Simplified HCV Treatment for All Genotypes

This is a PDF version of the following document:
Module 4: Treatment of Hepatitis C Infection
Lesson 2: Simplified HCV Treatment for All Genotypes

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Background

The advent of interferon-free, direct-acting antiviral (DAA) therapy in 2014-2015 revolutionized the landscape of hepatitis C virus (HCV) therapy, allowing for shorter, safer, and more effective treatment of chronic HCV. This success has led to a paradigm shift in HCV treatment, with national and international guidelines calling for the treatment of all adults with HCV, regardless of fibrosis stage or active substance use.[1,2]

In 2016, the World Health Organization (WHO) released strategic targets to help achieve the elimination of viral hepatitis by 2030.[3] In addition, in 2017, the National Academies of Sciences, Engineering, and Medicine similarly released a strategy to eliminate viral hepatitis in the United States, calling for a 90% reduction in HCV incidence by 2030.[4] Achieving these ambitious targets is predicated on expanding the available HCV treatment, a process that can be facilitated by simplified care pathways and treatment algorithms.

This lesson will review the simplified treatment approach for HCVin treatment-naïve adults (without cirrhosis or with compensated cirrhosis) based on guidance from the American Association for the Study of the Liver (AASLD) and Infectious Diseases Society of America (IDSA).[5,6,7] The simplified treatment approach applies to most patients with chronic HCV and can help streamline the pretreatment evaluation, treatment choices, and monitoring during and after treatment.[5,6,7]

Eligibility for Simplified HCV Treatment

The AASLD-IDSA HCV Guidance recommends treatment for all persons with chronic HCV, except for individuals who have a short (e.g., less than 12 months) life expectancy.[1] Therefore, all persons diagnosed with chronic HCV should be considered candidates for HCV treatment and evaluated as potential candidates for the simplified treatment approach. As summarized below, assessment of liver fibrosis is an important part of this process. We have outlined the general flow of evaluating a person with chronic HCV who may be a candidate for the simplified treatment algorithm. This initial assessment should include laboratory studies, evaluation of fibrosis status, and screening for the simplified treatment criteria. All individuals with cirrhosis should have further evaluation for evidence of hepatic decompensation. Once a person has been determined to meet the criteria for the simplified treatment approach, they can be stratified as (1) persons without cirrhosis or (2) persons with compensated cirrhosis.

Eligibility Criteria for Simplified Treatment Approach

The simplified treatment guidance primarily applies to adults with chronic HCV who are treatment naïve, including persons without cirrhosis and those with compensated cirrhosis.[5,6,7] Persons with decompensated cirrhosis are not eligible for the simplified treatment approach.[7] The simplified treatment approach utilizes the pangenotypic regimens glecaprevir-pibrentasvir and sofosbuvir-velpatasvir. Prior treatment experience excludes use of the simplified treatment approach because glecaprevir-pibrentasvir and sofosbuvir-velpatasvir are not uniformly appropriate for treatment-experienced patients.[7,8] Clinicians should follow the AASLD-IDSA HCV Guidance for treatment-experienced individuals, which is subdivided by the type of prior treatment.[8] Similarly, the simplified treatment guidelines are not intended for patients with chronic hepatitis B virus (HBV) coinfection due to the potential for HBV reactivation and the necessity for closer monitoring during treatment.[7,9] Further, the simplified algorithm does not apply to HCV treatment in pregnant women, given limited data for this approach in pregnancy.[7] Finally, any patient with known or suspected hepatocellular carcinoma (HCC) and those with a history of liver transplantation should not be treated under the simplified algorithm.[7] Patients with HCC require additional evaluation by a liver tumor specialist prior to undergoing HCV treatment, and they experience lower rates of sustained virologic response 12 weeks (SVR12) after completing HCV therapy than patients without HCC.[10] Similarly, patients with a history of liver transplantation require careful evaluation for drug interactions that may impact the pharmacokinetics of DAAs and common post-transplant immunosuppressant medications.[11]

Table 1. Eligibility Criteria for Simplified Treatment: AASLD/IDSA HCV Guidance

Who is Eligible for Simplified HCV Treatment Algorithm	Who is Excluded from Simplified HCV Treatment Algorithm
Adults with chronic HCV infection, including persons living with HIV: • Infected with any HCV genotype • Have NOT previously received HCV treatment • Without cirrhosis • With compensated cirrhosis (Child-Pugh*A) • The determination of cirrhosis can be based on the presence of any of the following: - Liver stiffness >12.5 kPa by FibroScan - FIB-4 >3.25 - Non-invasive serologic test (HCV FibroSure or enhanced liver fibrosis test) above proprietary cutoff - Liver biopsy showing cirrhosis - Liver nodularity or splenomegaly on imaging - Platelet count <150,000/mm^3 • The determination of compensated versus	**Adults with chronic HCV infection who have any of the following:** • Previously received HCV treatment • Hepatitis B surface antigen-positive • Compensated cirrhosis (Child-Pugh A*) with end-stage renal disease (eGFR <30 mL/min/m^2) • Current or prior decompensated cirrhosis, defined by Child-Pugh score ≥7 • Current pregnancy • Known or suspected hepatocellular carcinoma • Prior liver transplantation

Source: uncomplicated cirrhosis is based on Child-Pugh* score

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis. [AASLD-IDSA Hepatitis C Guidance]
- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis. [[AASLD-IDSA Hepatitis C Guidance]

Authors Note: The above table was generated from several resources from the AASLD-IDSA HCV Guidance.[5,6,7,12] In this table, we have clarified which criteria can be used to determine cirrhosis status and which criteria are used to distinguish compensated cirrhosis or decompensated cirrhosis. See the Fibrosis-4 (FIB-4) and Child-Turcotte-Pugh (CTP) calculators on this website.

Assessing Liver Fibrosis Status

For all persons diagnosed with HCV who are considering HCV treatment, it is essential to evaluate their liver fibrosis status as soon as possible after HCV diagnosis for the following four reasons:

1. Persons identified with cirrhosis need subsequent evaluation to determine whether they have compensated or decompensated cirrhosis, since persons with decompensated cirrhosis are not eligible for the simplified treatment approach, and they need a prompt referral to a liver specialist for expert management.
2. Once cirrhosis status is determined, the treatment-naïve patient with chronic HCV can be stratified into one of two categories: persons without cirrhosis or persons with compensated cirrhosis. The simplified treatment approach has a slightly different algorithm for persons without cirrhosis compared to those with compensated cirrhosis.
3. All persons identified with cirrhosis will need a liver ultrasound examination performed within 6 months prior to treatment to evaluate for hepatocellular carcinoma, as persons with hepatocellular carcinoma are not eligible for the simplified treatment approach and they need a referral to a liver cancer specialist.
4. All persons identified with cirrhosis need long-term, regular screening for hepatocellular carcinoma, typically every 6-month liver ultrasound, with or without alpha-fetoprotein.

