



CLINICAL GUIDELINES PROGRAM

NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV · HCV · SUBSTANCE USE · LGBT HEALTH

Treatment of Chronic HCV with Direct-Acting Antivirals

HCV Guideline Committee, updated August 2020

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Treatment of Chronic HCV with Direct-Acting Antivirals

Purpose of this Guideline

This guideline on treatment of chronic hepatitis C virus (HCV) infection was developed by the New York State (NYS) Department of Health (DOH) AIDS Institute (AI) to guide primary care providers and other practitioners in NYS in treating patients with chronic HCV infection. The guideline aims to achieve the following goals:

- Promote universal screening for HCV.
- Increase the number of NYS residents with chronic HCV infection treated for and cured of HCV.
- Increase compliance with the [2014 NYS public health law](#) that requires HCV antibody screening be offered to every individual born between 1945 and 1965 who receives healthcare services from a physician, physician assistant, or nurse practitioner in a primary care or inpatient hospital setting.
- Reduce the growing burden of morbidity and mortality associated with chronic HCV infection.
- Integrate current evidence-based clinical recommendations into the HCV-related implementation strategies of the [Ending the Epidemic \(ETE\) Initiative](#), which seeks to end the AIDS epidemic in NYS by the end of 2020.

The NYSDOH AI is publishing these guidelines at a critical time: 1) new treatments are available that can cure chronic HCV infection; 2) the burden of HCV disease is increasing in NYS [CDC 2016b]; and 3) primary care providers and other clinical care practitioners in NYS are playing an essential role in screening for and diagnosing chronic HCV infection and in providing state-of-the-art therapy for their patients.

New Standard of Care for Treatment of Chronic HCV Infection

The availability of safe and effective regimens of oral direct-acting antivirals (DAAs) has revolutionized HCV care. New DAA agents and new combinations of agents continue to be tested and approved, and these efficacious combinations have replaced earlier treatments as the standard of care for curing chronic HCV infection. The DAA regimens make cure possible for many patients, but these patients must first be identified, engaged in care, offered appropriate screening for status of their HCV infection/disease, and have access to treatment.

The goal of HCV therapy is a sustained virologic response (SVR), which is defined as the absence of detectable HCV RNA at least 12 weeks after completion of therapy. An SVR is the equivalent of cure. DAA regimens have been associated with an SVR rate of more than 90% and have excellent tolerability in both treatment-naïve and treatment-experienced patients with and without cirrhosis [Falade-Nwulia, et al. 2017].

Burden of HCV Disease

First isolated in 1989, HCV is the most common chronic blood-borne infection in the United States [Armstrong, et al. 2006; Chen SL and Morgan 2006], and research suggests that more than 50% of persons with HCV infection are unaware of their infection status [Denniston, et al. 2012]. Injection drug use is associated with the highest risk of contracting HCV [Alter 1999, 2007]. Other key routes of HCV transmission include receipt of infected blood or organs (before 1992) or blood products (before 1987), mother-to-child transmission (also known as vertical transmission), sexual transmission, and needle sticks/exposure in healthcare settings [CDC 1998]. According to National Health and Nutrition Examination Study (NHANES) data, among patients participating from 2001 to 2008, the prevalence of HCV infection in persons aged >20 years was 1.3% in the United States. After adjusting for populations not sampled in the NHANES surveys, such as the incarcerated and homeless, the researchers estimated that 3.5 million people were living with chronic HCV infection in the United States [CDC 2013; Edlin, et al. 2015]. Approximately 75% of reported cases were among persons born between 1945 and 1965 [Armstrong, et al. 2006; Denniston, et al. 2012; CDC 2013].

The Centers for Disease Control and Prevention (CDC) reported 162,863 cases of chronic HCV infection (past or present) nationwide in 2015 [Adams, et al. 2016]. The number of reported cases in New York State (excluding New York City) and New York City for 2017 are provided in *Box 1*.

Box 1: Acute and Chronic HCV Infection Cases* Reported in New York State and New York City	
New York State† [NYSDOH 2018]	New York City [NYCDHMH 2018]
<ul style="list-style-type: none"> • 138,106 cases reported from 2001 to 2017. • 2017 cases: 8,280 reported. <ul style="list-style-type: none"> – 32% (2,670) of cases reported from the 1945 to 1965 birth cohort, with 65% male and 35% female. – 29% (2,357) aged <30 years, with 55% male and 45% female. 	<ul style="list-style-type: none"> • 162,248 cases reported from 2001 to 2017. • 2017 cases: 5,308 reported <ul style="list-style-type: none"> – 41.5% (2,203) from the 1945 to 1965 birth cohort, with 63.1% male and 36.9% female. – 14.5% (766) aged <30 years, with 58.5% male and 41.4% female.
<p>*Cases meeting the CDC case definition for acute or chronic (NYS) or chronic (NYC), confirmed or probable cases of HCV. There may be duplication of individuals both within and between the NYS and NYC HCV surveillance systems, and the total cases reported in <i>Box 1</i> should not be interpreted as numbers of unique individuals reported with HCV.</p> <p>†Excluding New York City.</p>	

Ensuring access to effective DAA treatment for all individuals with chronic HCV and curing chronic HCV infection in as many as 90% of patients will prevent substantial morbidity and mortality. Approximately 25% to 30% of persons with untreated chronic HCV infection will advance to cirrhosis within 20 to 30 years, with progression occurring more quickly in men, in patients who use alcohol, in those who acquire HCV infection after age 40, and in patients with HIV/HCV coinfection [Klevens M, et al. 2015; Younossi, et al. 2015]. Of those with cirrhosis, >25% will develop end-stage liver disease or hepatocellular carcinoma (HCC), resulting in death if a liver transplant is not received [Klevens RM, et al. 2012].

Chronic HCV infection drives the development of HCC by inducing fibrosis and cirrhosis [El-Serag 2012]. From 1999 through 2013, deaths from primary liver cancer in the United States increased at the highest rate of all cancer sites, and liver cancer incidence rates increased sharply, second only to thyroid cancer [Ryerson, et al. 2016]. Men had more than twice the incidence rate of liver cancer than women, and rates increased with age for both sexes. Population modeling performed in 2011 posited that if new antiviral regimens consistently resulted in an 80% response rate, and if 50% of all HCV patients were treated, then, within 10 years, there would be a 15% reduction in cases of cirrhosis, a 30% reduction in cases of HCC, and 34% fewer deaths from liver disease, indicating the substantial effects that treatment would have in reducing liver disease morbidity [Rosen 2011].

In New York State (including New York City), the mortality rate associated with HCV increased from 4.0 per 100,000 population in 2001 to 5.5 per 100,000 population in 2015 [CDC 2016b]. The HCV-related mortality rate in New York State surpassed the HIV-related mortality rate in 2012, indicating the severity of disease burden and the urgency for wider treatment availability.

Role of NYS Primary Care Providers in Treatment of HCV

Primary care providers in New York State (NYS) are assuming a major role in the screening, diagnosis, treatment, and monitoring of patients with chronic HCV infection. When prescribing HCV antiviral therapy, clinical experience and appropriate continuing education are both important to ensure that HCV medications are prescribed safely and correctly and that all patients receive the highest quality of care.

This guideline covers screening, diagnosis, pretreatment assessment, treatment, and post-treatment monitoring for primary care providers treating patients with chronic HCV infection. The guideline includes recommendations for initial HCV treatment in patients with and without cirrhosis and for retreatment in patients with and without cirrhosis after previous treatment with DAA and non-DAA regimens has failed.

As stated in these recommendations, care providers new to HCV treatment should consult with a liver disease specialist when treating patients with chronic HCV infection and any of the following conditions:

- Compensated and decompensated cirrhosis.
- Concurrent hepatobiliary conditions.
- Extrahepatic manifestations of HCV, including renal, dermatologic, and rheumatologic manifestations.

- Significant renal impairment (creatinine clearance <30 mL/min) and/or undergoing hemodialysis.
- Active hepatitis B (HBV) infection, defined as HBV surface antigen–positive and detectable HBV DNA.
- Retreatment after any DAA treatment failure.

Care providers should refer patients with chronic HCV infection and decompensated liver disease and patients who are pre- or post-transplant to a liver disease specialist. Depending on their level of experience and expertise, care providers may also want to refer patients who have coexisting conditions (including HIV) that require treatment with complex drug regimens to a liver disease specialist.

→ **KEY POINT**

- Care providers should refer patients with chronic HCV infection and decompensated liver disease and patients who are pre- or post-transplant to a liver disease specialist.

Development of this Guideline

This guideline was developed by the New York State (NYS) Department of Health (DOH) AIDS Institute (AI) Clinical Guidelines Program, which is a collaborative effort between the NYSDOH AI Office of the Medical Director and the Johns Hopkins University School of Medicine, Division of Infectious Diseases.

Established in 1986, the goal of the Clinical Guidelines Program is to develop and disseminate evidence-based, state-of-the-art clinical practice guidelines to improve the quality of care provided to people with HIV, HCV, and STIs and to improve drug user health and LGBT health throughout the State of New York. NYSDOH AI guidelines are developed by committees of clinical experts through a consensus-driven process.

The NYSDOH AI Hepatitis C Virus Infection Guideline Committee was charged with developing evidence-based clinical recommendations for primary care providers in NYS who treat patients with chronic HCV infection. The resulting recommendations are based on an extensive review of the medical literature and reflect consensus among this panel of HCV experts. Each recommendation is rated for strength and for quality of the evidence (see below). If recommendations are based on expert opinion, the rationale for the opinion is included. See [About this Guideline](#) for a full description of the development process, including evidence collection and recommendation development.

AIDS Institute HIV Clinical Guidelines Program Recommendations Rating Scheme	
Strength of Recommendation	Quality of Supporting Evidence
A = Strong	1 = At least 1 randomized trial with clinical outcomes and/or validated laboratory endpoints
B = Moderate	2 = One or more well-designed, nonrandomized trial or observational cohort study with long-term clinical outcomes
C = Optional	3 = Expert opinion

Screening for HCV Infection

RECOMMENDATIONS

- Clinicians should perform HCV screening *at least once* for all patients aged 18 years and older who are not known to have HCV infection. (A2)
- Clinicians should repeat HCV screening in all patients who are planning to get pregnant (A2) or are currently pregnant (B3), and screening should be repeated with each pregnancy. (B3)
 - See the [Pregnancy and HCV](#) section of this guideline.

RECOMMENDATIONS

- Clinicians should offer repeat HCV screening based on individual exposure to the following risk factors, at least once if risk exposure is episodic and annually if it is ongoing.
 - Injection (A1) or intranasal (A2) drug use.
 - Hemodialysis. (A1)
 - HIV diagnosis. (A1)
 - Sex partner(s) with HCV infection. (A2)
 - Tattoo, piercing, or acupuncture obtained in a nonsterile setting. (A2)
 - Incarceration. (A2)
 - Unexplained liver disease or abnormal transaminase levels. (A1)
- Clinicians should offer repeat HCV screening *at least annually* to men who have sex with men (MSM) and to others who are not known to have HCV infection and:
 - Engage in receptive anal sex and other behaviors that may tear mucous membranes. (A2)
 - Have multiple sex partners. (A2)
 - Are taking pre-exposure prophylaxis (PrEP) to prevent HIV acquisition. (A3)
 - Are transgender women. (B3)
 - Engage in sex while using recreational mind-altering substances, particularly methamphetamine. (A2)
 - Have been diagnosed with another sexually transmitted infection (STI) within the previous 12 months. (A2)
- Clinicians should perform repeat HCV screening for individuals who are not known to have HCV infection and have a possible exposure in a healthcare setting, including those who:
 - Have a break in the skin caused by a sharp object that is contaminated with blood, visibly bloody fluid, or other potentially infectious material or that has been in the source patient's blood vessel. (A2)
 - Have been bitten by an individual with visible bleeding in the mouth that causes bleeding in the exposed worker. (A2)
 - Have been splashed on a mucosal surface with blood, visibly bloody fluid, or other potentially infectious material. (A2)
 - Have non-intact skin (e.g., dermatitis, chapped skin, abrasion, or open wound) that has been exposed to blood, visibly bloody fluid, or other potentially infectious material. (A2)

In the United States, chronic infection with hepatitis C virus (HCV) is highly prevalent, but approximately 50% of people with HCV may not be aware of their infection [CDC 2019; Hofmeister, et al. 2019; Kim, et al. 2019]. Reliable testing to identify HCV and pharmacologic treatment to cure the disease are available.

Given these findings, in June 2020, this Committee added a recommendation supporting HCV screening in all individuals aged 18 years and older, regardless of risk factors. The existing recommendation to screen all pregnant women during each pregnancy, added in February 2019, remains in place (see the [Pregnancy and HCV](#) section of this guideline). These recommendations are aligned with the current recommendations from the United States Preventive Services Task Force (USPSTF) and the Centers for Disease Control and Prevention (CDC) [Schillie, et al. 2020; USPSTF 2020]. Universal screening in individuals aged 18 years and older was demonstrated to be cost-effective compared with cohort- and risk-based screening, mainly by reducing cirrhosis- and liver-related mortality [Barocas, et al. 2018].

New York State (NYS) is actively seeking to identify people with chronic HCV infection and link them to treatment before irreversible liver damage occurs and, on a public health level, to eliminate HCV in the state (see [New York State Hepatitis C Elimination Task Force](#)). In response to the 2014 NYS law mandating HCV testing in all individuals born between 1945 and 1965, hospitals, clinics, health centers, and other primary care medical facilities established HCV screening programs. During the first year of implementing the law, there was a 51% increase in specimens submitted for HCV testing. Testing rates among active Medicaid clients increased by 52%. Among individuals with newly diagnosed HCV infection, linkage to care increased approximately 40% in NYS (excluding New York City) and 11% in New York City [Flanigan, et al. 2017].

People with HCV infection may face significant barriers to accessing care in clinical settings, including lack of health insurance, physical disability, ongoing substance use, mental health disorders, and housing instability. Locating HCV screening sites in a variety of community-based organizations, such as syringe exchange programs, sexually transmitted

disease (STI) clinics, and local health departments is integral to the effort to provide HCV screening, treatment, and education in diverse settings.

As part of HCV screening and diagnosis, a series of serologic and virologic tests are used, including laboratory-based antibody tests, point-of-care rapid HCV antibody tests for initial screening, and laboratory-based HCV RNA tests for HCV diagnosis (see the *Diagnosis of HCV Infection* section of this guideline).

→ KEY POINTS

- HCV screening in all patients aged 18 years and older is an essential first step in identifying and treating adults with HCV infection.
- Some patients may have ongoing or episodic risk that requires follow-up HCV screening.
- HCV testing is part of pregnancy planning and care for each pregnancy.
- HCV testing should be performed in individuals younger than 18 years of age who are at risk for infection (*see list of risk factors in recommendations*) [Schillie, et al. 2020; USPSTF 2020].

In the United States, an estimated 60% of chronic HCV infections result from use of shared needles, syringes, or other drug-use paraphernalia [CDC 1998]. Overall, sexual transmission accounts for approximately 5% of HCV infections, although transmission rates differ in select groups, as discussed below. Vertical transmission (transmission from mother to child) accounts for 5% to 6% of infection; receipt of contaminated organs or blood component transfusions before HCV testing of the blood supply began in 1992 accounts for approximately 5% of HCV infections [CDC 1998]. The average incidence of anti-HCV seroconversion after unintentional needle sticks or sharps exposures from a source with confirmed HCV infection is estimated at 1.8% [CDC 1998], and HCV infection has also resulted from unsterile skin piercing activities, such as tattoos in prisons (1%) [Alter 1999]. There are a few case reports that might suggest transmission during trauma, including biting [Dusheiko, et al. 1990] and fist fighting [Bourliere, et al. 2000], when there is potential for blood-to-blood transmission, but there are insufficient data to limit patients with HCV from participating in sports such as boxing or wrestling at this time.

Injection or intranasal drug use: Sharing of injection drug use (IDU) equipment is an efficient method of transmitting HCV. In the United States, a reduction in new HCV infections between 1992 and 2009 was attributed to expansions of syringe-access programs, safer injection practices among people who inject drugs (PWID), and increased enrollment in drug treatment programs [Klevens RM, et al. 2012]. However, HCV prevalence among PWID entering substance use treatment in New York City (n = 1,535) was 67% (95% confidence interval: 66% to 70%) during the 2006 to 2013 period and was not significantly different from that observed from 2000 to 2001 [Jordan, et al. 2015].

The demographics of IDU now include many young people living in suburban and rural regions [Klevens RM, et al. 2012]. Adolescents and young adults may advance to IDU after first becoming addicted to prescription oral opioids [Mateu-Gelabert, et al. 2015]. Reports from several states (including New York State), underscore the importance of awareness of HCV risk among adolescent and young adult patients and of offering HCV screening to this population [CDC 2008, 2011a, 2011b; Pollini, et al. 2011; CDC 2012; Zibbell, et al. 2015].

→ KEY POINTS

- Epidemics of HCV infection that parallel opioid-use epidemics have been observed among young male and female injection drug users, primarily in suburban and rural areas [CDC 2008, 2011a, 2011b; Pollini, et al. 2011; CDC 2012; Zibbell, et al. 2015].
- In 2015, 2,309 (27.2%) of HCV cases reported in New York State (excluding New York City) were in people <30 years of age [NYSDOH 2018]. Among those <30 for whom risk information is available, 91% reported a history of IDU.

In a systematic review of 28 studies on the prevalence of HCV in noninjecting drug users who smoked, sniffed, or snorted such drugs as heroin, powder or crack cocaine, or methamphetamine, investigators found HCV prevalence rates ranging from 2.3% to 35.3% [Scheinmann, et al. 2007; Stern, et al. 2008]. Among noninjecting drug users, sharing of oral and nasal drug use equipment is associated with an increased risk of HCV infection [Koblin, et al. 2003; Neaigus, et al. 2007; Macias, et al. 2008]. In addition, blood and HCV RNA have been confirmed in the nasal secretions and drug-sniffing paraphernalia of intranasal drug users with HCV infection [Aaron, et al. 2008].

Sexual transmission: Because many with HCV infection have a history of drug use, estimation of sexual transmission is a challenge (as reviewed in [Tohme and Holmberg 2010]). Sexual transmission of HCV among monogamous heterosexual couples is infrequent. The estimated maximum prevalence of HCV infection among sex partners of individuals with chronic HCV infection was only 1.2%, and the maximum incidence of HCV transmission through sex contact was 0.07% per year or approximately 1 per 190,000 sexual contacts [Terrault, et al. 2013]. Sexual transmission risk increases in the setting of multiple partners, STIs, HIV, and exposure to blood [Tohme and Holmberg 2010]. Several reports have demonstrated isolated outbreaks of sexual HCV transmission among MSM with HIV infection who engage in receptive anal intercourse [Urbanus, et al. 2009; van de Laar, et al. 2009; CDC 2011b; Wandeler, et al. 2012]. In a report from New York City on sexual transmission among MSM with HIV and no previous history of injection drug use, new HCV infections were highly correlated with receptive anal intercourse, engaging in sex while using methamphetamine, or participating in group sex [CDC 2011b].

