Hepatitis C Virus Management in the Post-Pipeline Era

By Michelle T. Martin, Pharm.D., FCCP, BCPS, BCACP

Reviewed by Bryan L. Love, Pharm.D., BCPS-AQ ID; Erin K. VanMeter, Pharm.D., BCACP; and Jordan Sedlacek, Pharm.D., BCACP, BC-ADM

LEARNING OBJECTIVES

1. Assess recent trends in transmission, screening, and management of hepatitis C virus (HCV).
2. Apply national guidance–based treatment strategies to develop and implement a patient-specific therapeutic plan for treating HCV in patients without cirrhosis.
3. Design optimal guidance-based HCV treatment for patients with cirrhosis, patients after transplantation, patients with HIV coinfection, or patients who have resistance.
4. Develop a plan to address and monitor drug interactions associated with HCV treatment.
5. Assess clinical outcomes and HCV treatment response.

ABBREVIATIONS IN THIS CHAPTER

AASLD	American Association for the Study of Liver Diseases
ADR	Adverse drug reaction
CTP	Child-Turcotte-Pugh
DAA	Direct-acting antiviral
DDI	Drug-drug interaction
ESRD	End-stage renal disease
GT	Genotype
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
PI	Protease inhibitor
RAS	Resistance-associated substitution
SVR	Sustained virologic response

Table of other common abbreviations.

INTRODUCTION

Hepatitis C virus (HCV) is a single-stranded, enveloped RNA virus from the Flaviviridae family of the *Hepacivirus* genus. Before HCV was discovered in 1989, it was identified as non-A, non-B hepatitis (Houghton 2009).

Hepatitis C is the most common bloodborne infection in the United States (CDC 2016). More Americans are infected with and die of HCV than 60 other nationally notifiable infectious conditions, including HIV (Ly 2016); however, HCV did not receive considerable public attention until the marketing of HCV direct-acting antiviral (DAA) agents. Chronic HCV infection is the second leading known reason for liver transplantation and the leading cause of end-stage liver disease, liver-related death, and hepatocellular carcinoma (HCC) in the United States (Kim 2018; Alter 2007).

Hepatitis C lacks a proofreading polymerase, allowing for frequent mutations during viral replication and evasion of the immune system. No vaccine is currently available for HCV, but researchers are investigating the cellular or humoral immune response in human trials (Shoukry 2018). No pre- or postexposure prophylaxis is available for HCV. Groundbreaking changes in HCV treatment have occurred since 2013 with the approval of several novel DAAs with improved sustained virologic response (SVR), or cure rates, and shorter treatment durations than historic treatment with pegylated interferon and ribavirin. Unlike other viral infections such as HIV, HCV is curable. Currently available HCV treatments have SVR rates in the high 90% range, depending on the patient's HCV genotype (GT), disease progression, and previous treatment experience (AASLD 2019). Medication adherence is imperative for successful response to HCV treatment. Medication access is vital, but the high cost of the new DAAs has increased health care costs. Some payers responded by limiting access, and many states' Medicaid plans still limit treatment to patients with advanced-stage disease.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Knowledge of biostatistics according to the BCACP blueprint
- Basic virology and replication of HCV
- Complications of cirrhosis

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- CDC. Interpretation of Hepatitis B Virus Serologies.
- American Association for the Study of Liver Diseases, Infectious Diseases Society of America, and International Antiviral Society-USA. Recommendations for testing, managing, and treating hepatitis C.

Box 1. Risk Factors for HCV Transmission

- Born 1945–1965
- Coinfection with HIV or HBV
- Hemodialysis
- Illicit intranasal drug use
- Intravenous drug use
- Occupational exposure
- Perinatal transmission (children born to mothers with HCV)
- Recipient of blood transfusions or solid organ transplants (before July 1992)
- Recipient of clotting factors (before 1987)
- Recipient of injections with used/contaminated needles
- Sexual transmission (multiple sex partners, men who have sex with men, or history of sexually transmitted disease)
- Tattoos, acupuncture, or body piercing with unsterilized instruments

HBV = hepatitis B virus; HCV = hepatitis C virus.

Information from: American Association for the Study of Liver Diseases, Infectious Diseases Society of America. Recommendations for Testing, Managing, and Treating Hepatitis C.

Epidemiology

The WHO estimates that 71 million people have HCV infection worldwide and that 399,000 people die of HCV-related causes annually (WHO 2018). These numbers have decreased in the past 3 years, but more progress is needed to eliminate the virus. A recent analysis estimates that HCV affects 2.4 million Americans, or 1% of the population (Hofmeister 2019). These HCV epidemiologic data were based on the National Health and Nutrition Examination Survey (which does not include homeless, incarcerated, active military, or institutionalized patients), and the authors included estimates from modeling studies of active duty military, homeless, incarcerated, and nursing home residents to yield a more accurate estimate of prevalence. However, only 50% of patients with HCV infection are given a diagnosis of and are aware of their HCV infection, and only a fraction have been prescribed HCV treatment (Yehia 2014). Moreover, an updated cascade of care is needed to assess the progress of HCV management in the DAA era.

Hepatitis C is associated with significant mortality; in 2016, HCV caused 18,153 deaths in the United States (CDC 2016). New HCV cases reported annually decreased from 291,000 in 1989 to 16,500 in 2011 but have since increased to 41,200 in 2016 (CDC 2016). The recent increase in HCV cases among patients younger than 30 years, especially in non-urban settings, is thought to be a result of increased heroin use among that population (Zibbell 2015). Injection drug use is the most common mode of HCV transmission in the United States, whereas unsafe injection or immunization practices, inadequate sterilization of medical equipment, and transfusion of unscreened blood and blood products are common causes of HCV in other less well-developed countries (WHO 2018). Box 1 lists risk factors and modes of HCV transmission.

Recent screening initiatives have been directed at patients with HCV infection who were born in 1945–1965 and were likely exposed to HCV from injection drug use or contaminated blood transfusions before the virus was discovered. Patients born within this age cohort account for about 75% of individuals with HCV infection. The American Association for the Study of Liver Diseases (AASLD), the CDC, the Centers for Medicare & Medicaid Services, and the U.S. Preventive Services Task Force endorse a one-time screening of patients born in 1945–1965, regardless of risk factors, in addition to screening all patients with risk factors (Moyer 2013; CDC 2012). Efforts have begun to push for universal screening to account for the bimodal incidence of HCV infection in younger patients with injection drug use in addition to baby boomers. In addition, universal screening of pregnant women is recommended. Because of the opioid crisis, the number of pregnant women with HCV has increased, as has the incidence of perinatal HCV transmission.

Hepatitis C has six major GTs that have treatment recommendations, but researchers have isolated more than six GTs and at least 67 different subtypes (e.g., GTs 1a, 1b, 2a, 2b, 2c, 3a) (Smith 2014). Genotype prevalence differs by geographic location. Genotype 1 is the most common form in the United States, accounting for about 76% of infections in North America; GT 1a is over 3-fold more prevalent than GT 1b. Genotypes 2 and 3 make up about 12% and 10%, respectively, of the HCV infections in North America (Messina 2015). Genotypes 1–3 are also the most common GTs in Europe. Genotype 4 is the predominant GT in the Middle East, GT 5 in Southern Africa, and GT 6 in Asia (Messina 2015).

Pathophysiology

Acute HCV Infection

After acute HCV infection, the virus is transferred by the blood to the liver, where it binds to host receptors on hepatocytes and enters the cell by receptor-mediated endocytosis. Fusion of the viral envelope and the cell membrane allows uncoating and release of viral RNA into the cell. Next, the RNA is translated into a large polyprotein, which is cleaved into smaller, functional proteins by the HCV protease complex, NS3/4A. The RNA is replicated, and the new virus is assembled. On release from the cell, the virus spreads to other hepatocytes for further replication (Ciesek 2011). In an infected liver, up to 1 trillion virions are produced every day. Although HCV can be found in non-liver cells, it mainly replicates in hepatocytes. The virus activates an immune response and inflammatory mediators leading to varying degrees of hepatic fibrosis over time.

Acute HCV may present with mild to severe nonspecific symptoms such as fatigue, nausea, vomiting, and diarrhea, as shown in Box 2. If symptoms occur, they usually present within the average incubation period of 6–7 weeks after HCV exposure but can appear any time 2–26 weeks after exposure. Up to 80% of patients have no symptoms after contracting the virus (WHO 2018).

Around 15%–25% of patients who are exposed to HCV will spontaneously clear the virus and eliminate the infection. The remaining 75%–85% of patients will develop chronic HCV, defined as detectable HCV viral RNA for more than 6 months (AASLD 2019; WHO 2018).

Box 2. Symptoms of Acute HCV

- Abdominal pain
- Dark urine/clay-colored stool
- Diarrhea
- Fatigue
- Fever
- Jaundice
- Loss of appetite/nausea/vomiting
- Myalgia/arthralgia

Information from: World Health Organization (WHO). Hepatitis C. 2018.

Chronic HCV Infection

Most patients are unaware of their infection as they transition from acute to chronic HCV infection (WHO 2018). Hepatitis C causes inflammation with progression of hepatic fibrosis, and the hepatocytes lose their ability to function. Chronic HCV infection can take decades to transform a healthy liver into a cirrhotic liver. Around 20% of patients with chronic HCV will develop cirrhosis; subsequently, portal hypertension can develop and result in esophageal varices. Other sequelae of advanced liver disease include ascites and encephalopathy. On physical examination, patients may have jaundice and spider angioma (WHO 2018). Patients with chronic HCV with cirrhosis are at risk of developing HCC, which occurs at the rate of about 1%–4% per year in this patient population (McHutchison 2005). Figure 1 shows the progression of HCV.

