



# CLINICAL GUIDELINES PROGRAM

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

## Pretreatment Assessment in Adults With Chronic Hepatitis C Virus Infection

### Updates, Authorship, and Related Guidelines

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Highlights of changes, additions, and updates in the October 6, 2022 edition	<ul style="list-style-type: none"><li>• Medical History and Physical Examination: Treatment after organ transplantation was added to patient conditions that suggest referral to a specialist. A recommendation was added on use of birth control during HCV treatment in individuals of childbearing capacity.</li><li>• Table 1: Key Elements of Patient History and Physical Examination: Assessing cardiac status is no longer recommended; birth control use during HCV treatment is now recommended.</li><li>• Note: The NYSDOH AI guideline Treatment of Chronic HCV with Direct-Acting Antivirals (July 2017 through October 2020) was replaced with 3 guidelines: 1) Hepatitis C Virus Screening, Testing and Diagnosis in Adults; 2) Pretreatment Assessment in Adults With Chronic Hepatitis C Virus Infection; and 3) Treatment of Chronic Hepatitis C Virus Infection in Adults</li></ul>
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**Committee:** [Hepatitis C Virus \(HCV\) Guideline Committee](#)

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## Purpose of This Guideline

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

- Provide evidence-based treatment guidelines to New York State clinicians to increase the number of New York State residents with chronic HCV who are treated and cured.
- Provide guidance to clinicians on key pretreatment assessment criteria to ensure that HCV medications are prescribed safely and correctly and that all patients receive the highest quality of care.
- Provide evidence-based clinical recommendations to support the goals of the [New York State Hepatitis C Elimination Plan \(NY Cures HepC\)](#).

## Medical History and Physical Examination

### RECOMMENDATIONS

#### Medical History and Physical Examination

- Clinicians should assess all patients with a confirmed diagnosis of chronic HCV infection, defined as a positive HCV surface antibody test result and detectable HCV RNA, for treatment. (A1)
- Clinicians should refer patients with chronic HCV and decompensated liver disease and patients who are pre- or post-liver transplant to a liver disease specialist. (A3)

**RECOMMENDATIONS**

- Clinicians new to treating chronic HCV infection should consult with a liver disease specialist when treating chronic HCV in patients with any of the following conditions (A3):
  - Compensated cirrhosis; concurrent hepatobiliary conditions
  - Extrahepatic manifestations of HCV, including renal, dermatologic, and rheumatologic manifestations
  - Significant renal impairment (CrCl <30 mL/min) or who are undergoing hemodialysis
  - Active HBV infection, defined as a positive HBsAg test result and detectable HBV DNA
  - Ongoing HCV infection after failure of treatment with DAAs
  - Treatment after organ transplantation

**Abbreviations:** CrCl, creatinine clearance; DAA, direct-acting antiviral; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

With few exceptions, nonpregnant patients with confirmed HCV are candidates for treatment [EASL 2020; Ghany and Morgan 2020]. Treatment of HCV infection reduces all-cause mortality, regardless of disease stage [Simmons, et al. 2015]. Patients who are not candidates for treatment with DAAs are those with a life expectancy of fewer than 12 months or for whom treatment or liver transplantation would not improve symptoms or prognosis [AASLD/IDSA 2021]. For recommendations for pregnant patients with chronic HCV and those who become pregnant while taking antiviral therapy for chronic HCV, see the NYSDOH AI guideline [Treatment of Chronic Hepatitis C Virus Infection in Adults > HCV Testing and Management in Pregnant Adults](#).

Screening for mental health and substance use disorders and providing treatment or referral as needed is essential but is not a reason to defer treatment. The approach to treating HCV infection in patients with mental health or substance use disorders is the same as for other patients with HCV. Patients with active substance use or mental health disorders can and should be successfully treated, although additional support for adherence, follow-up, and harm reduction may be necessary [Granozzi, et al. 2021; Hajarizadeh, et al. 2020; Torrens, et al. 2020; Gountas, et al. 2018; Sackey, et al. 2018; Tsui, et al. 2016].