PrEP: Individuals may have higher than average rates of baseline risk and ongoing risk for acquiring HCV due to ongoing IDU and high-risk sexual behavior. In a 2017 study of 375 men taking PrEP, 4.8% tested positive for HCV infection [Hoornenborg, et al. 2017]. Another study representing 304 person-years of PrEP use, reported an annual incidence rate of 0.7 per 100 patient-years among individuals who were initially not infected with HCV and did not report IDU [Volk, et al. 2015]. A recent report evaluated 14 MSM with no HIV infection taking PrEP, who were diagnosed with HCV infection from 2013 to 2018. Most participants were asymptomatic for HCV and most reported increases in sexual and drug use behaviors that put them at increased risk of exposure to HCV and bacterial STIs. These findings underline the need for consistent HCV screening and expanded prevention messages among MSM taking PrEP [Price, et al. 2019].

Transgender women: In one study of 571 transgender women in New York City, rates of HCV infection varied from 3.6% among Caucasian transgender women to as high as 15.7% among Hispanic transgender women [Nuttbrock and Hwahng 2017]. However, HCV screening rates among transgender women remain low. In a retrospective, multi-site study of gender-identity clinics in New York City, only 27% of participants were screened for HCV at baseline [Mangla, et al. 2017].

History of incarceration: Incarcerated populations are a significant but declining portion of the HCV epidemic in the United States [Larney, et al. 2013; Alvarez, et al. 2014; Varan, et al. 2014]. A study from 2009 to 2013 at two maximum-security prisons in New York State estimated an HCV prevalence of 10.1%; injection drug use, being the partner of a PWID, and HIV diagnosis were most strongly associated with HCV infection [Alvarez, et al. 2014]. In 2015, 22.2% of newly reported cases of chronic or acute HCV infection in New York State (excluding New York City) had a reported history of incarceration [NYSDOH 2018]. In New York City, the rate of newly reported chronic HCV infection in 2015 was 86.3 per 100,000. In the incarcerated population of the city, the rate was 964.3 per 100,000 for the same year [NYCDHMH 2016].

Exposure to blood in a healthcare setting: The average incidence of anti-HCV seroconversion after unintentional needle sticks or sharps exposures from a source with HCV infection is 1.8% [CDC 1998]. Healthcare-related transmission of HCV is documented infrequently in the United States [Henderson 2003; Tomkins, et al. 2012]. In 2014, among reported acute HCV cases that included information on exposure type, 1% was considered to be occupationally acquired [CDC 2017b].

Hemodialysis: The estimated 8% prevalence of anti-HCV antibodies among chronic hemodialysis patients is significantly higher than the estimated 1.6% prevalence in the general U.S. population [CDC 1998]. Nationally, 36 cases of acute HCV infection in 19 different hemodialysis clinics in 8 states were reported between 2014 and 2015, with epidemiologic and viral sequencing confirming transmission between patients [CDC 2016a]. The Centers for Disease Control and Prevention (CDC) recommend HCV antibody screening upon admission for chronic hemodialysis patients, followed by screening every 6 months thereafter [CDC 2016a, 2017a]. The National Kidney Foundation stratifies by prevalence and recommends antibody screening upon admission to facilities with a low HCV prevalence and consideration of HCV RNA testing upon admission to facilities with high HCV prevalence [KDIGO 2008].

Receipt of blood transfusion or organ transplant before 1992 or clotting factor concentrates from human plasma before 1987: Donor screening for HCV infection and inactivation procedures for pooled plasma and plasma derivative products have virtually eliminated the risk of HCV transmission through blood products in the United States [Watson, et al. 1992; CDC 1998].

Vertical transmission: A 2011 meta-analysis estimated that the risk of vertical HCV infection to children of HCV antibody-reactive and HCV RNA detectable women was 5.8% for children of women without HIV and 10.8% for children of women with HIV [Arshad, et al. 2011]. From 2011 to 2014, the national rate of HCV infection among women of childbearing age (15-44 years old) increased by 22% (from 139 to 169 per 100,000), and the national rate of infants born to women diagnosed with HCV infection increased by 68% (from 0.19% to 0.32%) [Koneru, et al. 2016]. Factors associated with an increased risk of perinatal transmission include HIV coinfection and higher maternal HCV viral loads [Arshad, et al. 2011;

Benova, et al. 2014]. Neither delivery by cesarean-section nor refraining from breastfeeding has been demonstrated to reduce vertical transmission [Koneru, et al. 2016].

Tattoos, piercings, or acupuncture obtained in nonsterile settings: Tattoos or piercings obtained in nonsterile settings, and especially those obtained during incarceration, have been associated with HCV infection, even after controlling for injection drug use and transfusion before 1992 [Tohme and Holmberg 2012; Carney, et al. 2013]. Low levels of HCV RNA have been detected on acupuncture needles from individuals known to have HCV infection [Lemos, et al. 2014], although acupuncture has not been established as a confirmed route of transmission.

HIV infection: HCV infection is common among persons with HIV because the routes of acquisition are similar. For decades, injection drug use has been recognized as the main risk factor for HIV/HCV coinfection, but an increasing number of sexually transmitted HCV infections have been documented in MSM with HIV [Breskin, et al. 2015; Fierer and Factor 2015; Hagan, et al. 2015]. In a recent study among MSM with HIV in Europe, Australia, and Canada, HCV incidence significantly increased from 1990 to 2014 [van de Laar, et al. 2009]. Analyses of data from the Multicenter AIDS Cohort Study (MACS) in the United States and from a cohort of MSM with HIV in San Diego demonstrated a similar rise in HCV incidence among MSM [Witt, et al. 2013; Chaillon, et al. 2017]. In this population, sexual acts that may tear mucous membranes, sex while using methamphetamines, and having other STIs have been associated with HCV infection [Fierer and Factor 2015; Hagan, et al. 2015].

Unexplained liver disease or abnormal transaminase levels: In primary care patients with an alanine transaminase (ALT) level 50 to 100 IU/L, HCV prevalence is 10-fold higher than in the general population, whereas hepatitis B (HBV) prevalence was not increased [Helsper, et al. 2012].

Diagnosis of HCV Infection

RECOMMENDATIONS

Screening Tests

- Clinicians should perform HCV screening using either a laboratory-based HCV antibody test or point-of-care rapid antibody test. (A1)

Confirmatory Testing

- If the HCV antibody test result is positive, clinicians should obtain confirmatory HCV RNA testing from a laboratory that uses a nucleic acid test (NAT) approved by the U.S. Food and Drug Administration (FDA). (A1)
- If HCV RNA is detected after a positive antibody result, the patient has confirmed HCV infection and clinicians should evaluate for treatment of chronic or acute HCV infection. (A2)
- If the HCV antibody test result is negative:
 - Clinicians should perform subsequent HCV screening based on individual patient risk factors (A3)
 - *And* if acute HCV infection is suspected, clinicians should perform a diagnostic HCV RNA test using an FDA-approved NAT. (A1)
- In patients with a history of a positive HCV antibody test, clinicians should use an HCV RNA test (not an HCV antibody test) for subsequent screening. (A1)

→ KEY POINT: REPORTING

- NYS Public Health law mandates that clinicians report all suspected or confirmed cases of HCV infection, specifying acute or chronic, to the local health department of the area where the patient resides.
 - See [NYSDOH Communicable Disease Reporting](#)

HCV Antibody Testing

HCV antibody testing is the first step in identifying whether a person has been exposed to the virus [CDC 2013] (see Centers for Disease Control and Prevention [CDC]: *Recommended Testing Sequence for Identifying Current HCV Infection*).

HCV antibody testing with a 3rd-generation enzyme immunoassay (EIA) is most frequently performed in the laboratory; this test has a sensitivity of approximately 99% even when used in low-prevalence populations [Lee, et al. 1995; Gretch 1997; Colin, et al. 2001; Abdel-Hamid, et al. 2002].

Reflex testing is an automatic HCV RNA test of the same specimen that is performed after a positive HCV antibody test. This testing provides confirmation or exclusion of active infection with a single laboratory test order, eliminating the need for the patient to return for follow-up testing and expediting linkage to care for those who have HCV (see *Table 1: Interpretation of HCV Test Results*, below). Knowledge of the laboratory's HCV reflex testing procedures is necessary, including the availability of reflex testing and, if available, whether it is performed automatically or must be requested. If reflex testing is not available, confirmatory HCV RNA testing should be performed soon as possible after a reactive HCV antibody test result is received.

Rapid, point-of-care HCV antibody screening tests are also available; they can be performed with a finger stick blood sample and produce results within 20 to 40 minutes. Sensitivities and specificities are equivalent to traditional EIA testing [Lee, et al. 2010]. The *NYSDOH HCV Rapid Testing Program* and others are using this simple and convenient testing method outside of traditional healthcare settings in drug treatment centers, syringe-exchange programs, and other community-based locations. The short testing process means the test can be performed and the result given while the patient is still present, and, if the patient is HCV antibody-positive, the follow-up appointment for confirmatory HCV RNA testing can be made.

If the HCV antibody test is negative, the immunocompetent patient does not have chronic HCV infection; ongoing individual risk factors will determine the need for future screening and the need for ongoing education about risk-reduction strategies. However, a false-negative antibody test result may occur in patients who may have been exposed to the virus within the previous 6 months and may be experiencing acute HCV infection (see the *Acute HCV Infection* section of this guideline) [Nastouli, et al. 2009]. HCV RNA is usually detectable within days to 2 weeks after an exposure [Wang TY, et al. 2002; Maheshwari and Thuluvath 2010], whereas it may take 2 to 6 months for HCV antibodies to be detectable ("window period") (for a graphic description of the "window period," please see the Association of Public Health Laboratories [APHL] *HCV Test Result Interpretation Guide*). False-negative antibody test results may also occur in patients who are immunocompromised due to advanced HIV infection, use of immunosuppressive therapy, long-term hemodialysis, or other conditions [Thomson, et al. 2009; Larouche, et al. 2012]. In these patients, confirmatory HCV RNA testing should be performed.

If the HCV antibody test is positive, confirmatory HCV RNA testing should be performed [Freiman, et al. 2016; Moorman, et al. 2017]. It is important to inform patients that the reactive antibody result does not confirm active HCV infection.

HCV RNA Testing

FDA-approved HCV RNA tests are available, and these tests can identify the presence of virus as early as 2 weeks post-exposure, rather than the 8 to 24 weeks needed for HCV antibodies to develop [Kamili, et al. 2012] (see American Association for the Study of Liver Disease [AASLD]: *FDA-Approved, Commercially Available Anti-HCV Screening Assays*). Ultrasensitive HCV quantitative RNA assays can detect as few as 5 copies/mm³.

If HCV RNA is not detected after a positive antibody test, then 1) the patient had previous exposure to HCV but has cleared the virus and does not have active HCV infection, or 2) the result of the HCV antibody test was falsely reactive. In these patients, ongoing HCV screening should occur based on individual risk factors. Because the presence of HCV antibodies can be lifelong, detection of current HCV infection in antibody-positive patients requires HCV RNA testing. Repeat HCV antibody testing is not useful in patients with previously reactive antibody tests.

If HCV RNA is detected after a positive antibody result, the patient has confirmed HCV infection and should be evaluated for treatment of chronic or *acute HCV infection* (see the *Pretreatment Assessment* section of this guideline). It is important to advise all patients with HCV viremia that they may be infectious and should take precautions to avoid transmitting HCV to others.

→ KEY POINTS: HCV ANTIBODIES

- The presence of HCV antibodies alone may not indicate active HCV infection.
- In patients with a history of a reactive HCV antibody test, subsequent screening requires an HCV RNA test, not an HCV antibody test, to detect infection.
- HCV antibodies do not prevent future HCV infections; prevention measures are needed for those with ongoing risk factors.

Table 1: Interpretation of HCV Test Results*

Anti-HCV Antibody	HCV RNA	Interpretation	Response
Positive	Detected	<ul style="list-style-type: none"> • Acute or chronic HCV infection. 	<ul style="list-style-type: none"> • Evaluate for treatment.
Positive	Not detected	<ul style="list-style-type: none"> • Resolution of HCV by spontaneous or treatment-related clearance, <i>or</i> • HCV infection during period of intermittent viremia, <i>or</i> • False-positive antibody screening result. 	<ul style="list-style-type: none"> • HCV RNA testing based on risk factors. • Repeat HCV RNA testing if acute exposure is known or suspected.
Negative	Detected	<ul style="list-style-type: none"> • Early acute HCV infection, <i>or</i> • Chronic HCV infection in setting of immunosuppressed state. 	<ul style="list-style-type: none"> • Evaluate for treatment if person has risk factors. • Repeat testing if person has no risk factors or exposure and false positive is suspected.
Negative	Unknown	<ul style="list-style-type: none"> • Presumed absence of HCV infection if the HCV RNA testing was not performed or the status is unknown. 	<ul style="list-style-type: none"> • HCV antibody test based on risk factors.

*Adapted from [CDC 2013].

For more information about interpreting HCV test results, see the [APHL HCV Test Result Interpretation Guide](#).

Acute HCV Infection

RECOMMENDATIONS

- Clinicians should suspect acute HCV infection if a patient who had a negative antibody test documented within the previous 6 months has a new positive antibody test or has detectable HCV RNA in the absence of a positive antibody test. (A3)
- Clinicians should not prescribe pre- or post-exposure prophylaxis to prevent HCV infection. (A1)
- If chronic HCV infection is established, clinicians should evaluate patients for treatment. (A1)
 - See the [Pretreatment Assessment](#) section of this guideline.
- Clinicians should screen all patients with possible acute HCV infection for HIV, hepatitis A virus (HAV), and hepatitis B virus (HBV) infections, given the similar risk factors for acquisition. (A3)
 - See the [Baseline Laboratory Testing](#) section of this guideline.

→ KEY POINTS

- Clinicians and their patients should determine the timing of HCV treatment with respect to the likelihood of spontaneous clearance and patient or care provider concerns regarding risk of transmission.
- Patient education should include the following information:
 - If patients have acute HCV infection, they may be infectious and should take precautions to avoid transmitting HCV to others.
 - HCV infection may clear spontaneously (i.e., without treatment).
 - Treatment options are available if HCV infection is established.

The acute phase is considered the first 6 months of HCV infection. Approximately 65% to 75% of patients with acute HCV infection are asymptomatic [Marcellin 1999]. When symptoms are present, they last a few weeks to months after exposure and may range from clinical hepatitis with jaundice, choloria (tea-colored urine), steatorrhea, and abdominal pain to only vague, nonspecific symptoms, such as fatigue, anorexia, low-grade fever, myalgias, arthralgia, mood disturbances, and nausea or vomiting [Marcellin 1999; Gerlach, et al. 2003; Loomba, et al. 2011]. As a result, in the absence of a clearly defined risk factor for transmission, the acute phase is rarely diagnosed. During acute infection, serum aminotransferase levels also vary and may be normal or up to 20 times the upper limit of normal [Maheshwari, et al. 2008].

An estimated 20% to 45% of patients with HCV infection will clear the virus spontaneously, generally within 12 to 16 weeks [Kamal 2008]. Approximately 11% of those who remain viremic 6 months after infection will eventually experience spontaneous clearance [Seeff 1997]. Predictors of spontaneous clearance include female sex, age <40 years, IL28B CC genotype (highest incidence in East and South Asians and Europeans, lowest in African Americans), symptomatic infection (jaundice), and a competent immune system (no immunosuppressive therapy or uncontrolled HIV) [Grebely, et al. 2014]. Because both aminotransferases and HCV viral load may fluctuate during the acute phase, durable spontaneous clearance, if it occurs, is not expected until 24 weeks after inoculation or exposure. Following spontaneous clearance, patients will remain antibody positive.

Known exposure: After a known exposure, which generally occurs in an occupational setting, baseline testing with both HCV RNA and antibody tests is reasonable to distinguish between acute or chronic infection.

Given the excellent response rates with current DAA therapy, at this time, there is no clear advantage to treatment of HCV in the acute phase [Naggie, et al. 2017]. It is reasonable to wait a minimum of 24 weeks to repeat HCV RNA and antibody tests to assess for spontaneous clearance or confirm infection. In some circumstances, clinicians and their patients may decide to initiate therapy sooner; however, if patients have an increased risk of transmitting HCV, are HIV-infected men who have sex with men (MSM), and/or use injection drugs, a minimum of 12 to 16 weeks is needed to assess for spontaneous clearance before initiation of therapy. Other factors influencing decisions to initiate early treatment may be current access to healthcare, concerns for delay due to family planning, and known cirrhosis or preexisting liver disease. The [recommended DAA regimens](#) used in these situations are the same as those indicated for chronic HCV therapy.

It is important to educate patients with potential acute HCV infection about the possibility of spontaneous clearance, the need to avoid or minimize hepatotoxic drugs (including alcohol), and the need to take precautions to prevent HCV transmission to others (see patient education information at [NYSDOH AI HCV Educational Materials](#)).

Pretreatment Assessment

RECOMMENDATIONS

Who to Assess for Treatment

- Clinicians should assess all patients with a confirmed diagnosis of chronic HCV infection for treatment. (A1)

When to Refer to a Liver Specialist

- Clinicians new to treating chronic HCV infection should consult with a liver disease specialist when treating chronic HCV infection in patients with any of the following conditions (A3):
 - Compensated and decompensated cirrhosis.
 - Concurrent hepatobiliary conditions.
 - Extrahepatic manifestations of HCV, including renal, dermatologic, and rheumatologic manifestations.
 - Significant renal impairment (creatinine clearance <30 mL/min) or who are undergoing hemodialysis.
 - Active hepatitis B virus (HBV) infection, defined as HBV surface antigen positive and detectable HBV DNA.
 - Ongoing HCV infection after failure of treatment with direct-acting antivirals (DAAs).
- Clinicians new to treating chronic HCV infection should consult with a liver disease specialist when evaluating patients for retreatment after any DAA treatment failure. (B3)
 - See the *Regimens for Retreatment After DAA Failure* section of this guideline.
- Clinicians should refer patients with chronic HCV infection and decompensated liver disease and patients who are pre- or post-transplant to a liver disease specialist. (A3)

With few exceptions, all patients with confirmed HCV infection are candidates for treatment [van der Meer, et al. 2012; Simmons, et al. 2015; Smith-Palmer, et al. 2015]. Treatment of HCV reduces all-cause mortality, regardless of disease stage [Simmons, et al. 2015]. The only patients who are not candidates for treatment with DAAs are those with a life expectancy of less than 12 months or for whom treatment would not improve symptoms or prognosis [AASLD/IDSA 2015].

Medical History and Physical Exam

The patient's medical history and physical examination are essential components of pretreatment assessment. *Table 2*, below, lists elements of the patient history and physical examination that apply specifically to pretreatment assessment of patients with chronic HCV infection.

Screening of mental health status and for alcohol/substance use and treating or referring patients with disorders is an essential component of patient care. The approach to patients with mental health or substance use disorders is the same for patients with HCV as for other patients. Mental health conditions that have been stabilized and substance use disorders that are being treated are not contraindications to HCV treatment.

- See New York State (NYS) Department of Health (DOH) AIDS Institute (AI) [Substance Use Guidelines](#) for more information.