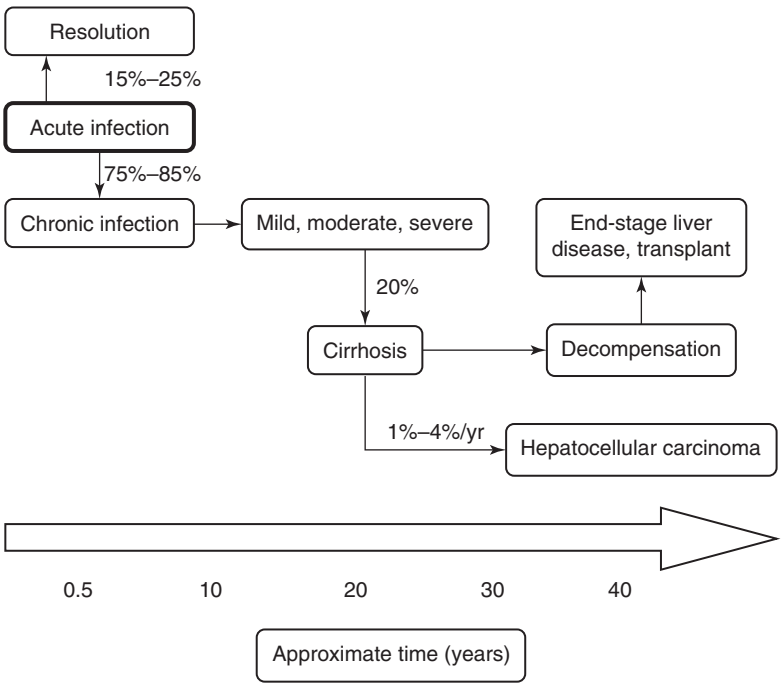

Figure 1. Progression of hepatitis C virus infection.

Information from: McHutchison JG, Bacon BR. Chronic hepatitis C: an age wave of disease burden. Am J Manag Care 2005;11:S286-S295.

CLINICAL EVALUATION AND DIAGNOSIS

HCV Screening Recommendations

The HCV antibody blood test is the initial screening test for determining HCV infection. All patients born between 1945–1965 and all patients with risk factors should be screened for HCV. Locations for HCV screening can include primary care and the ED. Colonoscopy suites typically have a vast opportunity to screen patients, given that most patients undergoing colonoscopy are included in age-cohort screening recommendations. Some drug manufacturers sponsor public screening events, provide grant funding for implementing screening programs, and advertise on television. The national goals for HCV elimination by 2030 include increased diagnoses with the hopes of funneling more patients into treatment and preventing transmission.

An FDA-approved Clinical Laboratory Improvement Amendments–waived point-of-care test is available for antibody screening (OraQuick HCV Rapid Antibody Test). Test sensitivity and specificity are 98% and 100%, results are available in about 20 minutes, and cost is about $20. This testing method is ideal when a venipuncture is not practical or possible, but a diagnosis of chronic HCV cannot be made with its use. Providers' concerns with point-of-care testing performed in a non–health center setting are that the patient may not receive appropriate education, support, and linkage to care for confirmation with HCV RNA testing and follow-up.

If the patient has a positive HCV antibody, a blood test for an HCV RNA quantitative viral load must be obtained to determine whether the patient has replicating virus (or current chronic HCV infection). Many laboratories have adopted the use of a reflexive test that will assess for HCV RNA if the antibody is present. This test is preferable because it reduces the number of steps needed to confirm diagnosis and minimizes the chance that the patient will be lost to follow-up before diagnosis.

Patients who have a chronic infection will have a detectable HCV RNA viral load 6 months or longer after the initial time of exposure to HCV. Patients who have been exposed to HCV will have a positive HCV antibody (detectable 4–10 weeks after exposure), regardless of whether they have chronic infection. Table 1 is a tool for interpreting these tests. Unlike antibodies for hepatitis A and B, the HCV antibody does not protect against future HCV infection. Because no protective immunoglobulin G antibodies develop in patients who have cleared HCV either spontaneously or through treatment, patients are at continued risk of HCV reinfection if reexposure occurs (AASLD 2019).

Patients with chronic infection will undergo an additional blood test to determine their HCV GT, which is used to select appropriate treatment. In the era of pangenotypic regimens, genotyping may be less vital in the future, and resource-limited settings may forgo the test. Genotype is currently used for treatment selection, for indication of when to check for resistance, and to complete payer forms. Viral load will be measured at 12 weeks after completing therapy to determine whether SVR was attained. If patients have an undetectable HCV viral load 12 weeks after completing treatment, they are considered cured.

Procedures and Noninvasive Measures of Disease Progression

Liver biopsy was previously considered the gold standard for evaluating both the degree of inflammation (grade) and the extent of scarring or fibrosis (stage) to evaluate the severity of the patient's liver disease. Severity of liver disease is often categorized according to the METAVIR fibrosis scores of F0 (no scarring) to F4 (cirrhosis), and activity, or inflammation, scores of A0 (no activity) to A3 (severe activity). The degree of fibrosis and inflammation can be estimated by liver biomarker blood tests (e.g., FibroSure, FibroTest, or FIBROSpect II) that measure components of the extracellular hepatic matrix (Poynard 2012). These tests use the METAVIR score to indicate the degree of scarring and inflammation in the liver. Other surrogate measures that can indicate the presence of cirrhosis include Plt concentrations below 150,000/mm^3, INR greater than 1 in the absence of anticoagulation, and albumin less than 3.5 g/dL. The FIB-4 index uses an equation of [(age x AST)/(Plt x ALT)] to assess the likelihood of fibrosis level; FIB-4 greater than 3.25 has been associated with advanced

Table 1. Interpretation of HCV Blood Tests

		HCV RNA Quantitative	
		Detectable	**Not Detected**
HCV antibody	Positive	Acute or chronic HCV infection	Resolved HCV infection (spontaneous resolution or successful treatment)
	Negative	Early acute infection or chronic HCV infection in an immunocompromised patient	No HCV infection

HCV = hepatitis C virus.

fibrosis. The AST to Plt ratio index (APRI) score can estimate the presence of cirrhosis: APRI values of 0.4 or less do not indicate significant fibrosis and cirrhosis, whereas values of 1.5 or greater indicate significant fibrosis (Snyder 2006).

Transient elastography (FibroScan) is an ultrasound-based technology that estimates the degree of liver stiffness, which is used as a marker of fibrosis. Transient elastography is a painless procedure that takes about 5 minutes and can be performed easily at the bedside or in a clinic setting. However, narrow intercostal space, obesity, ascites, and recent food consumption pose challenges or can inhibit accurate results. A liver stiffness measurement of over 12.5 kPa indicates cirrhosis in the setting of HCV, whereas scores of 2.5–7 kPa indicate mild or absent fibrosis (Castera 2008). The Child-Turcotte-Pugh (CTP) score is used to further assess patients with cirrhosis on the basis of mortality risk; class A is considered compensated cirrhosis; classes B and C are decompensated cirrhosis. Because of the invasiveness of a liver biopsy and its associated risks and costs, most patients and providers opt for noninvasive tests to estimate the degree of fibrosis and guide treatment options in the era of highly successful HCV treatment.

Patients with METAVIR stage F3 or F4 (cirrhosis) must undergo imaging of the liver every 6 months to screen for HCC (AASLD 2019). Abdominal ultrasonography is used to screen for lesions and can also identify splenomegaly, ascites, and other abnormalities. If lesions are detected on ultrasonography, a CT scan or MRI is used for more precise evaluation. Early detection and treatment of HCC yields better response rates. Ultrasonography and alfa-fetoprotein testing every 6 months resulted in a 90.2% sensitivity of HCC detection and a 63.4% sensitivity of early-stage HCC compared with 43.9% and 31.7%, respectively, with ultrasonography alone (Singal 2012). Therefore, some providers use this combination for HCC surveillance.

TREATMENT

The ultimate goal of HCV treatment is eradication of the HCV infection to prevent complications and death from liver disease. Successful treatment (with SVR) can halt the progression of liver fibrosis and prevent cirrhosis, end-stage liver disease, HCC, and the need for liver transplantation (AASLD 2019). Successful treatment of HCV infection can also reverse fibrosis caused by HCV infection. Even patients with late-stage fibrosis had decreased all-cause mortality after SVR (van der Meer 2012).

The AASLD, the International Antiviral Society (IAS), and the Infectious Diseases Society of America (IDSA) first published joint guidance for HCV management online in January 2014, which AASLD/IDSA updates with new recommendations when additional data are available. Pharmacologic treatment regimens and treatment duration differ depending on the HCV GT. Table 2, Table 3, and Table 4 show treatment options for treatment-naive and treatment-experienced patients (with pegylated interferon and ribavirin) without cirrhosis and with compensated cirrhosis, depending on the GT, as recommended by the June 2019 AASLD guidance. Levels of evidence are listed for each regimen in the guidance document, which is continuously updated. Readers are encouraged to visit the website for the latest information regarding treatment selection for clinical practice. Monotherapy is not effective in HCV treatment; regimens include a combination of two or three classes of DAAs. Genotype 1 has the most DAAs currently available for its treatment (Table 5). Current DAAs perform well in patients whose HCV treatment with pegylated interferon and ribavirin previously failed. Patients whose DAAs have failed have fewer options; see Table 4 for treatment options for protease inhibitors (PIs) and the AASLD guidance for more details. Prior exposure to a DAA can cause the emergence of resistance-associated substitutions (RASs) that cause decreased susceptibility to other DAAs within that class. Because SVR rates have increased drastically with the advent of DAAs, fewer patients have treatment failure while receiving these agents than with pegylated interferon and ribavirin treatment.

Hepatitis C treatment is usually not an urgent recommendation, except in peritransplant patients. Some providers prefer to treat before transplantation, especially if treatment may eliminate or defer the need for transplantation. Some providers defer HCV treatment until after transplantation to allow the donor pool to include patients with HCV-positive infection, and some programs may offer HCV-positive organ transplants to patients negative for HCV infection. Deferring HCV treatment may be an option in patients with no or minimal fibrosis and no evidence of significant extrahepatic disease. However, it is difficult to predict which patients will progress in their liver disease and at what rate. As of 2015, the guidance recommends treating all patients with HCV, except those with a short life expectancy. Several payers (i.e., some state Medicaid and Medicaid-managed care plans) implemented sobriety and provider restrictions, or only cover treatment for patients with F3 to F4, given that earlier guidance iterations recommended stratifying treatment by severity.