**Key elements of medical history and physical examination:** Table 1, below, lists components of the patient history and physical examination that apply specifically to pretreatment assessment of patients with chronic HCV.

<b>Table 1: Key Elements of Patient History and Physical Examination</b>	
<b>Elements of Patient History</b>	<b>Rationale</b>
Previous treatment for HCV infection	Previous regimen and treatment outcome will guide choice and duration of therapy.
History of hepatic decompensation	Warrants referral to a liver disease specialist.
History of renal disease	Findings may influence choice of regimen.
Medication history and current medications, including over-the-counter and herbal products	Carefully consider potential drug-drug interactions with DAAs. See <a href="#">American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA)</a> or <a href="#">University of Liverpool HEP Drug Interactions</a> .
Pregnancy status and plans	<ul style="list-style-type: none"> <li>• HCV treatment may be deferred during pregnancy [a].</li> <li>• Clinician could discuss the possibility of clinical trial participation and refer patient as appropriate (see <a href="#">Clinical Trials.gov</a>).</li> <li>• Birth control use is recommended during HCV treatment due to limited data on the safety of treatment during pregnancy.</li> <li>• For patients who have been exposed to DAA treatment during pregnancy, contact the <a href="#">Treatment in Pregnancy for Hepatitis C Registry</a>.</li> </ul>

<b>Table 1: Key Elements of Patient History and Physical Examination</b>	
<b>Elements of Patient History</b>	<b>Rationale</b>
HIV infection	<ul style="list-style-type: none"> <li>• If HIV infection is confirmed, offer the patient ART [b].</li> <li>• If the patient is being treated with antiretroviral medications, assess potential drug-drug interactions.</li> <li>• HIV infection may influence fibrosis assessment modality, choice of treatment, treatment duration, and monitoring.</li> </ul>
History of infection/vaccination status	<ul style="list-style-type: none"> <li>• HAV: Obtain HAV antibody test (IgG or total).</li> <li>• HBV: Obtain HBsAg, anti-HBs, and anti-HBc (total).</li> <li>• Pneumococcal: Administer pneumococcal polysaccharide vaccine [c] to all patients with cirrhosis, which is associated with increased susceptibility to bacterial infections [Jalan, et al. 2014].</li> <li>• Influenza: Administer annual influenza vaccine [d].</li> </ul>
<b>Elements of Pretreatment Physical Examination</b>	<b>Clinical Details</b>
Presence or absence of ankle edema, abdominal veins, jaundice, palmar erythema, gynecomastia, spider telangiectasia, ascites, encephalopathy, and asterixis	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	Presence may increase urgency of HCV treatment and may require additional evaluation and treatment needs [e].
Liver size by palpation or auscultation for hepatomegaly or splenomegaly, as well as tenderness or hepatic bruits	Size and tenderness may suggest the severity of liver disease and may require additional evaluation.
<p><b>Abbreviations:</b> anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; ART, antiretroviral therapy; DAA, direct-acting antiviral; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IgG, immunoglobulin G.</p> <p><b>Notes:</b></p> <p>a. See NYSDOH AI guideline <a href="#">Treatment of Chronic Hepatitis C Virus Infection in Adults &gt; HCV Testing and Management in Pregnant Adults</a>.</p> <p>b. See NYSDOH AI guideline <a href="#">Rapid ART Initiation</a>.</p> <p>c. As indicated in the Centers for Disease Control and Prevention <a href="#">Adult Immunization Schedule (recommendations for ages 19 years of older)</a>.</p> <p>d. See U.S. Food and Drug Administration <a href="#">Influenza Virus Vaccine Safety &amp; Availability</a>.</p> <p>e. See, for instance, Medscape <a href="#">Cutaneous Manifestations of Hepatitis C Clinical Presentation</a>.</p>	

## Mental Health, Substance Use, and Adherence

**Mental health:** Mental health disorders are not contraindications to treatment of chronic hepatitis C virus (HCV) infection with direct-acting antivirals (DAAs). Strategies to overcome mental health-related barriers to successful HCV treatment include counseling, 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 care providers provide HCV treatment and risk-reduction counseling has been effective [Sackey, et al. 2018; 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 regimen.