Table 2: Key Elements of a Pre-HCV Treatment Patient History and Physical Examination	
Elements of Patient History	Rationale
Previous treatment for HCV infection	<ul style="list-style-type: none"> • Previous regimen and treatment outcome will guide choice and duration of therapy
History of hepatic decompensation	<ul style="list-style-type: none"> • Warrants referral to a liver disease specialist
History of renal disease	<ul style="list-style-type: none"> • Findings may influence choice of regimen
Medication history and current medications, including over-the counter and herbal products	<ul style="list-style-type: none"> • Carefully consider drug-drug interactions with DAAs <ul style="list-style-type: none"> – See the <i>Drug-Drug Interactions</i> section of this guideline
Pregnancy status and plans (see <i>Pregnancy and HCV</i> section of this guideline)	<ul style="list-style-type: none"> • HCV treatment is deferred during pregnancy • Birth control use is essential during HCV treatment and for 6 months after treatment if patients are receiving ribavirin (RBV)
HIV infection	<ul style="list-style-type: none"> • If HIV infection is confirmed, offer the patient antiretroviral therapy (ART) <ul style="list-style-type: none"> – See the NYSDOH AI guideline <i>When to Initiate ART, With Protocol for Rapid Initiation</i> • If the patient is being treated with antiretroviral medications, assess potential drug-drug interactions <ul style="list-style-type: none"> – See the <i>Drug-Drug Interactions Between DAAs and ARVs</i> section of this guideline • Presence of HIV infection may influence fibrosis assessment modality, choice of treatment, duration, and monitoring
History of infection/vaccination status	<ul style="list-style-type: none"> • Hepatitis A virus (HAV): Obtain HAV antibody (immunoglobulin [IgG] or total) • Hepatitis B virus (HBV): Obtain hepatitis B surface antigen (HBsAg), antibody to HB surface antigen (anti-HBs), and anti-hepatitis B core antibody (anti-HBc) (total) • Administer pneumococcal polysaccharide vaccination (PPSV23) as follows: <ul style="list-style-type: none"> – All patients with cirrhosis, which is associated with increased susceptibility to bacterial infections [Jalan, et al. 2014] – As indicated in the <i>CDC/ACIP Recommended Immunization Schedule for Adults Aged 19 Years or Older</i> • Annual influenza <ul style="list-style-type: none"> – See U.S. Food and Drug Administration (FDA): <i>Influenza Virus Vaccine Safety & Availability</i>
Elements of a Pretreatment Physical Examination	Clinical Details
Presence or absence of ankle edema, abdominal veins, jaundice, palmar erythema, gynecomastia, spider telangiectasia, ascites, encephalopathy, and asterixis	<ul style="list-style-type: none"> • Presence may suggest cirrhosis or decompensated cirrhosis and may require additional evaluation and management or treatment
Presence or absence of physical signs related to extrahepatic manifestations of HCV, such as porphyria cutanea tarda, vasculitis, or lichen planus	<ul style="list-style-type: none"> • Presence may increase urgency of HCV treatment and may require additional evaluation and treatment needs <ul style="list-style-type: none"> – See, for instance, Medscape: <i>Cutaneous Manifestations of HCV Clinical Presentation</i>
Liver size by palpation or auscultation for hepatomegaly or splenomegaly, as well as tenderness or hepatic bruits	<ul style="list-style-type: none"> • Size and tenderness may suggest severity of liver disease and may require additional evaluation
Cardiac status	<ul style="list-style-type: none"> • Findings may influence choice of RBV-containing regimen, RBV dosing, or complete blood count (CBC) monitoring frequency

Mental Health, Substance Use, and Barriers to Adherence

Mental Health

If stabilized, mental health disorders are not contraindications to treatment of chronic HCV infection with DAAs. Strategies to overcome mental health-related barriers to successful HCV treatment include counseling and education and referral to psychiatry and behavioral health services. Patients with mental health disorders may need increased attention to management of adverse effects and coordination of care during HCV treatment. An integrated care model, in which mental health providers provide HCV treatment and risk reduction counseling, has been effective for treating HCV [Groessl, et al. 2013]. Few data are currently available regarding the effect of an existing psychiatric diagnosis on patient adherence to any oral HCV treatment regimens.

With interferon-free regimens, depression is no longer a common side effect of HCV treatment. However, antidepressant and antipsychotic drug-drug interactions have been reported with DAAs, so monitoring is necessary. Similarly, it is important to be aware of patient use of nonprescription medication: St. John's wort, an herbal self-remedy for depression, may decrease the effectiveness of DAA therapy [FDA 2015a, 2015b, 2015c, 2016b].

- See the *Drug-Drug Interactions* section of this guideline.

Alcohol and Other Substance Use

A history, or active use, of alcohol, tobacco, marijuana, and other substances is not a contraindication to HCV treatment unless the drug or alcohol use is believed to interfere with adherence to medications or appointments. Studies have demonstrated that active substance users who are receiving addiction treatment can be effectively treated for chronic HCV infection [Alavi, et al. 2013; Bojovic, et al. 2013; Brunner, et al. 2013; Newman, et al. 2013; Seidenberg, et al. 2013; Jerkeman, et al. 2014; Welzel, et al. 2015; Dore, et al. 2016].

Once a patient's alcohol consumption habits have been assessed, counseling may help the patient to reduce or eliminate alcohol use [EASL 2015]. It is important for patients with HCV infection who use alcohol to be made aware of the effects of alcohol on the course of HCV disease. Alcohol use has been associated with increased rates of liver disease progression and hepatocellular carcinoma (HCC) in persons with chronic HCV infection. In one such study, the risk of end-stage liver disease was higher in patients who reported ingesting more than 260 g (approximately 9 ounces) of alcohol per week [Vandenbulcke, et al. 2016]. Moderate alcohol intake is also associated with an increased risk of fibrosis progression [Westin, et al. 2002], and light-to-moderate alcohol intake is associated with an increased risk of HCC in patients with compensated cirrhosis [Vandenbulcke, et al. 2016]. There is no consensus on a safe level of alcohol ingestion for persons with chronic HCV infection, and no evidence is currently available regarding the effects of alcohol use on response to DAA treatment. Abstinence has been associated with improvement in chemical markers and decreased HCV RNA levels among previously heavy drinkers with HCV infection [Cromie, et al. 1996; Lieber 2001].

Barriers to Adherence

Though HCV treatment regimens are relatively short in duration, assessing a patient's readiness for treatment and ability to adhere to medications and medical appointments before initiating DAA therapy is essential. The purpose of the adherence assessment is to optimize support, not to deny access to treatment. After the pretreatment assessment and before treatment initiation, a plan can be developed with the patient to address potential barriers and/or to put support resources in place. Support groups and peer programs can promote increased patient engagement.

→ KEY POINTS

- The purpose of the adherence assessment is to optimize support, not to deny access to treatment.
- Though HCV treatment regimens are relatively short in duration, assessing a patient's readiness for treatment and ability to adhere to a medication regimen and medical care appointments before initiating DAA therapy is essential.
- After the pretreatment assessment and before treatment initiation, a plan can be developed with the patient to address potential barriers and/or to put support resources in place.

HCV Genotype

RECOMMENDATION

- Clinicians should obtain HCV genotype/subtype testing for all patients before starting treatment with DAAs. (A1)

HCV genotype influences the choice of DAA regimen and treatment duration in patients with chronic HCV infection; therefore, HCV genotype/subtype testing is needed for all patients being considered for HCV therapy [AASLD/IDSA 2015]. There are 6 common HCV genotypes and over 100 subtypes [Chevaliez and Pawlotsky 2007]. Approximately 70% of chronic HCV infections in the United States are genotype 1, the majority of which are subtype 1a [CDC 1998].

Fibrosis Assessment

RECOMMENDATIONS

- Clinicians should assess the degree of fibrosis in patients with chronic HCV infection to aid in determining the following (A1):
 - Need for pretreatment screening for varices and hepatocellular carcinoma (HCC).
 - Duration of antiviral treatment.
 - Need to include ribavirin (RBV) in the treatment regimen.
 - Need for post-treatment follow-up.
- Clinicians should assess patients with chronic HCV infection for decompensated liver disease. (A1)
- Clinicians should refer patients with decompensated cirrhosis to a liver disease specialist. (A3)

Fibrosis stage predicts HCV treatment response [Ogawa, et al. 2015]. An assessment of the degree of fibrosis should be performed regardless of alanine aminotransferase (ALT) patterns because significant fibrosis may be present in patients with repeatedly normal ALT [EASL 2015]. In one study, approximately 50% of HCV-infected persons born between 1945 and 1965 had severe fibrosis or cirrhosis as measured by fibrosis (FIB)-4 scoring [Klevens M, et al. 2015]. It is particularly important to identify patients with bridging fibrosis or cirrhosis; these findings may influence treatment selection and duration and may dictate post-treatment follow-up, such as the need for ongoing assessment for esophageal varices, hepatic function, and surveillance monitoring for HCC [Garcia-Tsao, et al. 2007; Bruix and Sherman 2011; AASLD/IDSA 2015]. Patients with lower severity of fibrosis have a higher likelihood of response to therapy and improved post-treatment prognosis [EASL 2015]. Patients known to have cirrhosis do not require repeat determination of degree of fibrosis before treatment.

Fibrosis stage can be assessed using noninvasive modalities, such as transient elastography, aspartate aminotransferase-to-platelet ratio index (APRI), FIB-4, and assays of direct markers of liver fibrosis using noninvasive tests other than transient elastography in patients with coinfection (see *Table 3: Methods for Staging Fibrosis*, below, and *Treatment of Patients with HIV/HCV Coinfection > Pre-HCV-Infection Treatment Assessment of Fibrosis in Patients with HIV* section of this guideline). Noninvasive modalities are well suited for rapid pretreatment assessment of chronic HCV infection in the primary care setting. Indirect serum markers use mathematical algorithms with different variables to predict fibrosis and are easily accessible in the primary care setting. Tests such as the APRI and FIB-4 index (age, AST, ALT, platelet count) appear efficacious in patients with little or no fibrosis and in those with cirrhosis. However, these tests have limited ability to discriminate between intermediate stages of fibrosis [Castera, et al. 2014; Patel and Shackel 2014; Schiavon Lde, et al. 2014]. Several studies have found FIB-4 to predict fibrosis more accurately than APRI [Shaikh, et al. 2009; Amorim, et al. 2012].

Liver biopsies are not routinely required. They are useful for patients with highly discordant results on noninvasive testing and in patients suspected of having a second etiology for liver disease in addition to HCV infection. Liver biopsy is an important instrument for diagnosing concurrent disease, such as metabolic nonalcoholic steatohepatitis (NASH), hemochromatosis (HHC), autoimmune primary biliary cholangitis (PBC), and autoimmune hepatitis (AIH). Although liver biopsy is safe and has a very low risk of complications (1/4,000 to 10,000), invasive procedures may be difficult to obtain in a timely fashion or may be unacceptably costly for uninsured patients [Seeff, et al. 2010].

An APRI calculator, FIB-4 index calculator, and other online clinical tools are available at [Hepatitis C Online](#). Assays of direct markers of liver fibrosis measure various combinations of liver matrix components in combination with standard biochemical markers. These assays (FibroSure, FibroTest, FibroMeter, FIBROSpect II, and HepaScore) appear efficacious in patients with little or no fibrosis and in those with cirrhosis, but, like FIB-4 and APRI, they have limited ability to discriminate between intermediate stages of fibrosis [Castera, et al. 2014; Patel and Shackel 2014; Schiavon Lde, et al. 2014]. These tests will provide an indication of disease progression over time and can be helpful in counseling patients who are considering treatment [Poynard, et al. 2014].

Vibration-controlled transient elastography (VCTE) measures shear wave velocity (expressed in kilopascals) and assesses a larger volume of liver parenchyma than liver biopsy. VCTE is most efficacious in F0-1 and F4 fibrosis but may be difficult to interpret in patients with F2 and F3 disease [Verveer, et al. 2012; Castera, et al. 2014; Schiavon Lde, et al. 2014; Tapper, et al. 2015]. Although VCTE is FDA-approved, it is not widely available. Other technologies, such as acoustic radiation force imaging, portal venous transit time, and MRI elastography, show promise for possible future use; these procedures are not recommended at this time because of their lack of sensitivity and specificity in early fibrosis, high cost, and limited availability [Bohte, et al. 2014; EASL 2015].

Table 3: Methods for Staging Fibrosis

Method	Procedure	Advantages	Disadvantages
Indirect serum markers	APRI, FIB-4*	Noninvasive; inexpensive	Limited ability to differentiate intermediate stages of fibrosis
Direct markers	FibroSure, FibroTest, FibroMeter, FIBROSpect II, and HepaScore	Noninvasive; easily accessible	Limited ability to differentiate intermediate stages of fibrosis
VCTE	Shear wave velocity	Noninvasive; assesses large volume of liver parenchyma	May be difficult to interpret in F2 and F3 liver disease; limited availability
Liver biopsy	Pathologic examination	Diagnostic standard; diagnoses concurrent liver disease	Invasive procedure; costly; sampling error

*See [Hepatitis C Online](#) for the following: [APRI Calculator](#) and [FIB-4 Calculator](#)

Cirrhosis Evaluation

RECOMMENDATIONS

- Clinicians should refer all patients with HCV-related cirrhosis for an upper endoscopy to screen for the presence of esophageal varices. (A3)
- Clinicians should screen for hepatocellular carcinoma (HCC) with ultrasound, computerized axial tomography (CT), or magnetic resonance imaging (MRI) every 6 months in patients with HCV-related bridging fibrosis or cirrhosis. (A3)

HCV treatment and the achievement of a sustained viral response (SVR) in patients with advanced liver disease dramatically decrease hepatic decompensation events, HCC, and liver-related mortality [AASLD/IDSA 2015]. To classify the severity of cirrhosis, the Model for End-Stage Liver Disease score ([MELD calculator](#)) or the Child-Turcotte-Pugh (CTP) score ([Table 4](#), below) may be used.

Table 4: Calculating the Child-Turcotte-Pugh (CTP) Score for Severity of Cirrhosis			
	1 point*	2 points*	3 points*
Encephalopathy	None	Stage 1 to 2 (or precipitant-induced)	Stage 3 to 4 (or chronic)
Ascites	None	Mild/moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	<2.0	2.0 to 3.0	>3.0
Albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Prothrombin time (sec prolonged) or INR	<4.0	4.0 to 6.0	>6.0
	<1.7	1.7 to 2.3	>2.3
<p>*CTP score is obtained by adding the score for each parameter. CTP class: A = 5 to 6 points (compensated, least severe liver disease) B = 7 to 9 points (decompensated, moderately severe liver disease) C = 10 to 15 points (decompensated, most severe liver disease) Adapted from: U.S. Department of Veterans Affairs: <i>Viral Hepatitis for Health Care Providers. Child-Turcotte-Pugh (CTP) Calculator.</i></p>			

Assessment for decompensation in patients with cirrhosis can be accomplished through medical history-taking and initial laboratory testing (see *Table 5: Evaluation and Follow-Up Screening for Patients with Cirrhosis*, below). Decompensation is defined as a MELD score of >15 or the presence of ascites, hepatic encephalopathy, portal hypertensive bleeding, HCC, intractable pruritus, hepatopulmonary syndrome, coagulopathy, or portopulmonary hypertension [Fox and Brown 2012]. Because of the clinical complexity of the condition, patients with a history or presence of decompensated cirrhosis should be referred to a liver disease specialist.

All patients with cirrhosis should undergo an upper endoscopy to screen for the presence of esophageal varices. Patients with HCV-related bridging fibrosis or cirrhosis are at increased risk of developing primary HCC and should undergo surveillance with an ultrasound every 6 months [Bruix and Sherman 2011; Shoreibah, et al. 2014]. Alpha-fetoprotein (AFP) determination lacks adequate sensitivity and specificity for effective use in surveillance and diagnosis of HCC. Elevated AFP levels may be seen in HCV infection in the absence of HCC [El-Serag and Mason 1999; EASL 2015].

For additional risk stratification and diagnosis information, see American Association of the Study of Liver Diseases (AASLD): *Practice Guidance on Portal Hypertensive Bleeding in Cirrhosis* [Garcia-Tsao, et al. 2017].

Table 5: Evaluation and Follow-Up Screening for Patients with Cirrhosis	
Type of Evaluation	Rationale
Assess for decompensation; refer to a liver disease specialist if history of decompensation or Child’s class B or C	<ul style="list-style-type: none"> Decompensation is defined as the presence (or history) of 1 of the following: <ul style="list-style-type: none"> MELD score of >15 Ascites Hepatic encephalopathy Portal hypertensive bleeding HCC Intractable pruritus Hepatopulmonary syndrome Portopulmonary hypertension
Abdominal ultrasound to screen for HCC	<ul style="list-style-type: none"> Ongoing HCC surveillance should be performed for patients with bridging fibrosis or cirrhosis according to standard guidelines every 6-12 months See AASLD Practice Guideline: <i>Management of Hepatocellular Carcinoma: An Update</i> [Bruix and Sherman 2011]
Upper endoscopy	<ul style="list-style-type: none"> Screen for varices

Baseline Laboratory Testing

Baseline laboratory testing essential to pre-HCV treatment is listed in *Table 6*, below.

Table 6: Baseline Laboratory Testing for Pre-HCV Treatment Assessment	
Test	Clinical Note
HCV RNA quantification	<ul style="list-style-type: none"> HCV RNA test confirms active HCV infection and determine HCV viral load.
Genotype/subtype	<ul style="list-style-type: none"> Genotype and subtype guide choice of regimen.
Complete blood count (CBC)	<ul style="list-style-type: none"> Low platelets (<140,000 platelets/μL) suggest cirrhosis and portal hypertension [Kaul and Munoz 2000; Ebell 2003]. Anemia may necessitate choice of a regimen that does not contain ribavirin (RBV).
Serum electrolytes with creatinine	<ul style="list-style-type: none"> Marked electrolyte abnormalities may suggest decompensated cirrhosis (e.g., hyponatremia). Renal function will influence choice of regimen.
Hepatic function panel	<ul style="list-style-type: none"> Elevated direct bilirubin suggests decompensated cirrhosis. Markedly elevated transaminases may suggest comorbidities.
International normalized ratio (INR)	<ul style="list-style-type: none"> Elevated INR suggests decompensated cirrhosis.
Pregnancy test for all individuals of childbearing potential (see <i>Pregnancy and HCV</i> section of this guideline)	<ul style="list-style-type: none"> If pregnant, suggest treatment deferral.
Hepatitis A virus (HAV) antibodies	<ul style="list-style-type: none"> Obtain HAV antibody (IgG or total) and administer the full HAV vaccine series in patients not immune to HAV.
Hepatitis B virus (HBV) antibodies	<ul style="list-style-type: none"> Obtain HBsAg, anti-HBs, and anti-HBc (total) and recommend administration of the HBV vaccine series (0, 1, and 6 months) for HBV-susceptible patients (negative for all serologies). <ul style="list-style-type: none"> In patients with positive HBsAg, perform HBV DNA testing to assess for active HBV infection. If HBV DNA is detectable, care providers new to HCV treatment should consult a liver disease specialist regarding treatment for HBV and HCV.
HIV test if status is unknown	<ul style="list-style-type: none"> If HIV infection is confirmed, offer patient antiretroviral therapy. <ul style="list-style-type: none"> See the NYSDOH AI guideline <i>When to Initiate ART, With Protocol for Rapid Initiation</i>.
Urinalysis	<ul style="list-style-type: none"> Protein may suggest extrahepatic manifestation of HCV.
Fibrosis serum markers	<ul style="list-style-type: none"> If not previously evaluated by biopsy or FibroScan.