Because current treatment options have almost 100% SVR rates, a short duration, and minimal adverse drug reactions (ADRs) compared with historic treatment, more patients may elect treatment. Some patients may be forced, by insurers, to wait until they have more advanced disease before beginning treatment.

Before 2011, the combination of pegylated interferon alfa-2a or alfa-2b with ribavirin was the standard of care for HCV treatment. Although pegylated interferon is no longer a treatment option within the guidelines, ribavirin still plays a role in improving SVR in cirrhotic GT 3 NS5A treatment failures, for patients with decompensated cirrhosis, and with some regimens for patients post-liver transplantation. Most regimens have eliminated the need for ribavirin. Ribavirin is

Table 2. Medication Options and Treatment Duration (in weeks) for Treatment-Naive Patients without Cirrhosis or with Compensated Cirrhosis (CTP class A), by HCV GT

Regimen	Stage	GT 1a	GT 1b	GT 2	GT 3	GT 4	GT 5/6
Recommended Regimens (*± Alternative Option*)							
EBR/GZR	Noncirrhotic	12 (if no NS5A RASs)	12	—	—	12	—
	Compensated cirrhotic	12 (if no NS5A RASs)	12	—	—	12	—
G/P	Noncirrhotic	8	8	8	8	8	8
	Compensated cirrhotic	12	12	12	12	12	12
LDV/SOF	Noncirrhotic	12 (or 8 if VL < 6 mill, not Black/ African American, no HIV)	12 (or 8 if VL < 6 mill, not Black/ African American, no HIV)	—	—	12	12
	Compensated cirrhotic	12	12	—	—	12	12
SOF/VEL	Noncirrhotic	12	12	12	12	12	12
	Compensated cirrhotic	12	12	12	12	12	12
Alternative Regimens							
DCV[b] + SOF	*Noncirrhotic*	*12[a]*	*12[a]*	*12[a]*	*12[a]*	—	—
	Compensated cirrhotic	—	—	*16–24[a]*	*24 ± wt-based RBV[a]*		—
EBR/GZR	*Noncirrhotic*	*16 + wt-based RBV[a,c]*					
	Compensated cirrhotic	*16 + wt-based RBV[a,c]*					
PrO[b,d]	*Noncirrhotic*	—	—		—	*12 + wt-based RBV[a]*	—
	Compensated cirrhotic	—	—		—	*12 + wt-based RBV[a]*	—
PrOD[b,d]	*Noncirrhotic*	*12 + wt-based RBV[a,c]*	*12[a]*	—	—	—	—
	Compensated cirrhotic	—	*12[a]*	—	—	—	—
SOF + SMV[b]	*Noncirrhotic*	*12[a]*	*12[a]*	—	—	—	—
	Compensated cirrhotic	—	—	—	—	—	—
SOF/VEL/VOX	*Noncirrhotic*	—	—	—	—	—	—
	Compensated cirrhotic	—	—	—	*12[a] (if Y93H mutation)*	—	-—

[a]Alternative regimen.

[b]No longer commercially available in the United States.

[c]If NS5A RASs present.

[d]Contraindicated in patients with decompensated cirrhosis.

CTP = Child-Turcotte-Pugh; DCV = daclatasvir; EBR = elbasvir; G/P = glecaprevir/pibrentasvir; GT = genotype; GZR = grazoprevir; LDV = ledipasvir; PrO = paritaprevir/ritonavir/ombitasvir; PrOD = paritaprevir/ritonavir/ombitasvir/dasabuvir; RAS = resistance-associated substitution; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; VEL = velpatasvir; VL = viral load; VOX = voxilaprevir.

Information from: AASLD/IDSA. Recommendations for Testing, Managing, and Treating Hepatitis C. Available at www.hcvguidelines.org. Accessed June 4, 2019.

Table 3. Medication Options and Treatment Duration (in Weeks) for Treatment-Experienced (with PegIFN and RBV) Patients without Cirrhosis or with Compensated Cirrhosis (CTP class A), by HCV GT[a]

Regimen	Stage	GT 1a	GT 1b	GT 2	GT 3	GT 4	GT 5/6
Recommended Regimens (*± Alternative Option*)							
EBR/GZR	Noncirrhotic	12 (if no NS5A RASs)	12	—	—	12 (if relapsed)	—
	Compensated cirrhotic	12 (if no NS5A RASs)	12	—	12 with SOF	12 wk (if relapsed)	—
G/P	Noncirrhotic	8	8	8	*16*[a]	8	8
	Compensated cirrhotic	12	12	12	*16*[a]	12	12
LDV/SOF	Noncirrhotic	12	12	—	—	12	12
	Compensated cirrhotic	*12*[a]	*12*[a]	—	—	*12 + wt-based RBV*[a]	12
SOF/VEL	Noncirrhotic	12	12	12	12[b]	12	12
	Compensated cirrhotic	12	12	12	*12 + wt-based RBV*[a]	12	12
SOF/VEL/VOX	*Noncirrhotic*	—	—	—	*12*[a] *(if Y93H mutation)*	—	—
	Compensated cirrhotic	—	—	—	12	—	-—
Alternative Regimens							
DCV[c] *+ SOF*	*Noncirrhotic*	*12*[a]	*12*[a]	12[a]	12[a,b]	—	—
	Compensated cirrhotic	—	—	*16–24*[a]	—	—	—
EBR/GZR	*Noncirrhotic*	*16 + wt-based RBV*[a,d]				*16 + wt-based RBV (if virologic failure)*[a]	
	Compensated cirrhotic	*16 + wt-based RBV*[a,d]				*16 + wt-based RBV (if virologic failure)*[a]	
PrO[c,e]	*Noncirrhotic*	—	—		—	*12 + wt-based RBV*[a]	—
	Compensated cirrhotic	—	—		—	*12 + wt-based RBV*[a]	—
PrOD[c,e]	*Noncirrhotic*	*12 + wt-based RBV*[a]	*12*[a]	—	—	—	—
	Compensated cirrhotic	—	*12*[a]	—	—	—	—
SOF + SMV[c]	*Noncirrhotic*	*12*[a]	*12*[a]	—	—	—	—
	Compensated cirrhotic	—	—	—	—	—	—

[a]Alternative regimen.
[b]RAS testing indicated.
[c]No longer commercially available in the United States.
[d]If NS5A RASs present.
[e]Contraindicated in patients with decompensated cirrhosis.
PegIFN = pegylated interferon.
Information from: AASLD/IDSA. Recommendations for Testing, Managing, and Treating Hepatitis C. Available at www.hcvguidelines.org. Accessed June 4, 2019.

Table 4. Medication Options for Treatment-Experienced Patients with GT 1, without Cirrhosis or with Compensated Cirrhosis, Treated with a PI (i.e., telaprevir, boceprevir, or simeprevir) + PegIFN + RBV

Regimen		GT 1
Recommended Regimens (*± Alternative Option*)		
G/P	Noncirrhotic	12 wk
	Compensated cirrhosis	12 wk
LDV/SOF	Noncirrhotic	12 wk
	Compensated cirrhosis	*12 wk + wt-based RBV*[a]
SOF/VEL	Noncirrhotic	12 wk
	Compensated cirrhosis	12 wk
Alternative Regimen		
EBR/GZR	*Noncirrhotic*	*12 wk + wt-based RBV (in GT 1b or GT 1a no NS5A RASs)*[a] *or 16 wk + wt-based RBV (in GT 1a with NS5A RASs)*[a]
	Compensated cirrhosis	*12 wk + wt-based RBV (in GT 1b or GT 1a no NS5A RASs)*[a] *or 16 wk + wt-based RBV (in GT 1a with NS5A RASs)*[a]

[a]Alternative regimen.

Information from: AASLD/IDSA. Recommendations for Testing, Managing, and Treating Hepatitis C. Available at www.hcvguidelines.org/. Accessed June 4, 2019.

a guanosine analog that inhibits RNA synthesis; its antiviral action supports DAAs, and it must not be used as monotherapy for HCV. Full weight-based oral dosing is 1200 mg in two divided doses daily for patients weighing 75 kg or more and 1000 mg in two divided doses for patients weighing less than 75 kg. Ribavirin can be dosed orally daily (if the total daily dose is up to 600 mg), or twice daily (recommended if the total daily dose is higher than 600 mg). Ribavirin dose adjustments are made to 200 mg or 400 mg daily in the setting of decreased renal function (CrCl 30–50 mL/minute) and to 200 mg daily in patients receiving dialysis or with a CrCl less than 30 mL/minute. Ribavirin causes hemolytic anemia; recovery is delayed after ribavirin dose reduction because of its half-life of 120–170 hours. Ribavirin can cause a rash. Ribavirin is also teratogenic; pregnancy must be avoided, and two forms of contraception must be used during treatment and for 6 months after the last ribavirin dose regardless of whether the patient is male or female.

HCV Medication Classes: PIs/NS5B Polymerase Inhibitors/NS5A Replication Complex Inhibitors

The NS3/4A PIs (glecaprevir, grazoprevir, paritaprevir, simeprevir, voxilaprevir) prevent the virus from cleaving the replicated polyprotein into smaller proteins and thus interfere with the virus's ability to replicate by inhibiting the NS3/4A complex (Ciesek 2011).

Protease inhibitors can cause drug-drug interactions (DDIs) because they inhibit CYP3A4. See Table 5 for the pharmacokinetics of HCV agents. As an example, Box 3 contains a list of medications that have DDIs with glecaprevir/pibrentasvir. See the package inserts and www.hep-druginteractions.org for more information regarding DDI management with PIs. Patients must be counseled on the importance of disclosing all medications and supplements with their health care providers to avoid potentially dangerous interactions.

