvir levels may be altered by agents that suppress gastric acid.</td>
</tr>
<tr>
<td>Sofosbuvir/simeprevir</td>
<td>400/150 mg once daily</td>
<td>12 weeks</td>
<td>Simeprevir: Screen patients for Q80K mutation in GT 1a; possible increase in bilirubin levels; increased risk of rash or photosensitivity in East Asian patients.</td>
</tr>
<tr>
<td>Sofosbuvir/daclatasvir</td>
<td>400/60 mg once daily</td>
<td>12 weeks</td>
<td>Avoid use with strong CYP3A4-inducing or -inhibiting agents.</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir*</td>
<td>400/100 mg once daily</td>
<td>12 weeks</td>
<td>Avoid use with strong CYP3A4-inducing or -inhibiting agents; medications that increase gastric pH may lower concentrations of velpatasvir.</td>
</tr>
<tr>
<td>Elbasvir/ grazoprevir*</td>
<td>50/100 mg once daily</td>
<td>12 weeks</td>
<td>Avoid use in the presence of CTP stage B or C, inhibitors of organic anion transporting polypeptide, strong CYP3A4 inducers.</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir/dasabuvir, plus ribavirin</td>
<td>150/100/25/250 mg, plus weight-based ribavirin</td>
<td>12 weeks</td>
<td>Avoid use in strong CYP3A4- or CYP2C8- inducing or inhibiting agents; avoid use in the presence of CTP stage B or C; monitor closely for elevations in ALT and discontinue if &gt; 10 times ULN; many potential drug–drug interactions secondary to ritonavir component.</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; CTP = Child–Turcotte–Pugh; CYP = cytochrome P450; GT = genotype; ULN = upper limit of normal.
* Indicates single-tablet combinations

Table 5  Genotype 2, 3, and 4 Approved Regimens: Treatment-Naïve and Noncirrhotic Patients

<table>
<thead>
<tr>
<th>Medications</th>
<th>Dosing</th>
<th>Duration</th>
<th>Contraindications or Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir*</td>
<td>400/100 mg once daily</td>
<td>12 weeks in noncirrhotic patients and those with compensated cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/daclatasvir</td>
<td>400/60 mg once daily</td>
<td>12 weeks in noncirrhotic patients and 16–24 weeks in those with compensated cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Genotype 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir*</td>
<td>400/100 mg once daily</td>
<td>12 weeks in noncirrhotic patients and those with compensated cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/daclatasvir</td>
<td>400/60 mg once daily</td>
<td>12 weeks in noncirrhotic patients and 24 weeks ± RBV in those with compensated cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Genotype 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir*</td>
<td>400/90 mg once daily</td>
<td>12 weeks in noncirrhotic patients and those with compensated cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir*</td>
<td>400/100 mg once daily</td>
<td>12 weeks in noncirrhotic patients and those with compensated cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Elbasvir/ grazoprevir*</td>
<td>50/100 mg once daily</td>
<td>12 weeks in noncirrhotic patients and those with compensated cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir/dasabuvir, plus ribavirin</td>
<td>150/100/25 mg; ribavirin dosed by weight</td>
<td>12 weeks in noncirrhotic patients and those with compensated cirrhosis</td>
<td></td>
</tr>
</tbody>
</table>

* Indicates single-tablet combinations

may arise from the adverse effects of RBV therapy, such as hemolytic anemia, which may require use of an erythropoietin-stimulating agent or increased laboratory monitoring.

While the AWPs quoted in Table 3 are high, it is important to note that this is rarely the final cost for the patient or health care system. Negotiations involving insurance, pharmacy benefit managers, state governments (for Medicaid), and national contracts (Veterans Affairs, Department of Defense, federal prisons) often result in substantially reduced pricing for achieving SVR12. Given the wide range of factors that influence pricing and the dynamic nature of insurance or state medical coverage, it is difficult to speak definitively about treatment costs. In addition, many relevant contracts are confidential, making price assessment difficult. However, a report from the U.S. Senate Finance Committee quoted Gilead Sciences as negotiating average discounts with payers of 22% and 46% of the wholesale acquisition cost (WAC) in 2014 and 2015, respectively. This suggests that the true cost of curing HCV may be lower than the suggested AWP or WAC, and this cost likely has been reduced further following the introduction of new therapies to the market.10,68