Cardiac, Renal, HAV/HBV, Pregnancy, and Metabolic Status

RECOMMENDATIONS

Cardiovascular Status

- For individuals with chronic HCV infection who are aged >50 years, clinicians should perform cardiovascular risk assessment before initiation of treatment with ribavirin (RBV). (A2)

Renal Status

- Clinicians should assess creatinine clearance in all patients with HCV infection. (A1)
- Clinicians new to HCV treatment should consult a liver disease specialist when treating patients with severe renal impairment (creatinine clearance <30 mL/min). (A3)

RECOMMENDATIONS**Hepatitis A (HAV) and/or Hepatitis B (HBV) Immunity Status**

- Clinicians should obtain HAV antibody (IgG or total) and administer the full HAV vaccine series in patients who are not immune to HAV. (A3)
- Clinicians should obtain HBV surface antigen (HBsAg), anti-hepatitis B surface (HBs), and anti-hepatitis B core antigen (HBc), total, and recommend administration of the anti-hepatitis B virus (HBV) vaccine series (0, 1, and 6 months) for HBV-susceptible patients (negative for all serologies). (A3)
 - In patients with positive HBsAg, clinicians should perform HBV DNA testing to assess for active HBV infection. (A1)
 - If HBV DNA is detectable, clinicians new to HCV treatment should consult a clinician experienced in the management of both HBV and HCV. (A1)

Pregnancy Status and Contraception (see the *Pregnancy and HCV* section of this guideline)

- Before initiating ribavirin (RBV), clinicians should (A2):
 - Confirm a negative pregnancy test.
 - Advise patients to use 2 methods of birth control to avoid pregnancy during therapy and for 6 months after completion of therapy.
 - Counsel female and male patients on effective contraceptive use.
- **Contraindication:** Clinicians should not prescribe RBV in treatment of the following patients:
 - Any individual who is planning conception within 6 months of the last dose of RBV. (A2)
 - Male patients who have pregnant partners. (A2)

Cardiovascular Status

Cardiovascular disease and congestive heart failure may be worsened by possible anemia associated with the use of RBV-containing regimens. Individuals taking RBV-containing regimens may be at risk of anemia and subsequent high-output failure, as well as decreased oxygen-carrying capacity and subsequent ischemia [Kaul and Munoz 2000]. In patients being considered for RBV-containing regimens, it is important to assess for underlying cardiac disease and, if unstable cardiac disease is present, stabilize these patients before initiation of RBV.

Drug-drug interactions between direct-acting antiviral (DAA) medications and cardiovascular medications have been reported and may require adjustments or changes before initiation of therapy (see the *Drug-Drug Interactions* section of this guideline).

Renal Status

A patient's renal status will influence the choice of DAA regimen. Evaluation for renal disease includes assessing HCV-related causes of kidney disease such as membranoproliferative glomerulonephritis and membranous glomerulonephritis, even if patients have other comorbidities also associated with kidney disease, such as diabetes and hypertension.

HAV and/or HBV Immunity Status

Completion of HAV and HBV vaccination is not a pretreatment mandate and is appropriate during or after treatment for chronic HCV infection. Coinfection with HCV and either HAV or HBV may result in additional liver inflammation and pathology, and vaccination against HAV and HBV is important for patients with HCV infection to prevent acute decompensation and the sequelae of chronic superinfection by HBV [Lau and Hewlett 2005]. Approximately 40% to 50% of patients with HCV have no documented immunity against HAV or HBV [Henkle, et al. 2015].

If a patient is susceptible to both HAV and HBV infection, the combined vaccination series should be initiated. The laboratory assessment and vaccination (as appropriate) for HAV and HBV should be performed as soon as possible, but completion of the vaccination series is not necessary before initiation of HCV treatment. For more information, see *Hepatitis C Online*.

Vaccination of patients with a positive anti-HBc and negative HBsAg and anti-HBs (i.e., isolated anti-HBc) is controversial because results are subject to several interpretations. In patients from regions in which HBV infection is highly endemic or in patients with risk factors for acquiring HBV, a positive anti-HBc result may represent acute or chronic active HBV or serologic clearance of anti-HBs after a prior infection. In patients who have no risk factors or who are from regions in which HBV infection rates are low, a positive anti-HBc result may represent a false-positive result. In patients with isolated anti-HBc, HBV DNA testing to assess for active HBV infection is recommended, with subsequent vaccination if results are negative.

HBV reactivation and HBV-related hepatic flares, sometimes fulminant, have been reported both during and after DAA therapy in patients who were not receiving concurrent HBV treatment [Collins, et al. 2015; Ende, et al. 2015; De Monte, et al. 2016; Hayashi, et al. 2016; Sulkowski MS, et al. 2016; Takayama, et al. 2016; Wang C, et al. 2017]. Studies have demonstrated that HCV has a suppressive effect on HBV replication, and previous interferon-based treatments were active against both viruses [Shih, et al. 1993; Chu, et al. 1998; Chen SY, et al. 2003; Liu and Hou 2006]. However, unlike interferon, DAAs are not active against HBV, and when HCV is eradicated, HBV may be able to replicate. For more information about the risk of HBV reactivation, see [U.S. Food and Drug Administration \(FDA\) Drug Safety Warning](#).

→ KEY POINT

- For patients with active HBV infection, treatment of both HBV and HCV should be provided in consultation with a clinician experienced in the management of both HCV and HBV.

Pregnancy Status and Contraception

The data on use of DAA therapy in pregnancy is limited, and treatment of individuals who are pregnant is currently not recommended (see [Pregnancy and HCV](#) section of this guideline).

For all women and men planning conception within 6 months of treatment, use of RBV is contraindicated due to the teratogenic effects of the drug [FDA 2011]. Before prescribing an RBV-containing regimen for an individual of childbearing potential, a negative pregnancy test is required immediately before initiation of therapy and 2 forms of contraception or abstinence are advised during therapy and for 6 months after. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of therapy in female patients and in female partners of male patients who are taking RBV.

→ KEY POINTS

- RBV is contraindicated in female and male patients planning conception within 6 months of treatment [FDA 2011].
- To use an RBV-containing regimen in women of childbearing potential or in the male sex partners of these women, extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of therapy:
 - A negative pregnancy test is required immediately before initiation of therapy; and
 - Two forms of contraception or abstinence are advised during, and for 6 months after, therapy.

Metabolic Status

Obesity does not affect treatment of HCV with DAAs. Among individuals with HCV infection, both obesity and hepatic steatosis have been associated with progression of fibrosis and increased risk of advanced liver disease [Bressler, et al. 2003; Charlton, et al. 2006; Goossens and Negro 2014; Dyal, et al. 2015].

Chronic HCV infection appears to be associated with an increased risk of development of type 2 diabetes mellitus (DM2) in predisposed individuals [Mehta, et al. 2000; Mehta, et al. 2003; Lecube, et al. 2004]. Insulin resistance (IR) and diabetes are associated with increased liver fibrosis [Moucari, et al. 2008; Petta, et al. 2008; Patel, et al. 2011], cirrhosis [Gordon, et al. 2015], and hepatocellular carcinoma [Tazawa, et al. 2002; Veldt, et al. 2008; Donadon, et al. 2009; Hung, et al. 2011] in patients with HCV infection. Successful treatment of chronic HCV infection may be associated with improved IR, reduced incidence of DM2, and potentially decreased DM2-associated renovascular complications [Arase, et al. 2009; Thompson, et al. 2012; Hsu, et al. 2014]. No serious drug-drug interactions have been reported with DAA agents and insulin-sensitizing or diabetic medications.

Pregnancy and HCV

RECOMMENDATIONS

- Clinicians should repeat HCV screening in all patients who are planning to get pregnant (A2) or are currently pregnant (B3), and screening should be repeated with each pregnancy (B3).
 - See the *Diagnosis of HCV Infection* section of this guideline.
- Clinicians should advise pregnant patients with HCV to defer treatment with direct-acting antivirals (DAAs) until they are no longer pregnant or breastfeeding. (A2)
- If an individual with HCV becomes pregnant during DAA treatment, clinicians should (A3):
 - Advise that the use of DAAs is not currently recommended during pregnancy because no data are currently available on the effects of medications on the fetus.
 - Discuss the risks and benefits of continuing treatment.
- Clinicians should refer pregnant patients who are diagnosed with HCV (HCV antibody and HCV RNA positive), or who are known to have HCV and become pregnant before or during DAA treatment, to a specialist experienced in counseling about HCV in pregnancy. (A3) Specialists may include, but are not limited to, hepatologists, gastroenterologists, infectious disease specialists, or high-risk obstetricians.
- If a pregnant patient with HCV has a substance use disorder, the clinician should provide substance use treatment, including harm reduction services, or refer the patient for these services. (A3)
- Clinicians should advise pregnant and postpartum individuals with HCV mono-infection that breastfeeding is considered safe, and HCV is not transmitted through breast milk. (B3)
- Clinicians should advise patients that if they have or develop cracked or bleeding nipples, breastfeeding should be discontinued, and milk should be expressed and discarded until bleeding has resolved. (B3)
- Clinicians should refer infants born to mothers with HCV to clinicians with experience in HCV care for further counseling and testing and notify the clinician of the mother's HCV status; see *CDC Hepatitis C, Perinatal Infection 2018 Case Definition* and *IDSA/AASLD HCV in Pregnancy*. (A3)

→ KEY POINT

- Report perinatal exposure to ribavirin (RBV) to the *Ribavirin Pregnancy Registry*.

In 2017, 59% (1,914) of all new female cases of HCV reported in New York State (excluding New York City) were among women of childbearing age [NYSDOH 2018]. In New York City, in 2017, 38.7% (783) of all new female cases of HCV in were among women of childbearing age [NYCDHMH 2018].

These data raise concerns about reaching and treating this population and the potential for mother-to-child (vertical) HCV transmission. Data indicate that in areas of high HCV prevalence, 10% to 28% of pregnant individuals with HCV infection are not identified by risk-based screening [Thomas 2013; Waruingi, et al. 2015; Fernandez, et al. 2016].

Thus, in alignment with the CDC recommendations [Schillie, et al. 2020], this Committee recommends universal screening for HCV infection in individuals who are pregnant or planning to get pregnant and that screening should be repeated during each pregnancy. Identifying HCV presents an opportunity to ensure linkage to care, guide obstetric clinicians on the maternal and fetal risks in pregnant patients with HCV. In addition, based on a modeling study, universal HCV screening during pregnancy appears to be cost-effective compared to current practice [Tasillo, et al. 2019].

This Committee recommends universal HCV testing for all individuals who are pregnant or planning pregnancy and disclosure of positive results to an individual's OB-GYN and/or an HCV specialist, but recognizes the risk for stigma toward an individual who is pregnant and diagnosed with HCV. The effects of stigma cannot be underestimated. One cannot assume that HCV infection is associated with current or past injection drug use. Such assumptions can result in personal, family, and legal consequences for the patient, particularly among pregnant individuals. It is important to recognize and acknowledge the influence of stigma when caring for patients.

HCV Infection During Pregnancy

There are no published data on DAA treatment for HCV infection in pregnancy, and treatment of pregnant individuals is not currently recommended. If an individual becomes pregnant during DAA treatment, clinicians should discuss with the patient the risks (e.g., no information on the effects of the medication on the fetus) and benefits (e.g., probable HCV cure) of continuing treatment. Clinical trials are underway to evaluate the use of DAAs for the treatment of HCV during pregnancy. Patients may consider enrolling in a clinical trial if available.

HCV infection, as compared to no HCV infection, is associated with a higher incidence of intrahepatic cholestasis in pregnancy. Intrahepatic cholestasis in pregnancy has significant maternal and fetal morbidity [Wijarnpreecha, et al. 2017], and patients with HCV and this condition should be followed by a liver specialist and/or an obstetrician experienced in managing high-risk pregnancies [Wijarnpreecha, et al. 2017]. HCV infection during pregnancy has been associated with other adverse maternal and fetal outcomes, including gestational diabetes, low birth weight, small for gestational age, impaired intrauterine fetal growth, preterm delivery, miscarriage, and congenital anomalies [Connell, et al. 2011]. Researchers note that the specific role of HCV in determining these outcomes is unclear because the data may be confounded by comorbid polysubstance use [Connell, et al. 2011]. Patients with HCV and recent or active substance use during pregnancy should be referred to care providers experienced in managing substance use during pregnancy for evaluation, treatment, and harm reduction services.

Vertical Transmission of HCV Infection

Approximately 1% to 3.6% of pregnant individuals in the United States have HCV infection [Floreani 2013; Edlin, et al. 2015], and the risk of mother-to-child transmission is estimated at 6% for patients with HCV mono-infection and more than 10% for patients with HIV/HCV coinfection [Arshad, et al. 2011; Pawlowska 2015]. Currently, there is no antiviral treatment available to reduce the transmission of HCV during pregnancy.

→ KEY POINTS

- All pregnant individuals should be tested for HCV during each pregnancy.
- If patients engage in ongoing high-risk behaviors during pregnancy, rescreening during pregnancy or the postpartum period is appropriate.
 - See section on [Screening for HCV Infection](#)

Intrauterine, intrapartum, and postpartum HCV transmission to the fetus have been reported, but postpartum transmission is believed to be rare [Gibb, et al. 2000]. In utero transmission may occur during all 3 trimesters, and risk of transmission may be associated with higher maternal HCV RNA levels [Elrazek, et al. 2017]. During pregnancy, when maternal immune response is altered, HCV RNA levels usually increase during the second and third trimesters, and there is a synchronous decrease in maternal alanine transaminase (ALT) levels [Gervais, et al. 2000]. HCV RNA levels decline after delivery, and rare spontaneous postpartum clearance of the HCV infection in the mother has been reported [Prasad and Honegger 2013; Hashem, et al. 2017].

Data are limited on intrauterine HCV transmission during invasive procedures, such as fetal scalp monitoring, intrauterine pressures, chorionic villi sampling, and amniocentesis. Conditions such as premature rupture of membranes during pregnancy have been associated with increased risk of HCV transmission [Mast, et al. 2005]. However, observational studies have demonstrated that mode of delivery (Cesarean section [C-section] or vaginal) is not associated with the rate of mother-to-child HCV transmission [EPHCVN 2001; Mast, et al. 2005; Ghamar Chehreh, et al. 2011]. The [Society for Maternal Fetal Medicine \(SMFM\) and American College of Obstetricians and Gynecologists \(ACOG\) guidelines](#) recommend against performing a C-section simply for the purpose of reducing the risk of HCV transmission [Cottrell, et al. 2013; Hughes, et al. 2017]. For postpartum individuals with HCV mono-infection, breastfeeding is an option and is not associated with an increased risk of HCV transmission to the infant [Cottrell, et al. 2013]. It should be noted, however, that if the postpartum individual has cracked or bleeding nipples, HCV transmission may occur during breastfeeding through blood or non-intact skin exposure [CDC 2018]. Early discussion with lactation consultants during or after pregnancy may be helpful to minimize difficulties with breastfeeding. For pregnant patients with HIV/HCV coinfection, clinicians should consult the [American College of Obstetricians and Gynecologists obstetric HIV guidelines](#).

Treatment Options

The treatment of chronic HCV infection has evolved significantly in recent years following advances in the understanding of the HCV genome and HCV proteins [Pockros 2018]. As a result, new, highly effective therapies are available for patients who are treatment-naïve and -experienced, who do and do not have cirrhosis, and who have any HCV genotype (see *Box 2*, below). Before the availability of these new therapies, many patients and practitioners had been reluctant to initiate therapy for chronic HCV infection due to suboptimal sustained virologic response (SVR) rates and significant rates of adverse events. These concerns are no longer applicable with direct-acting antivirals (DAAs).

DAAs are molecules that work at different stages of the HCV lifecycle, targeting and inhibiting specific nonstructural proteins of HCV to disrupt viral replication and infection [Pockros 2018]. The classes of DAAs are defined by their mechanism of action and therapeutic target.

Current* direct-acting antivirals (DAAs) for treatment of HCV:

- Protease inhibitors (-previrs): Glecaprevir, voxilaprevir.
- NS5A inhibitors (-asvirs): Ledipasvir, velpatasvir, pibrentasvir.
- NS5B nucleoside polymerase inhibitor (-buvir): Sofosbuvir.

*As of August 2020, the following DAAs are no longer used in the United States: Boceprevir, daclatasvir, dasabuvir, elbasvir, grazoprevir, ombitasvir, paritaprevir, simeprevir, and telaprevir.

Goals of Treatment and DAA Regimen Choice

The goal of treatment in patients with chronic HCV infection is to attain a virologic cure, as evidenced by an SVR, in order to reduce all-cause mortality and liver-related complications, including end-stage liver disease, hepatocellular carcinoma (HCC), and the morbidity and mortality associated with the extrahepatic manifestation of chronic HCV infection. With the significant advances in treatment, all patients with chronic HCV infection, regardless of fibrosis stage, are considered candidates for antiviral therapy [van der Meer, et al. 2012; Simmons, et al. 2015; Smith-Palmer, et al. 2015].

This guideline includes recommendations for treating patients with chronic HCV infection, with consideration of individual characteristics, such as viral genotype, presence of cirrhosis, and previous treatment history. There are several options for treatment in each category, and no single regimen in any given category is prioritized or recommended over another. Regimens are listed alphabetically. The choice of treatment is based on specific individual patient factors, such as concomitant medical conditions, potential drug-drug interactions, and cost/coverage.

→ KEY POINTS

- Clinicians can increase their patients' ability to understand treatment-related information and to participate in decision-making if they communicate with language that is clear, easily understood, jargon-free, and culturally sensitive.
- Patient preferences are central to all treatment decisions.

Considerations

RECOMMENDATIONS

Considerations in HCV Treatment

- Clinicians should assess creatinine clearance before initiating antiviral therapy. (A1)
- Clinicians new to HCV treatment should consult a liver disease or experienced viral hepatitis specialist when treating patients who:
 - Have severe renal impairment (creatinine clearance <30 mL/min) and/or are undergoing hemodialysis. (A3)
 - Require retreatment after treatment failure of any DAA regimen. (B3)

RECOMMENDATIONS

○ See the *Regimens for Retreatment After DAA Failure* section of this guideline.

- Clinicians should prescribe ribavirin (RBV) with caution for patients with a creatinine clearance <50 mL/min. (A1)
 - If prescribed, a reduced dose of 200 mg per day is required.
 - Non-RBV-containing regimens can be prescribed without dose adjustments for patients with creatinine clearance ≥30 mL/min.

Contraindications

- Clinicians should not prescribe RBV in treatment of the following patients:
 - Female or male patients planning conception within 6 months of the last dose of RBV. (A2)
 - Male patients who have pregnant partners. (A2)

→ KEY POINT

- Sex, age, viral load levels, substance use disorders, mental health disorders, pill burden, and HIV coinfection are not considerations in selecting HCV treatment regimens. The most suitable regimen for any individual patient depends on the patient's preference and the clinician's assessment of comorbidities, such as chronic kidney disease, potential drug-drug interactions with the patient's current prescription and over-the-counter medications (see the *Drug-Drug Interactions* section of this guideline); medication tolerability and adverse event profile; and duration of treatment. Sex, age, viral load levels, substance use disorders, mental health disorders, pill burden, and HIV coinfection are not considerations in selecting HCV treatment regimens.

Selection of a treatment regimen for patients with chronic HCV infection is based on viral genotype, the presence of cirrhosis, treatment history (treatment-naïve vs -experienced), the potential for *drug-drug interactions*, and other specific considerations, noted previously, such as the presence of cardiac disease, renal function, and choice of contraception.