For the purpose of the simplified treatment algorithm, the FIB-4 can be used to identify patients with or without cirrhosis. This simple, noninvasive test utilizes the patient's age, aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level, and platelet count to calculate a score that estimates the degree of fibrosis. In clinical studies, a lower cutoff value of 1.45 (FIB-4 score 3.25) has been shown to be 97% specific for advanced fibrosis with a positive predictive value of 65%.[13] Patients with a FIB-4 score of >3.25 should be considered to have cirrhosis and follow the simplified treatment algorithm outlined in this section.[13] In addition, the AASLD-IDSA HCV Guidance notes the following finding, even if they were previously obtained, establishes a presumptive diagnosis of cirrhosis:[5,6,7]

- FibroScan indicates liver stiffness with a score greater than 12.5 kPa
- Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (e.g., FibroSure, Enhanced Liver Fibrosis test)
- Evidence of cirrhosis on imaging (e.g., liver nodularity and/or splenomegaly or a platelet count less than 150,000/mm^3, etc.)
- Prior liver biopsy showing cirrhosis

Evaluation for Decompensated Cirrhosis

All persons identified with cirrhosis should have a clinical and laboratory evaluation to determine whether the cirrhosis is compensated or decompensated. In the setting of presumptive or confirmed cirrhosis (or advanced fibrosis), clinicians should calculate a Child-Turcotte-Pugh (CTP) score. See the CTP Calculator on this website. This score, which is a proxy of overall liver function, takes into consideration both laboratory values (bilirubin, albumin, and international normalized ratio [INR]) and clinical manifestations (encephalopathy and ascites). A CTP score of 7 or greater (class B or C) indicates decompensated cirrhosis.[6,14] Although studies note that many patients with decompensated cirrhosis experience improvement in clinical and laboratory markers of liver disease following treatment with DAAs, they remain at high risk for liver-related death and may progress to need transplantation regardless of HCV treatment.[15,16] Furthermore, DAA regimens containing a protease inhibitor (e.g., **glecaprevir**-pibrentasvir, sofosbuvir-velpatasvir-**voxilaprevir**, elbasvir-**grazoprevir**) are not recommended for use in patients with decompensated cirrhosis, because of the risk of hepatotoxicity and hepatic decompensation.[17,18] As such, patients with decompensated cirrhosis are not eligible for the simplified treatment approach, and they should be managed by a hepatologist (or another health professional who has expertise in liver disease), ideally at a liver transplantation center.[19]

Pretreatment Assessment for Adults without Cirrhosis

Most pretreatment laboratory studies will have been conducted during the initial assessment to determine eligibility for the simplified treatment algorithm. Nevertheless, it is important to ensure all pretreatment laboratory studies and recommended education have been completed and reviewed prior to initiating treatment. In addition, individuals who qualify for the simplified treatment algorithm should have a comprehensive medication reconciliation performed, which includes a review of over-the-counter medications.[5,12] This medication review serves to identify potential drug-drug interactions with commonly used DAA regimens. Resources to screen for drug interactions are available online, including in the Monitoring Section on the AASLD/IDSA guidance website and the University of Liverpool Hep Drug Interactions website (a resource that can also be downloaded as an app on mobile devices). The necessary pretreatment laboratory studies for persons without cirrhosis, as recommended in the AASLD-IDSA HCV Guidance, are listed in the table below.[5]

Table 2. Pretreatment Assessment for Treatment-Naïve Adults without Cirrhosis: AASLD/IDSA HCV Guidance

Before Initiating Antiviral Therapy
• Calculate a FIB-4 score[a]
• Assess for Cirrhosis[b]
• Obtain CBC
• Obtain hepatic function panel ◦ Total and direct bilirubin ◦ Albumin ◦ ALT, AST
• Determine eGFR
• Perform medication reconciliation[c]
• Assess for drug-drug interactions[d]
• Check quantitative HCV RNA (viral load)
• Obtain HIV-1/2 antigen-antibody test
• Check hepatitis B surface antigen (*see Author's Notes*)
• Obtain serum pregnancy testing and counsel about pregnancy risk and DAAs
• Educate about DAA administration and adherence, prevention of reinfection, and avoiding excess alcohol
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; DAA = direct-acting antiviral; eGFR = estimated glomerular filtration rate; FIB-4 = fibrosis-4 index for liver fibrosis; HCV = hepatitis C virus; INR = international normalized ratio. [a] FIB-4 is a noninvasive measure of hepatic fibrosis that is calculated using age (years), AST, ALT, and platelet count. [b] A patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 or if they have any of the following from a previously performed test: transient elastography indicating cirrhosis (i.e., liver stiffness >12.5 kPa), noninvasive serologic test above the proprietary cutoff indicating cirrhosis (e.g., FibroSure, enhanced liver fibrosis test), clinical evidence of cirrhosis (e.g., liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm^3), or prior liver biopsy showing cirrhosis. [c] Medication reconciliation should record currently prescribed medications, over-the-counter drugs, and herbal/dietary supplements. [d] Drug-drug interaction assessment should be performed using the table in the Monitoring Section of the HCV Guidance website or the University of Liverpool drug interaction checker.

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C.

Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis. [[AASLD-IDSA Hepatitis C Guidance]]

Authors Notes:

1. As noted in the table above, the AASLD/IDSA recommends checking hepatitis B surface antigen. In 2023, the Centers for Disease Control and Prevention (CDC) issued updated hepatitis B screening recommendations using the triple screen with hepatitis B surface antigen HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc).[20]

Simplified Treatment Regimens for Adults without Cirrhosis

Routine genotype assessment is not part of the simplified HCV treatment algorithm for patients without cirrhosis according to the AASLD-IDSA HCV Guidance.[5,7] The following two pangenotypic regimens are recommended as HCV treatment for persons without cirrhosis who have met eligibility for the simplified treatment approach.[5,7]

Table 3. AASLD-IDSA HCV Simplified Guidance for All Genotypes: Initial Treatment
Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis

Regimens listed alphabetically

Recommended for Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis
Glecaprevir-Pibrentasvir **Fixed-dose combination of glecaprevir-pibrentasvir. Take 3 tablets daily for 8 weeks. Total daily dose = 300 mg of glecaprevir and 120 mg of pibrentasvir.*
Note: *Take with food

Recommended for Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis
Sofosbuvir-Velpatasvir ***Fixed-dose combination of sofosbuvir-velpatasvir. Take 1 tablet once daily for 12 weeks. Total daily dose = 400 mg of sofosbuvir and 100 mg of velpatasvir.*
Note: **Take with or without food

Source: AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis. [[AASLD-IDSA Hepatitis C Guidance]

The glecaprevir-pibrentasvir and sofosbuvir-velpatasvir regimens have proven efficacy in treatment-naïve patients without cirrhosis, regardless of genotype. Below is a brief summary of the main registration trials of glecaprevir-pibrentasvir and sofosbuvir-velpatasvir in treatment-naïve patients without cirrhosis.