The NS5B polymerase inhibitors (sofosbuvir, dasabuvir) block the RNA polymerase enzyme that is needed for replication. Sofosbuvir is a component of five of the eight HCV regimens; older treatment included combination with simeprevir or daclatasvir; sofosbuvir is also co-formulated with ledipasvir for the treatment of GTs 1, 4, 5, and 6; and with velpatasvir, and with velpatasvir/voxilaprevir for the treatment of patients with GTs 1–6. Because sofosbuvir does not depend on CYP for metabolism, DDIs are generally limited and involve medications that induce P-gp because sofosbuvir is a P-gp substrate. Examples of these agents include carbamazepine, phenytoin, phenobarbital, oxcarbazepine, rifamycins, and St. John's wort, all of which can potentially decrease sofosbuvir concentrations. Use of sofosbuvir is contraindicated with amiodarone because of the risk of severe bradycardia. For more details, see the package insert for a listing of contraindicated drugs and drug classes. See the combination

Table 5. DAA HCV Medications Available in the United States

	Single Agent[a]		Fixed-Dose Combination			
Medication	Sofosbuvir (SOF) [Sovaldi]	Ledipasvir (LDV)/ sofosbuvir (SOF) [Harvoni]	Elbasvir (EBR)/ grazoprevir (GZR) [Zepatier]	Sofosbuvir (SOF)/ velpatasvir (VEL) [Epclusa]	Sofosbuvir (SOF)/velpatasvir (VEL)/voxilaprevir (VOX) [Vosevi]	Glecaprevir/ pibrentasvir (G/P) [Mavyret]
Mechanism of action	NS5B polymerase inhibitor	NS5A replication complex inhibitor + NS5B polymerase inhibitor	NS5A replication complex inhibitor + NS3/4A PI	NS5B polymerase inhibitor + NS5A replication complex inhibitor	NS5B polymerase inhibitor + NS5A replication complex inhibitor + NS3/4A PI	NS3/4A PI + NS5A replication complex inhibitor
Dose and dosage forms	400-mg tablet by mouth once daily[a]	90-mg/400-mg fixed-dose combination tablet by mouth once daily	50-mg/100-mg fixed-dose combination tablet by mouth once daily	100-mg/400-mg fixed-dose combination tablet by mouth once daily	100-mg/400-mg/100-mg fixed-dose combination tablet by mouth once daily with food	Three 100-mg/40-mg fixed-dose combination tablets once daily with food
Common ADRs	• Fatigue • Headache	• Fatigue • Headache • Asthenia	• Fatigue • Headache • Nausea • Anemia (with RBV)	• Fatigue • Headache	• Fatigue • Headache • Diarrhea • Nausea	• Fatigue • Headache
Cautions	Not labeled for use in patients with CrCl < 30 mL/min Do not use concurrently with amiodarone	Not labeled for use in patients with CrCl < 30 mL/min Do not use concurrently with amiodarone	Do not use with OATP1B1/3 inhibitors, strong CYP3A inducers, and efavirenz. Contraindicated in CTP class B or C	Not labeled for use in patients with CrCl < 30 mL/min Do not use concurrently with amiodarone	Not labeled for use in patients with CrCl < 30 mL/min Do not use concurrently with rifampin or amiodarone Not labeled for use in CTP class B or C	Contraindicated in CTP class C Do not use concurrently with atazanavir or rifampin
Half-life	0.5 hr for SOF; 25–27 hr for active metabolite GS-331007	LDV: 47 hr	EBR: 24 hr GZR: 31 hr	VEL: 15 hr	VOX: 33 hr	GLE: 6 hr; PIB: 13 hr
Metabolism	Substrate of P-gp Non-CYP, non-UGT mediated metabolism	LDV: Slow oxidative metabolism; unknown mechanism	EBR: Oxidation, substrate of CYP3A4 and P-gp GZR: Oxidation, substrate of CYP3A4 and P-gp	VEL: Substrate of CYP2B6, CYP2C8, and CYP3A4	VOX: Substrate of CYP3A4	GLE: Substrate of CYP3A4
Elimination	Renal excretion primary Urine 80%; 78% as GS-331007 Fecal excretion 14% Expired air 2.5%	LDV: Biliary excretion primary Fecal 86%; 70% unchanged	EBR: Fecal 90% Urine < 1% GZR: Fecal 90% Urine < 1%	VEL: Biliary excretion Fecal 94% (77% as parent drug)	VOX: Biliary excretion Fecal 94% (40% as parent drug)	GLE: Biliary Fecal 92.1%; PIB: Biliary Fecal 96.6%
FDA approval date	12/6/2013	10/10/2014	1/28/2016	6/28/2016	7/18/2017	8/3/2017

[a]Must be used in combination with at least one other DAA.

ADR = adverse drug reaction; BCRP = breast cancer resistance protein; DAA = direct-acting antiviral; DDI = drug-drug interaction; GLE = glecaprevir; NS3/4A = nonstructural protein 3/4A; NS5B = nonstructural protein 5B; OATP1B1/3 = organic anion transporting polypeptide 1B1/1B3; P-gp = *P-glycoprotein*; PI = protease inhibitor; PIB = pibrentasvir; UGT = uridine diphosphate glucuronyl transferase.

Information from: manufacturer's package inserts.

Box 3. Potentially Significant DDIs[a] with G/P Administration According to FDA Prescribing Information

- Atazanavir[b]
- Atorvastatin[c]
- Carbamazepine[c]
- Cyclosporine
- Dabigatran[c]
- Darunavir[c]
- Digoxin
- Efavirenz[c]
- Ethinyl estradiol–containing medications[c]
- Fluvastatin
- Lopinavir[c]
- Lovastatin[c]
- Pitavastatin
- Pravastatin
- Rifampin[b]
- Ritonavir[c]
- Rosuvastatin
- Simvastatin[c]
- St. John's wort[c]

[a]This list is not all-inclusive. These medications have interactions; some require monitoring, some are not recommended, and some are contraindicated. However, other drugs metabolized by similar enzyme systems may also have significant drug interactions requiring dose adjustments and additional monitoring (see prescribing guidelines for additional information).

[b]Contraindicated with G/P according to package insert and www.hep-druginteractions.org.

[c]Coadministration not recommended with G/P according to package insert.

DDI = drug-drug interaction; G/P = glecaprevir/pibrentasvir,

Information from: Mavyret [package insert]. North Chicago, IL: AbbVie, July 2017.

For more information, see: University of Liverpool. Hepatitis C Drug Interactions.

DAA section for details on clinical trials with sofosbuvir-containing regimens. Discontinuation rates because of adverse events were low in sofosbuvir-based regimens. Of note, NS5B RASs were not clinically relevant with sofosbuvir.

The NS5A inhibitors (e.g., ledipasvir, daclatasvir, ombitasvir, elbasvir, velpatasvir, pibrentasvir) prevent new replication complexes, which are sites of RNA synthesis for HCV. Overall class benefits include fewer ADRs and DDIs than with PIs. Resistance is a concern with this medication class; second-generation NS5A inhibitors (e.g., elbasvir, velpatasvir, pibrentasvir) have improved barriers to resistance compared with first-generation NS5As (e.g., ledipasvir, ombitasvir, daclatasvir).

Recommended Agents

Ledipasvir/Sofosbuvir

Ledipasvir/sofosbuvir was the first fixed-dose combination DAA; it simplified HCV treatment to 1 tablet once daily. Ledipasvir/sofosbuvir is also one of two regimens that can be as short as 8 weeks, depending on patient characteristics. Treatment-naive patients with HCV monoinfection without cirrhosis with baseline HCV RNA viral loads less than 6 million IU/mL may be considered for 8 weeks of treatment, given that 97% of these 123 patients achieved SVR in ION-3; the AASLD guidance also suggests that 8-week therapy be limited to non-black patients without HIV coinfection. This therapy has few DDIs, but its need for an acidic environment for absorption can be complicated for patients receiving acid-suppressive therapy. Restrictions on acid-lowering therapy include the following items. (1) Patients must take no more than an equivalent proton pump inhibitor (PPI) dose of omeprazole 20 mg daily concurrently with ledipasvir/sofosbuvir on an empty stomach. (2) Patients should take no more than the equivalent histamine-2 receptor antagonist (H_2RA) dose of famotidine 40 mg twice daily (first dose taken concurrently with ledipasvir/sofosbuvir, second dose of the H_2RA spaced 12 hours later). (3) Patients should space antacids 4 hours from ledipasvir/sofosbuvir administration. The TRIO real-world data analyses suggested that SVR did not differ between once-daily PPI users and PPI nonusers (97.3% vs. 97.2%); only the SVR rates of patients taking high-dose twice-daily PPIs were decreased (Afdhal 2016). Use of ledipasvir/sofosbuvir is more limited after the FDA approval of subsequent pangenotypic agents. Genotype 1a remains a challenge for the use of ledipasvir/sofosbuvir because of resistance and lower SVR rates than with GT 1b.

Elbasvir/Grazoprevir

Advantages of elbasvir/grazoprevir include its use in patients with end-stage renal disease (ESRD) and low pill burden. Elbasvir/grazoprevir must be stored in the original blister package to protect it from moisture and light. Patients whose elbasvir/grazoprevir therapy fails should not be re-treated with glecaprevir/pibrentasvir because it contains the same DAA mechanisms, and patients may develop NS5A and PI resistance. See the Resistance Testing section for details; this is the only DAA regimen that may need both adjustment to the length of therapy and the addition of ribavirin if the patient has RASs.

Sofosbuvir/Velpatasvir

Sofosbuvir/velpatasvir was the first available pangenotypic 12-week regimen; it resulted in an SVR rate of 99% in patients with GT 1, 2, 4, 5, or 6 in the ASTRAL-1 phase III trial, and SVR rates did not differ by cirrhosis status or treatment history (Feld 2015). Drug-drug interactions with acid suppression must be addressed by providers. Use of this regimen with ribavirin is also an option for patients with decompensated cirrhosis.