→ KEY POINT

- Cardiac disease and other comorbidities may affect a patient's ability to tolerate RBV-induced anemia and should be considered before initiating an RBV-containing regimen.

Renal Impairment

For patients with a creatinine clearance <50 mL/min, RBV should be used with caution; if used, a reduced dose of 200 mg per day is recommended [FDA 2011]. No dose adjustment of ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, or glecaprevir/pibrentasvir is required in patients with mild, moderate, or severe renal impairment [FDA 2015b, 2016b, 2017, 2020].

Resistance Testing

At present, testing for resistance-associated variants (RAV) is not universally recommended. RAVs are also referred to as resistance analysis populations (RAP) and resistance-associated substitutions (RAS). RAV testing is performed when retreatment is considered for patients for whom treatment with a DAA regimen containing an NS5A or NS5B inhibitor has failed (see the *Regimens for Retreatment After DAA Failure* section of this guideline).

NS5A testing is recommended in patients with HCV genotype 3 who are being considered for 12 weeks of sofosbuvir/velpatasvir and are either treatment-naïve and have cirrhosis, or are treatment-experienced and do not have cirrhosis (see the *Genotype 3* section of this guideline) [Foster, et al. 2015a; Hezode, et al. 2018]. If the Y93H RAS is present, weight-based ribavirin should be added to the regimen or another regimen should be selected.

- For more information on HCV resistance, please see the *AASLD/IDSA HCV Resistance Primer*.

Pregnancy and Contraception

For all women and men planning conception within 6 months of treatment, use of RBV is contraindicated due to the teratogenic effects of the drug [FDA 2011]. Before prescribing an RBV-containing regimen for an individual of childbearing potential, a negative pregnancy test is required immediately before initiation of therapy and 2 forms of contraception or abstinence are advised during therapy and for 6 months after. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of therapy in female patients and in female partners of male patients who are taking RBV.

Recommended DAA Regimens for Adults

All regimens listed in this guideline were available as of August 2020.

These recommendations on treatment of chronic HCV in adults aged 18 and older were developed by the NYSDOH AI HCV Guideline Committee to guide primary care providers and other clinicians in NYS in treating patients with chronic HCV infection. Treatment guidelines for patients aged 17 years and younger are available at the *American Association of the Study of Liver Diseases/Infectious Disease Society of America (AASLD/IDSA) HCV Guidance*.

HIV/HCV coinfection: Recommendations for treatment of chronic HCV infection in patients with HIV are the same as those for patients who do not have HIV, but attention to potential drug-drug interactions between direct-acting antivirals (DAAs) and antiretrovirals is needed (see the *Drug-Drug Interactions > Drug-Drug Interactions Between DAAs and ARVs* section of this guideline). Clinicians are encouraged to consult a specialist in treatment of liver disease or viral hepatitis and an *experienced HIV care provider* as needed.

→ KEY POINTS: CHOOSING AN ANTI-HCV TREATMENT REGIMEN

- Treatment regimen recommendations are organized according to HCV genotype and subtype, the presence or absence of compensated cirrhosis, and HCV treatment history.
- The recommended regimens within each list are in alphabetical order, not in order of preference.
- No single regimen is recommended over another within each list of options; data on direct comparisons of treatment regimens have not been published.
- The choice of regimen should be based on individual pretreatment assessment findings, the general considerations detailed above, and insurance coverage.
- The regimens recommended for retreatment are for patients who have been treated previously with DAAs or pegylated interferon (PEG-IFN) plus ribavirin (RBV).

Undetectable or indeterminate genotype: Rarely, laboratories report the results of an HCV genotype test as “undetectable” or “indeterminate” for a patient with detectable HCV viral load [Germer, et al. 2011]. These HCV genotype reports are consistent with active HCV infection. The laboratory may be able to clarify the specific reason for the result; for example, an “undetectable” result may be due to the lower sensitivity of the genotype test compared with the HCV RNA test or a level of HCV RNA that is too low to perform the assay for genotype.

Data on treating patients with HCV who have an undetectable or indeterminate genotype are limited. All patients should be assessed for the degree of fibrosis. In terms of HCV treatment, one option is to repeat the genotype and HCV viral load tests in 3 months and then make a determination regarding the initiation of therapy. A second option is to offer these patients DAA therapy with a pangenotypic regimen such as glecaprevir/pibrentasvir or sofosbuvir/velpatasvir at the same dose and duration recommended for treatment-naïve patients with genotype 3 HCV infection, taking into consideration the degree of fibrosis (see *Tables 19 and 20 > Genotype 3* in this guideline). At present, there are not sufficient data to offer ribavirin to these patients.

Recommended oral DAAs are listed in *Table 7*, below. All regimens listed in drug regimen tables for all HCV genotypes refer to oral medications.

Table 7: Recommended Oral Direct-Acting Antiviral Drugs and Drug Regimens for Adults [a] With Chronic HCV (August 2020)

Drug/Combination	Trade Name
Glecaprevir/pibrentasvir	Mavyret [b]
Ledipasvir/sofosbuvir	Multiple brands [b]
Sofosbuvir/velpatasvir	Multiple brands
Sofosbuvir/velpatasvir/voxilaprevir	Vosevi

a. Aged 18 years and older.
b. Glecaprevir/pibrentasvir (GLE/PIB; Mavyret) is indicated for individuals 12 years of age and older or weighing ≥ 45 kg with chronic HCV genotype 1, 2, 3, 4, 5, or 6; ledipasvir/sofosbuvir (LED/SOF; multiple brands) is indicated for individuals 3 years of age and older with chronic HCV genotype 1, 4, 5, or 6. See prescribing information for full indications and information.

Genotype 1a

RECOMMENDATIONS

- Based on the results of the pretreatment assessment, clinicians should choose from among the treatment regimens for patients with HCV genotype 1a listed in Tables 8 through 11, below.
- If a regimen with weight-based ribavirin (RBV) is chosen, clinicians should dose as follows: (A1)
 - <75 kg: RBV 400 mg once daily plus 600 mg once daily (total daily dose: 1000 mg)
 - ≥ 75 kg: RBV 600 mg twice daily (total daily dose: 1200 mg)

Recommended regimens: The recommendations are organized by previous HCV treatment (treatment-naïve or treatment-experienced) and whether or not the patient has compensated cirrhosis. All drugs in the recommended regimens below are oral medications.

Treatment interruption and adherence: Before initiating treatment with a DAA regimen, it is essential to develop an adherence plan with the patient, address potential barriers, and make support available if it is needed. Clinicians are advised to consult an HCV treatment specialist if a patient’s DAA treatment is interrupted.

Drug names: Use of a “/” between two drug names indicates a co-formulated tablet. Use of the word “plus” indicates two separate drugs.

Rating of regimens: All regimen choices listed below are rated A1 (strong recommendation, with high quality evidence from at least 1 randomized trial with clinical outcomes and/or validated laboratory endpoints) except where indicated.

Table 8: Genotype 1a • Treatment-naïve • No cirrhosis

Choose 1 of the following regimens (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Gane E, et al. 2016a; Forns, et al. 2017; Zeuzem, et al. 2018; Brown, et al. 2019; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Feld, et al. 2015; Lawitz, et al. 2015; Sulkowski M, et al. 2015] (SOF/VEL; multiple brands)	12 weeks
For patients who are non-black, HIV-uninfected, and have HCV RNA <6 million copies/mL (Rating: A2): Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Kowdley, et al. 2014; FDA 2015b; Terrault, et al. 2016; Kowdley, et al. 2017] (LED/SOF; multiple brands)	8 weeks
For patients who are black, HIV-infected, or have HCV RNA ≥ 6 million copies/mL: Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Kowdley, et al. 2014; FDA 2015b; Terrault, et al. 2016; Kowdley, et al. 2017] (LED/SOF; multiple brands)	12 weeks

Table 9: Genotype 1a • Treatment-naive • Compensated cirrhosis	
Choose 1 of the following regimens (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Gane E, et al. 2016a; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Bourliere, et al. 2015; Reddy, et al. 2015] (LED/SOF; multiple brands)	12 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Feld, et al. 2015] (SOF/VEL; multiple brands)	12 weeks

Table 10: Genotype 1a • Prior failure with PEG-IFN* • No cirrhosis	
Choose 1 of the following regimens for <i>retreatment</i> (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Kwo, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Afdhal, et al. 2014] (LED/SOF; multiple brands)	12 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Feld, et al. 2015] (SOF/VEL; multiple brands)	12 weeks
*Pegylated interferon plus ribavirin.	

Table 11: Genotype 1a • Prior failure with PEG-IFN plus RBV* • Compensated cirrhosis	
Choose 1 of the following regimens for <i>retreatment</i> (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Kwo, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	12 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Bourliere, et al. 2014; Bourliere, et al. 2015] (LED/SOF; multiple brands)	24 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg once daily plus weight-based ribavirin twice daily [Bourliere, et al. 2014; Bourliere, et al. 2015] (LED/SOF; multiple brands plus RBV; Copegus)	12 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Feld, et al. 2015] (SOF/VEL; multiple brands)	12 weeks
*Pegylated interferon plus ribavirin.	

Genotype 1b

RECOMMENDATIONS
<ul style="list-style-type: none"> Based on the results of the pretreatment assessment, clinicians should choose from among the treatment regimens for patients with HCV genotype 1b listed in <i>Tables 12 through 15</i>, below. If a regimen with weight-based ribavirin (RBV) is chosen, clinicians should dose as follows: (A1) <ul style="list-style-type: none"> <75 kg: RBV 400 mg once daily plus 600 mg once daily (total daily dose: 1000 mg) ≥75 kg: RBV 600 mg twice daily (total daily dose: 1200 mg)

Recommended regimens: The recommendations are organized by previous HCV treatment (treatment-naive or treatment-experienced) and whether or not the patient has compensated cirrhosis. All drugs in the recommended regimens below are oral medications.

Treatment interruption and adherence: Before initiating treatment with a DAA regimen, it is essential to develop an adherence plan with the patient, address potential barriers, and make support available if it is needed. Clinicians are advised to consult an HCV treatment specialist if a patient’s DAA treatment is interrupted.

Drug names: Use of a “/” between two drug names indicates a co-formulated tablet. Use of the word “plus” indicates two separate drugs.

Rating of regimens: All regimen choices listed are rated A1 (strong recommendation, with high-quality evidence from at least 1 randomized trial with clinical outcomes and/or validated laboratory endpoints) except where indicated.

Table 12: Genotype 1b • Treatment-naive • No cirrhosis	
Choose 1 of the following regimens (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Kwo, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Feld, et al. 2015] (SOF/VEL; multiple brands)	12 weeks
For patients who are non-black, HIV-uninfected, and have HCV RNA <6 million copies/mL (Rating: A2): Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Kowdley, et al. 2014; FDA 2015b; Terrault, et al. 2016; Kowdley, et al. 2017] (LED/SOF; multiple brands)	8 weeks
For patients who are black, HIV-infected, or have HCV RNA ≥6 million copies/mL: Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Kowdley, et al. 2014; FDA 2015b; Terrault, et al. 2016; Kowdley, et al. 2017] (LED/SOF; multiple brands)	12 weeks

Table 13: Genotype 1b • Treatment-naive • Compensated cirrhosis	
Choose 1 of the following regimens (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Forns, et al. 2017; Zeuzem, et al. 2018; Brown, et al. 2019; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Bourliere, et al. 2015; Reddy, et al. 2015] (LED/SOF; multiple brands)	12 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Feld, et al. 2015] (SOF/VEL; multiple brands)	12 weeks

Table 14: Genotype 1b • Prior failure with PEG-IFN plus RBV* • No cirrhosis	
Choose 1 of the following regimens for retreatment (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Poordad, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Afdhal, et al. 2014; Lawitz, et al. 2014] (LED/SOF; multiple brands)	12 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Feld, et al. 2015] (SOF/VEL; multiple brands)	12 weeks
*Pegylated interferon plus ribavirin.	

Table 15: Genotype 1b • Prior failure with PEG-IFN plus RBV* • Compensated cirrhosis	
Choose 1 of the following regimens for retreatment (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily [FDA 2020] (GLE/PIB; Mavyret)	12 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Bourliere, et al. 2014; Bourliere, et al. 2015] (LED/SOF; multiple brands)	24 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg once daily plus weight-based ribavirin twice daily [Bourliere, et al. 2014; Bourliere, et al. 2015] (LED/SOF; multiple brands plus RBV; Copegus)	12 weeks

Table 15: Genotype 1b • Prior failure with PEG-IFN plus RBV* • Compensated cirrhosis	
Choose 1 of the following regimens for <i>retreatment</i> (A1):	Duration
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Feld, et al. 2015] (SOF/VEL; multiple brands)	12 weeks
*Pegylated interferon plus ribavirin.	

Genotype 2

<input checked="" type="checkbox"/> RECOMMENDATION
<ul style="list-style-type: none"> Based on the results of the pretreatment assessment, clinicians should choose from among the treatment regimens for patients with HCV genotype 2 listed in <i>Tables 16 through 18</i>, below.

Recommended regimens: The recommendations are organized by previous HCV treatment (treatment-naïve or treatment-experienced) and whether or not the patient has compensated cirrhosis. All drugs in the recommended regimens below are oral medications.

Treatment interruption and adherence: Before initiating treatment with a DAA regimen, it is essential to develop an adherence plan with the patient, address potential barriers, and make support available if it is needed. Clinicians are advised to consult an HCV treatment specialist if a patient’s DAA treatment is interrupted.

Drug names: Use of a “/” between two drug names indicates a co-formulated tablet. Use of the word “plus” indicates two separate drugs.

Rating of regimens: All regimen choices listed below are rated A1 (strong recommendation, with high-quality evidence from at least 1 randomized trial with clinical outcomes and/or validated laboratory endpoints).

Table 16: Genotype 2 • Treatment-naïve • No cirrhosis	
Choose 1 of the following regimens (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Kwo, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Foster, et al. 2015a] (SOF/VEL; multiple brands)	12 weeks

Table 17: Genotype 2 • Treatment-naïve • Compensated cirrhosis	
Choose 1 of the following regimens (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Forns, et al. 2017; Asselah, et al. 2018; Brown, et al. 2019; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Foster, et al. 2015a] (SOF/VEL; multiple brands)	12 weeks

Table 18: Genotype 2 • Prior failure with PEG-IFN plus RBV* • No cirrhosis OR compensated cirrhosis	
Choose 1 of the following regimens for <i>retreatment</i> (A1):	Duration
No cirrhosis: Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Kwo, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Compensated cirrhosis: Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Kwo, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	12 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Foster, et al. 2015a] (SOF/VEL; multiple brands)	12 weeks

Table 18: Genotype 2 • Prior failure with PEG-IFN plus RBV* • No cirrhosis OR compensated cirrhosis

Choose 1 of the following regimens for <i>retreatment</i> (A1):	Duration
*Pegylated interferon plus ribavirin.	

Genotype 3

RECOMMENDATION

- Based on the results of the [pretreatment assessment](#), clinicians should choose from among the treatment regimens for patients with HCV genotype 3 listed in *Tables 19 through 22*, below.
- Clinicians should order NS5A testing in patients with HCV genotype 3 who are being considered for 12 weeks of sofosbuvir/velpatasvir and are either treatment-naïve and have cirrhosis, or are treatment-experienced and do not have cirrhosis. (A1)
 - If the Y93H resistance-associated substitution (RAS) is present, weight-based ribavirin should be added to the regimen or another regimen should be selected. (A1)

Recommended regimens: The recommendations are organized by previous HCV treatment (treatment-naïve or treatment-experienced) and whether or not the patient has compensated cirrhosis. All drugs in the recommended regimens below are oral medications.

Treatment interruption and adherence: Before initiating treatment with a DAA regimen, it is essential to develop an adherence plan with the patient, address potential barriers, and make support available if it is needed. Clinicians are advised to consult an HCV treatment specialist if a patient’s DAA treatment is interrupted.

Drug names: Use of a “/” between two drug names indicates a co-formulated tablet. Use of the word “plus” indicates two separate drugs.

Rating of regimens: All regimen choices listed below are rated A1 (strong recommendation, with high-quality evidence from at least 1 randomized trial with clinical outcomes and/or validated laboratory endpoints).

Sustained virologic response (SVR) rate: SVR rates are listed from studies of patients with HCV genotype 3 (reference numbers are cited in each table). These data have been included only for genotype 3 because, to date, achievement of an SVR in these patients, especially those with cirrhosis, has proven to be more difficult than it is in patients with other HCV genotypes.

Table 19: Genotype 3 • Treatment-naïve • No cirrhosis

Choose 1 of the following regimens (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily (SVR, 83% to 94%) [FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Sofosbuvir 400/velpatasvir 100 mg once daily (SVR, 98%) [Foster, et al. 2015b] (SOF/VEL; multiple brands)	12 weeks

Table 20: Genotype 3 • Treatment-naïve • Compensated cirrhosis

Choose 1 of the following regimens (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily (SVR, 98%) [Zeuzem, et al. 2018; Brown, et al. 2019; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily* (SVR, 93%) [Foster, et al. 2015b] (SOF/VEL; multiple brands)	12 weeks
*NS5A testing is recommended before initiating treatment. If the Y93H RAS is present, weight-based ribavirin should be added or an alternate regimen should be selected.	

Table 21: Genotype 3 • Prior failure with Peg-IFN plus RBV* • No cirrhosis	
Choose 1 of the following regimens for retreatment (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily (SVR, 98%) [FDA 2020] (GLE/PIB; Mavyret)	16 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily† (SVR, 91%) [Foster, et al. 2015b] (SOF/VEL; multiple brands)	12 weeks
*Pegylated interferon plus ribavirin. †NS5A testing is recommended before initiating treatment. If the Y93H RAS is present, weight-based ribavirin should be added or an alternate regimen should be selected.	

Table 22: Genotype 3 • Prior failure with PEG-IFN plus RBV* • Compensated cirrhosis	
Choose 1 of the following regimens for retreatment (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily (SVR, 98%) [FDA 2020] (GLE/PIB; Mavyret)	16 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily† (SVR, 89%) [Foster, et al. 2015a] (SOF/VEL; multiple brands)	12 weeks
*Pegylated interferon plus ribavirin. †NS5A testing is recommended before initiating treatment. If the Y93H RAS is present, weight-based ribavirin should be added or an alternate regimen should be selected.	

Genotype 4

RECOMMENDATIONS
<ul style="list-style-type: none"> Based on the results of the pretreatment assessment, clinicians should choose from among the treatment regimens for patients with HCV genotype 4 listed in <i>Tables 23 and 24</i>, below. If a regimen with weight-based ribavirin (RBV) is chosen, clinicians should dose as follows: (A1) <ul style="list-style-type: none"> <75 kg: RBV 400 mg once daily plus 600 mg once daily (total daily dose: 1000 mg) ≥75 kg: RBV 600 mg twice daily (total daily dose: 1200 mg)

Recommended regimens: The recommendations are organized by previous HCV treatment (treatment-naïve or treatment-experienced) and whether or not the patient has compensated cirrhosis. All drugs in the recommended regimens below are oral medications.

Treatment interruption and adherence: Before initiating treatment with a DAA regimen, it is essential to develop an adherence plan with the patient, address potential barriers, and make support available if it is needed. Clinicians are advised to consult an HCV treatment specialist if a patient’s DAA treatment is interrupted.