For those who require assistance covering expenses related to HCV care, Gilead offers its SUPPORT PATH program for eligible U.S. patients to receive access to SOF, SOF/LVD, or SOF/VEL. This program includes copay assistance for eligible patients with private insurance and may provide medications at no charge for eligible and qualified patients without insurance. AbbVie has assistance programs for Viekira and Technivie for qualifying patients through its ProCeed program. Bristol-Myers Squibb has set up Patient Support Connect to assist with daclatasvir access, and Janssen offers its CarePath program of financial support for simeprevir. A copayment assistance program has...
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### Table 6: Recommended Regimens for Special Populations

<table>
<thead>
<tr>
<th>Patients who require stomach acid suppression therapy</th>
<th>Use of PPI not recommended as it may lower ledipasvir concentrations; if HCV therapy used concomitantly, administer dose at same time as PPI at equivalent dose of omeprazole 20 mg or lower</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>No interaction documented</td>
</tr>
<tr>
<td>Sofosbuvir + simeprevir</td>
<td>Use of PPI not recommended as it may lower velpatasvir concentrations; if HCV therapy used concomitantly, administer dose four hours before PPI with food, and do not exceed PPI dose of omeprazole 20 mg or equivalent</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir + dasabuvir</td>
<td>Use of PPI not recommended as concentrations of both ombitasvir and dasabuvir are increased when given with omeprazole</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with renal failure (CrCL &lt; 30 mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a</td>
</tr>
</tbody>
</table>
| Genotype 1b                                   | • Elbasvir 50 mg/grazoprevir 100 mg for 12 weeks  
• Paritaprevir 150 mg + ritonavir 100 mg + ombitasvir 25 mg + dasabuvir 250 mg twice daily + ribavirin for 12 weeks |
| Genotype 4                                    | Elbasvir 50 mg/grazoprevir 100 mg for 12 weeks |
| Genotypes 2, 3, 5, and 6                       | Pegylated-interferon and dose-adjusted ribavirin |

** Decompensated liver disease **

| Genotypes 1 or 4                               | • Sofosbuvir 400 mg/ledipasvir 90 mg + low-dose ribavirin (600 mg; increase as tolerated) for 12 weeks  
• Sofosbuvir 400 mg/velpatasvir 100 mg + weight-based ribavirin for 12 weeks  
• Sofosbuvir 400 mg + daclatasvir 60 mg + low-dose ribavirin (600 mg; increase as tolerated) for 12 weeks |
| Genotypes 1 or 4 who cannot tolerate ribavirin | • Sofosbuvir 400 mg/ledipasvir 90 mg for 24 weeks  
• Sofosbuvir 400 mg/velpatasvir 100 mg for 24 weeks  
• Sofosbuvir 400 mg + daclatasvir 60 mg for 24 weeks |
| Genotypes 2 or 3                               | • Sofosbuvir 400 mg/velpatasvir 100 mg + weight-based ribavirin for 12 weeks  
• Sofosbuvir 400 mg + daclatasvir 60 mg + low-dose ribavirin (600 mg; increase as tolerated) for 12 weeks |

HCV = hepatitis C virus; PPI = proton pump inhibitor

also been established for elbasvir/grazoprevir that could lower a patient’s costs to as little as $5 per prescription or possibly no cost if the patient qualifies. The American Liver Foundation provides references and resources for financial assistance programs offered by the pharmaceutical industry, nonprofit organizations, and states at: http://hepc.liverfoundation.org/resources/what-if-i-need-financial-assistance-to-pay-for-treatment.