Sofosbuvir/Velpatasvir/Voxilaprevir

Recommended use of this combination is reserved for patients with GT 1a whose sofosbuvir therapy failed, patients with GT 3 with cirrhosis whose pegylated interferon and

ribavirin therapy failed, and patients GTs 1 and 3–6 whose DAA therapy failed. This combination is also listed as an alternative regimen for treatment-naive patients with GT 3 and cirrhosis with Y93 NS5A resistance and GT 3 pegylated interferon and ribavirin therapy failures with Y93 NS5A resistance. This combination is the only fixed-dose single-tablet combination that combines all three DAA mechanisms, and it must be administered with food. Drug-drug interactions with acid-suppressive agents must be addressed with this regimen.

Glecaprevir/Pibrentasvir

Glecaprevir/pibrentasvir is approved for both treatment-naive patients and patients whose DAA therapy has failed. Glecaprevir/pibrentasvir has the lowest wholesale acquisition cost and offers 8-week treatment for all treatment-naive patients without cirrhosis. Glecaprevir/pibrentasvir is also safe in patients with ESRD, and labeled-use treatment is never combined with ribavirin. Glecaprevir/pibrentasvir is packaged in a blister pack and must be administered with food. Treatment-experienced patients with GT 3 remain a challenging patient population; guidance recommends 12 weeks of glecaprevir/pibrentasvir therapy for those whose pegylated interferon and ribavirin therapy failed but only 8 weeks for patients with other GTs.

Alternative Agents

Paritaprevir/Ritonavir/Ombitasvir with or without Dasabuvir

Paritaprevir/ritonavir/ombitasvir/dasabuvir and paritaprevir/ritonavir/ombitasvir were discontinued in the United States on January 1, 2019, yet twice-daily paritaprevir/ritonavir/ombitasvir/dasabuvir is still available outside the United States, and guidelines still reference them as alternerative regimens at the time of this chapter's publication.

Paritaprevir/ritonavir/ombitasvir/dasabuvir was approved for use in GT 1 in December 2014, and paritaprevir/ritonavir/ombitasvir was approved for GT 4 in July 2015. Use was limited because of extensive DDIs (because of coformulation with ritonavir), twice-daily dosing of paritaprevir/ritonavir/ombitasvir/dasabuvir (yet it was reformulated for once-daily administration in July 2016), and need for coadministration of ribavirin with paritaprevir/ritonavir/ombitasvir/dasabuvir in GT 1a.

Sofosbuvir and Simeprevir

Simeprevir was discontinued in the United States on May 25, 2018, yet guidelines still referenced its use as an alternative agent at the time of this chapter's publication. The combination of sofosbuvir and simeprevir was used extensively after the AASLD guidance recommended its off-label use in January 2014, given that the combination was the only dual DAA oral regimen available at the time. Clinical trials found that the Q80K polymorphism caused resistance to simeprevir in patients with GT 1a. Use of sofosbuvir and simeprevir decreased after the approval of ledipasvir/sofosbuvir in October 2014.

Sofosbuvir and Daclatasvir

Daclatasvir was discontinued in the United States in June 2019, yet daclatasvir is still available outside of the United States and guidelines still referenced its use with sofosbuvir (as an alternative regimen in most cases) at the time of this chapter's publication. Daclatasvir is the only DAA whose dose was able to be adjusted for DDIs. The cost of two DAAs and its relatively lower efficacy in some difficult-to-cure patients with GT 3 decreased its use after newer agents were approved.

Table 6. HCV Medication Options for Patients with Decompensated Cirrhosis (CTP classes B and C) by GT[a]

DAA Regimen	RBV Dose	Length of Therapy	Genotypes
LDV/SOF	RBV 600 mg daily (increased as tolerated)	12 wk with RBV or 24 wk if RBV-ineligible	1, 4, 5, 6
SOF/VEL	Wt-based RBV[b]	12 wk with RBV or 24 wk if RBV-ineligible	1–6
DCV[c] + SOF	RBV 600 mg daily (increased as tolerated)	12 wk with RBV or 24 wk if RBV-ineligible	1–4

[a]All regimens include RBV.
[b]In GTs 1, 4, 5, 6: CTP class C: RBV 600 mg daily (increased as tolerated).
[c]No longer commercially available in the United States
Information from: AASLD/IDSA. Recommendations for Testing, Managing, and Treating Hepatitis C.

Treatment Selection Considerations

Decompensated Cirrhosis

Guidelines recommend that patients with decompensated cirrhosis (CTP class B or C) be referred to an experienced provider, ideally at a liver transplant center. Patients who undergo treatment before developing cirrhosis usually tolerate treatment better than patients with cirrhosis. In some trials, SVR rates in patients with cirrhosis are slightly lower than in patients without cirrhosis, and SVR rates of patients with decompensated cirrhosis are even lower. Protease inhibitors should not be used in patients with decompensated cirrhosis (CTP class B or C). Table 6 contains treatment recommendations for patients with decompensated cirrhosis. Patients with decompensated cirrhosis for whom sofosbuvir- or NS5A-based treatment failed should be treated for 24 weeks with sofosbuvir/velpatasvir and ribavirin (weight-based in CTP class B, and low-dose 600 mg daily, increased as tolerated in CTP class C).

Renal Impairment and ESRD

In 2016, the first DAA was approved for use in patients with ESRD and patients receiving dialysis. The C-SURFER trial with elbasvir/grazoprevir showed efficacy and safety in patients with ESRD; previous regimens lacked FDA approval in this population. The SVR rate was 94% in 122 patients with stage 4 or 5 chronic kidney disease who completed 12 weeks of elbasvir/grazoprevir; six patients discontinued for reasons unrelated to the treatment, and one patient relapsed. Adverse events included headache, nausea, fatigue, insomnia, dizziness, and diarrhea. Efficacy was not affected by hemodialysis, GT 1a versus 1b, or diabetes (Roth 2015).

Glecaprevir/pibrentasvir was approved for use in 2017. The EXPEDITION-3 trial of 104 patients with stage 4 or 5 chronic kidney disease yielded an SVR rate of 98% after 12 weeks of glecaprevir/pibrentasvir treatment. Adverse events included pruritus, nausea, and fatigue (Gane 2017).

Sofosbuvir-based regimens are not FDA approved in patients receiving dialysis or patients with a CrCl less than 30 mL/minute, yet clinical trial results may lead the manufacturer to file for a change in FDA approval in the future.

Liver Transplantation

Ideally, HCV should be eliminated before OLT (orthotopic liver transplantation) or living donor liver transplantation in order to protect the new liver from HCV infection. If patients either cannot receive HCV treatment or cannot achieve SVR before transplantation, HCV treatment should be initiated post-transplantation because the post-transplant liver has accelerated rates of fibrosis with HCV infection. Successful HCV treatment in the posttransplant setting can protect graft function and extend the time between transplantation and liver decompensation. Alternatively, some physicians may postpone HCV treatment until after transplantation to widen the donor pool to include HCV-positive livers, now that treatment is highly effective in the post-liver transplant patient population.

Recommendations for the treatment of patients with GT 1–6 posttransplantation include glecaprevir/pibrentasvir for 12 weeks in patients without cirrhosis and ledipasvir/sofosbuvir with weight-based ribavirin for 12 weeks in patients without cirrhosis and with compensated cirrhosis with GT 1 and GTs 4–6. See the AASLD guidelines for the alternative regimens.

HIV/HCV Coinfection

Patients with HIV/HCV coinfection should be treated for HCV, given that SVR has been shown to prevent accelerated hepatic fibrosis. Patients with HIV/HCV coinfection can be treated with the same regimens as patients with HCV monoinfection, given that SVR rates do not differ between these two groups with the use of modern DAAs.

Drug-drug interactions are common among HCV DAAs and antiretroviral medications, particularly with PIs and nonnucleoside reverse transcriptase inhibitors. Providers must carefully assess patient-specific factors such as stage of liver disease, previous HCV treatment, comorbid conditions, HIV viral load, immunodeficiency status, HIV GT/phenotype, and medication access when making decisions on managing the DDIs between HCV and HIV medications. One strategy is to select alternative HCV agents that do not interact with the patient's antiretroviral therapy (ART). Another approach is to substitute the patient's HIV treatment with an alternative regimen that does not interact with the HCV DAAs. This approach should only be used in collaboration with or by the patient's infectious diseases prescriber because it requires assessment of the patient's ART history and HIV GT/phenotype. The DAAs that do not rely on CYP for metabolism, such as sofosbuvir, have fewer DDIs. In the second scenario, HCV PIs should generally be avoided because they are CYP3A4 inhibitors and consequently have many DDIs with ART. Delaying HCV treatment should only be considered if the severity of the patient's liver disease does not warrant immediate treatment. See the AASLD guidance and AIDS information guidelines for more information on DDIs with HCV DAAs and ART; a DDI table is shown on the website to indicate HCV treatment compatibility with HIV treatment.

Resistance Testing

Resistance testing is only required in a few patient groups. Guidance no longer recommends NS3/4A resistance testing because the use of earlier PIs is out of practice. Because of the lack of clinical significance, NS5B resistance testing was never recommended. In patients with GT 1a for whom treatment with elbasvir/grazoprevir is considered, baseline testing for NS5A RASs is necessary before initiating treatment to determine the treatment duration and whether ribavirin should be added to the regimen. The testing costs around $700 in U.S. dollars and can be avoided with use of

a different regimen. NS5A RASs at positions M28, Q30, L31, or Y93 were associated with reduced efficacy with 12-week elbasvir/grazoprevir treatment. Adding ribavirin and extending the treatment length to 16 weeks achieved favorable SVR rates, yet guidance lists the extended regimen as alternative therapy because of the use of ribavirin and the availability of shorter therapy. The C-EDGE TN trial resulted in an SVR rate of 95% in the 316 treatment-naive patients with and without cirrhosis after treatment with 12 weeks of elbasvir/grazoprevir. Fifty-seven percent of 151 patients with GT 1a and 19% of 129 patients with GT 1b had baseline NS3 RASs; 12% of 154 patients with GT 1a and 14% of 130 patients with GT 1b had baseline NS5A RASs. The SVR rate was reduced to 22% in 9 patients with GT 1a with baseline NS5A RASs, resulting in a greater than 5-fold potency loss to NS5As (Zeuzem 2015). These data show that RASs exist in treatment-naive patients, and the impact of NS5A RASs on SVR in patients with GT 1a can be catastrophic in a dual DAA regimen.