Glecaprevir-Pibrentasvir

- ENDURANCE-1: This phase 3, single-arm open-label trial evaluated the safety and efficacy of 8 versus 12 weeks of glecaprevir-pibrentasvir in 703 genotype 1 patients without cirrhosis, 62% of whom were treatment naïve.[21] Among the 336 patients enrolled in the 8-week arm, 99.1% achieved an SVR12, compared with 99.7% of the 334 patients enrolled in the 12-week arm.[21]
- SURVEYOR-II (Part 4): This phase-3, single-arm, open-label trial evaluated the safety and efficacy of 8 weeks of glecaprevir-pibrentasvir in 203 adults without cirrhosis and with genotype 2, 4, 5, or 6.[22] In the intention-to-treat analysis, the overall SVR12 rate was 96% across all genotypes.[22]
- ENDURANCE-3: This phase-3, randomized trial compared the safety and efficacy of 8 or 12 weeks of glecaprevir-pibrentasvir versus 12 weeks of sofosbuvir and daclatasvir in treatment-naïve adults without cirrhosis and with HCV genotype 3.[21] In total, 157 people were assigned to 8 weeks of

glecaprevir-pibrentasvir, of whom 95% achieved an SVR12.[21] Similar results were observed in the 12-week arm.[21]

Sofosbuvir-Velpatasvir

- ASTRAL-1: This phase-3 trial randomized treatment-naïve and treatment-experienced adults with hepatitis C genotypes 1, 2, 4, 5, or 6 to receive 12 weeks of sofosbuvir-velpatasvir versus placebo.[23] Among the 624 people who received sofosbuvir-velpatasvir, 99% achieved an SVR12.[23]
- ASTRAL-3: This phase-3 randomized, open-label trial compared sofosbuvir-velpatasvir for 12 weeks versus sofosbuvir plus ribavirin for 24 weeks in adults with genotype 3.[24] Among the 206 treatment-naïve participants, 97% achieved an SVR12, which was significantly higher than the 87% of treatment-naïve patients who received sofosbuvir plus ribavirin.[24]
- MINMON (ACTGA5360): This international phase 4, open-label, single-arm trial used a simplified treatment approach to provide a 12-week course of sofosbuvir-velpatasvir for 399 treatment-naïve adults with chronic HCV.[25] This trial included persons with HIV and/or compensated cirrhosis, comprising 42% and 9% of participants, respectively.[25] In this trial, key elements of the simplified approach included use of FIB-4 to assess for cirrhosis, absence of pretreatment genotyping, and dispensing the entire course of sofosbuvir-velpatasvir before treatment began. In addition, no scheduled on-treatment labs or in-person visits were performed, and participants had remote contact (e.g., phone call) with the care teams at weeks 4 and 22; the SVR12 labs were drawn at week 24.[25] Overall, 95% of study participants were cured of HCV, including 95% with HCV monoinfection and 95% with HCV and HIV coinfection.[25] Among the participants without cirrhosis, 96% were cured.[25]

Monitoring Patients without Cirrhosis

Monitoring While On Treatment

Limited on-treatment monitoring is needed for treatment-naïve and noncirrhotic patients while on DAA therapy. Testing HCV RNA levels or hepatic enzymes/function is not necessary during treatment, as these results have not been shown to change management in patients without cirrhosis.[5] Treatment of HCV with DAAs has been shown to improve glycemic control in patients with chronic HCV, and, thus, patients undergoing treatment with DAAs who are concomitantly taking medications for diabetes should be informed about the potential for symptomatic hypoglycemia, and monitoring for hypoglycemia is recommended.[5,26] Although neither glecaprevir-pibrentasvir nor sofosbuvir-velpatasvir is likely to affect the pharmacokinetics of warfarin, close monitoring of INR is recommended for patients on warfarin therapy, given that it may change as a result of improved liver function.[27,28]

Table 4. Simplified Treatment, Without Cirrhosis, Monitoring On-Treatment: AASLD/IDSA HCV Guidance

Monitoring On-Treatment
• Monitor for hypoglycemia in patients taking medications for diabetes.
• Monitor for sub-therapeutic INR in patients taking warfarin.
• No laboratory monitoring is required for other patients.
• In-person or remote (telehealth/phone) visits may be scheduled, as needed, for patient support and to assess tolerance of new medications.
Abbreviations: INR – international normalized ratio

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis. [[AASLD-IDSA Hepatitis C Guidance]]

Post-Treatment Assessment of Cure

A follow-up HCV RNA level and repeat liver function tests are recommended 12 weeks or longer following the completion of therapy to assess for cure and ongoing evidence of liver inflammation, respectively.[5,7] If the HCV RNA level is undetectable 12 or more weeks following the completion of therapy, this is considered a sustained virologic response or cure. Although SVR12 has been the gold standard for assessing cure, real-world studies indicate that up to 25% of treated individuals can be lost to follow-up before SVR12 can be assessed.[29] To mitigate this loss, an SVR4, which has very high concordance with SVR12 (>99%), can be measured for an earlier determination of cure.[30] The AASLD-IDSA HCV Guidance offers SVR4 as an acceptable option for patients without cirrhosis or prior treatment experience.[5] If transaminase levels remain elevated despite achieving an SVR, further investigation is warranted to assess for other causes of liver disease.[5,7]

Table 5. Simplified Treatment, Without Cirrhosis, Post-Treatment Assessment of Cure: AASLD/IDSA HCV Guidance

Post-Treatment Monitoring
• Obtain quantitative HCV RNA and hepatic function panel 12 weeks or later following completion of HCV therapy.
• If quantitative HCV RNA is undetectable 12+ weeks following completion of HCV therapy, the patient is considered to have achieved an SVR, also known as a cure.

• Assess for other causes of liver disease if transaminase levels remain elevated after achieving an SVR.
Abbreviations: SVR = sustained virologic response

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis. [[AASLD-IDSA Hepatitis C Guidance]]

Post-Treatment Follow-Up After Virologic Cure

Patients without cirrhosis who achieve a virologic cure do not require any screening or monitoring for hepatocellular carcinoma.[7,31] Patients should, however, be counseled that they are not immune to HCV following successful treatment and are susceptible to reinfection.[5,7] Patients with ongoing risk factors (e.g., people who inject drugs, men who have sex with men and engage in condomless anal intercourse) should be screened annually for reinfection using HCV RNA testing.[7,32]

Table 6. Simplified Treatment, Without Cirrhosis, Cure after Treatment: AASLD/IDSA HCV Guidance

Post-Treatment Follow-Up After Achieving Virologic Cure
• No liver-specific follow-up is needed for patients without advanced fibrosis following SVR.
• Patients with ongoing risk factors for HCV should be counseled regarding their risk for reinfection and undergo testing for HCV RNA annually and with any elevation in ALT, AST or bilirubin.
• Patients should be advised to avoid excessive alcohol.
Abbreviations: SVR = sustained virologic response

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis. [[AASLD-IDSA Hepatitis C Guidance]]

Post-Treatment Follow-Up When Virologic Cure Not Achieved

If initial treatment fails to achieve a virologic cure, patients should be referred to a specialist who can evaluate them for repeat treatment.[7] In the setting of prior treatment experience, patients are not eligible for the simplified treatment algorithm, and the treatment plan should follow the AASLD-IDSA HCV Guidance for repeat treatment.[8] While a patient is awaiting repeat treatment, a complete blood count (CBC), and hepatic function panel, with or without an INR, should be obtained every 6 to 12 months.[5,7]

Table 7. Simplified Treatment, Without Cirrhosis, No Cure after Treatment: AASLD/IDSA HCV Guidance

Post-Treatment Follow-Up for Patients who Do *NOT* Achieve Virologic Cure
• When initial HCV treatment fails to achieve a cure (SVR), patients should be evaluated for retreatment by a specialist, in accordance with AASLD/IDSA HCV guidance.
• Assess disease progression with a CBC, hepatic function panel, and INR every 6 – 12 months until retreatment occurs.
• Patients should be advised to avoid excessive alcohol.
Abbreviations: SVR = sustained virologic response; CBC = complete blood count; INR = international

normalized ratio

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis. [[AASLD-IDSA Hepatitis C Guidance]]