With interferon-free regimens, depression is no longer a common adverse effect of HCV treatment. However, antidepressant and antipsychotic drug-drug interactions have been reported with DAAs, so monitoring is necessary; see [Table 1: Key Elements of Patient History and Physical Examination](#) for resources for identifying drug-drug interactions.

Similarly, it is important to be aware of patient use of nonprescription medication. St. John’s wort (*Hypericum perforatum*), an herbal self-remedy for depression, may decrease the effectiveness of DAA therapy [FDA 2019; FDA 2017; FDA 2016].

**Substance use:** A history of or active use of alcohol, tobacco, marijuana, and other substances is not a contraindication to HCV treatment unless the drug or alcohol use significantly interferes with adherence to medications or appointments. Studies have demonstrated that individuals who are receiving [substance use treatment](#) can be effectively treated for chronic HCV infection [Coffin, et al. 2019; Grebely, et al. 2018; Tsui, et al. 2016].

Once a patient’s alcohol consumption habits have been assessed, counseling may help the patient reduce or eliminate alcohol use. It is important for patients with HCV 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 people with chronic HCV. Moderate alcohol intake is 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 people with chronic HCV.

**Barriers to adherence:** 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 put support resources in place [Al-Khazraji, et al. 2020]. 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, 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 put support resources in place.

## Baseline Laboratory Testing

Hepatitis C virus (HCV) genotype may influence the [choice of direct-acting antiviral regimen and treatment duration](#) in patients with chronic HCV; however, given the availability of pangenotypic regimens, genotyping is not required to initiate treatment in treatment-naïve patients. Baseline genotyping may also help in understanding treatment options if a sustained viral response is not attained because it may help distinguish reinfection from virologic relapse.

There are 6 common HCV genotypes [Chevaliez and Pawlotsky 2007]. Based on data from 8,140 participants (≥18 years old) in the U.S.-based Chronic Hepatitis Cohort Study, genotype 1 was most common (75.4%), followed by genotypes 2 (12.6%) and 3 (10.2%); genotypes 4 (1.5%) and 6 (0.3%) were less prevalent [Gordon, et al. 2019]. The single participant with genotype 5 was excluded from the study. Distribution varied significantly by geography and demographics; birth decade, race, and study site were independently associated with genotype distribution ( $P < 0.01$ ).

Additional baseline laboratory testing essential to pre-HCV treatment is listed in Table 2, below.

Test	Clinical Note
Quantitative HCV RNA	Confirms active HCV infection and determines HCV viral load.
Genotype/subtype	Genotype and subtype guide choice of regimen.
Complete blood count	<ul style="list-style-type: none"> <li>• Low platelet count (&lt;140,000 platelets/<math>\mu</math>L) suggests cirrhosis and portal hypertension [Ebell 2003; Kaul and Munoz 2000].</li> <li>• Anemia may necessitate choice of a regimen that does not contain ribavirin.</li> </ul>