** Pricing strategies for these medications have caused fierce debate regarding health care costs and resource allocation. Many state Medicaid programs require patients to demonstrate extensive liver disease (F3 or F4) before qualifying for treatment coverage. Evaluation of restrictions in Medicare plans that utilize fee-for-service or managed care organization services showed in 2014 that 31 of 34 states (91%) with known restrictions required patients to demonstrate F3 or F4 disease to qualify for coverage, but this number declined to 23 of 44 (50%) in 2016.69 The number of states with unknown restrictions declined from 17 to seven during the same time, demonstrating a trend toward states improving access to HCV treatment.69 Other barriers to treatment include required patient sobriety from substances ranging from alcohol to injection drugs, restrictions on the type of practitioners who can prescribe treatment, or restrictions involving patients who develop reinfection.70

Early treatment of patients with HCV can also be viewed as a preventive strategy. Chronic HCV is the most common reason patients require a liver transplant, and curing HCV lowers the need for this procedure.71 The estimated cost of a liver transplant is more than $739,000 based on 2014 billing charges, and this does not account for the subsequent life-long anti-rejection medications required afterward.72 Additionally, HCV is a leading cause of HCC, and the median costs associated with cancer treatment were shown to be $176,456 (interquartile range, $84,489–$292,192).73 Achieving SVR has demonstrated a substantial reduction in patients’ risk of developing HCC compared with patients not achieving SVR (hazard ratio, 0.24; 95% CI, 0.18–0.31; P < 0.001).74 Chronic HCV has also been linked to the development of hepatic steatosis, insulin resistance, and subsequent diabetes mellitus.75 Eradication of HCV has been shown to reduce the number of patients who develop type-2 diabetes as well as reduce cardiovascular- and renal-related outcomes in patients who are already diagnosed with diabetes.76,77 However, many of these long-term outcome studies were conducted in patients who achieved SVR with PEG-IFN and RBV therapy, and long-term data using all-oral regimens are lacking because many of these agents have been available for only a few years.

In summary, patients who achieve SVR attain numerous long-term benefits; however, these benefits may not fully satisfy payers in part because those payers may not benefit from treating patients early if the patient switches to a different health care provider later in life when the costs of untreated HCV might otherwise have come due.78

** THE PLACE OF REGIMENS IN THERAPY **

The decision of which agent to use in the setting of HCV should be based largely on individual patient factors, such as comorbid disease states, potential drug–drug interactions, and insurance coverage and affordability, because the available
medications have relatively similar rates of cure. Comorbidities to consider include cirrhosis status, HIV, and CKD. The efficacy and tolerability of the available regimens are especially comparable in GT 1 patients who are noncirrhotic and treatment naive. Prior to starting any patient on medication, a thorough analysis for drug–drug interactions should be conducted, ideally by a pharmacist trained in infectious diseases. Multiple types of interactions may exist aside from typical CYP-mediated interactions, such as altered gastric pH affecting bioavailability, P-gp inhibition or induction, or RAVs affecting medication efficacy in experienced patients.

Tables 4, 5, and 6 are provided to summarize available and recommended regimens for GTs 1–4 and in selected disease states.

CONCLUSION

The HCV treatment arena is extremely dynamic at this moment, with new data being published continuously and new therapies expected to come to market over the next few years. Several resources can keep clinicians up to date, including HCV guidance from the AASLD and IDSA that is available online and continuously updated (www.hcvguidelines.org). The University of Liverpool maintains an HCV drug–drug interaction database online (www.hep-druginteractions.org) that is also available as an app (Liverpool HEP iChart) for both iOS and Android devices. These resources can help guide the practitioner in selecting an appropriate and safe regimen for all patients seeking care, which should be administered by a multidisciplinary team that can include pharmacists, nurse practitioners, or physician assistants to allow for more patients to be screened, educated, and treated.

The cost of treatment cannot be ignored, and practitioners must be vigilant about ensuring patient access whether through insurance or patient-assistance programs. Partnering with specialty pharmacies may help facilitate patient access because these pharmacies have experience in obtaining insurance coverage and stock these high-cost medications. In the coming years, competition between companies can be expected to drive costs down, especially with more agents projected to come to market.

Over the past decade, HCV has evolved from a major global cause of morbidity and mortality, with treatments that were largely ineffective, complicated, and intolerable, to a disease that can be eradicated with simple, tolerable, and highly efficacious therapies. The progress achieved in the 30 years between that can be eradicated with simple, tolerable, and highly efficacious therapies. The progress achieved in the 30 years between the discovery of this disease and the development of targeted medications represents the amazing potential of medicine.

REFERENCES

Hepatitis C: A Review of Current Therapies