Pretreatment Assessment for Adults with Compensated Cirrhosis

Individuals with compensated cirrhosis who qualify for the simplified treatment algorithm should have a pretreatment laboratory evaluation similar to that in patients without cirrhosis. A comprehensive medication reconciliation should also be performed, as this serves to identify potential drug interactions with commonly used DAA regimens.[6,12] Resources to screen for drug interactions are available online, including in the Monitoring Section on the AASLD/IDSA guidance website and the University of Liverpool Hep Drug Interactions website. The main distinction for patients with compensated cirrhosis is that a baseline HCV genotype is recommended when considering the use of sofosbuvir-velpatasvir, as resistance-associated substitutions (RAS) can adversely impact SVR12 rates among genotype 3 patients with compensated cirrhosis.[24,33,34] The necessary pretreatment laboratory studies for persons with cirrhosis, as recommended in the AASLD-IDSA HCV Guidance, are listed in the table below.[5]

Table 8. Pretreatment Assessment for Treatment-Naïve Adults With Compensated Cirrhosis: AASLD/IDSA HCV Guidance

Assessment Before Initiating Antiviral Therapy
• Calculate a Child-Pugh Score[a] (*see Authors Notes*)
• Perform liver ultrasound
• Obtain complete blood count (CBC)
• Check international normalized ratio (INR)
• Obtain hepatic function panel ◦ Total and direct bilirubin ◦ Albumin ◦ ALT, AST
• Determine eGFR
• Perform medication reconciliation[c]
• Assess for drug-drug interactions[d]
• Check quantitative HCV RNA
• Obtain HIV-1/2 antigen-antibody test
• Check hepatitis B surface antigen (*see Authors Notes*)
• Check HCV genotype (if treating with sofosbuvir-velpatasvir)
• Obtain serum pregnancy testing and counsel about pregnancy risk and DAAs
• Educate about DAA administration and adherence, prevention of reinfection, and avoiding excess alcohol
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; DAA = direct-acting antiviral; eGFR = estimated glomerular filtration rate; FIB-4 = fibrosis-4 index for liver fibrosis; HCV = hepatitis C virus; INR = international normalized ratio. [a] Child–Pugh score based on presence of ascites, hepatic encephalopathy, total bilirubin >2.0 mg/dL, albumin ≤3.5 g/dL, or INR ≥1.7. Patients with a Child–Pugh score ≥7 (ie, Child–Pugh B or C) have decompensated cirrhosis; this simplified treatment approach is not recommended for patients with decompensated cirrhosis. [b] Obtain liver ultrasound within 6 months prior to initiating antiviral treatment to exclude hepatocellular carcinoma and subclinical ascites. This simplified treatment approach is not recommended for patients with hepatocellular carcinoma and/or decompensated cirrhosis [c] Medication reconciliation should record currently prescribed medications, over-the-counter drugs, and herbal/dietary supplements. [d] Drug-drug interaction assessment should be performed using the table in the Monitoring Section of the HCV Guidance website or the University of Liverpool drug interaction checker.

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis. [AASLD-IDSA Hepatitis C Guidance]
- Bhattacharya D, Aronsohn A, Price J, Lo Re V. Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clin Infect Dis. 2023;ciad319. [PubMed Abstract]

Authors Note:

- For patients with cirrhosis, clinicians should calculate a Child-Turcotte-Pugh (CTP) score (see the CTP calculator) that includes total bilirubin, albumin, and INR, as well as clinical severity of encephalopathy or ascites if present.[14] Use of DAA regimens containing a protease inhibitor (e.g., glecaprevir-pibrentasvir, sofosbuvir-velpatasvir-voxilaprevir, elbasvir-grazoprevir) is not recommended for use in patients with decompensated cirrhosis, owing to the risk of hepatic decompensation and overall limited data.[17,18]

Simplified Treatment Regimens for Adults with Compensated Cirrhosis

The AASLD-IDSA HCV Guidance recommends the following two pangenotypic regimens for persons with compensated cirrhosis who have met eligibility for the simplified treatment approach: glecaprevir-pibrentasvir or sofosbuvir-velpatasvir.[6,7] If sofosbuvir-velpatasvir is planned for the treatment of a patient with compensated cirrhosis, an HCV genotype should be performed. If HCV genotype 3 is identified, then baseline resistance-associated substitution (RAS) testing is recommended. If the patient has compensated cirrhosis, HCV genotype 3 HCV, and a baseline Y93H mutation, sofosbuvir-velpatasvir should not be used alone, due to evidence of decreased efficacy in this specific setting.[6,24] Weight-based ribavirin could be added to sofosbuvir-velpatasvir to avoid ribavirin toxicity. In this situation, to avoid the potential ribavirin-associated toxicity, use of glecaprevir-pibrentasvir would be preferred. In addition, if baseline NS5A resistance-associated substitution testing is not sent or not available, then glecaprevir-pibrentasvir should be used.[6]

Table 9. AASLD-IDSA HCV Simplified Guidance for All Genotypes: Initial Treatment
Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis^

Regimens listed alphabetically

Recommended for Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis^
Glecaprevir-Pibrentasvir **Fixed-dose combination of glecaprevir-pibrentasvir. Take 3 tablets once daily for 8 weeks. Total daily dose = 300 mg of glecaprevir and 120 mg of pibrentasvir.*
For Genotypes 1-6 Note: *Take with food

Recommended for Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis^
Sofosbuvir-Velpatasvir ***Fixed-dose combination of sofosbuvir-velpatasvir. Take 1 tablet once daily for 12 weeks. Total daily dose = 400 mg of sofosbuvir and 100 mg of velpatasvir.*
Patients with compensated cirrhosis and HCV genotype 3 require baseline NS5A RAS testing prior to use of sofosbuvir-velpatasvir. Those with a Y93H mutation require the addition of weight-based ribavirin. Note: **Take with or without food

^For patients with decompensated cirrhosis, refer to a liver specialist and see the AASLD-IDSA Guidance: Unique Populations—Patients with Decompensated Cirrhosis.

Source: AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis. [AASLD-IDSA Hepatitis C Guidance]

Both glecaprevir-pibrentasvir and sofosbuvir-velpatasvir have proven efficacy in treatment-naïve patients with cirrhosis. The following is a brief summary of the main registration trials of glecaprevir-pibrentasvir and sofosbuvir-velpatasvir in treatment-naïve patients with compensated cirrhosis.

Glecaprevir-Pibrentasvir

- EXPEDITION-8: This was a single-arm, multicenter, phase 3b trial evaluating the efficacy of glecaprevir-pibrentasvir for 8 weeks in treatment-naïve participants with compensated cirrhosis and genotypes 1-6.[35] Among the 343 people included in this trial, 97.7% achieved an SVR12 in the per protocol analysis.[35]
- Pooled Analysis in Cirrhosis: In an integrated analysis of pooled phase 2/3 trial data, a total of 308 patients with cirrhosis and a range of genotypes received either 12 weeks (80%) or 16 weeks (20%) of glecaprevir-pibrentasvir.[36] No incidents of hepatic injury were noted, and 96.4% achieved an SVR12.[36]