**Table 2: Pretreatment Laboratory Testing**

Test	Clinical Note
Serum electrolytes with creatinine	<ul style="list-style-type: none"> <li>Marked electrolyte abnormalities may suggest decompensated cirrhosis (e.g., hyponatremia).</li> <li>Renal function will influence choice of regimen.</li> </ul>
Hepatic function panel	<ul style="list-style-type: none"> <li>Elevated direct bilirubin suggests decompensated cirrhosis.</li> <li>Markedly elevated transaminases may suggest comorbidities.</li> </ul>
INR	Elevated INR suggests decompensated cirrhosis.
Pregnancy test for all individuals of childbearing potential	If patient is pregnant, suggest treatment deferral [a].
HAV antibodies	Obtain HAV antibody test (IgG or total) and administer the full HAV vaccine series in patients not immune to HAV.
HBV antibodies	<ul style="list-style-type: none"> <li>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).</li> <li>In patients with a positive HBsAg test result, perform HBV DNA testing to assess for active HBV infection.</li> <li>If HBV DNA is detectable, care providers new to HCV treatment should consult a liver disease specialist regarding treatment for HBV and HCV.</li> </ul>
HIV test if status is unknown	If HIV infection is confirmed, offer the patient antiretroviral therapy [b].
Urinalysis	Protein may suggest extrahepatic manifestation of HCV.
Fibrosis serum markers	If not previously evaluated by biopsy or FibroScan.
<p><b>Abbreviations:</b> anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; ART, antiretroviral therapy; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IgG, immunoglobulin G; INR, international normalized ratio.</p> <p><b>Notes:</b></p> <p>a. See NYSDOH AI guideline <a href="#">Treatment of Chronic Hepatitis C Virus Infection in Adults &gt; HCV Testing and Management in Pregnant Adults</a>.</p> <p>b. See NYSDOH AI guideline <a href="#">Rapid ART Initiation</a>.</p>	

## Fibrosis Assessment

### RECOMMENDATIONS

#### Fibrosis Assessment

- Clinicians should assess the degree of fibrosis in patients with chronic HCV infection to aid in determining the need for pretreatment varices and HCC screening, the duration of antiviral treatment, whether the regimen should include RBV, and post-treatment follow-up. (A1)
- Clinicians should assess patients with chronic HCV for decompensated liver disease (A1) and, if present, refer patients with decompensated cirrhosis to a liver disease specialist. (A3)

**Abbreviations:** HCC, hepatocellular carcinoma; HCV, hepatitis C virus; RBV, ribavirin.

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 2020]. In 1 study, approximately 50% of people with HCV born between 1945 and 1965

had severe fibrosis or cirrhosis as measured by Fibrosis-4 (FIB-4) index scoring [Klevens, et al. 2016]. 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 [AASLD/IDSA 2021; Bruix and Sherman 2011; Garcia-Tsao, et al. 2007]. Patients known to have cirrhosis do not require repeat determination of the degree of fibrosis before treatment.

Fibrosis stage can be assessed using noninvasive modalities, such as transient elastography, aspartate aminotransferase (AST)-to-platelet ratio index (APRI), FIB-4 index, and assays of direct markers of liver fibrosis (see Table 3, below). 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 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 the FIB-4 index to predict fibrosis more accurately than the APRI [Amorim, et al. 2012; Shaikh, et al. 2009].

Liver biopsies are not routinely required but 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 diseases, such as metabolic nonalcoholic steatohepatitis, hemochromatosis, autoimmune primary biliary cholangitis, and autoimmune hepatitis. Although liver biopsy is safe and has a very low risk of complications, invasive procedures may be difficult to obtain in a timely fashion or 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 those with cirrhosis, but, like the FIB-4 index and APRI, these assays 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 to F1 and F4 fibrosis but may be difficult to interpret in F2 and F3 disease [Loomba, et al. 2023; Tapper, et al. 2015; Castera, et al. 2014; Schiavon Lde, et al. 2014; Vermeer, et al. 2012]. Although VCTE is approved by the U.S. Food and Drug Administration, it is not yet available in all settings and, although highly accurate, is not as cost-effective as laboratory liver fibrosis determinations [Schmid, et al. 2015]. There may also be limitations for patients with obesity [Lai and Afdhal 2019]. Other technologies, such as acoustic radiation force imaging, portal venous transit time, and magnetic resonance imaging elastography or a combination of modalities, 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 [EASL 2020; Agbim and Asrani 2019; Bohte, et al. 2014].

