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

Date of current publication	October 6, 2022
Highlights of changes, additions, and updates in the October 6, 2022 edition	• 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. • 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. • 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
Intended users	Clinicians in New York State who treat adults with chronic HCV
Lead author	Christine A. Kerr, MD
Writing group	Joshua S. Aron, MD; David E. Bernstein, MD; Colleen Flanigan, RN, MS; Christopher J. Hoffmann, MD, MPH; Charles J. Gonzalez, MD
Author and writing group conflict of interest disclosures	None
Date of original publication	October 6, 2022
Committee	Hepatitis C Virus (HCV) Guideline Committee
Developer and funder	New York State Department of Health AIDS Institute (NYSDOH AI)
Development process	See Supplement: Guideline Development and Recommendation Ratings
Related NYSDOH AI guidelines	• Prevention and Management of Hepatitis B Virus Infection in Adults With HIV • Rapid ART Initiation • Substance Use Screening, Risk Assessment, and Use Disorder Diagnosis in Adults • Treatment of Chronic Hepatitis C Virus Infection in Adults

Pretreatment Assessment in Adults With Chronic Hepatitis C Virus Infection

Date of current publication: October 6, 2022
Lead author: Christine A. Kerr, MD
Writing group: Joshua S. Aron, MD; David E. Bernstein, MD; Colleen Flanigan, RN, MS; Christopher J. Hoffmann, MD, MPH; Charles J. Gonzalez, MD
Committee: Hepatitis C Virus (HCV) Guideline Committee
Date of original publication: October 6, 2022

Contents

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.

Table 1: Key Elements of Patient History and Physical Examination

Elements of Patient History	Rationale
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 American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) or University of Liverpool HEP Drug Interactions.
Pregnancy status and plans	• HCV treatment may be deferred during pregnancy [a]. • Clinician could discuss the possibility of clinical trial participation and refer patient as appropriate (see Clinical Trials.gov). • Birth control use is recommended during HCV treatment due to limited data on the safety of treatment during pregnancy. • For patients who have been exposed to DAA treatment during pregnancy, contact the Treatment in Pregnancy for Hepatitis C Registry.

Table 1: Key Elements of Patient History and Physical Examination	
Elements of Patient History	**Rationale**
HIV infection	• If HIV infection is confirmed, offer the patient ART [b]. • If the patient is being treated with antiretroviral medications, assess potential drug-drug interactions. • HIV infection may influence fibrosis assessment modality, choice of treatment, treatment duration, and monitoring.
History of infection/vaccination status	• HAV: Obtain HAV antibody test (IgG or total). • HBV: Obtain HBsAg, anti-HBs, and anti-HBc (total). • Pneumococcal: Administer pneumococcal polysaccharide vaccine [c] to all patients with cirrhosis, which is associated with increased susceptibility to bacterial infections [Jalan, et al. 2014]. • Influenza: Administer annual influenza vaccine [d].
Elements of Pretreatment Physical Examination	**Clinical Details**
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.

Abbreviations: 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.

Notes:

a. See NYSDOH AI guideline Treatment of Chronic Hepatitis C Virus Infection in Adults > HCV Testing and Management in Pregnant Adults.
b. See NYSDOH AI guideline Rapid ART Initiation.
c. As indicated in the Centers for Disease Control and Prevention Adult Immunization Schedule (recommendations for ages 19 years of older).
d. See U.S. Food and Drug Administration Influenza Virus Vaccine Safety & Availability.
e. See, for instance, Medscape Cutaneous Manifestations of Hepatitis C Clinical Presentation.

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-naive 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.

Table 2: Pretreatment Laboratory Testing

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	• Low platelet count (<140,000 platelets/µL) suggests cirrhosis and portal hypertension [Ebell 2003; Kaul and Munoz 2000]. • Anemia may necessitate choice of a regimen that does not contain ribavirin.

Table 2: Pretreatment Laboratory Testing	
Test	**Clinical Note**
Serum electrolytes with creatinine	• Marked electrolyte abnormalities may suggest decompensated cirrhosis (e.g., hyponatremia). • Renal function will influence choice of regimen.
Hepatic function panel	• Elevated direct bilirubin suggests decompensated cirrhosis. • Markedly elevated transaminases may suggest comorbidities.
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	• 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). • In patients with a positive HBsAg test result, 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	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.