Sofosbuvir-Velpatasvir

- ASTRAL-1: This was a randomized, placebo-controlled, phase 3 trial using a fixed-dose combination of sofosbuvir-velpatasvir for 12 weeks in treatment-naïve and treatment-experienced patients with genotypes 1, 2, 4, 5, or 6.[23] Both patients without cirrhosis and those with compensated cirrhosis were included. Ninety-nine percent of patients with compensated cirrhosis achieved an SVR12, including 99% of those with baseline NS5A RASs.[23]
- ASTRAL-3: This randomized, placebo-controlled, open-label, phase 3 trial compared sofosbuvir-velpatasvir for 12 weeks to sofosbuvir plus ribavirin for 24 weeks in genotype 3 patients with and without compensated cirrhosis.[24] Ninety-three percent of treatment-naïve patients with compensated cirrhosis achieved an SVR12 in the sofosbuvir-velpatasvir arm comparison with 73% in the sofosbuvir plus ribavirin arm.[24] Among those who received sofosbuvir-velpatasvir and had baseline NS5A RASs, 88% achieved an SVR12, compared with 97% of those without baseline substitutions.[24]
- POLARIS-3 This open-label, randomized, phase 3 trial compared the efficacy of sofosbuvir-velpatasvir-voxilaprevir for 8 weeks versus sofosbuvir-velpatasvir for 12 weeks in patients with compensated cirrhosis and genotype 3.[37] Among treatment-naïve patients receiving sofosbuvir-velpatasvir, 99% achieved an SVR12. Four patients in the sofosbuvir-velpatasvir arm had a baseline Y93H mutation, all of whom achieved an SVR12.[37]
- Sofosbuvir-Velpatasvir in Patients with Compensated Cirrhosis and HCV Genotype 3 (Spain): This was a phase 2 trial of sofosbuvir-velpatasvir for 12 weeks versus sofosbuvir-velpatasvir plus ribavirin for 12 weeks in 204 patients with genotype 3 HCV and compensated cirrhosis.[33] Among the patients who received 12 weeks of sofosbuvir-velpatasvir, the SVR12 rate was 91%; participants who received sofosbuvir-velpatasvir and ribavirin had an SVR12 rate of 96%.[33] Among participants in the sofosbuvir-velpatasvir arm, 19 had NS5A RASs, 16 (84%) achieved an SVR12.[33]

Monitoring Patients with Compensated Cirrhosis

Monitoring While On Treatment

Due to the rare but potential risk for hepatic decompensation among patients with compensated cirrhosis on DAA therapy, the AASLD-IDSA HCV Guidance recommend providers consider monitoring for liver injury during treatment.[6,38] Patients should be referred to a specialist if they develop jaundice, ascites, encephalopathy, significant liver laboratory abnormalities, or other signs and symptoms of hepatic decompensation. Treatment with DAAs has been shown to improve glycemic control in patients with chronic HCV, and patients taking any medication for diabetes should be informed about the potential for symptomatic hypoglycemia, and monitoring of blood sugars is recommended.[6,26] Although neither glecaprevir-pibrentasvir nor sofosbuvir-velpatasvir is likely to affect the pharmacokinetics of warfarin, close monitoring of INR is recommended for patients on warfarin therapy, given that it may change as a result of improved liver function.[28,39]

Table 10. Simplified Treatment, Compensated Cirrhosis, Monitoring On-Treatment: AASLD/IDSA HCV Guidance

On-Treatment Monitoring
• Health care providers may order blood tests to monitor for liver injury or hepatic decompensation, both of which occur rarely among patients with cirrhosis undergoing antiviral treatment for HCV
• Patients should see a liver specialist if they develop jaundice, ascites, encephalopathy, other new liver-related symptoms, or worsening liver blood tests (e.g., AST, ALT, bilirubin) during treatment.
• Monitor for hypoglycemia in patients taking medications for diabetes.
• Monitor for subtherapeutic INR in patients taking warfarin.
• No laboratory monitoring is required for other patients.
• In-person or remote (telehealth/phone) visits may be scheduled, as needed, for patient support and to assess tolerance of new medications.
Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase; INR – international normalized ratio

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis. [AASLD-IDSA Hepatitis C Guidance]

Post-Treatment Assessment of Cure

A follow-up HCV RNA level and liver function tests are recommended 12 weeks after the completion of therapy to assess for cure and ongoing evidence of liver inflammation, respectively. If the HCV RNA level is undetectable 12 or more weeks following the completion of therapy, this is considered a sustained virologic response or cure. An HCV RNA level 4 weeks post-treatment (SVR4) is not routinely advised for patients with cirrhosis given more limited data for SVR12 concordance in that subgroup. If transaminase levels remain elevated despite the achievement of an SVR, further investigation is warranted to assess for other causes of liver disease.[6]

Table 11. Simplified Treatment, Compensated Cirrhosis, Assessment of Cure: AASLD/IDSA HCV Guidance

Post-Treatment Monitoring: Assessment of Cure
• Obtain quantitative HCV RNA and hepatic function panel 12 weeks or later following completion of HCV therapy.
• If quantitative HCV RNA is undetectable at least 12 weeks following completion of HCV therapy, the

patient is considered to have achieved a sustained virologic response (SVR), also known as a cure.
• Assess for other causes of liver disease if transaminase levels remain elevated after achieving an SVR.
Abbreviations: SVR = sustained virologic response

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis. [AASLD-IDSA Hepatitis C Guidance]

Monitoring After Achieving Virologic Cure (SVR)

Patients with cirrhosis require ongoing monitoring for hepatocellular carcinoma, even after achieving an SVR12.[31] This is done via a hepatic ultrasound every 6 months, with an alpha-fetoprotein level, in accordance with AASLD guidelines on screening for hepatocellular carcinoma.[40] Patients should also be counseled that they are not immune to HCV following successful treatment and are susceptible to reinfection. Individuals with ongoing risk factors (e.g., people who inject drugs, men who have sex with men and engage in condomless anal intercourse) should be screened annually for reinfection using HCV RNA.[32]

Table 12. Simplified Treatment, Compensated Cirrhosis, Follow-Up After Cure: AASLD/IDSA HCV Guidance

Post-Treatment Follow-up After Achieving Virologic Cure
• The AASLD recommends ultrasound surveillance for HCC (with alpha-fetoprotein testing) every 6 months in patients with cirrhosis.
• An upper endoscopy should be performed for surveillance of esophageal varices in certain patients, in accordance with the AASLD guidelines on portal hypertensive bleeding in cirrhosis.
• Patients with ongoing risk factors for HCV should be counseled regarding their risk for reinfection and undergo testing for HCV RNA annually and with any elevation in ALT, AST or bilirubin.
• Patients should be advised to avoid excessive alcohol.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; HCC = hepatocellular carcinoma

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis. [AASLD-IDSA Hepatitis C Guidance]
- Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. 2023;78:1922-65. [AASLD]

Post-Treatment Follow-Up When Virologic Cure Not Achieved

If initial treatment fails to achieve a virologic cure, patients should be evaluated for repeat treatment.[8] In the setting of prior treatment experience, patients with compensated cirrhosis are not eligible for the simplified treatment algorithm, and patients should be evaluated by a specialist in accordance with AASLD/IDSA guidance.[6] Similarly, as mentioned above, patients with cirrhosis should undergo ultrasound surveillance for hepatocellular carcinoma every six months, with an alpha-fetoprotein level.[40] This surveillance is performed for all patients with advanced fibrosis, regardless of SVR12 status. While a patient is awaiting repeat treatment, a CBC, hepatic function panel, creatinine, and INR should be obtained every 6 to

12 months.