Drug names: Use of a “/” between two drug names indicates a co-formulated tablet. Use of the word “plus” indicates two separate drugs.

Rating of regimens: All regimen choices listed below are rated A1 (strong recommendation, with high-quality evidence from at least 1 randomized trial with clinical outcomes and/or validated laboratory endpoints).

Table 23: Genotype 4 • Treatment-naïve • No cirrhosis OR compensated cirrhosis	
Choose 1 of the following regimens (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Forns, et al. 2017; Kwo, et al. 2017; Asselah, et al. 2018; Brown, et al. 2019; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Kohli, et al. 2015; Abergel, et al. 2016] (LED/SOF; multiple brands)	12 weeks

Table 23: Genotype 4 • Treatment-naïve • No cirrhosis OR compensated cirrhosis	
Choose 1 of the following regimens (A1):	Duration
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Feld, et al. 2015] (SOF/VEL; multiple brands)	12 weeks

Table 24: Genotype 4 • Prior failure with Peg-IFN plus RBV* • No cirrhosis OR compensated cirrhosis	
Choose 1 of the following regimens for <i>retreatment</i> (A1):	Duration
No cirrhosis: Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Kwo, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Compensated cirrhosis: Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Kwo, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	12 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Kohli, et al. 2015] (LED/SOF; multiple brands)	12 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Feld, et al. 2015] (SOF/VEL; multiple brands)	12 weeks
*Pegylated interferon plus ribavirin.	

Genotype 5

<input checked="" type="checkbox"/> RECOMMENDATION
<ul style="list-style-type: none"> Based on the results of the pretreatment assessment, clinicians should choose from among the treatment regimens for patients with HCV genotype 5 listed in <i>Tables 25 and 26</i>, below.

Recommended regimens: The recommendations are organized by previous HCV treatment (treatment-naïve or treatment-experienced) and whether or not the patient has compensated cirrhosis. All drugs in the recommended regimens below are oral medications.

Treatment interruption and adherence: Before initiating treatment with a DAA regimen, it is essential to develop an adherence plan with the patient, address potential barriers, and make support available if it is needed. Clinicians are advised to consult an HCV treatment specialist if a patient’s DAA treatment is interrupted.

Drug names: Use of a “/” between two drug names indicates a co-formulated tablet. Use of the word “plus” indicates two separate drugs.

Rating of regimens: All regimen choices listed below are rated A1 (strong recommendation, with high-quality evidence from at least 1 randomized trial with clinical outcomes and/or validated laboratory endpoints).

Table 25: Genotype 5 • Treatment-naïve • No cirrhosis OR compensated cirrhosis	
Choose 1 of the following regimens (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Forns, et al. 2017; Kwo, et al. 2017; Asselah, et al. 2018; Brown, et al. 2019; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Abergel, et al. 2016] (LED/SOF; multiple brands)	12 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Feld, et al. 2015] (SOF/VEL; multiple brands)	12 weeks

Table 26: Genotype 5 • Prior failure with PEG-IFN plus RBV* • No cirrhosis OR compensated cirrhosis	
Choose 1 of the following regimens for retreatment (A1):	Duration
No cirrhosis: Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Kwo, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Compensated cirrhosis: Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Kwo, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	12 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Abergel, et al. 2016] (LED/SOF; multiple brands)	12 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Feld, et al. 2015] (SOF/VEL; multiple brands)	12 weeks

*Pegylated interferon plus ribavirin.

Genotype 6

RECOMMENDATION
<ul style="list-style-type: none"> Based on the results of the pretreatment assessment, clinicians should choose from among the treatment regimens for patients with HCV genotype 6 listed in <i>Tables 27 and 28</i>, below.

Recommended regimens: The recommendations are organized by previous HCV treatment (treatment-naive or treatment-experienced) and whether or not the patient has compensated cirrhosis. All drugs in the recommended regimens below are oral medications.

Treatment interruption and adherence: Before initiating treatment with a DAA regimen, it is essential to develop an adherence plan with the patient, address potential barriers, and make support available if it is needed. Clinicians are advised to consult an HCV treatment specialist if a patient’s DAA treatment is interrupted.

Drug names: Use of a “/” between two drug names indicates a co-formulated tablet. Use of the word “plus” indicates two separate drugs.

Rating of regimens: All regimen choices listed below are rated A1 (strong recommendation, with high-quality evidence from at least 1 randomized trial with clinical outcomes and/or validated laboratory endpoints).

Table 27: Genotype 6 • Treatment-naive • No cirrhosis OR compensated cirrhosis	
Choose 1 of the following regimens (A1):	Duration
Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Forns, et al. 2017; Kwo, et al. 2017; Asselah, et al. 2018; Brown, et al. 2019; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Gane EJ, et al. 2015] (LED/SOF; multiple brands)	12 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Feld, et al. 2015] (SOF/VEL; multiple brands)	12 weeks

Table 28: Genotype 6 • Prior failure with PEG-IFN plus RBV* • No cirrhosis OR compensated cirrhosis	
Choose 1 of the following regimens for retreatment (A1):	Duration
No cirrhosis: Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Kwo, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	8 weeks
Compensated cirrhosis: Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Kwo, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	12 weeks

Table 28: Genotype 6 • Prior failure with PEG-IFN plus RBV* • No cirrhosis OR compensated cirrhosis

Choose 1 of the following regimens for <i>retreatment</i> (A1):	Duration
Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Gane EJ, et al. 2015] (LED/SOF; multiple brands)	12 weeks
Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Feld, et al. 2015] (SOF/VEL; multiple brands)	12 weeks

*Pegylated interferon plus ribavirin.

Regimens for Retreatment After DAA Failure

RECOMMENDATIONS

- Clinicians new to HCV treatment should consult a liver disease or experienced viral hepatitis specialist when retreating patients in whom prior treatment with any DAA regimen has failed. (B3) Failure is defined as detectable HCV RNA 12 weeks after the conclusion of HCV treatment.
- If a regimen with weight-based ribavirin (RBV) is chosen, clinicians should dose as follows: (A1)
 - <75 kg: RBV 400 mg once daily plus 600 mg once daily (total daily dose: 1000 mg).
 - ≥75 kg: RBV 600 mg twice daily (total daily dose: 1200 mg).

Treatment regimens are now approved and available for patients with HCV genotypes 1, 2, 3, 4, 5, and 6 whose previous treatment with direct-acting antivirals (DAAs) failed (see *Tables 29 to 32*). Recommendations for treatment dose and duration are based on previous exposure to either NS3/4A protease inhibitors or NS5A polymerase inhibitors. None of the regimens approved for retreatment after DAA treatment failure requires resistance testing or the addition of ribavirin.

Regimens for Use After DAA Treatment Failure

All drugs in the recommended regimens below are oral medications. In addition to the patient’s previous treatment regimen(s), the presence of cirrhosis and patient preferences influence the choice of regimen.

Treatment interruption and adherence: Before initiating treatment with a DAA regimen, it is essential to develop an adherence plan with the patient, address potential barriers, and make support available if it is needed. Clinicians are advised to consult an HCV treatment specialist if a patient’s DAA treatment is interrupted.

Drug names: Use of a “/” between two drug names indicates a co-formulated tablet. Use of the word “plus” indicates two separate drugs.

Rating of regimens: All regimen choices listed below are rated A1 (strong recommendation, with high quality evidence from at least 1 randomized trial with clinical outcomes and/or validated laboratory endpoints).

Table 29: Prior failure with an NS5A inhibitor*-containing regimen

Choose 1 of the following regimens for <i>retreatment</i> (A1):			
Genotype	Cirrhosis Status	Regimens	Duration
1	No cirrhosis; compensated cirrhosis	No previous treatment with NS3/4A protease inhibitors[§]: Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Poordad, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	16 weeks
3	Compensated cirrhosis	Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg once daily plus weight-based ribavirin twice daily [Bourliere, et al. 2017] (SOF/VEL/VOX; Vosevi plus RBV; Copegus)	12 weeks

Table 29: Prior failure with an NS5A inhibitor*-containing regimen			
Choose 1 of the following regimens for <i>retreatment</i> (A1):			
Genotype	Cirrhosis Status	Regimens	Duration
1,2,3,4,5,6	No cirrhosis; compensated cirrhosis	Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg once daily [Gane EJ, et al. 2016b; Bourliere, et al. 2017] (SOF/VEL/VOX; Vosevi)	12 weeks
*NS5A polymerase inhibitors: daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, and velpatasvir §NS3/4A protease inhibitors: glecaprevir, grazoprevir, paritaprevir, and voxilaprevir			

Table 30: Prior failure with an NS3/4A inhibitor*-containing regimen that <i>did not contain</i> an NS5A inhibitor[§] • No cirrhosis OR compensated cirrhosis			
Choose 1 of the following regimens for <i>retreatment</i> (A1):			
Genotype	Cirrhosis Status	Regimens	Duration
1	No cirrhosis; compensated cirrhosis	Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Poordad, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	12 weeks
	No cirrhosis; compensated cirrhosis	Sofosbuvir 400 mg/velpatasvir 100 mg once daily [Bourliere, et al. 2017] (SOF/VEL; multiple brands)	12 weeks
	No cirrhosis	Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Osinusi, et al. 2014] (LED/SOF; multiple brands)	12 weeks
	Compensated cirrhosis	Ledipasvir 90 mg/sofosbuvir 400 mg once daily plus weight-based ribavirin twice daily [Wyles, et al. 2015] (LED/SOF; multiple brands plus RBV; Copegus)	12 weeks
	Compensated cirrhosis	Ledipasvir 90 mg/sofosbuvir 400 mg once daily [Bourliere, et al. 2014; Bourliere, et al. 2015] (LED/SOF; multiple brands)	24 weeks
1,2,3,4,5,6	No cirrhosis; compensated cirrhosis	Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg once daily [Gane E, et al. 2016a; Bourliere, et al. 2017] (SOF/VEL/VOX; Vosevi)	12 weeks
*NS3/4A protease inhibitors: glecaprevir, grazoprevir, paritaprevir, and voxilaprevir §NS5A polymerase inhibitors: daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, and velpatasvir			

Table 31: Failure with a sofosbuvir-containing regimen that <i>did not contain</i> an NS5A inhibitor* • No cirrhosis OR compensated cirrhosis			
Choose 1 of the following regimens for <i>retreatment</i> (A1):			
Genotype	Cirrhosis Status	Regimens	Duration
1	No cirrhosis	No previous treatment with NS3/4A protease inhibitors[§]: Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Poordad, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	12 weeks
1	Compensated cirrhosis	No previous treatment with NS3/4A protease inhibitors[§]: Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Poordad, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	16 weeks
1,2,3,4,5,6	No cirrhosis; compensated cirrhosis	Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg once daily [Gane EJ, et al. 2016b] (SOF/VEL/VOX; Vosevi)	12 weeks

Table 31: Failure with a sofosbuvir-containing regimen that *did not contain* an NS5A inhibitor* • No cirrhosis OR compensated cirrhosis

*NS5A polymerase inhibitors: daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, and velpatasvir
 §NS3/4A protease inhibitors: glecaprevir, grazoprevir, paritaprevir, and voxilaprevir

Table 32: Failure with PEG-IFN plus RBV* and sofosbuvir • No cirrhosis OR compensated cirrhosis

Choose 1 of the following regimens for *retreatment* (A1):

Genotype	Cirrhosis Status	Regimens	Duration
1,2,4,5,6	No cirrhosis; compensated cirrhosis	Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Poordad, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	12 weeks
3		Glecaprevir 300 mg/pibrentasvir 120 mg once daily [Poordad, et al. 2017; FDA 2020] (GLE/PIB; Mavyret)	16 weeks
1,2,3,4,5,6		Sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg once daily [Gane EJ, et al. 2016b; Bourliere, et al. 2017] (SOF/VEL/VOX; Vosevi)	12 weeks

*Pegylated interferon plus ribavirin

Monitoring During DAA Treatment

RECOMMENDATIONS

Monitoring of Patients Taking RBV

- While patients are taking ribavirin (RBV), clinicians should perform hemoglobin testing at weeks 2 and 4 of treatment and every 4 weeks thereafter until therapy is complete. (A1)

Monitoring for HBV Reactivation

- In patients who are hepatitis B virus surface antigen (HBsAg) positive and have no detectable HBV DNA, clinicians should monitor for HBV reactivation by performing aspartate aminotransferase (AST), ALT, and HBV DNA tests every 4 weeks during HCV treatment. (A3)
- Clinicians new to HCV treatment should consult a liver disease or experienced viral hepatitis specialist for further evaluation of patients who develop detectable HBV DNA. (A3)

Pregnancy

- If an individual becomes pregnant during therapy with a regimen containing RBV, clinicians should stop the RBV. (A1)
- If an individual becomes pregnant during therapy with any DAA regimen, clinicians should discuss the benefits and risks of using DAAs during pregnancy. (A3)

The adverse events associated with DAA treatment are listed in *Table 33*, below, and most are manageable. Patients who are taking RBV and experience insomnia may need to adjust the timing of the dose to earlier in the afternoon to avoid any sleep disruption.

→ KEY POINT

- HCV RNA testing is needed only at baseline and at least 12 weeks after treatment is finished; HCV RNA testing is not necessary during or at the completion of treatment.

Transient transaminase and bilirubin elevations may occur during the normal course of DAA therapy, but severe laboratory value elevations and rare hepatic decompensation have been reported with protease inhibitors during the treatment of patients with cirrhosis [FDA 2016c; Hayashi, et al. 2016; FDA 2017, 2020]. Therefore, if at 4 weeks after treatment is initiated, the ALT level is elevated above baseline, testing should be repeated and levels monitored according to the drug’s prescribing information [FDA 2016c; Hayashi, et al. 2016; FDA 2017, 2020].

HBV reactivation and HBV-related hepatic flares have occurred both during and after DAA therapy in patients who were not receiving HBV treatment [Collins, et al. 2015; Ende, et al. 2015; Sulkowski MS, et al. 2016; Wang C, et al. 2017]. The U.S. Food and Drug Administration (FDA) has issued a [drug safety warning](#) regarding these risks.

Table 33: Adverse Events Associated with DAAs

Drug or Combination (brand name)	Most Common Adverse Reactions (proportion observed)
Glecaprevir/pibrentasvir (GLE/PIB; Mavyret)	<ul style="list-style-type: none"> • Headache and fatigue (>10%)
Ledipasvir/sofosbuvir (LED/SOF; multiple brands)	<ul style="list-style-type: none"> • Asthenia, headache, and fatigue (≥10%)
Ribavirin (Copegus)	<ul style="list-style-type: none"> • Fatigue/asthenia, pyrexia, myalgia, and headache in adults receiving combination therapy (>40%)
Sofosbuvir/velpatasvir (SOF/VEL; multiple brands)	<ul style="list-style-type: none"> • With velpatasvir/sofosbuvir: headache and fatigue (≥10%, all grades) • With velpatasvir/sofosbuvir and ribavirin in patients decompensated cirrhosis: fatigue, anemia, nausea, headache, insomnia, and diarrhea (≥10%, all grades)
Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX; Vosevi)	<ul style="list-style-type: none"> • Headache, fatigue, diarrhea, and nausea (≥10%)

Sources: [FDA 2011, 2015b, 2016b, 2016c; Hayashi, et al. 2016; FDA 2017, 2020]

Drug-Drug Interactions

The charts contained in this section are meant to provide guidance on significant interactions between DAAs and common primary care medications. While these guidelines can be helpful, they are not a substitute for sound clinical judgment and practice.

In some cases, the medications listed below are *contraindicated* in the U.S. Food and Drug Administration (FDA) labeling for the medication, or the label may state elsewhere that co-administration is not recommended. For some, the recommendation may be to “Avoid Co-administration,” but in some clinical situations it may be necessary to use the medications concurrently. When this is the case, clinicians are encouraged to consult additional references or a liver disease specialist for additional guidance.

For more information on drug-drug interactions in patients with HIV/HCV coinfection see the [Drug-Drug Interactions Between DAAs and ARVs](#) section of this guideline.

→ KEY POINT

- Although significant interactions associated with the use of direct-acting antivirals (DAAs) and drugs used commonly in the treatment of substance use disorders are unlikely, care providers should always monitor for excess sedation when making alterations to a patient’s drug therapy while he/she is taking methadone, buprenorphine, naltrexone, and naloxone.

The links below open pages with tables for each of the following drugs:

- [Glecaprevir/Pibrentasvir](#)
- [Ledipasvir/Sofosbuvir](#)
- [Sofosbuvir/Velpatasvir](#)
- [Sofosbuvir/Velpatasvir/Voxilaprevir](#)

Box 2: Online Resources for Identifying Drug-Drug Interactions between DAAs and Common Medications

- [American Association for the Study of Liver Diseases \(AASLD\)/Infectious Diseases Society of America \(IDSA\)](#): Includes charts listing all DAAs
- [University of Liverpool HEP Drug Interactions](#): Provides guidance on managing HCV drug interactions, especially in those coinfecting with HIV; may not include all medications available in the United States

Note: As of May 2019, the following DAAs are no longer used in the United States: Boceprevir, daclatasvir, dasabuvir, elbasvir, grazoprevir, ombitasvir, paritaprevir, simeprevir, and telaprevir.