Abbreviations: 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.

Notes:

a. See NYSDOH AI guideline Treatment of Chronic Hepatitis C Virus Infection in Adults > HCV Testing and Management in Pregnant Adults.
b. See NYSDOH AI guideline Rapid ART Initiation.

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; Verveer, 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].

Table 3: Methods for Staging Fibrosis

Method	Procedure	Advantages	Disadvantages
Indirect serum markers	APRI, FIB-4 [a]	• 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

Table 3: Methods for Staging Fibrosis			
Method	**Procedure**	**Advantages**	**Disadvantages**
Liver biopsy	Pathologic examination	• Diagnostic standard • Diagnoses concurrent liver disease	• Invasive procedure • Costly • Sampling error

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:

a. Adapted from U.S. Department of Veterans Affairs Viral Hepatitis and Liver Disease: Child-Turcotte-Pugh Calculator.
b. 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: • CTP class B or C • MELD score of >15 • Ascites • Hepatic encephalopathy • Portal hypertensive bleeding • HCC • Intractable pruritus • Hepatopulmonary syndrome • Portopulmonary hypertension
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.

Abbreviations: 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.

References

AASLD/IDSA. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. 2021 Oct. https://www.hcvguidelines.org/ [accessed 2022 Aug 29]

Agbim U, Asrani SK. Non-invasive assessment of liver fibrosis and prognosis: an update on serum and elastography markers. *Expert Rev Gastroenterol Hepatol* 2019;13(4):361-74. [PMID: 30791772] https://pubmed.ncbi.nlm.nih.gov/30791772

Al-Khazraji A, Patel I, Saleh M, et al. Identifying barriers to the treatment of chronic hepatitis C infection. *Dig Dis* 2020;38(1):46-52. [PMID: 31422405] https://pubmed.ncbi.nlm.nih.gov/31422405

Amorim TG, Staub GJ, Lazzarotto C, et al. Validation and comparison of simple noninvasive models for the prediction of liver fibrosis in chronic hepatitis C. *Ann Hepatol* 2012;11(6):855-61. [PMID: 23109448] https://pubmed.ncbi.nlm.nih.gov/23109448

Andres J, Barros M, Arutunian M, et al. Treatment of hepatitis C virus and long-term effect on glycemic control. *J Manag Care Spec Pharm* 2020;26(6):775-81. [PMID: 32463777] https://pubmed.ncbi.nlm.nih.gov/32463777

Arase Y, Suzuki F, Suzuki Y, et al. Sustained virological response reduces incidence of onset of type 2 diabetes in chronic hepatitis C. *Hepatology* 2009;49(3):739-44. [PMID: 19127513] https://pubmed.ncbi.nlm.nih.gov/19127513

Belperio PS, Shahoumian TA, Mole LA, et al. Evaluation of hepatitis B reactivation among 62,920 veterans treated with oral hepatitis C antivirals. *Hepatology* 2017;66(1):27-36. [PMID: 28240789] https://pubmed.ncbi.nlm.nih.gov/28240789

Bohte AE, de Niet A, Jansen L, et al. Non-invasive evaluation of liver fibrosis: a comparison of ultrasound-based transient elastography and MR elastography in patients with viral hepatitis B and C. *Eur Radiol* 2014;24(3):638-48. [PMID: 24158528] https://pubmed.ncbi.nlm.nih.gov/24158528

Bressler BL, Guindi M, Tomlinson G, et al. High body mass index is an independent risk factor for nonresponse to antiviral treatment in chronic hepatitis C. *Hepatology* 2003;38(3):639-44. [PMID: 12939590] https://pubmed.ncbi.nlm.nih.gov/12939590

Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;53(3):1020-22. [PMID: 21374666] https://pubmed.ncbi.nlm.nih.gov/21374666

Butt AA, Yan P, Shaikh OS, et al. Hepatitis B reactivation and outcomes in persons treated with directly acting antiviral agents against hepatitis C virus: results from ERCHIVES. *Aliment Pharmacol Ther* 2018;47(3):412-20. [PMID: 29181838] https://pubmed.ncbi.nlm.nih.gov/29181838