Table 13. Simplified Treatment, Compensated Cirrhosis, Follow-Up After No Cure: AASLD/IDSA HCV Guidance

Post-Treatment Monitoring for Patients who Do *NOT* Achieve Virologic Cure
• The AASLD recommends ultrasound surveillance for HCC (with alpha-fetoprotein testing) every 6 months in patients with cirrhosis.
• When initial HCV treatment fails to achieve a cure (SVR), patients should be evaluated for retreatment by a specialist, in accordance with AASLD/IDSA HCV guidance.
• Assess disease progression with a CBC, hepatic function panel, and INR every 6–12 months until retreatment occurs.
• Patients should be advised to avoid excessive alcohol.
Abbreviations: SVR = sustained virologic response; HCC = hepatocellular cancer; CBC = complete blood count; INR = international normalized ratio

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis. [AASLD-IDSA Hepatitis C Guidance]
- Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. 2023;78:1922-65. [AASLD]

Treatment Interruptions

Incomplete adherence to DAAs is relatively common among persons receiving HCV treatment and has the potential to impact SVR rates.[41,42] Although short periods of nonadherence (e.g., 1-2 days) are very unlikely to affect treatment responses, longer periods of nonadherence can lead to virologic failure.[43,44]

Recommendations for Management of Treatment Interruptions

Based on a literature review and expert consensus, the AASLD-IDSA HCV Guidance has addressed this important issue and developed recommendations for managing nonadherence events that consider the duration and timing of nonadherence.[7] This guidance is specific to whether the interruption occurred before or after the person received 28 days of DAA therapy.[7] In addition, this guidance is only applicable to DAA-treatment-naïve individuals and is intended to reflect recommendations for management of nonadherence events in patients who qualify for the AASLD/IDSA simplified treatment algorithms (e.g., simplified HCV treatment for treatment-naïve individuals without cirrhosis and with compensated cirrhosis) who are receiving glecaprevir-pibrentasvir or sofosbuvir-velpatasvir.[7] Management of incomplete adherence in patients who fall outside of this guidance should be done in consultation with an HCV specialist. The following table summarizes the 2023 AASLD HCC Guidance for the management of treatment interruptions in persons while receiving glecaprevir-pibrentasvir or sofosbuvir-velpatasvir in the simplified treatment approach.[7]

Table 14. Management of Treatment Interruptions: AASLD/IDSA HCV Guidance

Recommended Management of DAA Treatment Interruptions for Treatment-Naive Patients without Cirrhosis or with Compensated Cirrhosis Receiving Glecaprevir-Pibrentasvir or Sofosbuvir-Velpatasvir
Interruptions Before Receiving 28 Days of DAA Therapy
Missed ≤7 Days • **Restart** DAA therapy immediately. Complete therapy for originally planned duration (8 or 12 weeks).
Missed ≥8 Days • **Restart** DAA therapy immediately. Restarting DAA takes precedence over obtaining HCV RNA level. • **Obtain** HCV RNA test as soon as possible, preferably the same day as restarting the DAA therapy. ◦ If HCV RNA is negative (undetectable), complete originally planned DAA treatment course (8 or 12 weeks; total planned dosage[a]). Recommend extending DAA treatment for an additional 4 weeks for patients with genotype 3 infection and/or compensated cirrhosis. ◦ If HCV RNA is positive (>25 IU/L) or not obtained, extend DAA treatment for an additional 4 weeks.
Interruptions After Receiving ≥28 Days of DAA Therapy
Missed ≤7 Days • **Restart** DAA therapy immediately. Complete therapy for originally planned duration (8 or 12 weeks).
Missed 8-20 Consecutive Days • **Restart** DAA therapy immediately. Restarting DAA takes precedence over obtaining HCV RNA level. • **Obtain** HCV RNA test as soon as possible, preferably the same day as restarting the DAA therapy. ◦ If HCV RNA is negative (undetectable), complete originally planned DAA treatment course (8 or 12 weeks; total planned dosage[a]). Recommend extending DAA treatment for an additional 4 weeks for patients with genotype 3 infection and/or compensated cirrhosis. ◦ If HCV RNA is positive (>25 IU/L) or not obtained, **stop** DAA treatment and retreat according to recommendations in the Retreatment Section in the AASLD-IDSA Guidance.

Missed ≥21 Consecutive Days

- **Stop** DAA treatment and assess for SVR12. If SVR12 not achieved, retreat according to recommendations in the Retreatment Section.

Abbreviations: DAA = direct-acting antiviral; HCV = hepatitis C virus; SVR = sustained virologic response
[a]Extend duration of therapy such that the patient receives the total planned dosage (i.e., the total number of daily pills). For example, if a patient missed 10 days of a planned 8-week course of therapy, treatment would be extended to 8 weeks plus 10 days.

Source:

- Bhattacharya D, Aronsohn A, Price J, Lo Re V. Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clin Infect Dis. 2023;ciad319. [PubMed Abstract]

Summary Points

- The AASLD/IDSA simplified HCV treatment algorithm can help streamline treatment initiation and on-treatment monitoring in select populations of treatment-naïve individuals.
- For the purposes of the simplified treatment assessment, a patient is presumed to have cirrhosis if their FIB-4 score is greater than 3.25.
- An HCV genotype is not necessary to obtain in noncirrhotic treatment-naïve patients eligible for the simplified HCV treatment algorithm.
- The use of 8 weeks of glecaprevir-pibrentasvir or 12 weeks of sofosbuvir-velpatasvir is recommended for treatment-naïve patients without cirrhosis as part of the AASLD/IDSA simplified HCV treatment algorithm.
- On-treatment monitoring of hepatic function tests or HCV viral load is not necessary for treatment-naïve patients without cirrhosis who are eligible for the simplified treatment algorithm.
- Genotype 1, 2, 4, 5, or 6 cirrhotic patients on the simplified treatment algorithm can be treated with either 8 weeks of glecaprevir-pibrentasvir or 12 weeks of sofosbuvir-velpatasvir.
- For patients with genotype 3 HCV and compensated cirrhosis, sofosbuvir-velpatasvir should not be used alone if a baseline Y93H mutation is present. If baseline RAS testing is not available, 8 weeks of glecaprevir-pibrentasvir should be used.
- Providers may elect to check on-treatment hepatic function tests for patients with compensated cirrhosis on the simplified treatment regimen, given that hepatic decompensation and liver injury rarely occur in cirrhotic patients during antiviral therapy.
- Patients with cirrhosis should undergo ongoing surveillance for HCC with liver ultrasound with or without the addition of a serum alpha-fetoprotein level every 6 months, regardless of HCV cure.

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Table 1. Eligibility Criteria for Simplified Treatment: AASLD/IDSA HCV Guidance

Who is Eligible for Simplified HCV Treatment Algorithm	Who is Excluded from Simplified HCV Treatment Algorithm
Adults with chronic HCV infection, including persons living with HIV: • Infected with any HCV genotype • Have NOT previously received HCV treatment • Without cirrhosis • With compensated cirrhosis (Child-Pugh*A) • The determination of cirrhosis can be based on the presence of any of the following: - Liver stiffness >12.5 kPa by FibroScan - FIB-4 >3.25 - Non-invasive serologic test (HCV FibroSure or enhanced liver fibrosis test) above proprietary cutoff - Liver biopsy showing cirrhosis - Liver nodularity or splenomegaly on imaging - Platelet count <150,000/mm^3 • The determination of compensated versus uncomplicated cirrhosis is based on Child-Pugh* score	**Adults with chronic HCV infection who have any of the following:** • Previously received HCV treatment • Hepatitis B surface antigen-positive • Compensated cirrhosis (Child-Pugh A*) with end-stage renal disease (eGFR <30 mL/min/m^2) • Current or prior decompensated cirrhosis, defined by Child-Pugh score ≥7 • Current pregnancy • Known or suspected hepatocellular carcinoma • Prior liver transplantation