Glecaprevir/Pibrentasvir

Table 34: Glecaprevir/Pibrentasvir (Mavyret) Drug-Drug Interactions

Avoid co-administration; see clinical comments

Class (medications)	Clinical Comments
Anticonvulsants (carbamazepine, phenobarbital, phenytoin)	<ul style="list-style-type: none"> • Carbamazepine: Significant decrease in glecaprevir/pibrentasvir levels expected • Phenobarbital, phenytoin: Significant decrease in glecaprevir/pibrentasvir levels possible
Antimycobacterial (rifampin)	<ul style="list-style-type: none"> • Significant decrease in glecaprevir/pibrentasvir levels expected
Ethinyl estradiol	<ul style="list-style-type: none"> • Increased risk of ALT elevations
Herbal therapy (St. John’s Wort)	<ul style="list-style-type: none"> • Decreased glecaprevir/pibrentasvir levels expected
HIV medications (efavirenz, atazanavir, darunavir, lopinavir, saquinavir, tipranavir)	<ul style="list-style-type: none"> • Efavirenz: Significant decrease in glecaprevir/pibrentasvir levels expected • Atazanavir: Significant increase in glecaprevir/pibrentasvir levels expected; increased ALT elevations • Darunavir, lopinavir/ritonavir, other HIV protease inhibitors: Significant increase in glecaprevir/pibrentasvir levels expected
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	<ul style="list-style-type: none"> • Increased levels of atorvastatin, lovastatin, and simvastatin expected; do not co-administer • See note below regarding use of alternative statins

Co-administration possible; see clinical comments

Class (medications)	Clinical Comments
Antiarrhythmic (digoxin)	<ul style="list-style-type: none"> • Increased digoxin levels likely; reduce digoxin dosage 50% • Measure serum digoxin level prior to initiating therapy with glecaprevir/pibrentasvir
Anticoagulant (dabigatran etexilate)	<ul style="list-style-type: none"> • Refer to dabigatran prescribing information; follow dosage recommendations for concurrent use with P-glycoprotein inhibitors
HMG-CoA reductase inhibitors (fluvastatin, pitavastatin, pravastatin, rosuvastatin)	<ul style="list-style-type: none"> • Fluvastatin, pitavastatin: Increased statin levels likely; use lowest statin dosage and monitor for adverse events (e.g., myopathy) • Pravastatin: Increased statin level likely; reduce pravastatin dosage by 50% prior to initiating therapy with glecaprevir/pibrentasvir • Rosuvastatin: Increased statin level likely; do not exceed rosuvastatin 10 mg daily when combined with glecaprevir/pibrentasvir
Immunosuppressant (cyclosporine)	<ul style="list-style-type: none"> • Increased levels of glecaprevir/pibrentasvir expected; do not co-administer in patients requiring cyclosporine doses >100 mg daily

Table 34: Glecaprevir/Pibrentasvir (Mavyret) Drug-Drug Interactions

Source: FDA. Mavyret (glecaprevir and pibrentasvir) tablets, for oral use.
http://www.natap.org/2017/HCV/mavyret_pi.pdf [accessed 2019 May 9]

Ledipasvir/Sofosbuvir

Table 35: Ledipasvir/Sofosbuvir (multiple brands) Drug-Drug Interactions

Avoid co-administration; see clinical comments

Class (medications)	Clinical Comments
Antiarrhythmic (amiodarone)	<ul style="list-style-type: none"> Significant bradycardia, especially in patients who are taking beta-blockers, have underlying cardiac abnormalities, or have advanced liver disease If concurrent use is required, cardiac monitoring is recommended See package insert for additional information
Herbal product (St. John's wort)	<ul style="list-style-type: none"> Significant decrease in ledipasvir/sofosbuvir levels
Anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin)	<ul style="list-style-type: none"> Significant decrease in ledipasvir/sofosbuvir levels
Antimycobacterials (rifampin, rifabutin, rifapentine)	<ul style="list-style-type: none"> Significant decrease in ledipasvir/sofosbuvir levels
HMG-CoA reductase inhibitor (rosuvastatin)	<ul style="list-style-type: none"> Significant increase in rosuvastatin level
NS3/4A HCV protease inhibitor (simeprevir)	<ul style="list-style-type: none"> Significant increases in ledipasvir levels

Co-administration possible; see clinical comments

Class (medications)	Clinical Comments
Antacids	<ul style="list-style-type: none"> Ledipasvir solubility decreases as pH increases Separate administration of aluminum- and magnesium-containing antacids and ledipasvir/sofosbuvir by 4 hours
Antiarrhythmic (digoxin)	<ul style="list-style-type: none"> Increase in digoxin level expected Monitor digoxin level
H2-receptor antagonists	<ul style="list-style-type: none"> Administer simultaneously with, or 12 hours apart from, ledipasvir/sofosbuvir Do not exceed doses comparable to famotidine 40 mg twice daily
Proton-pump inhibitors	<ul style="list-style-type: none"> If co-administration is required, doses comparable to omeprazole 20 mg or lower can be administered simultaneously with ledipasvir/sofosbuvir under fasting conditions

Source: FDA. Harvoni (ledipasvir and sofosbuvir) tablets, for oral use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205834s024lbl.pdf [accessed 2019 May 9]

Sofosbuvir/Velpatasvir

Table 36: Sofosbuvir/Velpatasvir (multiple brands) Drug-Drug Interactions

Avoid co-administration; see clinical comments

Class (medications)	Clinical Comments
Antiarrhythmic (amiodarone)	<ul style="list-style-type: none"> Significant bradycardia, especially in patients who are taking beta-blockers, have underlying cardiac abnormalities, or have advanced liver disease If concurrent use is required, cardiac monitoring is recommended See package insert for additional information
Anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin)	<ul style="list-style-type: none"> Significant decrease in sofosbuvir level expected, leading to reduced sofosbuvir and/or velpatasvir drug levels
Antimycobacterials (rifampin, rifabutin, rifapentine)	<ul style="list-style-type: none"> Potential significant decrease in sofosbuvir and/or velpatasvir drug levels
Herbal product (St. John's wort)	<ul style="list-style-type: none"> May significantly decrease sofosbuvir and/or velpatasvir drug levels

Co-administration possible; see clinical comments

Class (medications)	Clinical Comments
Antacids (aluminum and magnesium hydroxide)	<ul style="list-style-type: none"> May decrease concentration of velpatasvir Separate administration of antacid and velpatasvir/sofosbuvir by 4 hours
Antiarrhythmic (digoxin)	<ul style="list-style-type: none"> Increase in digoxin level expected Monitor digoxin level
Anticancer (topotecan)	<ul style="list-style-type: none"> Significant increase in topotecan expected
H2-receptor antagonist (famotidine)	<ul style="list-style-type: none"> Velpatasvir solubility decreases as pH increases May decrease concentration of velpatasvir H2-receptor antagonists may be administered simultaneously with, or 12 hours apart from velpatasvir/sofosbuvir, at a dose that does not exceed doses comparable to famotidine 40 mg twice daily
HMG-CoA reductase inhibitor (rosuvastatin)	<ul style="list-style-type: none"> May significantly increase the concentration of rosuvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis Rosuvastatin may be administered at a dose not greater than 10 mg daily
Proton-pump inhibitor (omeprazole)	<ul style="list-style-type: none"> May decrease concentration of velpatasvir Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with velpatasvir/sofosbuvir under fasting conditions

Source: FDA. Epclusa (sofosbuvir and velpatasvir) tablets, for oral use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208341s000lbl.pdf [accessed 2019 May 9]

Sofosbuvir/Velpatasvir/Voxilaprevir

Table 37: Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi) Drug-Drug Interactions

Avoid co-administration; see clinical comments

Class (medications)	Clinical Comments
Antiarrhythmic (amiodarone)	<ul style="list-style-type: none"> Potential for significant bradycardia, especially in patients who are taking beta-blockers, have underlying cardiac abnormalities, or have advanced liver disease If concurrent use is required, cardiac monitoring is recommended
Herbal product (St. John's wort)	<ul style="list-style-type: none"> Significant decrease in sofosbuvir/velpatasvir/voxilaprevir levels
Anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin)	<ul style="list-style-type: none"> Significant decrease in sofosbuvir/velpatasvir/voxilaprevir levels
Antimycobacterials (rifampin, rifabutin, rifapentine)	<ul style="list-style-type: none"> Significant decrease in sofosbuvir/velpatasvir/voxilaprevir levels
HIV medications (efavirenz, atazanavir, tipranavir)	<ul style="list-style-type: none"> Efavirenz: Significant decrease in velpatasvir and voxilaprevir levels expected Atazanavir: Significant increase in voxilaprevir level expected Tipranavir: Significant decrease in sofosbuvir and voxilaprevir levels expected
HMG-CoA reductase inhibitor (pitavastatin, rosuvastatin)	<ul style="list-style-type: none"> Significant increase in pitavastatin and rosuvastatin levels expected when combined with sofosbuvir/velpatasvir/voxilaprevir
Immunosuppressant (cyclosporine)	<ul style="list-style-type: none"> Significant increases in cyclosporine level expected

Co-administration possible; see clinical comments

Class (medications)	Clinical Comments
Acid reducing medications: <ul style="list-style-type: none"> Aluminum- and magnesium hydroxide- containing antacids H2-receptor antagonists Proton pump inhibitor 	<ul style="list-style-type: none"> Separate administration of antacids and sofosbuvir/velpatasvir/voxilaprevir by 4 hours H2-receptor antagonists may be administered simultaneously with or staggered from sofosbuvir/velpatasvir/voxilaprevir at a dose that does not exceed a comparable dose of famotidine 40 mg twice daily Omeprazole 20 mg can be administered with sofosbuvir/velpatasvir/voxilaprevir: <ul style="list-style-type: none"> Use with other proton pump inhibitors has not been studied Use with lowest doses of other proton pump inhibitors is unlikely to interact
Antiarrhythmic (digoxin)	<ul style="list-style-type: none"> Sofosbuvir/velpatasvir/voxilaprevir may increase digoxin levels; monitor digoxin levels closely prior to and during therapy
HIV medication (tenofovir disoproxil fumarate [TDF])	<ul style="list-style-type: none"> Significant increase in TDF levels expected; monitor for tenofovir-related adverse events
HMG-CoA reductase inhibitor (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin)	<ul style="list-style-type: none"> Atorvastatin, fluvastatin, lovastatin, simvastatin: Potential increase levels of statins when combined with sofosbuvir/velpatasvir/voxilaprevir; use lowest statin dosage Pravastatin: Potential increased levels of pravastatin when combined with sofosbuvir/velpatasvir/voxilaprevir; do not exceed pravastatin 40 mg daily when combined

Source: FDA. Vosevi (sofosbuvir and velpatasvir and voxilaprevir) tablets, for oral use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209195s000lbl.pdf [accessed 2019 May 9]

Drug-Drug Interactions Between DAAs and ARVs

Use of DAAs concurrently with ART may lead to clinically relevant drug interactions. *Table 38*, below, lists the potential drug-drug interactions between DAA regimens and select ART regimens and *Box 3*, below, lists other resources on drug-drug interactions in patients with HIV/HCV coinfection.

Tenofovir is a nucleoside reverse transcriptase inhibitor used extensively in the treatment of HIV and HBV. Tenofovir drug concentrations, when taken in the disoproxil fumarate form (TDF), are increased in the setting of renal failure and when taken with elvitegravir and cobicistat and are highest with concurrent ritonavir use [German, et al. 2015]. Use of TDF with velpatasvir or ledipasvir also increases the level of tenofovir [FDA 2015b, 2016a]. When ledipasvir/sofosbuvir is administered with TDF concurrently with efavirenz or ritonavir-boosted atazanavir or darunavir, the TDF exposure may increase even further, raising concern for development of TDF-related nephrotoxicity [German, et al. 2014; German, et al. 2015]. These interactions are also likely to occur with the sofosbuvir/velpatasvir combination [FDA 2016a]. In addition, the use of TDF with sofosbuvir/velpatasvir/voxilaprevir may also increase tenofovir levels; switching from TDF to TAF, changing TDF to ABC, or monitoring for adverse renal effects would be appropriate in this setting [FDA 2017].

Close monitoring of creatinine clearance is recommended when ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, or sofosbuvir/velpatasvir/voxilaprevir must be co-administered with TDF and efavirenz or a ritonavir-boosted protease inhibitor. Care providers should consider changing the patient’s ART regimen by switching from TDF to TAF or abacavir if the HIV virus is susceptible to these drugs. TAF is associated with much lower peak serum tenofovir concentrations [Garrison, et al. 2015]. The current FDA label allows TAF formulations to be used in patients whose CrCl is as low as 30 mL/min [FDA 2016a].

Box 3: Online Resources for Identifying Drug-Drug Interactions between DAAs and ARVs

- Northeast Caribbean AETC Antiretroviral Clinical Support Tools: DAA Drug Interactions Quick Guides for Clinicians:
 - Glecaprevir/pibrentasvir (Mavyret)
 - Ledipasvir/sofosbuvir (Harvoni)
 - Sofosbuvir/velpatasvir (Epclusa)
 - Sofosbuvir/velpatasvir/voxilaprevir (Vosevi)
- HCV Guidance: American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA): Includes charts listing all DAAs and their compatibility with ARVs
- University of Liverpool HEP Drug Interactions: Provides guidance on managing HCV drug interactions, especially in those who also have HIV; may not include all medications available in the United States)

Table 38: Compatibility of Select ART and DAA Regimens [a] for Nonpregnant Adults (August 2020)

ART Regimen	Concurrent DAA Regimen and Clinical Comment
<i>Preferred Initial ART Regimens</i>	
Abacavir/lamivudine/dolutegravir (ABC/3TC/DTG; Triumeq)	<ul style="list-style-type: none"> • All DAA regimens are compatible.
Tenofovir alafenamide/emtricitabine/bictegravir (TAF 25 mg/FTC/BIC; Biktarvy)	<ul style="list-style-type: none"> • All DAA regimens are compatible, but see note [b] regarding concomitant use of LED or VEL and tenofovir.
Tenofovir alafenamide/emtricitabine and dolutegravir (TAF 25 mg/FTC and DTG; Descovy and Tivicay)	<ul style="list-style-type: none"> • All DAA regimens are compatible, but see note [b] regarding concomitant use of LED or VEL and tenofovir.
Tenofovir alafenamide/emtricitabine and raltegravir (TAF 25 mg/FTC and RAL HD; Descovy and Isentress HD)	<ul style="list-style-type: none"> • All DAA regimens are compatible. • GLE/PIB may increase the serum concentration of RAL but no action is needed. • See note [b] regarding concomitant use of LED or VEL and tenofovir.

Table 38: Compatibility of Select ART and DAA Regimens [a] for Nonpregnant Adults (August 2020)

ART Regimen	Concurrent DAA Regimen and Clinical Comment
<i>Alternative Initial ART Regimens [b]</i>	
Tenofovir alafenamide/emtricitabine/cobicistat/darunavir (TAF 10 mg/FTC/COBI/DRV; Symtuza)	<ul style="list-style-type: none"> Do not co-administer with GLE/PIB. When combining SOF/VEL/VOX with COBI-boosted DRV, levels of VOX may be increased. Until more safety data become available, patients who are taking the combination should be monitored for hepatotoxicity during therapy. See note [b] regarding concomitant use of LED or VEL and tenofovir.
Tenofovir alafenamide/emtricitabine/cobicistat/elvitegravir (TAF 10 mg/FTC/COBI/EVG; Genvoya)	<ul style="list-style-type: none"> When combining GLE/PIB with COBI-boosted EVG, levels of GLE/PIB may be increased. Until more safety data become available, patients who are taking the combination should be monitored for hepatotoxicity during therapy. See note [b] regarding concomitant use of LED or VEL and tenofovir.
Tenofovir alafenamide/emtricitabine/rilpivirine (TAF 25 mg/FTC/RPV; Odefsey)	<ul style="list-style-type: none"> All DAA regimens are compatible, but see note [b] regarding concomitant use of LED or VEL and tenofovir.
Tenofovir disoproxil fumarate/lamivudine/doravirine (TDF/3TC/DOR; Delstrigo)	<ul style="list-style-type: none"> All DAA regimens are considered to be compatible, but there are limited data evaluating the use of doravirine with SOF/VEL or GLE/PIB. See note [b] regarding concomitant use of LED or VEL and tenofovir.
Abacavir/lamivudine and doravirine (ABC/3TC and DOR; Epzicom and Pifeltro)	<ul style="list-style-type: none"> All DAA regimens are considered to be compatible, but there are limited data evaluating the use of doravirine with SOF/VEL or GLE/PIB.
Tenofovir alafenamide/emtricitabine and doravirine (TAF 25 mg/FTC and DOR; Descovy and Pifeltro)	<ul style="list-style-type: none"> All DAA regimens are considered to be compatible, but there are limited data evaluating the use of doravirine with SOF/VEL or GLE/PIB. See note [b] regarding concomitant use of LED or VEL and tenofovir.
Tenofovir disoproxil fumarate/emtricitabine and dolutegravir (TDF/FTC and DTG; Truvada and Tivicay)	<ul style="list-style-type: none"> All DAA regimens are compatible, but see note [b] regarding concomitant use of LED or VEL and tenofovir.
Tenofovir disoproxil fumarate/emtricitabine and raltegravir (TDF/FTC and RAL HD; Truvada and Isentress HD)	<ul style="list-style-type: none"> All DAA regimens are compatible, but see note [b] regarding concomitant use of LED or VEL and tenofovir.
<p>ARV abbreviation key: Abacavir (ABC); bicitgravir (BIC); cobicistat (COBI); darunavir (DRV); dolutegravir (DTG); elvitegravir (EVG); emtricitabine (FTC); lamivudine (3TC); raltegravir (RAL); rilpivirine (RPV); tenofovir alafenamide (TAF); tenofovir disoproxil fumarate (TDF).</p>	
<p>Notes:</p> <ol style="list-style-type: none"> Available DAA regimens as of August 2020: Glecaprevir/pibrentasvir (GLE/PIB; Mavyret); ledipasvir/sofosbuvir (LED/SOF; multiple brands); sofosbuvir/velpatasvir (SOF/VEL; multiple brands); sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX; Vosevi). Concomitant use of LED or VEL and tenofovir: When using TAF or TDF concurrently with a DAA regimen containing LED or VEL, renal function should be evaluated with CrCl testing at baseline and 4 weeks after the start of DAA treatment. When LED or VEL is taken with TDF or TAF, the serum concentration of tenofovir may be increased, which may lead to tenofovir-related renal side effects. Concurrent use of a LED- or VEL-containing DAA and TDF should be avoided in patients with a CrCl < 50 mL/min. Options include switching TDF to TAF [c], substituting ABC if patient is HLAB*5701 negative and has no evidence of ABC resistance, or using a different DAA regimen. Substitutions: 1) In all cases, FTC and 3TC are interchangeable. 2) TAF 10 mg and TAF 25 mg are not interchangeable. 3) COBI and RTV should not be considered interchangeable because of their drug-interaction profiles. See the NYSDOH AI guideline <i>Selecting an Initial ART Regimen</i>. 	

As new drug approvals for HIV ARVs and HCV DAAs continue, it is important that clinicians stay current on potential drug-drug interactions. Useful online resources for looking up potential drug-drug interactions and for monitoring for new information on drug-drug interactions are listed in *Box 3*, above.

Post-Treatment Care

RECOMMENDATIONS

Evaluating the Response to HCV Treatment

- Clinicians should perform HCV RNA testing 12 weeks after treatment is complete to verify that a sustained virologic response (SVR) has been achieved. (A1)
- If SVR is achieved, as established by undetectable HCV RNA at 12 weeks after treatment, clinicians should:
 - Inform their patients that the HCV infection has been cured. (A2)
 - Explain the risk of HCV reinfection and that HCV antibodies are not protective against reinfection. (A1)
- To assess for reinfection in patients with **ongoing risk factors**, clinicians should perform follow-up screening with HCV RNA testing (not HCV antibody testing) at least annually, even with a history of an SVR. (A1)
- If HCV RNA is detectable at 12 weeks after treatment, clinicians should:
 - Inform patients that treatment has failed. (A1)
 - If new to HCV treatment, consult with a liver disease specialist for retreatment evaluation. (B3)
 - See the *Regimens for Retreatment After DAA Failure* section of this guideline.

Post-Treatment Monitoring

- For patients taking ribavirin (RBV)-containing HCV treatment regimens, clinicians should:
 - Advise female and male patients to take extreme care to avoid pregnancy for 6 months after completion of therapy. (A2)
 - Counsel female and male patients on effective contraceptive use. (A2)
- If an individual becomes pregnant within 6 months of completing an RBV-containing HCV treatment, clinicians should discuss the risks of using DAAs and RBV during pregnancy. (A3)

Patients with Persistent Liver Disease

- Clinicians should evaluate patients with persistent abnormal transaminase levels after SVR for other causes of liver disease and consult with a liver disease specialist. (A3)
- In patients with underlying bridging fibrosis or cirrhosis, clinicians should screen for hepatocellular carcinoma (HCC) every 6 months. (A1)

After treatment for chronic HCV infection, follow-up care is based on individual patient factors, including response to recent treatment, previous treatment history, degree of hepatic fibrosis, comorbidities, and cofactors for other sources of liver injury, such as alcohol use or fatty liver disease.