Consideration for use of ledipasvir/sofosbuvir in GT 1a also warrants resistance testing in treatment-experienced patients; a different regimen (i.e., sofosbuvir/velpatasvir or glecaprevir/pibrentasvir) should be selected if clinically relevant RASs are present.

Patients with GT 3 should be tested for resistance when considering use of sofosbuvir/velpatasvir (treatment-naive patients with cirrhosis and any treatment-experienced patients) or, historically, daclatasvir plus sofosbuvir (treatment-naive patients with cirrhosis and treatment-experienced patients without cirrhosis). If Y93H is present, ribavirin should be added to the regimen, or a different regimen should be selected (glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir – see AASLD guidance for more details.

PATIENT AND PROVIDER EDUCATION

Pharmacoeconomics

Cost-effectiveness of HCV treatment was an increasing concern because of the high prices of the DAA agents approved in 2013 and 2014 (i.e., $84,000 for 12 weeks of sofosbuvir alone and $94,500 for 12 weeks of ledipasvir/sofosbuvir). The competitive price of $54,600 for 12 weeks of elbasvir/grazoprevir in January 2016 and then $26,400 for 8 weeks of glecaprevir/pibrentasvir in August 2017 continued the trend for lower prices. In October 2018, notice was released of the availability of $24,000 authorized generics for 12 weeks of sofosbuvir/velpatasvir and 8 weeks of ledipasvir/sofosbuvir. Several cost-effectiveness reports have been published in the past few years; some compare DAA groups, and some compare DAAs with pegylated interferon–based treatment, which is no longer the standard of care. A cost-effectiveness analysis (CEA) often uses the wholesale acquisition cost of HCV medications. However, few insurers actually pay this price; most have negotiated significant discounts with the manufacturers, which are not disclosed to the public. Using the wholesale acquisition cost (instead of the actual prices paid by insurers) in the CEA calculations may skew the results to conclude that the incremental cost-effectiveness ratio (ICER) of dollars per quality-adjusted life-years (QALYs) gained is unaffordable. The general assumption for willingness to pay is $50,000 per QALY. The HCV guidelines site lists examples of CEAs for GTs 1–4, with ICERs ranging from cost savings to more than $400,000 per QALY gained, depending on patient characteristics and assumptions of the model (AASLD 2019). Some studies offer insight into the cost to treat HCV in a percentage of patients with a diagnosis of HCV, versus all patients versus stratifying treatment on the basis of stage of fibrosis (Chahal 2015). Because many CEA studies are available, readers should recognize the limitations and assumptions of each analysis.

Given the high prices of HCV treatment, some providers find it challenging to gain insurance approval for treating some patients. To minimize the financial burden of HCV treatment, several insurance plans have implemented HCV therapy formulary restrictions, high copays, or cost sharing for specialty pharmacy medications. Most insurance plans require the completion of multiple-page prior authorization forms, limit the duration of approval time, and request additional clinical documentation or justification from the prescribers before medication approval. Some plans limit lifetime HCV treatment coverage to one course, and others deny coverage for off-label DAA regimens, even though these regimens are recommended by the HCV guidelines.

The State of Hep C website lists state requirements for Medicaid and Medicaid-managed care plans. Several states still limit HCV medication approval to patients with cirrhosis or F3 to F4 staging and deny coverage for patients with less severe disease. States often require additional documentation, such as negative urine drug screens, adherence letters signed by patients, and documentation of sobriety for 6–12 months. The Centers for Medicare & Medicaid Services issued a letter to state insurers in November 2015 to urge a decrease in limitations for access to HCV treatment. Many plans have not yet changed their restrictions for HCV treatment, but progress has been made in the past 3 years; however, litigation has been the impetus for change in some states.

In some situations, patients cannot afford the out-of-pocket copay amount. Other patients lack insurance coverage. Most manufacturers offer patient assistance programs, copay cards, and coupons; other nonprofit organizations also offer assistance. The extent of some manufacturers' patient assistance coverage has changed with time. Box 4 lists resources. Pharmacists can facilitate use of these programs in community and clinical settings. Pharmacists can also decrease the cost burden to payers by correcting inappropriate prescribing.

Box 4. HCV Resources for Patients and Providers

HCV Guidelines
- AASLD, IDSA, and IAS-USA
  www.hcvguidelines.org

DDI Sources
- Lexicomp, Inc.
  www.lexi.com
- Micromedex Solutions
  www.micromedex.com
- University of Liverpool
  www.hep-druginteractions.org
  www.hiv-druginteractions.org

Government-Sponsored HCV Information
- Centers for Disease Control and Prevention
  www.cdc.gov/hepatitis/HCV/index.htm
- U.S. Department of Veterans Affairs
  www.hepatitis.va.gov/

HIV and Hepatitis Information
- HIVandHepatitis.com
  http://hivandhepatitis.com/hepatitis-c
- National AIDS Treatment Advocacy Project
  www.natap.org

Online HCV Courses
- University of Washington
  http://hepatitisc.uw.edu/

Free Online HCV Textbook
- *in*Practice Hepatology
  https://www.inpractice.com/Textbooks/Hepatology.aspx

HCV Clinical Information
- Clinical Care Options
  www.clinicaloptions.com/Hepatitis.aspx
- ViralEd
  www.viraled.com/

Patient Support Groups
- American Liver Foundation
  www.liverfoundation.org
- HCV Support
  www.hcvsupport.org

24-Hr Telephone Patient Assistance and Financial Assistance Programs
- AbbVie
  https://www.abbvie.com/patients/patient-assistance.html
  1-800-222-6885
  1-855-687-7503
- Gilead Sciences
  www.mysupportpath.com
  1-855-7-MYPATH (1-855-769-7284)
- Merck
  www.merckhelps.com/
  1-800-727-5400
  https://www.merckaccessprogram-zepatier.com/hcc/
  1-866-251-6013

Medication Selection and Approval

The pharmacist can help guide providers in selecting appropriate HCV medications to allow for maximum medication access. Clinical pharmacists are responsible for selecting and managing HCV treatment for patients in some institutions, whereas other clinical pharmacists may provide variations of referral evaluations for appropriateness of therapy to aid in proper prescribing (Sebhatu 2016). The pharmacist should be aware of current treatment recommendations and ensure that patients are prescribed a regimen appropriate for their GT, treatment status, comorbidities, medications, and other patient concerns. See Box 4 for additional resources for HCV education for both patients and providers.

Because of insurance restrictions, approval of HCV medication may be challenging. Most insurance companies require the completion of time-consuming prior authorization forms before approving high-cost HCV medications. External specialty pharmacies may use technicians to assist with prior authorization forms, given that the margin earned with dispensing HCV medications more than funds the time spent on medication approval. Health system–based specialty pharmacies may use technicians and pharmacy students to assist with the high burden of paperwork and telephone calls to insurers (Martin 2016). Nurses, medical assistants, and even pharmacists may assist in other clinic settings. Medication denials can be appealed with letters of medical necessity. The approval process can take from hours to days to weeks, depending on the insurance plan. Referral to patient assistance programs may be the final step in attempting medication approval.

Drug Interactions

Patients are counseled on the need to inform the pharmacist and any other health care providers about their current HCV medications in order to allow providers to monitor for and prevent DDIs. Several resources aid providers in detecting and explaining DDIs with HCV medications. See Box 4 for a list of selected resources. Access to drug information resources such as Lexicomp and Micromedex is provided by many employers, and several databases offer convenient applications for handheld devices. The University of Liverpool has an extensive free online interactive DDI information system. Users may select the proposed hepatitis or HIV regimens and add additional medications to review for DDIs. Prescribers may also use a variety of other available sources; these are examples of sources with information specific to HCV and HIV.

Adherence

Adherence is required for HCV treatment success; nonadherence negatively affects SVR rates (Weiss 2009) and potentially leads to development of resistance, yet data for an optimal adherence rate have not been published. If delaying treatment is not harmful to a patient's condition, providers can recommend waiting until the patient is fully committed to adhering to HCV treatment before prescribing HCV medications. The importance of medication adherence should be emphasized at treatment initiation, at all follow-up visits, and

at the time of medication refills. The pharmacist can counsel the patient on the importance of adherence to minimize the risk of treatment failure. Patients should be encouraged to use adherence aids such as pillboxes, alarms, and medication charts and be given specific instructions for what to do if they miss a dose of HCV treatment (i.e., take the dose as soon as possible when remembered; do not double the dose if it is time for the next dose). The pharmacist's expertise and provision of education to providers and patients increases the likelihood of appropriate treatment candidate selection and patient adherence to the HCV regimen.

Patient Counseling

Patients should understand the mode of HCV transmission and be counseled on avoiding behaviors that can lead to spread of the virus and reinfection. Pharmacists can provide group patient education classes, extensive one-on-one patient education at the initiation of HCV treatment, and ongoing follow-up assessment to aid in patient comprehension and safety (Sebhatu 2016). The patient should be informed about the meaning of HCV laboratory results, SVR, the next step for treatment if the patient's current treatment fails, and how the disease may progress. The pharmacist is the ideal provider to inform patients about the proper storage and administration of their HCV medications, DDIs, potential ADRs of the treatment, steps that can be taken to alleviate or minimize ADRs, and procedure to follow if an ADR occurs. Patients who are successfully treated should be counseled that no immunity is conferred and that reinfection is possible with reexposure.