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis. [AASLD-IDSA Hepatitis C Guidance]
- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis. [[AASLD-IDSA Hepatitis C Guidance]

Table 2. Pretreatment Assessment for Treatment-Naïve Adults without Cirrhosis: AASLD/IDSA HCV Guidance

Before Initiating Antiviral Therapy
• Calculate a FIB-4 score[a]
• Assess for Cirrhosis[b]
• Obtain CBC
• Obtain hepatic function panel ◦ Total and direct bilirubin ◦ Albumin ◦ ALT, AST
• Determine eGFR
• Perform medication reconciliation[c]
• Assess for drug-drug interactions[d]
• Check quantitative HCV RNA (viral load)
• Obtain HIV-1/2 antigen-antibody test
• Check hepatitis B surface antigen (*see Author's Notes*)
• Obtain serum pregnancy testing and counsel about pregnancy risk and DAAs
• Educate about DAA administration and adherence, prevention of reinfection, and avoiding excess alcohol
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; DAA = direct-acting antiviral; eGFR = estimated glomerular filtration rate; FIB-4 = fibrosis-4 index for liver fibrosis; HCV = hepatitis C virus; INR = international normalized ratio. [a] FIB-4 is a noninvasive measure of hepatic fibrosis that is calculated using age (years), AST, ALT, and platelet count. [b] A patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 or if they have any of the following from a previously performed test: transient elastography indicating cirrhosis (i.e., liver stiffness >12.5 kPa), noninvasive serologic test above the proprietary cutoff indicating cirrhosis (e.g., FibroSure, enhanced liver fibrosis test), clinical evidence of cirrhosis (e.g., liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm^3), or prior liver biopsy showing cirrhosis. [c] Medication reconciliation should record currently prescribed medications, over-the-counter drugs, and herbal/dietary supplements. [d] Drug-drug interaction assessment should be performed using the table in the Monitoring Section of the HCV Guidance website or the University of Liverpool drug interaction checker.

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis. [[AASLD-IDSA Hepatitis C Guidance]]

Table 3. AASLD-IDSA HCV Simplified Guidance for All Genotypes: Initial Treatment
Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis

Regimens listed alphabetically

Recommended for Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis
Glecaprevir-Pibrentasvir **Fixed-dose combination of glecaprevir-pibrentasvir. Take 3 tablets daily for 8 weeks. Total daily dose = 300 mg of glecaprevir and 120 mg of pibrentasvir.*
Note: *Take with food

Recommended for Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis
Sofosbuvir-Velpatasvir ***Fixed-dose combination of sofosbuvir-velpatasvir. Take 1 tablet once daily for 12 weeks. Total daily dose = 400 mg of sofosbuvir and 100 mg of velpatasvir.*
Note: **Take with or without food

Source: AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis. [[AASLD-IDSA Hepatitis C Guidance]]

Table 4. Simplified Treatment, Without Cirrhosis, Monitoring On-Treatment: AASLD/IDSA HCV Guidance

Monitoring On-Treatment
• Monitor for hypoglycemia in patients taking medications for diabetes.
• Monitor for sub-therapeutic INR in patients taking warfarin.
• No laboratory monitoring is required for other patients.
• In-person or remote (telehealth/phone) visits may be scheduled, as needed, for patient support and to assess tolerance of new medications.
Abbreviations: INR – international normalized ratio

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis. [[AASLD-IDSA Hepatitis C Guidance]]

Table 5. Simplified Treatment, Without Cirrhosis, Post-Treatment Assessment of Cure: AASLD/IDSA HCV Guidance

Post-Treatment Monitoring
• Obtain quantitative HCV RNA and hepatic function panel 12 weeks or later following completion of HCV therapy.
• If quantitative HCV RNA is undetectable 12+ weeks following completion of HCV therapy, the patient is considered to have achieved an SVR, also known as a cure.
• Assess for other causes of liver disease if transaminase levels remain elevated after achieving an SVR.
Abbreviations: SVR = sustained virologic response

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis. [[AASLD-IDSA Hepatitis C Guidance]]

Table 6. Simplified Treatment, Without Cirrhosis, Cure after Treatment: AASLD/IDSA HCV Guidance

Post-Treatment Follow-Up After Achieving Virologic Cure
• No liver-specific follow-up is needed for patients without advanced fibrosis following SVR.
• Patients with ongoing risk factors for HCV should be counseled regarding their risk for reinfection and undergo testing for HCV RNA annually and with any elevation in ALT, AST or bilirubin.
• Patients should be advised to avoid excessive alcohol.
Abbreviations: SVR = sustained virologic response

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis. [[AASLD-IDSA Hepatitis C Guidance]]

Table 7. Simplified Treatment, Without Cirrhosis, No Cure after Treatment: AASLD/IDSA HCV Guidance

Post-Treatment Follow-Up for Patients who Do *NOT* Achieve Virologic Cure
• When initial HCV treatment fails to achieve a cure (SVR), patients should be evaluated for retreatment by a specialist, in accordance with AASLD/IDSA HCV guidance.
• Assess disease progression with a CBC, hepatic function panel, and INR every 6 – 12 months until retreatment occurs.
• Patients should be advised to avoid excessive alcohol.
Abbreviations: SVR = sustained virologic response; CBC = complete blood count; INR = international normalized ratio

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis. [[AASLD-IDSA Hepatitis C Guidance]]

Table 8. Pretreatment Assessment for Treatment-Naïve Adults With Compensated Cirrhosis: AASLD/IDSA HCV Guidance

Assessment Before Initiating Antiviral Therapy
• Calculate a Child-Pugh Score[a] (*see Authors Notes*)
• Perform liver ultrasound
• Obtain complete blood count (CBC)
• Check international normalized ratio (INR)
• Obtain hepatic function panel ◦ Total and direct bilirubin ◦ Albumin ◦ ALT, AST
• Determine eGFR
• Perform medication reconciliation[c]
• Assess for drug-drug interactions[d]
• Check quantitative HCV RNA
• Obtain HIV-1/2 antigen-antibody test
• Check hepatitis B surface antigen (*see Authors Notes*)
• Check HCV genotype (if treating with sofosbuvir-velpatasvir)
• Obtain serum pregnancy testing and counsel about pregnancy risk and DAAs
• Educate about DAA administration and adherence, prevention of reinfection, and avoiding excess alcohol
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; DAA = direct-acting antiviral; eGFR = estimated glomerular filtration rate; FIB-4 = fibrosis-4 index for liver fibrosis; HCV = hepatitis C virus; INR = international normalized ratio. [a] Child–Pugh score based on presence of ascites, hepatic encephalopathy, total bilirubin >2.0 mg/dL, albumin ≤3.5 g/dL, or INR ≥1.7. Patients with a Child–Pugh score ≥7 (ie, Child–Pugh B or C) have decompensated cirrhosis; this simplified treatment approach is not recommended for patients with decompensated cirrhosis. [b] Obtain liver ultrasound within 6 months prior to initiating antiviral treatment to exclude hepatocellular carcinoma and subclinical ascites. This simplified treatment approach is not recommended for patients with hepatocellular carcinoma and/or decompensated cirrhosis [c] Medication reconciliation should record currently prescribed medications, over-the-counter drugs, and herbal/dietary supplements. [d] Drug-drug interaction assessment should be performed using the table in the Monitoring Section of the HCV Guidance website or the University of Liverpool drug interaction checker.