Castera L, Winnock M, Pambrun E, et al. Comparison of transient elastography (FibroScan), FibroTest, APRI and two algorithms combining these non-invasive tests for liver fibrosis staging in HIV/HCV coinfected patients: ANRS CO13 HEPAVIH and FIBROSTIC Collaboration. *HIV Med* 2014;15(1):30-39. [PMID: 24007567] https://pubmed.ncbi.nlm.nih.gov/24007567

Charlton MR, Pockros PJ, Harrison SA. Impact of obesity on treatment of chronic hepatitis C. *Hepatology* 2006;43(6):1177-86. [PMID: 16729327] https://pubmed.ncbi.nlm.nih.gov/16729327

Chevaliez S, Pawlotsky JM. Hepatitis C virus: virology, diagnosis and management of antiviral therapy. *World J Gastroenterol* 2007;13(17):2461-66. [PMID: 17552030] https://pubmed.ncbi.nlm.nih.gov/17552030

Coffin PO, Santos GM, Behar E, et al. Randomized feasibility trial of directly observed versus unobserved hepatitis C treatment with ledipasvir-sofosbuvir among people who inject drugs. *PLoS One* 2019;14(6):e0217471. [PMID: 31158245] https://pubmed.ncbi.nlm.nih.gov/31158245

Collins JM, Raphael KL, Terry C, et al. Hepatitis B virus reactivation during successful treatment of hepatitis C virus with sofosbuvir and simeprevir. *Clin Infect Dis* 2015;61(8):1304-6. [PMID: 26082511] https://pubmed.ncbi.nlm.nih.gov/26082511

De Monte A, Courjon J, Anty R, et al. Direct-acting antiviral treatment in adults infected with hepatitis C virus: reactivation of hepatitis B virus coinfection as a further challenge. *J Clin Virol* 2016;78:27-30. [PMID: 26967675] https://pubmed.ncbi.nlm.nih.gov/26967675

Donadon V, Balbi M, Zanette G. Hyperinsulinemia and risk for hepatocellular carcinoma in patients with chronic liver diseases and type 2 diabetes mellitus. *Expert Rev Gastroenterol Hepatol* 2009;3(5):465-67. [PMID: 19817667] https://pubmed.ncbi.nlm.nih.gov/19817667

Dyal HK, Aguilar M, Bhuket T, et al. Concurrent obesity, diabetes, and steatosis increase risk of advanced fibrosis among HCV patients: a systematic review. *Dig Dis Sci* 2015;60(9):2813-24. [PMID: 26138651] https://pubmed.ncbi.nlm.nih.gov/26138651

EASL. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;69(1):182-236. [PMID: 29628281] https://pubmed.ncbi.nlm.nih.gov/29628281

EASL. EASL recommendations on treatment of hepatitis C: final update of the series. *J Hepatol* 2020;73(5):1170-1218. [PMID: 32956768] https://pubmed.ncbi.nlm.nih.gov/32956768

Ebell MH. Probability of cirrhosis in patients with hepatitis C. *Am Fam Physician* 2003;68(9):1831-33. [PMID: 14620604] https://pubmed.ncbi.nlm.nih.gov/14620604

El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999;340(10):745-50. [PMID: 10072408] https://pubmed.ncbi.nlm.nih.gov/10072408

Ende AR, Kim NH, Yeh MM, et al. Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report. *J Med Case Rep* 2015;9:164. [PMID: 26215390] https://pubmed.ncbi.nlm.nih.gov/26215390

FDA. Epclusa (sofosbuvir and velpatasvir) tablets, for oral use. 2016 Jun. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208341s000lbl.pdf [accessed 2022 Feb 1]

FDA. Vosevi (sofosbuvir, velpatasvir, and voxilaprevir) tablets, for oral use. 2017 Jul. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209195s000lbl.pdf [accessed 2022 Feb 1]

FDA. Harvoni (ledipasvir and sofosbuvir) tablets, for oral use. 2019 Aug. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212477s000lbl.pdf [accessed 2022 Feb 1]

Fox AN, Brown RS, Jr. Is the patient a candidate for liver transplantation? *Clin Liver Dis* 2012;16(2):435-48. [PMID: 22541708] https://pubmed.ncbi.nlm.nih.gov/22541708

Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, an management: 2016 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2017;65(1):310-35. [PMID: 27786365] https://pubmed.ncbi.nlm.nih.gov/27786365

Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007;46(3):922-38. [PMID: 17879356] https://pubmed.ncbi.nlm.nih.gov/17879356

Ghany MG, Morgan TR. Hepatitis C guidance 2019 update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America recommendations for testing, managing, and treating hepatitis C virus infection. *Hepatology* 2020;71(2):686-721. [PMID: 31816111] https://pubmed.ncbi.nlm.nih.gov/31816111

Goossens N, Negro F. The impact of obesity and metabolic syndrome on chronic hepatitis C. *Clin Liver Dis* 2014;18(1):147-56. [PMID: 24274870] https://pubmed.ncbi.nlm.nih.gov/24274870

Gordon SC, Lamerato LE, Rupp LB, et al. Prevalence of cirrhosis in hepatitis C patients in the Chronic Hepatitis Cohort Study (CHeCS): a retrospective and prospective observational study. *Am J Gastroenterol* 2015;110(8):1169-77; quiz 1178. [PMID: 26215529] https://pubmed.ncbi.nlm.nih.gov/26215529

Gordon SC, Trudeau S, Li J, et al. Race, age, and geography impact hepatitis C genotype distribution in the United States. *J Clin Gastroenterol* 2019;53(1):40-50. [PMID: 28737649] https://pubmed.ncbi.nlm.nih.gov/28737649

Gountas I, Sypsa V, Blach S, et al. HCV elimination among people who inject drugs. Modelling pre- and post-WHO elimination era. *PLoS One* 2018;13(8):e0202109. [PMID: 30114207] https://pubmed.ncbi.nlm.nih.gov/30114207

Granozzi B, Guardigni V, Badia L, et al. Out-of-hospital treatment of hepatitis C increases retention in care among people who inject drugs and homeless persons: an observational study. *J Clin Med* 2021;10(21):4955. [PMID: 34768474] https://pubmed.ncbi.nlm.nih.gov/34768474

Grebely J, Dalgard O, Conway B, et al. Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use (SIMPLIFY): an open-label, single-arm, phase 4, multicentre trial. *Lancet Gastroenterol Hepatol* 2018;3(3):153-61. [PMID: 29310928] https://pubmed.ncbi.nlm.nih.gov/29310928

Groessl EJ, Sklar M, Cheung RC, et al. Increasing antiviral treatment through integrated hepatitis C care: a randomized multicenter trial. *Contemp Clin Trials* 2013;35(2):97-107. [PMID: 23669414] https://pubmed.ncbi.nlm.nih.gov/23669414

Hajarizadeh B, Cunningham EB, Valerio H, et al. Hepatitis C reinfection after successful antiviral treatment among people who inject drugs: a meta-analysis. *J Hepatol* 2020;72(4):643-57. [PMID: 31785345] https://pubmed.ncbi.nlm.nih.gov/31785345

Hayashi K, Ishigami M, Ishizu Y, et al. A case of acute hepatitis B in a chronic hepatitis C patient after daclatasvir and asunaprevir combination therapy: hepatitis B virus reactivation or acute self-limited hepatitis? *Clin J Gastroenterol* 2016;9(4):252-56. [PMID: 27329484] https://pubmed.ncbi.nlm.nih.gov/27329484

Henkle E, Lu M, Rupp LB, et al. Hepatitis A and B immunity and vaccination in chronic hepatitis B and C patients in a large United States cohort. *Clin Infect Dis* 2015;60(4):514-22. [PMID: 25371489] https://pubmed.ncbi.nlm.nih.gov/25371489

Hsu YC, Wu CY, Lane HY, et al. Determinants of hepatocellular carcinoma in cirrhotic patients treated with nucleos(t)ide analogues for chronic hepatitis B. *J Antimicrob Chemother* 2014;69(7):1920-27. [PMID: 24576950] https://pubmed.ncbi.nlm.nih.gov/24576950

Hung CH, Lee CM, Wang JH, et al. Impact of diabetes mellitus on incidence of hepatocellular carcinoma in chronic hepatitis C patients treated with interferon-based antiviral therapy. *Int J Cancer* 2011;128(10):2344-52. [PMID: 20669224] https://pubmed.ncbi.nlm.nih.gov/20669224

Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. *J Hepatol* 2014;60(6):1310-24. [PMID: 24530646] https://pubmed.ncbi.nlm.nih.gov/24530646

Kaul VV, Munoz SJ. Coagulopathy of liver disease. *Curr Treat Options Gastroenterol* 2000;3(6):433-38. [PMID: 11096602] https://pubmed.ncbi.nlm.nih.gov/11096602

Klevens RM, Canary L, Huang X, et al. The burden of hepatitis C infection-related liver fibrosis in the United States. *Clin Infect Dis* 2016;63(8):1049-55. [PMID: 27506688] https://pubmed.ncbi.nlm.nih.gov/27506688

Lai M, Afdhal NH. Liver fibrosis determination. *Gastroenterol Clin North Am* 2019;48(2):281-89. [PMID: 31046975] https://pubmed.ncbi.nlm.nih.gov/31046975

Lau DT, Hewlett AT. Screening for hepatitis A and B antibodies in patients with chronic liver disease. *Am J Med* 2005;118 Suppl 10A:28s-33s. [PMID: 16271538] https://pubmed.ncbi.nlm.nih.gov/16271538

Lecube A, Hernandez C, Genesca J, et al. High prevalence of glucose abnormalities in patients with hepatitis C virus infection: a multivariate analysis considering the liver injury. *Diabetes Care* 2004;27(5):1171-75. [PMID: 15111540] https://pubmed.ncbi.nlm.nih.gov/15111540

Li(a) J, Gordon SC, Rupp LB, et al. Sustained virological response does not improve long-term glycaemic control in patients with type 2 diabetes and chronic hepatitis C. *Liver Int* 2019;39(6):1027-32. [PMID: 30570808] https://pubmed.ncbi.nlm.nih.gov/30570808

Li(b) J, Gordon SC, Rupp LB, et al. Sustained virological response to hepatitis C treatment decreases the incidence of complications associated with type 2 diabetes. *Aliment Pharmacol Ther* 2019;49(5):599-608. [PMID: 30650468] https://pubmed.ncbi.nlm.nih.gov/30650468

Loomba R, Huang DQ, Sanyal AJ, et al. Liver stiffness thresholds to predict disease progression and clinical outcomes in bridging fibrosis and cirrhosis. *Gut* 2023;72(3):581-89. [PMID: 36750244] https://pubmed.ncbi.nlm.nih.gov/36750244

Mehta SH, Brancati FL, Strathdee SA, et al. Hepatitis C virus infection and incident type 2 diabetes. *Hepatology* 2003;38(1):50-56. [PMID: 12829986] https://pubmed.ncbi.nlm.nih.gov/12829986

Mehta SH, Brancati FL, Sulkowski MS, et al. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med* 2000;133(8):592-99. [PMID: 11033586] https://pubmed.ncbi.nlm.nih.gov/11033586

Minami T, Tateishi R, Fujiwara N, et al. Impact of obesity and heavy alcohol consumption on hepatocellular carcinoma development after HCV eradication with antivirals. *Liver Cancer* 2021;10(4):309-19. [PMID: 34414119] https://pubmed.ncbi.nlm.nih.gov/34414119

Moucari R, Asselah T, Cazals-Hatem D, et al. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. *Gastroenterology* 2008;134(2):416-23. [PMID: 18164296] https://pubmed.ncbi.nlm.nih.gov/18164296

Ogawa E, Furusyo N, Shimizu M, et al. Non-invasive fibrosis assessment predicts sustained virological response to telaprevir with pegylated interferon and ribavirin for chronic hepatitis C. *Antivir Ther* 2015;20(2):185-92. [PMID: 24941012] https://pubmed.ncbi.nlm.nih.gov/24941012

Patel K, Shackel NA. Current status of fibrosis markers. *Curr Opin Gastroenterol* 2014;30(3):253-59. [PMID: 24671009] https://pubmed.ncbi.nlm.nih.gov/24671009