Method	Procedure	Advantages	Disadvantages
Indirect serum markers	APRI, FIB-4 [a]	<ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Inexpensive</li> </ul>	Limited ability to differentiate intermediate stages of fibrosis
Direct markers	FibroSure, FibroTest, FibroMeter, FIBROSpect II, and HepaScore	<ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Easily accessible</li> </ul>	Limited ability to differentiate intermediate stages of fibrosis
VCTE	Shear wave velocity	<ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Assesses large volume of liver parenchyma</li> </ul>	<ul style="list-style-type: none"> <li>• May be difficult to interpret in F2 and F3 liver disease</li> <li>• Limited availability</li> </ul>

**Table 3: Methods for Staging Fibrosis**

Method	Procedure	Advantages	Disadvantages
Liver biopsy	Pathologic examination	<ul style="list-style-type: none"> <li>Diagnostic standard</li> <li>Diagnoses concurrent liver disease</li> </ul>	<ul style="list-style-type: none"> <li>Invasive procedure</li> <li>Costly</li> <li>Sampling error</li> </ul>

**Abbreviations:** APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, Fibrosis-4; VCTE, vibration-controlled transient elastography.

**Note:**

a. See [Hepatitis C Online](#) for APRI and FIB-4 index calculators.

## Cirrhosis Evaluation

### RECOMMENDATIONS

#### Cirrhosis Evaluation

- Clinicians should determine the severity of cirrhosis (A1) and refer patients with a history of decompensation or decompensated cirrhosis (CTP class B or C) to a liver disease specialist. (A3)
- 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 HCC with ultrasound, CT, or MRI every 6 months in patients with HCV-related bridging fibrosis or cirrhosis. (A3)

**Abbreviations:** CTP, Child-Turcotte-Pugh; CT, computerized axial tomography; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MRI, magnetic resonance imaging.

The Model for End-Stage Liver Disease (MELD) score ([MELD calculator](#)) or the CTP score (see Table 4, below) may be used to classify the severity of cirrhosis.

**Table 4: Calculating the Child-Turcotte-Pugh (CTP) Score for Severity of Cirrhosis [a]**

	1 point [b]	2 points [b]	3 points [b]
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 international normalized ratio (INR)	<4.0	4.0 to 6.0	>6.0
	<1.7	1.7 to 2.3	>2.3

**Notes:**

- Adapted from U.S. Department of Veterans Affairs [Viral Hepatitis and Liver Disease: Child-Turcotte-Pugh Calculator](#).
- 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)



Assessment for decompensation in patients with cirrhosis can be accomplished through medical history-taking and initial laboratory testing (see Table 5, 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 [Shoreibah, et al. 2014; Bruix and Sherman 2011]. Alpha-fetoprotein (AFP) testing 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 [EASL 2018; El-Serag and Mason 1999].

For additional risk stratification and diagnosis information, see the American Association of the Study for Liver Diseases practice guidance on portal hypertensive bleeding in cirrhosis [Garcia-Tsao, et al. 2017].

**Table 5: Baseline 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 or current decompensation	Decompensation is defined as the presence (or history) of 1 of the following: <ul style="list-style-type: none"> <li>• CTP class B or C</li> <li>• MELD score of &gt;15</li> <li>• Ascites</li> <li>• Hepatic encephalopathy</li> <li>• Portal hypertensive bleeding</li> <li>• HCC</li> <li>• Intractable pruritus</li> <li>• Hepatopulmonary syndrome</li> <li>• Portopulmonary hypertension</li> </ul>
Abdominal ultrasound to screen for HCC	Ongoing HCC surveillance should be performed for patients with bridging fibrosis or cirrhosis every 6 to 12 months.
Upper endoscopy	Refer to a liver disease specialist to screen for varices.
<b>Abbreviations:</b> CTP, Child-Turcotte-Pugh; HCC, hepatocellular carcinoma; MELD, Model of End-Stage Liver Disease.	