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis. [AASLD-IDSA Hepatitis C Guidance]
- Bhattacharya D, Aronsohn A, Price J, Lo Re V. Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clin Infect Dis. 2023;ciad319. [PubMed Abstract]

Table 9. AASLD-IDSA HCV Simplified Guidance for All Genotypes: Initial Treatment
Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis^

Regimens listed alphabetically

Recommended for Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis^
Glecaprevir-Pibrentasvir **Fixed-dose combination of glecaprevir-pibrentasvir. Take 3 tablets once daily for 8 weeks. Total daily dose = 300 mg of glecaprevir and 120 mg of pibrentasvir.*
For Genotypes 1-6 Note: *Take with food

Recommended for Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis^
Sofosbuvir-Velpatasvir ***Fixed-dose combination of sofosbuvir-velpatasvir. Take 1 tablet once daily for 12 weeks. Total daily dose = 400 mg of sofosbuvir and 100 mg of velpatasvir.*
Patients with compensated cirrhosis and HCV genotype 3 require baseline NS5A RAS testing prior to use of sofosbuvir-velpatasvir. Those with a Y93H mutation require the addition of weight-based ribavirin. Note: **Take with or without food

^For patients with decompensated cirrhosis, refer to a liver specialist and see the AASLD-IDSA Guidance: Unique Populations—Patients with Decompensated Cirrhosis.

Source: AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis. [AASLD-IDSA Hepatitis C Guidance]

Table 10. Simplified Treatment, Compensated Cirrhosis, Monitoring On-Treatment: AASLD/IDSA HCV Guidance

On-Treatment Monitoring
• Health care providers may order blood tests to monitor for liver injury or hepatic decompensation, both of which occur rarely among patients with cirrhosis undergoing antiviral treatment for HCV
• Patients should see a liver specialist if they develop jaundice, ascites, encephalopathy, other new liver-related symptoms, or worsening liver blood tests (e.g., AST, ALT, bilirubin) during treatment.
• Monitor for hypoglycemia in patients taking medications for diabetes.
• Monitor for subtherapeutic INR in patients taking warfarin.
• No laboratory monitoring is required for other patients.
• In-person or remote (telehealth/phone) visits may be scheduled, as needed, for patient support and to assess tolerance of new medications.
Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase; INR – international normalized ratio

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis. [AASLD-IDSA Hepatitis C Guidance]

Table 11. Simplified Treatment, Compensated Cirrhosis, Assessment of Cure: AASLD/IDSA HCV Guidance

Post-Treatment Monitoring: Assessment of Cure
• Obtain quantitative HCV RNA and hepatic function panel 12 weeks or later following completion of HCV therapy.
• If quantitative HCV RNA is undetectable at least 12 weeks following completion of HCV therapy, the patient is considered to have achieved a sustained virologic response (SVR), also known as a cure.
• Assess for other causes of liver disease if transaminase levels remain elevated after achieving an SVR.
Abbreviations: SVR = sustained virologic response

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis. [AASLD-IDSA Hepatitis C Guidance]

Table 12. Simplified Treatment, Compensated Cirrhosis, Follow-Up After Cure: AASLD/IDSA HCV Guidance

Post-Treatment Follow-up After Achieving Virologic Cure
• The AASLD recommends ultrasound surveillance for HCC (with alpha-fetoprotein testing) every 6 months in patients with cirrhosis.
• An upper endoscopy should be performed for surveillance of esophageal varices in certain patients, in accordance with the AASLD guidelines on portal hypertensive bleeding in cirrhosis.
• Patients with ongoing risk factors for HCV should be counseled regarding their risk for reinfection and undergo testing for HCV RNA annually and with any elevation in ALT, AST or bilirubin.
• Patients should be advised to avoid excessive alcohol.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; HCC = hepatocellular carcinoma

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis. [AASLD-IDSA Hepatitis C Guidance]
- Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. 2023;78:1922-65. [AASLD]

Table 13. Simplified Treatment, Compensated Cirrhosis, Follow-Up After No Cure: AASLD/IDSA HCV Guidance

Post-Treatment Monitoring for Patients who Do *NOT* Achieve Virologic Cure
• The AASLD recommends ultrasound surveillance for HCC (with alpha-fetoprotein testing) every 6 months in patients with cirrhosis.
• When initial HCV treatment fails to achieve a cure (SVR), patients should be evaluated for retreatment by a specialist, in accordance with AASLD/IDSA HCV guidance.
• Assess disease progression with a CBC, hepatic function panel, and INR every 6–12 months until retreatment occurs.
• Patients should be advised to avoid excessive alcohol.
Abbreviations: SVR = sustained virologic response; HCC = hepatocellular cancer; CBC = complete blood count; INR = international normalized ratio

Source:

- AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Simplified HCV Treatment for Treatment-Naive Adults With Compensated Cirrhosis. [AASLD-IDSA Hepatitis C Guidance]
- Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology. 2023;78:1922-65. [AASLD]

Table 14. Management of Treatment Interruptions: AASLD/IDSA HCV Guidance

Recommended Management of DAA Treatment Interruptions for Treatment-Naive Patients without Cirrhosis or with Compensated Cirrhosis Receiving Glecaprevir-Pibrentasvir or Sofosbuvir-Velpatasvir
Interruptions Before Receiving 28 Days of DAA Therapy
Missed ≤7 Days • **Restart** DAA therapy immediately. Complete therapy for originally planned duration (8 or 12 weeks).
Missed ≥8 Days • **Restart** DAA therapy immediately. Restarting DAA takes precedence over obtaining HCV RNA level. • **Obtain** HCV RNA test as soon as possible, preferably the same day as restarting the DAA therapy. ◦ If HCV RNA is negative (undetectable), complete originally planned DAA treatment course (8 or 12 weeks; total planned dosage[a]). Recommend extending DAA treatment for an additional 4 weeks for patients with genotype 3 infection and/or compensated cirrhosis. ◦ If HCV RNA is positive (>25 IU/L) or not obtained, extend DAA treatment for an additional 4 weeks.
Interruptions After Receiving ≥28 Days of DAA Therapy
Missed ≤7 Days • **Restart** DAA therapy immediately. Complete therapy for originally planned duration (8 or 12 weeks).
Missed 8-20 Consecutive Days • **Restart** DAA therapy immediately. Restarting DAA takes precedence over obtaining HCV RNA level. • **Obtain** HCV RNA test as soon as possible, preferably the same day as restarting the DAA therapy. ◦ If HCV RNA is negative (undetectable), complete originally planned DAA treatment course (8 or 12 weeks; total planned dosage[a]). Recommend extending DAA treatment for an additional 4 weeks for patients with genotype 3 infection and/or compensated cirrhosis. ◦ If HCV RNA is positive (>25 IU/L) or not obtained, **stop** DAA treatment and retreat according to recommendations in the Retreatment Section in the AASLD-IDSA Guidance.
Missed ≥21 Consecutive Days • **Stop** DAA treatment and assess for SVR12. If SVR12 not achieved, retreat according to recommendations in the Retreatment Section.
Abbreviations: DAA = direct-acting antiviral; HCV = hepatitis C virus; SVR = sustained virologic response [a]Extend duration of therapy such that the patient receives the total planned dosage (i.e., the total number of daily pills). For example, if a patient missed 10 days of a planned 8-week course of therapy, treatment would be extended to 8 weeks plus 10 days.

Source:

- Bhattacharya D, Aronsohn A, Price J, Lo Re V. Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clin Infect Dis. 2023;ciad319. [PubMed Abstract]