Patel K, Thompson AJ, Chuang WL, et al. Insulin resistance is independently associated with significant hepatic fibrosis in Asian chronic hepatitis C genotype 2 or 3 patients. *J Gastroenterol Hepatol* 2011;26(7):1182-88. [PMID: 21410752] https://pubmed.ncbi.nlm.nih.gov/21410752

Petta S, Camma C, Di Marco V, et al. Insulin resistance and diabetes increase fibrosis in the liver of patients with genotype 1 HCV infection. *Am J Gastroenterol* 2008;103(5):1136-44. [PMID: 18477344] https://pubmed.ncbi.nlm.nih.gov/18477344

Poynard T, Vergniol J, Ngo Y, et al. Staging chronic hepatitis C in seven categories using fibrosis biomarker (FibroTest) and transient elastography (FibroScan(R)). *J Hepatol* 2014;60(4):706-14. [PMID: 24291240] https://pubmed.ncbi.nlm.nih.gov/24291240

Sackey B, Shults JG, Moore TA, et al. Evaluating psychiatric outcomes associated with direct-acting antiviral treatment in veterans with hepatitis C infection. *Ment Health Clin* 2018;8(3):116-21. [PMID: 29955556] https://pubmed.ncbi.nlm.nih.gov/29955556

Schiavon Lde L, Narciso-Schiavon JL, de Carvalho-Filho RJ. Non-invasive diagnosis of liver fibrosis in chronic hepatitis C. *World J Gastroenterol* 2014;20(11):2854-66. [PMID: 24659877] https://pubmed.ncbi.nlm.nih.gov/24659877

Schmid P, Bregenzer A, Huber M, et al. Progression of liver fibrosis in HIV/HCV co-infection: a comparison between non-invasive assessment methods and liver biopsy. *PLoS One* 2015;10(9):e0138838. [PMID: 26418061] https://pubmed.ncbi.nlm.nih.gov/26418061

Seeff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. *Clin Gastroenterol Hepatol* 2010;8(10):877-83. [PMID: 20362695] https://pubmed.ncbi.nlm.nih.gov/20362695

Shaikh S, Memon MS, Ghani H, et al. Validation of three non-invasive markers in assessing the severity of liver fibrosis in chronic hepatitis C. *J Coll Physicians Surg Pak* 2009;19(8):478-82. [PMID: 19651008] https://pubmed.ncbi.nlm.nih.gov/19651008

Shoreibah MG, Bloomer JR, McGuire BM, et al. Surveillance for hepatocellular carcinoma: evidence, guidelines and utilization. *Am J Med Sci* 2014;347(5):415-19. [PMID: 24759379] https://pubmed.ncbi.nlm.nih.gov/24759379

Simmons B, Saleem J, Heath K, et al. Long-term treatment outcomes of patients infected with hepatitis C virus: a systematic review and meta-analysis of the survival benefit of achieving a sustained virological response. *Clin Infect Dis* 2015;61(5):730-40. [PMID: 25987643] https://pubmed.ncbi.nlm.nih.gov/25987643

Sulkowski MS, Chuang WL, Kao JH, et al. No evidence of reactivation of hepatitis B virus among patients treated with ledipasvir-sofosbuvir for hepatitis C virus infection. *Clin Infect Dis* 2016;63(9):1202-4. [PMID: 27486112] https://pubmed.ncbi.nlm.nih.gov/27486112

Takayama H, Sato T, Ikeda F, et al. Reactivation of hepatitis B virus during interferon-free therapy with daclatasvir and asunaprevir in patient with hepatitis B virus/hepatitis C virus co-infection. *Hepatol Res* 2016;46(5):489-91. [PMID: 26297529] https://pubmed.ncbi.nlm.nih.gov/26297529

Tapper EB, Castera L, Afdhal NH. FibroScan (vibration-controlled transient elastography): where does it stand in the United States practice. *Clin Gastroenterol Hepatol* 2015;13(1):27-36. [PMID: 24909907] https://pubmed.ncbi.nlm.nih.gov/24909907

Tazawa J, Maeda M, Nakagawa M, et al. Diabetes mellitus may be associated with hepatocarcinogenesis in patients with chronic hepatitis C. *Dig Dis Sci* 2002;47(4):710-15. [PMID: 11991597] https://pubmed.ncbi.nlm.nih.gov/11991597