Evaluating the Response to HCV Treatment

All treated individuals should have HCV RNA testing performed 12 weeks after treatment. If there is no detectable HCV RNA at 12 weeks, HCV infection has been cured. In the absence of recurrent risk factors, subsequent HCV testing is not required. However, with late relapse reported in rare (<0.5%) cases, some clinicians may choose to retest at 24 and/or 48 weeks after end of treatment [Jacobson, et al. 2017].

Successful treatment of chronic HCV infection results in no detectable HCV RNA, but antibodies to HCV are typically retained for life. It is important for treated individuals to understand that they will continue to have antibodies but not active HCV infection. It is also important for patients to understand that, although antibodies to HCV will continue to be present after treatment, HCV antibodies do not offer protection from HCV reinfection. All individuals with no detectable HCV RNA are considered susceptible to reinfection if re-exposed to HCV. While the overall rate of reinfection is low, it is elevated among populations at higher risk [Martinello, et al. 2017]. A meta-analysis of 59 studies reporting on recurrence after an SVR in 9,049 patients found that the summary 5-year risk of HCV reinfection among high-risk populations was 10.67% [Simmons, et al. 2016]. High risk was defined as having one or more risk factors, currently or formerly, for reinfection (injection drug use, imprisonment, and being a man who has sex with other men). Among low-risk

populations, defined as those with no known risk factors, the summary 5-year recurrence risk of was 0.95% [Simmons, et al. 2016]. For discussion of risk factors, see the *Screening for HCV Infection* and *Diagnosis of HCV Infection* sections of this guideline.

Post-Treatment Monitoring

It is important to monitor for the resolution of patients' HCV treatment-related adverse events. RBV-containing regimens are teratogenic; patients receiving RBV-containing regimens and their partners should be counseled to avoid pregnancy during treatment and up to 6 months post-treatment. Two forms of effective birth control should be used [FDA 2011].

See *Monitoring During DAA Treatment > Table 33: Adverse Events Associated with DAAs* for a list of adverse events associated with DAA regimens. During treatment with RBV, patients may experience hemolytic anemia, nausea, cough, shortness of breath, rash, dry skin, pruritus, lactic acidosis, or pancreatitis [FDA 2011]. Patients should be monitored through the follow-up period for resolution of any symptoms.

Hepatitis B virus (HBV) reactivation: HBV-related hepatic flares have been reported during and after DAA therapy in patients who were not receiving concurrent HBV treatment [Collins, et al. 2015; Ende, et al. 2015; De Monte, et al. 2016; Hayashi, et al. 2016; Sulkowski MS, et al. 2016; Takayama, et al. 2016; Wang C, et al. 2017]. The U.S. Food and Drug Administration (FDA) has issued a [drug safety warning](#) regarding these risks. Although data are insufficient to make a definitive recommendation regarding monitoring in the setting of isolated anti-HBc [AASLD/IDSA 2015], it is important to consider HBV reactivation as part of the differential diagnosis for patients with HBV infection who experience unexplained increases in liver enzymes either during or after completion of DAA treatment.

Patients with Persistent Liver Disease

While cessation of the progression of fibrosis and histological improvement are among the benefits of treating chronic HCV infection [Toccali, et al. 2003; George, et al. 2009], patients should still be monitored for potential risk of post-treatment decompensation [Jacobson, et al. 2017].

Individuals in whom HCV infection is cured remain at risk of liver disease progression if their baseline fibrosis is sufficiently advanced or if they have comorbidities, such as metabolic syndrome, alcohol use, or uncontrolled coinfection with HIV or HBV or are at risk of liver injury from drugs or dietary supplements [Vandenbulcke, et al. 2016].

Although there is wide individual variation in the time needed for fibrosis progression to occur in chronic HCV infection, it is important to maintain an elevated level of suspicion for progression of fibrosis and the complications associated with hepatic decompensation, particularly in individuals with long-term chronic HCV infection or comorbidities that would predispose them to faster progression. Transient elastography is not available in all clinical settings, but once it is more widely available, it will aid in monitoring fibrosis progression after HCV treatment.

For patients with bridging fibrosis or cirrhosis, an ultrasound should be performed every 6 months, regardless of SVR, to screen for HCC [Jacobson, et al. 2017]. The risk of HCC for patients with stage 3 or higher fibrosis is 1.5% to 5% per year, but it is not known whether the histologic improvement after successful treatment mitigates this risk [Bruix and Sherman 2011].

All Recommendations

ALL RECOMMENDATIONS: TREATMENT OF CHRONIC HCV WITH DIRECT-ACTING ANTIVIRALS

Screening for HCV

- Clinicians should perform HCV screening *at least once* for all patients aged 18 years and older who are not known to have HCV infection. (A2)
- Clinicians should repeat HCV screening in all patients who are planning to get pregnant (A2) or are currently pregnant (B3), and screening should be repeated with each pregnancy. (B3)
 - See the *Pregnancy and HCV* section of this guideline.

☑ ALL RECOMMENDATIONS: TREATMENT OF CHRONIC HCV WITH DIRECT-ACTING ANTIVIRALS

- Clinicians should offer repeat HCV screening based on individual exposure to the following risk factors, at least once if risk exposure is episodic and annually if it is ongoing.
 - Injection (A1) or intranasal (A2) drug use.
 - Hemodialysis. (A1)
 - HIV diagnosis. (A1)
 - Sex partner(s) with HCV infection. (A2)
 - Tattoo, piercing, or acupuncture obtained in a nonsterile setting. (A2)
 - Incarceration. (A2)
 - Unexplained liver disease or abnormal transaminase levels. (A1)
- Clinicians should offer repeat HCV screening *at least annually* to men who have sex with men (MSM) and to others who are not known to have HCV infection and:
 - Engage in receptive anal sex and other behaviors that may tear mucous membranes. (A2)
 - Have multiple sex partners. (A2)
 - Are taking pre-exposure prophylaxis (PrEP) to prevent HIV acquisition. (A3)
 - Are transgender women. (B3)
 - Engage in sex while using recreational mind-altering substances, particularly methamphetamine. (A2)
 - Have been diagnosed with another sexually transmitted infection (STI) within the previous 12 months. (A2)
- Clinicians should perform repeat HCV screening for individuals who are not known to have HCV infection and have a possible exposure in a healthcare setting, including those who:
 - Have a break in the skin caused by a sharp object that is contaminated with blood, visibly bloody fluid, or other potentially infectious material or that has been in the source patient’s blood vessel. (A2)
 - Have been bitten by an individual with visible bleeding in the mouth that causes bleeding in the exposed worker. (A2)
 - Have been splashed on a mucosal surface with blood, visibly bloody fluid, or other potentially infectious material. (A2)
 - Have non-intact skin (e.g., dermatitis, chapped skin, abrasion, or open wound) that has been exposed to blood, visibly bloody fluid, or other potentially infectious material. (A2)

Screening Tests

- Clinicians should perform HCV screening using either a laboratory-based HCV antibody test or point-of-care rapid antibody test. (A1)

Confirmatory Testing

- If the HCV antibody test result is positive, clinicians should obtain confirmatory HCV RNA testing from a laboratory that uses a nucleic acid test (NAT) approved by the U.S. Food and Drug Administration (FDA). (A1)
- If HCV RNA is detected after a positive antibody result, the patient has confirmed HCV infection and clinicians should evaluate for treatment of chronic or acute HCV infection. (A2)
- If the HCV antibody test result is negative:
 - Clinicians should perform subsequent HCV screening based on individual patient risk factors (A3)
 - *And* if acute HCV infection is suspected, clinicians should perform a diagnostic HCV RNA test using an FDA-approved NAT. (A1)
- In patients with a history of a positive HCV antibody test, clinicians should use an HCV RNA test (not an HCV antibody test) for subsequent screening. (A1)

Acute HCV Infection

- Clinicians should suspect acute HCV infection if a patient who had a negative antibody test documented within the previous 6 months has a new positive antibody test or has detectable HCV RNA in the absence of a positive antibody test. (A3)

☑ ALL RECOMMENDATIONS: TREATMENT OF CHRONIC HCV WITH DIRECT-ACTING ANTIVIRALS

- Clinicians should not prescribe pre- or post-exposure prophylaxis to prevent HCV infection. (A1)
- If chronic HCV infection is established, clinicians should evaluate patients for treatment. (A1)
 - See the *Pretreatment Assessment* section of this guideline.
- Clinicians should screen all patients with possible acute HCV infection for HIV, hepatitis A virus (HAV), and hepatitis B virus (HBV) infections, given the similar risk factors for acquisition. (A3)
 - See the *Baseline Laboratory Testing* section of this guideline.

Who to Assess for Treatment

- Clinicians should assess all patients with a confirmed diagnosis of chronic HCV infection for treatment. (A1)

When to Refer to a Liver Specialist

- Clinicians new to treating chronic HCV infection should consult with a liver disease specialist when treating chronic HCV infection in patients with any of the following conditions (A3):
 - Compensated and decompensated cirrhosis.
 - Concurrent hepatobiliary conditions.
 - Extrahepatic manifestations of HCV, including renal, dermatologic, and rheumatologic manifestations.
 - Significant renal impairment (creatinine clearance <30 mL/min) or who are undergoing hemodialysis.
 - Active hepatitis B virus (HBV) infection, defined as HBV surface antigen positive and detectable HBV DNA.
 - Ongoing HCV infection after failure of treatment with direct-acting antivirals (DAAs).
- Clinicians new to treating chronic HCV infection should consult with a liver disease specialist when evaluating patients for retreatment after any DAA treatment failure. (B3)
 - See the *Regimens for Retreatment After DAA Failure* section of this guideline.
- Clinicians should refer patients with chronic HCV infection and decompensated liver disease and patients who are pre- or post-transplant to a liver disease specialist. (A3)

Medical History and Physical Exam

See *Table 2: Key Elements of a Pre-HCV Treatment Patient History and Physical Examination*

HCV Genotype Testing

- Clinicians should obtain HCV genotype/subtype testing for all patients before starting treatment with DAAs. (A1)

Fibrosis Assessment

- Clinicians should assess the degree of fibrosis in patients with chronic HCV infection to aid in determining the following (A1):
 - Need for pretreatment screening for varices and hepatocellular carcinoma (HCC).
 - Duration of antiviral treatment.
 - Need to include ribavirin (RBV) in the treatment regimen.
 - Need for post-treatment follow-up.
- Clinicians should assess patients with chronic HCV infection for decompensated liver disease. (A1)
- Clinicians should refer patients with decompensated cirrhosis to a liver disease specialist. (A3)

Cirrhosis Evaluation

- Clinicians should refer all patients with HCV-related cirrhosis for an upper endoscopy to screen for the presence of esophageal varices. (A3)
- Clinicians should screen for hepatocellular carcinoma (HCC) with ultrasound, computerized axial tomography (CT), or magnetic resonance imaging (MRI) every 6 months in patients with HCV-related bridging fibrosis or cirrhosis. (A3)

Baseline Laboratory Testing

See *Table 6: Baseline Laboratory Testing for Pre-HCV Treatment Assessment*

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Cardiovascular Status

- For individuals with chronic HCV infection who are aged >50 years, clinicians should perform cardiovascular risk assessment before initiation of treatment with ribavirin (RBV). (A2)

Renal Status

- Clinicians should assess creatinine clearance in all patients with HCV infection. (A1)
- Clinicians new to HCV treatment should consult a liver disease specialist when treating patients with severe renal impairment (creatinine clearance <30 mL/min). (A3)

Hepatitis A (HAV) and/or Hepatitis B (HBV) Immunity Status

- Clinicians should obtain HAV antibody (IgG or total) and administer the full HAV vaccine series in patients who are not immune to HAV. (A3)
- Clinicians should obtain HBV surface antigen (HBsAg), anti-hepatitis B surface (HBs), and anti-hepatitis B core antigen (HBc), total, and recommend administration of the anti-hepatitis B virus (HBV) vaccine series (0, 1, and 6 months) for HBV-susceptible patients (negative for all serologies). (A3)
 - In patients with positive HBsAg, clinicians should perform HBV DNA testing to assess for active HBV infection. (A1)
 - If HBV DNA is detectable, clinicians new to HCV treatment should consult a clinician experienced in the management of both HBV and HCV. (A1)

Pregnancy Status and Contraception (see the *Pregnancy and HCV* section of this guideline)

- Before initiating ribavirin (RBV), clinicians should (A2):
 - Confirm a negative pregnancy test.
 - Advise patients to use 2 methods of birth control to avoid pregnancy during therapy and for 6 months after completion of therapy.
 - Counsel female and male patients on effective contraceptive use.
- **Contraindication:** Clinicians should not prescribe RBV in treatment of the following patients:
 - Any individual who is planning conception within 6 months of the last dose of RBV. (A2)
 - Male patients who have pregnant partners. (A2)

Pregnancy and HCV

- Clinicians should repeat HCV screening in all patients who are planning to get pregnant (A2) or are currently pregnant (B3), and screening should be repeated with each pregnancy (B3).
 - See the *Diagnosis of HCV Infection* section of this guideline.
- Clinicians should advise pregnant patients with HCV to defer treatment with direct-acting antivirals (DAAs) until they are no longer pregnant or breastfeeding. (A2)
- If an individual with HCV becomes pregnant during DAA treatment, clinicians should (A3):
 - Advise that the use of DAAs is not currently recommended during pregnancy because no data are currently available on the effects of medications on the fetus.
 - Discuss the risks and benefits of continuing treatment.
- Clinicians should refer pregnant patients who are diagnosed with HCV (HCV antibody and HCV RNA positive), or who are known to have HCV and become pregnant before or during DAA treatment, to a specialist experienced in counseling about HCV in pregnancy. (A3) Specialists may include, but are not limited to, hepatologists, gastroenterologists, infectious disease specialists, or high-risk obstetricians.
- If a pregnant patient with HCV has a substance use disorder, the clinician should provide substance use treatment, including harm reduction services, or refer the patient for these services. (A3)
- Clinicians should advise pregnant and postpartum individuals with HCV mono-infection that breastfeeding is considered safe, and HCV is not transmitted through breast milk. (B3)

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- Clinicians should advise patients that if they have or develop cracked or bleeding nipples, breastfeeding should be discontinued, and milk should be expressed and discarded until bleeding has resolved. (B3)
- Clinicians should refer infants born to mothers with HCV to clinicians with experience in HCV care for further counseling and testing and notify the clinician of the mother's HCV status; see *CDC Hepatitis C, Perinatal Infection 2018 Case Definition* and *IDSA/AASLD HCV in Pregnancy*. (A3)

Considerations in HCV Treatment

- Clinicians should assess creatinine clearance before initiating antiviral therapy. (A1)
- Clinicians new to HCV treatment should consult a liver disease or experienced viral hepatitis specialist when treating patients who:
 - Have severe renal impairment (creatinine clearance <30 mL/min) and/or are undergoing hemodialysis. (A3)
 - Require retreatment after treatment failure of any DAA regimen. (B3)
 - See the *Regimens for Retreatment After DAA Failure* section of this guideline.
- Clinicians should prescribe ribavirin (RBV) with caution for patients with a creatinine clearance <50 mL/min. (A1)
 - If prescribed, a reduced dose of 200 mg per day is required.
 - Non-RBV-containing regimens can be prescribed without dose adjustments for patients with creatinine clearance ≥30 mL/min.

Contraindications

- Clinicians should not prescribe RBV in treatment of the following patients:
 - Female or male patients planning conception within 6 months of the last dose of RBV. (A2)
 - Male patients who have pregnant partners. (A2)

Recommended DAA Regimens

- Based on the results of the *pretreatment assessment*, clinicians should choose from among the treatment regimens for patients with HCV genotypes 1a through 6 listed in *Tables 8 through 28*.
- If a regimen with weight-based RBV is chosen, clinicians should dose as follows: (A1)
 - <75 kg: RBV 400 mg once daily + 600 mg once daily (total daily dose: 1000 mg)
 - ≥75 kg: RBV 600 mg twice daily (total daily dose: 1200 mg)
- Clinicians should order NS5A testing in patients with HCV genotype 3 who are being considered for 12 weeks of sofosbuvir/velpatasvir and are either treatment-naïve and have cirrhosis, or are treatment-experienced and do not have cirrhosis. (A1)
 - If the Y93H RAS is present, weight-based ribavirin should be added to the regimen or another regimen should be selected. (A1)

Retreatment After Failure with Any DAA

- Clinicians new to HCV treatment should consult a liver disease or experienced viral hepatitis specialist when retreating in whom prior treatment with any DAA regimen has failed. (B3) Failure is defined as detectable HCV RNA 12 weeks after the conclusion of HCV treatment.
- If a regimen with weight-based ribavirin (RBV) is chosen, clinicians should dose as follows: (A1)
 - <75 kg: RBV 400 mg once daily plus 600 mg once daily (total daily dose: 1000 mg).
 - ≥75 kg: RBV 600 mg twice daily (total daily dose: 1200 mg).

Monitoring of Patients Taking RBV

- While patients are taking ribavirin (RBV), clinicians should perform hemoglobin testing at weeks 2 and 4 of treatment and every 4 weeks thereafter until therapy is complete. (A1)

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Monitoring for HBV Reactivation

- In patients who are hepatitis B virus surface antigen (HBsAg) positive and have no detectable HBV DNA, clinicians should monitor for HBV reactivation by performing aspartate aminotransferase (AST), ALT, and HBV DNA tests every 4 weeks during HCV treatment. (A3)
- Clinicians new to HCV treatment should consult a liver disease or experienced viral hepatitis specialist for further evaluation of patients who develop detectable HBV DNA. (A3)

Pregnancy

- If an individual becomes pregnant during therapy with a regimen containing RBV, clinicians should stop the RBV. (A1)
- If an individual becomes pregnant during therapy with any DAA regimen, clinicians should discuss the benefits and risks of using DAAs during pregnancy. (A3)

Evaluating the Response to HCV Treatment

- Clinicians should perform HCV RNA testing 12 weeks after treatment is complete to verify that a sustained virologic response (SVR) has been achieved. (A1)
- If SVR is achieved, as established by undetectable HCV RNA at 12 weeks after treatment, clinicians should:
 - Inform their patients that the HCV infection has been cured. (A2)
 - Explain the risk of HCV reinfection and that HCV antibodies are not protective against reinfection. (A1)
- To assess for reinfection in patients with **ongoing risk factors**, clinicians should perform follow-up screening with HCV RNA testing (not HCV antibody testing) at least annually, even with a history of an SVR. (A1)
- If HCV RNA is detectable at 12 weeks after treatment, clinicians should:
 - Inform patients that treatment has failed. (A1)
 - If new to HCV treatment, consult with a liver disease specialist for retreatment evaluation. (B3)
 - See the *Regimens for Retreatment After DAA Failure* section of this guideline.

Post-Treatment Monitoring

- For patients taking ribavirin (RBV)-containing HCV treatment regimens, clinicians should:
 - Advise female and male patients to take extreme care to avoid pregnancy for 6 months after completion of therapy. (A2)
 - Counsel female and male patients on effective contraceptive use. (A2)
- If an individual becomes pregnant within 6 months of completing an RBV-containing HCV treatment, clinicians should discuss the risks of using DAAs and RBV during pregnancy. (A3)

Patients with Persistent Liver Disease

- Clinicians should evaluate patients with persistent abnormal transaminase levels after SVR for other causes of liver disease and consult with a liver disease specialist. (A3)
- In patients with underlying bridging fibrosis or cirrhosis, clinicians should screen for hepatocellular carcinoma (HCC) every 6 months. (A1)

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