Education about the importance of lifestyle changes can also be provided by the pharmacist. Overweight patients and patients with obesity should be encouraged to make healthy diet choices and engage in regular exercise to achieve a healthy BMI. Patients with obesity are more likely to have nonalcoholic fatty liver disease, which is a risk factor for HCV fibrosis progression (Ortiz 2002). Alcohol consumption accelerates scarring of the liver, and all patients with HCV should be counseled to abstain from alcohol consumption upon HCV diagnosis because no safe amount of alcohol consumption has been established (AASLD 2019). Patients should ideally abstain from illicit drug use for overall health. However, clinical trials showed high adherence in patients with injection drug use, and guidelines state that drug use is not a contraindication for treatment. From a public health perspective, some clinics are trying to treat active drug users in order to decrease the transmission of HCV. Smoking is associated with a risk of developing HCC; patients who use tobacco products should be offered smoking cessation services according to stage of readiness to quit (Koh 2011). Similarly, daily marijuana smoking is associated with progression of fibrosis and should be discouraged (Hézode 2005). Patients should be counseled to avoid herbal supplements because they lack FDA approval, can be hepatotoxic, and may interact with HCV regimens. See Box 4 for additional resources for HCV education for both patients and providers.

Monitoring

Table 7 provides selected guidance recommendations on laboratory monitoring for HCV treatment. Many current DAA regimens do not require specific monitoring, though providers (and insurers) may request HCV RNA viral loads at week 4 to detect efficacy and adherence; guidelines support this. Guidance (on the basis of expert opinion and concern for resistance, not published clinical trial evidence) recommends rechecking the HCV RNA viral load at week 6 if it is positive at week 4. Discontinuation is recommended if the week 6 HCV RNA viral load exceeds the week 4 viral load by 1 log (10-fold); no recommendations are made for altering the therapy duration if the viral load at week 6 is lower than at week 4.

All HCV DAAs have a black box warning regarding hepatitis B virus (HBV) reactivation; hence, all patients must be screened for HBV before treatment initiation (Pockros 2017). Patients must be monitored during treatment if they have a positive core antibody (but negative surface antigen), and reactivation should be considered if they have an unexplained increase in liver enzymes during or after HCV treatment. Patients must be monitored or treated for HBV if they have a positive surface antigen; the HBV DNA viral load must be checked before HCV treatment initiation. If patients meet the HBV treatment criteria according to the AASLD HBV guidelines, HBV treatment should be started before or at the same time as HCV treatment (Terrault 2018). See the AASLD guidance for more details.

Patients receiving elbasvir/grazoprevir may be at increased risk of ALT elevations; thus, hepatic function should be monitored at treatment week 8 and week 12 (if receiving 16 weeks of therapy). Renal function should be monitored in patients with a decreased CrCl because sofosbuvir-based regimens are currently only recommended in patients with a CrCl greater than 30 mL/minute. In patients taking ribavirin, renal function and Hgb should be monitored at week 4 and as clinically indicated during treatment – usually every 4 weeks.

Providers should document follow-up visits, education provided, laboratory assessments, DDIs, medication changes, ADRs, and management plans in the patient's medical record to facilitate communication among providers.

HCV ELIMINATION

The WHO's proposed seven steps to eliminate HCV and HBV are listed in Table 8. The NASEM Phase One Report lists three goals for eliminating HCV and HBV in the United States by 2030: end transmission, eliminate chronic infection, and reduce morbidity and mortality (NASEM 2016). The NASEM Phase Two Report evaluates the feasibility of achieving these goals; it calls for a 90% reduction in HCV incidence (vs. the

Table 7. Laboratory Monitoring During HCV Treatment

Laboratory Test	Any Time Before HCV Treatment	Within 12 Wk Before Treatment	Baseline (and as clinically indicated)	Week 4 of HCV Treatment	12 Wk After HCV Treatment Completion
HCV GT and subtype	X				
HCV PCR quantitative	X			X	X
CBC with differential		X		X (and as clinically indicated in patients receiving RBV)	
Creatinine; calculated glomerular filtration rate		X		X (and as clinically indicated)	
INR		X			
Hepatic function panel (albumin, total and direct bilirubin, ALT, AST, and ALK concentrations)		X		X[a] (and as clinically indicated; check at week 8 if EBR/GZR for 12 wk, and again at week 12 if EBR/GZR for 16 wk)	
Pregnancy test (women of childbearing capacity starting RBV)			X		
Hepatitis B surface antigen, antibody, and core antibody total	X			Check HBV DNA throughout and after treatment if hepatitis B surface antigen is positive	

[a]Discontinue treatment at week 4 if there is a 10-fold increase in ALT, or if a < 10-fold increase in ALT is accompanied by any weakness, nausea, vomiting, jaundice, or significantly increased bilirubin, ALK, or INR. Asymptomatic < 10-fold increases in ALT should be monitored closely and repeated at weeks 6 and 8; consider discontinuation if persistent elevations.

Information from: AASLD/IDSA. Recommendations for Testing, Managing, and Treating Hepatitis C. Available at www.hcvguidelines.org. Accessed June 4, 2019.

Table 8. WHO's 7 Steps to Eliminate HBV and HCV by 2030

Step No.	Description	Details
1	Global action, national plans	Specific action to combat viral hepatitis
2	Testing for HBV and HCV	9% (HBV) and 20% (HCV) diagnosed in 2015 à goal 30% diagnosed by 2020 and 90% diagnosed by 2030 for viral hepatitis
3	Treatment	7.4% treated in 2015 à goal 80% by 2030
4	HBV vaccination	Goal 90% by 2030
5	Preventing mother-to-child transmission	Further research
6	Blood safety	Goal 100% screening of blood products and 0% unsafe injection practices
7	Harm reduction	Needle exchange

Information from: World Health Organization (WHO). 7 Steps to Eliminate Hepatitis B and C by 2030.

Table 9. DHHS National Viral Hepatitis Action Plan 2017–2020[a]

Goal No.	Description	Details
1	Prevent new viral hepatitis infections	60% decrease in new HCV infections from 30,500 to 10,889
2	Reduce deaths and improve the health of people living with viral hepatitis	Increased awareness of HCV infection from 54% to 66% 25% decrease in HCV-related death from 19,659 to 14,744
3	Reduce viral hepatitis health disparities	25% decrease in HCV-related death in: 55- to 74-year-old patients, American Indians/Alaska Natives, and African Americans 60% decrease in new HCV infections: 20- to 39-year-old patients, American Indians/Alaska Natives
4	Coordinate, monitor, and report on implementation of viral hepatitis activities	

[a]2014 → 2020 goals.

Information from: Department of Health & Human Services (DHHS). National Viral Hepatitis Action Plan 2017-2020.

2015 data) and a 65% reduction in mortality (NASEM 2017). To achieve this, diagnosis rates must be 110,000 per year through 2020, almost 89,000 annually in 2020–2024, and over 70,000 annually in 2025–2030. These diagnoses rates require high levels of HCV screening. Screening opportunities must be implemented across practice sites. Emergency departments, primary care settings, and community pharmacies are examples of locations where HCV screening has been successfully implemented. Universal screening is a strategy that can assist with diagnosing patients. Table 9 summarizes the Department of Health &Human Services (DHHS) National Viral Hepatitis Action plan with specific goals to achieve in 2017–2020.

CONCLUSION

Hepatitis C virus affects millions of Americans, yet only half are aware of the infection. Recent advances in DAA treatment have greatly increased SVR rates in patients with all HCV GTs, with the drawback of high treatment cost. Pharmacists can play an integral role in HCV treatment and elimination.

Patient Care Scenario

A 48-year-old woman with HCV GT 1a without cirrhosis presents to the liver clinic to discuss HCV treatment options. She was treated once with pegylated interferon and ribavirin in 2009 but had to discontinue treatment at week 4 because of psychiatric adverse events that led to a suicide attempt, and she did not achieve SVR. Her medical history includes depression and hypertension. She takes sertraline 25 mg daily and amlodipine 10 mg daily. Her laboratory test results include hepatitis B surface antigen (HBsAg) negative, hepatitis B surface antibody (anti-HBs) negative, and hepatitis B core antibody (anti-HBc) positive; CrCl 89 mL/minute; and Hgb 14.5 g/dL. Her liver function tests are within normal limits, and the Y93H mutation is detected. Which is best to recommend for this patient?

A. Administer the HBV vaccination series before initiating HCV treatment.
B. Check the HBV DNA viral load every 4 weeks during HCV treatment.
C. Check the ALT concentration every 4 weeks during HCV treatment.
D. Initiate tenofovir for HBV treatment concurrently with HCV treatment.

ANSWER

Answer C is preferred because it is important to monitor for an unexplained ALT elevation as a possible sign of HBV reactivation. This patient does not have a positive HBsAg, so many providers would not assess for HBV DNA viral loads. Answer A is incorrect; it is not necessary to vaccinate a patient with anti-HBc positivity. Answer B is incorrect; guidance only recommends assessing HBV DNA in patients with a positive HBsAg. Answer D is incorrect; the patient does not have a positive HBsAg, so HBV treatment is not indicated. See Table 7, the AASLD guidelines, and the figure in Pockros (2017) for recommendations regarding HBV serologies.

- **AASLD/IDSA. Recommendations for Testing, Managing, and Treating Hepatitis C. Available at www.hcvguidelines.org. Accessed June 4, 2019.**
- **Pockros PJ. Black box warning for possible HBV reactivation during DAA therapy for chronic HCV infection. Gastroenterol Hepatol 2017;13:536-40.**

Practice Points

- **Readers are urged to review the current treatment guidelines at www.hcvguidelines.org/ for the most up-to-date HCV information for clinical practice.**
- **Pharmacists are the ideal providers to assist with the challenges of HCV treatment.**
- **Modern DAA regimens are well tolerated, yet access and DDIs can complicate treatment.**
- **DAAs have high efficacy, yet adherence is important.**
- **SVR does not prevent against reinfection.**
- **Patients should be instructed to contact their health care team before starting any new medications, OTC agents, supplements, or herbals. The University of Liverpool's hepatitis drug interaction source is available at www.hep-druginteractions.org.**
- **HCV elimination strategies are multifaceted and will required buy-in from key stakeholders.**
- **Current guidelines recommend HCV treatment in almost all patients, but treatment may not be feasible for all patients at this time, including:**
  - **Patients with restrictive insurance plans; some insurers create barriers for treatment**
  - **Patients without insurance coverage who do not qualify for financial assistance programs**
  - **Patients without interest in or dedication to treatment**

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Self-Assessment Questions

1. A 56-year-old woman who has just moved to a different state is establishing care with her new health care provider. Her medical records are not available. At her initial clinic visit, the patient is found to have a remote history of intravenous drug use and now has worsening fatigue. In addition to a positive HCV antibody, which one of the following additional assessments or results is most needed to confirm the diagnosis of chronic HCV?