Thompson AJ, Patel K, Chuang WL, et al. Viral clearance is associated with improved insulin resistance in genotype 1 chronic hepatitis C but not genotype 2/3. *Gut* 2012;61(1):128-34. [PMID: 21873466] https://pubmed.ncbi.nlm.nih.gov/21873466

Torrens M, Soyemi T, Bowman D, et al. Beyond clinical outcomes: the social and healthcare system implications of hepatitis C treatment. *BMC Infect Dis* 2020;20(1):702. [PMID: 32972393] https://pubmed.ncbi.nlm.nih.gov/32972393

Tsui JI, Williams EC, Green PK, et al. Alcohol use and hepatitis C virus treatment outcomes among patients receiving direct antiviral agents. *Drug Alcohol Depend* 2016;169:101-9. [PMID: 27810652] https://pubmed.ncbi.nlm.nih.gov/27810652

Vandenbulcke H, Moreno C, Colle I, et al. Alcohol intake increases the risk of HCC in hepatitis C virus-related compensated cirrhosis: a prospective study. *J Hepatol* 2016;65(3):543-51. [PMID: 27180899] https://pubmed.ncbi.nlm.nih.gov/27180899

Veldt BJ, Chen W, Heathcote EJ, et al. Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. *Hepatology* 2008;47(6):1856-62. [PMID: 18506898] https://pubmed.ncbi.nlm.nih.gov/18506898

Verveer C, Zondervan PE, ten Kate FJ, et al. Evaluation of transient elastography for fibrosis assessment compared with large biopsies in chronic hepatitis B and C. *Liver Int* 2012;32(4):622-28. [PMID: 22098684] https://pubmed.ncbi.nlm.nih.gov/22098684

Wang C, Ji D, Chen J, et al. Hepatitis due to reactivation of hepatitis B virus in endemic areas among patients with hepatitis C treated with direct-acting antiviral agents. *Clin Gastroenterol Hepatol* 2017;15(1):132-36. [PMID: 27392759] https://pubmed.ncbi.nlm.nih.gov/27392759

Westin J, Lagging LM, Spak F, et al. Moderate alcohol intake increases fibrosis progression in untreated patients with hepatitis C virus infection. *J Viral Hepat* 2002;9(3):235-41. [PMID: 12010513] https://pubmed.ncbi.nlm.nih.gov/12010513

Yuan M, Zhou J, Du L, et al. Hepatitis C virus clearance with glucose improvement and factors affecting the glucose control in chronic hepatitis C patients. *Sci Rep* 2020;10(1):1976. [PMID: 32029793] https://pubmed.ncbi.nlm.nih.gov/32029793

Zhou Y, Xie W, Zheng C, et al. Hypoglycemia associated with direct-acting anti-hepatitis C virus drugs: an epidemiologic surveillance study of the FDA adverse event reporting system (FAERS). *Clin Endocrinol (Oxf)* 2022;96(5):690-97. [PMID: 34913180] https://pubmed.ncbi.nlm.nih.gov/34913180

Supplement: Guideline Development and Recommendation Ratings

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Developer	New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program
Funding source	NYSDOH AI
Program manager	Clinical Guidelines Program, Johns Hopkins University School of Medicine, Division of Infectious Diseases. See Program Leadership and Staff.
Mission	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.
Expert committees	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.
Committee structure	• 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 • Contributing members • Guideline writing groups: Lead author, coauthors if applicable, and all committee leaders
Disclosure and management of conflicts of interest	• 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. • 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.
Evidence collection and review	• Literature search and review strategy is defined by the guideline lead author based on the defined scope of a new guideline or update. • 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. • A targeted search and review to identify recently published evidence is conducted for guidelines published within the previous 3 years. • 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.

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Recommendation development	• The lead author drafts recommendations to address the defined scope of the guideline based on available published data. • Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations. • When published data are not available, support for a recommendation may be based on the committee's expert opinion. • 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.
Review and approval process	• Following writing group approval, draft guidelines are reviewed by all contributors, program liaisons, and a volunteer reviewer from the AI Community Advisory Committee. • 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. • Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.
External reviews	• External review of each guideline is invited at the developer's discretion. • External reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback.
Update process	• 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. • 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.

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†	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.