## Renal, HAV/HBV, Metabolic, and Cardiovascular Status

### RECOMMENDATIONS

#### Renal Status

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

#### HAV and HBV Immunity Status

- Clinicians should obtain HAV antibody (IgG or total) testing and administer the full HAV vaccine series in patients who are not immune to HAV. (A3)
- Clinicians should obtain HBsAg, anti-HBs, and anti-HBc test results (total) and should recommend administration of the HBV vaccine series (at 0, 1, and 6 months) for HBV-susceptible patients (negative for all serologies). (A3)
- In patients with positive HBsAg test results, clinicians should perform HBV DNA testing to assess for active HBV infection. (A1)

## RECOMMENDATIONS

- If HBV DNA is detectable, clinicians new to HCV treatment should consult a clinician experienced in managing both HBV and HCV. (A1)

**Abbreviations:** anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; CrCl, creatinine clearance; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IgG, immunoglobulin G.

**Renal status:** A patient's renal status will influence the choice of direct-acting antiviral (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 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; vaccination against HAV and HBV is important for patients with HCV 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 vaccine 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 vaccine series is not necessary before initiation of HCV treatment.

Vaccination of patients with positive anti-HBc and negative HBsAg and anti-HBs (i.e., isolated anti-HBc) test results is controversial because results are subject to several interpretations. In patients from regions where 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 are from regions where 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 [Butt, et al. 2018; Belperio, et al. 2017; Wang, et al. 2017; De Monte, et al. 2016; Hayashi, et al. 2016; Sulkowski, et al. 2016; Takayama, et al. 2016; Collins, et al. 2015; Ende, et al. 2015]. Studies have demonstrated that HCV has a suppressive effect on HBV replication. For more information about the risk of HBV reactivation, see the U.S. Food and Drug Administration [Drug Safety Communication](#).

## → KEY POINT

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

**Metabolic status:** Obesity does not affect the treatment of HCV with DAAs. Among individuals with HCV, both obesity and hepatic steatosis have been associated with progression of fibrosis, increased risk of advanced liver disease, and hepatocellular carcinoma (HCC) [Minami, et al. 2021; Dyal, et al. 2015; Goossens and Negro 2014; Charlton, et al. 2006; Bressler, et al. 2003].

Chronic HCV infection appears to be associated with an increased risk of developing type 2 diabetes mellitus (DM2) in predisposed individuals [Lecube, et al. 2004; Mehta, et al. 2003; Mehta, et al. 2000]. Insulin resistance (IR) and diabetes are associated with increased liver fibrosis [Patel, et al. 2011; Moucari, et al. 2008; Petta, et al. 2008], cirrhosis [Gordon, et al. 2015], and HCC [Hung, et al. 2011; Donadon, et al. 2009; Veldt, et al. 2008; Tazawa, et al. 2002] in patients with HCV. Successful treatment of chronic HCV infection may be associated with improved IR, reduced incidence of DM2, and potentially decreased DM2-associated renovascular complications [Hsu, et al. 2014; Thompson, et al. 2012; Arase, et al. 2009]. No serious drug-drug interactions have been reported with DAA agents and insulin-sensitizing or diabetic medications. However, because of the potential for improved glycemic control, diabetic patients have a higher risk for hypoglycemia during or after treatment with DAAs [Zhou, et al. 2022; Andres, et al. 2020; Yuan, et al. 2020; Li(a), et al. 2019; Li(b), et al. 2019] and should be counseled to monitor blood sugars during and after treatment.

**Cardiovascular status:** Although cardiovascular disease and congestive heart failure may be worsened by possible anemia associated with the use of ribavirin (RBV)-containing regimens, no such concern is noted with DAA regimens that do not contain RBV. However, [drug-drug interactions](#) between DAA medications and cardiovascular medications have been reported and may require adjustments or changes before initiation of therapy.