   A. Transient elastography (FibroScan)
   B. Liver biopsy
   C. Detectable HCV RNA viral load
   D. Detectable HCV RNA viral load and FibroSure

2. A group of providers collaborate to work toward HCV elimination in their region of the United States. Which one of the following charges best aligns with the National Academies of Sciences recommendations for HCV elimination?

   A. Treat 80% of HCV-infected patients by 2030.
   B. Reduce HCV incidence by 90% and reduce mortality by 65% by 2030.
   C. Achieve 90% diagnosis of HCV-infected patients and 90% HBV vaccination rates by 2030.
   D. Reduce viral hepatitis health disparities by decreasing death by 25% and new HCV infections by 60% in African Americans, American Indians/Alaska Natives.

3. A 54-year-old treatment-naive man with decompensated cirrhosis (Child-Turcotte-Pugh [CTP] class B) with HCV GT 1a presents to the hepatology clinic for treatment. The patient's laboratory values include CrCl 57 mL/minute, Hgb 11.7 g/dL, INR 1.2, albumin 2.9 g/dL, and total bilirubin 1.9 mg/dL. The hepatologist would like to treat the patient's HCV. Which one of the following is best to recommend for this patient?

   A. Daclatasvir and sofosbuvir with weight-based ribavirin for 12 weeks
   B. Ledipasvir/sofosbuvir with weight-based ribavirin for 12 weeks
   C. Glecaprevir/pibrentasvir for 12 weeks
   D. Sofosbuvir/velpatasvir with weight-based ribavirin for 12 weeks

4. A 65-year-old treatment-naive white man (weight 78 kg) has HCV GT 1a and a medical history significant for an orthotopic liver transplant (OLT) in 2012, hypertension, and diabetes. His current medications include tacrolimus, lisinopril, insulin glargine, insulin aspart, a multivitamin, and cholecalciferol. Laboratory values include SCr 0.71 mg/dL, Hgb 12.8 g/dL, ALT 19 IU/L, AST 24 IU/L, ALK 70 IU/L, FK506 5.3, and FibroSure F3 (noncirrhotic). Which one of the following is best to recommend for this patient's HCV treatment?

   A. Daclatasvir plus sofosbuvir and weight-based ribavirin for 12 weeks
   B. Sofosbuvir/velpatasvir and weight-based ribavirin for 12 weeks
   C. Ledipasvir/sofosbuvir and ribavirin 600 mg daily for 12 weeks
   D. Glecaprevir/pibrentasvir for 12 weeks

5. A 52-year-old treatment-naive Hispanic woman with GT 1a without cirrhosis with a HCV RNA viral load of 3.9 million IU/mL presents to the hepatology clinic to discuss treatment options. Which one of the following best depicts the shortest possible length of HCV treatment that is appropriate for treating this patient's infection?

   A. 6 weeks of triple DAA therapy
   B. 8 weeks of dual DAA therapy
   C. 8 weeks of dual DAA therapy with ribavirin
   D. 12 weeks of dual DAA therapy

6. Which one of the following U.S. patients has the greatest risk of developing HCV infection?

   A. Infant born at 32 weeks' gestation to a 27-year-old mother with HCV
   B. 33-year-old man who uses intravenous heroin
   C. 49-year-old man who has sex with men
   D. 66-year-old woman with chronic kidney disease receiving dialysis

7. A physician would like to initiate a multidisciplinary team to aid in HCV screening and diagnosis at a health system; she asks for your assistance with recommending the most strategic location. Which one of the following locations would most likely identify the highest prevalence rate of patients with HCV-positive infection with guidance-recommended HCV screening?

   A. Dialysis center
   B. General medicine clinic
   C. Colonoscopy suite
   D. Psychiatry clinic

8. A 47-year-old treatment-experienced woman with compensated cirrhosis with HCV GT 2 receiving treatment with glecaprevir/pibrentasvir presents to the clinic after her week 4 blood test. Her HCV RNA viral load is 105 IU/mL. The patient claims adherence to therapy. Which one of the following is best to recommend for this patient?

   A. Discontinue HCV treatment because the HCV RNA viral load is detectable.

B. Add ribavirin to the patient's regimen as rescue therapy.
C. Extend HCV treatment to a 24-week course of glecaprevir/pibrentasvir.
D. Recheck HCV RNA viral load at or after week 6; discontinue treatment if the viral load is greater than 1 log higher than week 4.

9. A 48-year-old man without cirrhosis has a medical history of HIV/HCV coinfection. He uses methamphetamine and has unprotected sex with men. The patient had an undetectable HCV RNA after completing 12 weeks of HCV treatment with ledipasvir/sofosbuvir for HCV GT 1a in late 2017. He returns 36 weeks after completing treatment with a viral load of 5,500,000 IU/mL; a reflex GT test reports GT 3. Which one of the following best explains this patient's viral load?

A. The patient's virus relapsed after HCV treatment.
B. The patient was reinfected after completing treatment.
C. The wrong GT was reported because of a laboratory error.
D. The patient had a super-infection with GTs 1a and 3 at baseline.

10. A 33-year-old treatment-naive African American man (weight 79 kg) with compensated cirrhosis (CTP class A) with HCV GT 1b presents for continued evaluation of HCV and requests HCV treatment. The patient's CrCl is 53 mL/minute and Hgb is 12.7 g/dL. The patient is a heroin user who reports that he usually does not share injection paraphernalia. The patient has shown appointment adherence and medication adherence in the past 6 months. According to the guidelines, which one of the following is best to recommend for this patient?

A. Treat with ledipasvir/sofosbuvir for 12 weeks, counsel on adherence, and enroll in needle exchange.
B. Treat with glecaprevir/pibrentasvir for 8 weeks, counsel on adherence, and enroll in needle exchange.
C. Do not treat; the patient is likely to be reinfected through continued injection drug use.
D. Do not treat; the patient is likely to be nonadherent to HCV treatment because of drug use.

11. A health care provider is evaluating the outcomes of several studies of HCV regimens. Which one of the following best depicts the difference in sustained virologic response (SVR) rates that is statistically significant?

A. Drug A versus drug B – odds ratio for SVR 1.83 (95% CI, 1.04–2.78)
B. Drug A versus drug B – rate difference in SVR 9% (95% CI, -0.98% to 14%)
C. Drug C versus drug D – odds ratio for SVR 1.43 (95% CI, 0.93–2.06)
D. Drug C versus drug D – rate difference in SVR 5% (95% CI, -1.3% to 9.2%)

12. A clinical pharmacist would like to measure the degree of patient satisfaction in patients with HCV who were treated by clinical pharmacists throughout HCV treatment compared with patients who were treated by a physician during HCV treatment. Patients are asked to indicate their agreement with satisfaction with the HCV care provider using a Likert scale (1 = highly satisfied, through 5 = highly dissatisfied). Which one of the following statistical tests would best compare these data?

A. Chi-square test
B. McNemar test
C. Paired student t-test
D. Wilcoxon rank sum test

13. A 66-year-old treatment-naive man without cirrhosis with HIV/HCV coinfection presents to the liver clinic for HCV treatment evaluation. The patient's HIV regimen consists of efavirenz 600 mg at bedtime, zidovudine 300 mg twice daily, and lamivudine 50-mg solution twice daily. He also takes ergocalciferol 50,000 units once weekly, budesonide/formoterol 160/4.5 mcg 2 puffs twice daily, and albuterol 90-mcg inhalation as needed. Laboratory values include CrCl 8.9 mL/minute on hemodialysis Mondays, Wednesdays, and Fridays and Hgb 9.6 g/dL. Which one of the following is best to recommend for this patient with HCV GT 1b?

A. Consult with the infectious diseases clinic to adjust his HIV regimen before initiating HCV treatment.
B. Administer sofosbuvir/velpatasvir for 12 weeks.
C. Administer glecaprevir/pibrentasvir for 8 weeks.
D. Administer elbasvir/grazoprevir for 12 weeks.

14. A 60-year-old man is presents for HCV treatment initiation with sofosbuvir/velpatasvir for 12 weeks for GT 4 infection. He has a history of dyspepsia, hypertension, hyperlipidemia, and erectile dysfunction. The patient's home drugs include amlodipine 10 mg daily, hydrochlorothiazide 25 mg daily, omeprazole 20 mg daily, atorvastatin 10 mg daily, and sildenafil 25 mg as needed. Laboratory values include TC 154 mg/dL, TG 200 mg/dL, LDL 67 mg/dL, and CrCl 85 mL/minute. Which one of the following is best to recommend for this patient's successful HCV treatment?

A. Discontinue atorvastatin.
B. Advise patient to discontinue omeprazole, if possible, but if medically necessary to continue, dose sofosbuvir/velpatasvir with food 4 hours before a maximum of omeprazole 20 mg daily.

C. Advise patient to discontinue sildenafil during HCV treatment.
D. Change amlodipine to an alternative antihypertensive agent.

15. Which one of the following patients would most require counseling on the importance of using two forms of contraception during HCV treatment and for 6 months after completing treatment?

A. 29-year-old woman taking ledipasvir/sofosbuvir plus ribavirin
B. 37-year-old woman taking elbasvir/grazoprevir
C. 63-year-old woman taking sofosbuvir plus daclatasvir plus ribavirin
D. 42-year-old woman taking glecaprevir/pibrentasvir