# All Recommendations

## ☑ ALL RECOMMENDATIONS: PRETREATMENT ASSESSMENT IN ADULTS WITH CHRONIC HCV INFECTION

### Medical History and Physical Examination

- Clinicians should assess all patients with a confirmed diagnosis of chronic HCV infection, defined as a positive HCV surface antibody test result and detectable HCV RNA, for treatment. (A1)
- Clinicians should refer patients with chronic HCV and decompensated liver disease and patients who are pre- or post-liver transplant to a liver disease specialist. (A3)
- Clinicians new to treating chronic HCV infection should consult with a liver disease specialist when treating chronic HCV in patients with any of the following conditions (A3):
  - Compensated cirrhosis; concurrent hepatobiliary conditions
  - Extrahepatic manifestations of HCV, including renal, dermatologic, and rheumatologic manifestations
  - Significant renal impairment (CrCl <30 mL/min) or who are undergoing hemodialysis
  - Active HBV infection, defined as a positive HBsAg test result and detectable HBV DNA
  - Ongoing HCV infection after failure of treatment with DAAs
  - Treatment after organ transplantation

### Fibrosis Assessment

- Clinicians should assess the degree of fibrosis in patients with chronic HCV infection to aid in determining the need for pretreatment varices and HCC screening, the duration of antiviral treatment, whether the regimen should include RBV, and post-treatment follow-up. (A1)
- Clinicians should assess patients with chronic HCV for decompensated liver disease (A1) and, if present, refer patients with decompensated cirrhosis to a liver disease specialist. (A3)

### Cirrhosis Evaluation

- Clinicians should determine the severity of cirrhosis (A1) and refer patients with a history of decompensation or decompensated cirrhosis (CTP class B or C) to a liver disease specialist. (A3)
- 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 HCC with ultrasound, CT, or MRI every 6 months in patients with HCV-related bridging fibrosis or cirrhosis. (A3)

### Renal Status

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

### HAV and HBV Immunity Status

- Clinicians should obtain HAV antibody (IgG or total) testing and administer the full HAV vaccine series in patients who are not immune to HAV. (A3)
- Clinicians should obtain HBsAg, anti-HBs, and anti-HBc test results (total) and should recommend administration of the HBV vaccine series (at 0, 1, and 6 months) for HBV-susceptible patients (negative for all serologies). (A3)
- In patients with positive HBsAg test results, 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 managing both HBV and HCV. (A1)

**Abbreviations:** anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; CTP, Child-Turcotte-Pugh; CrCl, creatinine clearance; CT, computerized axial tomography; DAA, direct-acting antiviral; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IgG, immunoglobulin G; MRI, magnetic resonance imaging.

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# Supplement: Guideline Development and Recommendation Ratings

**Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program**

<b>Developer</b>	<a href="#">New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program</a>
<b>Funding source</b>	NYSDOH AI
<b>Program manager</b>	Clinical Guidelines Program, Johns Hopkins University School of Medicine, Division of Infectious Diseases. See <a href="#">Program Leadership and Staff</a> .
<b>Mission</b>	To produce and disseminate evidence-based, state-of-the-art clinical practice guidelines that establish uniform standards of care for practitioners who provide prevention or treatment of HIV, viral hepatitis, other sexually transmitted infections, and substance use disorders for adults throughout New York State in the wide array of settings in which those services are delivered.
<b>Expert committees</b>	The NYSDOH AI Medical Director invites and appoints committees of clinical and public health experts from throughout New York State to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of New York State, all relevant clinical practice settings, key New York State agencies, and community service organizations.
<b>Committee structure</b>	<ul style="list-style-type: none"> <li>• Leadership: AI-appointed chair, vice chair(s), chair emeritus, clinical specialist(s), JHU Guidelines Program Director, AI Medical Director, AI Clinical Consultant, AVAC community advisor</li> <li>• Contributing members</li> <li>• Guideline writing groups: Lead author, coauthors if applicable, and all committee leaders</li> </ul>
<b>Disclosure and management of conflicts of interest</b>	<ul style="list-style-type: none"> <li>• Annual disclosure of financial relationships with commercial entities for the 12 months prior and upcoming is required of all individuals who work with the guidelines program, and includes disclosure for partners or spouses and primary professional affiliation.</li> <li>• The NYSDOH AI assesses all reported financial relationships to determine the potential for undue influence on guideline recommendations and, when indicated, denies participation in the program or formulates a plan to manage potential conflicts. Disclosures are listed for each committee member.</li> </ul>
<b>Evidence collection and review</b>	<ul style="list-style-type: none"> <li>• Literature search and review strategy is defined by the guideline lead author based on the defined scope of a new guideline or update.</li> <li>• A comprehensive literature search and review is conducted for a new guideline or an extensive update using PubMed, other pertinent databases of peer-reviewed literature, and relevant conference abstracts to establish the evidence base for guideline recommendations.</li> <li>• A targeted search and review to identify recently published evidence is conducted for guidelines published within the previous 3 years.</li> <li>• Title, abstract, and article reviews are performed by the lead author. The JHU editorial team collates evidence and creates and maintains an evidence table for each guideline.</li> </ul>



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<b>Recommendation development</b>	<ul style="list-style-type: none"> <li>• The lead author drafts recommendations to address the defined scope of the guideline based on available published data.</li> <li>• Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations.</li> <li>• When published data are not available, support for a recommendation may be based on the committee’s expert opinion.</li> <li>• The writing group assigns a 2-part rating to each recommendation to indicate the strength of the recommendation and quality of the supporting evidence. The group reviews the evidence, deliberates, and may revise recommendations when required to reach consensus.</li> </ul>
<b>Review and approval process</b>	<ul style="list-style-type: none"> <li>• Following writing group approval, draft guidelines are reviewed by all contributors, program liaisons, and a volunteer reviewer from the AI Community Advisory Committee.</li> <li>• Recommendations must be approved by two-thirds of the full committee. If necessary to achieve consensus, the full committee is invited to deliberate, review the evidence, and revise recommendations.</li> <li>• Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.</li> </ul>
<b>External reviews</b>	<ul style="list-style-type: none"> <li>• External review of each guideline is invited at the developer’s discretion.</li> <li>• External reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback.</li> </ul>
<b>Update process</b>	<ul style="list-style-type: none"> <li>• JHU editorial staff ensure that each guideline is reviewed and determined to be current upon the 3-year anniversary of publication; guidelines that provide clinical recommendations in rapidly changing areas of practice may be reviewed annually. Published literature is surveilled to identify new evidence that may prompt changes to existing recommendations or development of new recommendations.</li> <li>• If changes in the standard of care, newly published studies, new drug approval, new drug-related warning, or a public health emergency indicate the need for immediate change to published guidelines, committee leadership will make recommendations and immediate updates and will invite full committee review as indicated.</li> </ul>

**Table S2: Recommendation Ratings and Definitions**

Strength	Quality of Evidence	
A: Strong B. Moderate C: Optional	1	Based on published results of at least 1 randomized clinical trial with clinical outcomes or validated laboratory endpoints.
	*	Based on either a self-evident conclusion; conclusive, published, in vitro data; or well-established practice that cannot be tested because ethics would preclude a clinical trial.
	2	Based on published results of at least 1 well-designed, nonrandomized clinical trial or observational cohort study with long-term clinical outcomes.
	2 <sup>†</sup>	Extrapolated from published results of well-designed studies (including nonrandomized clinical trials) conducted in populations other than those specifically addressed by a recommendation. The source(s) of the extrapolated evidence and the rationale for the extrapolation are provided in the guideline text. One example would be results of studies conducted predominantly in a subpopulation (e.g., one gender) that the committee determines to be generalizable to the population under consideration in the guideline.
	3	Based on committee expert opinion, with rationale provided in the guideline text.