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Hepatitis C Care for Primary Care Providers

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The incidence of acute hepatitis C virus (HCV) infection has risen in recent years, largely due to the opioid epidemic and rising rates of intravenous drug use.[1] According to the Center for Disease Control and Prevention (CDC), the number of reported cases of HCV infection in 2021 had doubled since 2014, rising by 129%.[2] In 2021, there were 69,900 estimated acute HCV infections in the United States, of which 57% reported a history of intravenous drug use. Due to the growing incidence and prevalence of hepatitis C, it is imperative that healthcare professionals can recognize risk factors, understand management strategies, and act as a resource for patients. To meet global HCV elimination goals, healthcare providers in primary care settings are essential to provide the necessary outreach, screening, treatment and follow up along the HCV continuum of care. The purpose of this newsletter is to review recommendations for screening, treatment, and monitoring in patients with HCV and assist in risk stratification for treatment in the primary care setting.

HCV Screening

Since many patients with HCV remain asymptomatic **(Table 1)**, a major component of preventing the spread of HCV is ensuring that at-risk patient populations are screened for HCV.[3] According to the American Association for the Study of Liver Disease (AASLD) and the Infectious Diseases Society of America (IDSA), anti-HCV antibody testing remains the gold standard with 99% sensitivity and specificity.[4] Patient eligibility for HCV testing is outlined in **Table 1**.

Table 1: Patients Eligible to Receive HCV Testing[4]

Testing	Population
Annual Testing	Patients who inject drugs, who have HIV and have sex with men, and men who have sex with men taking pre-exposure prophylaxis
One time testing	All adults ≥18 years of age should be screened once, and during each pregnancy
Periodic and/or Situational Testing	Patients <18 years of age at an increased risk* of HCV infection
	Patients who engage in high-risk activities* or are at high risk of exposure should be tested periodically

*Additional risk factors: incarceration, infants born to a person with hepatitis C, long-term dialysis, needle stick injuries in the hospital
Abbreviations: HCV = hepatitis C virus; HIV = human immunodeficiency virus

In cases with a reactive HCV antibody, a follow-up reflex HCV ribonucleic acid (RNA) polymerase chain reaction (PCR) test should be performed.[4] If the HCV RNA is detected, the patient should be linked to care and initiated on treatment.

Pre-Treatment Patient Evaluation

Evaluation of liver disease severity is essential prior to treatment and may be initially assessed with noninvasive biomarkers and baseline workup (Table 2). Clinical calculations using routine blood tests, known as the fibrosis-4 (FIB-4) and Aspartate aminotransferase (AST) to Platelet Ratio Index (APRI), can rule out advanced fibrosis and cirrhosis.[4] Liver ultrasound with elastography is recommended in cases that have equivocal evidence of advanced fibrosis, based on intermediate FIB-4 and ARPI tests, or high pretest probability (e.g., longer duration of disease, heavy alcohol use, hepatitis B virus (HBV) or human immunodeficiency virus (HIV) coinfection) or if there are clinical symptoms consistent with hepatic decompensation. A liver biopsy is rarely needed to assess the staging of hepatic fibrosis. The stage of hepatic fibrosis facilitates decision making regarding HCV treatment strategies and can help to identify patients who require additional interventions, including hepatocellular carcinoma and variceal screening. Lastly, it is important to test for HBV coinfection due to the risk of HBV reactivation during treatment for HCV. With the availability of effective pangenotypic regimens, genotype testing is not needed for most treatment naïve individuals without cirrhosis.

Table 2: Pre-Treatment Patient Workup[4]

Assessment	Details
Baseline Labs	▪ Complete blood count (CBC) ▪ International normalized ratio (INR) ▪ Hepatic function panel ○ Serum albumin, total/direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase levels ▪ Kidney function tests ▪ HCV baseline viral load ▪ HIV screening ▪ Pregnancy testing if appropriate
Staging of Hepatic Fibrosis	• Fibrosis 4 (FIB-4) score • AST to Platelet Ratio Index (ARPI) • Transient elastography • Liver imaging • Physical Exam
Hepatitis B serology*	• Hepatitis B surface antigen • Hepatitis B core antibody • Hepatitis B surface antibody

*Reactive hepatitis B surface antigen consistent with active hepatitis B coinfection. Reactive hepatitis B core antibody consistent with evidence of prior infection.

When to Refer to A Specialist

Patients with evidence of hepatic decompensation or decompensated cirrhosis (e.g. Child-Turcotte Pugh Class B or Class C) should be referred to a specialist.[4] During treatment, those who display clinical deterioration or changes in labs (increases in alanine aminotransferase [ALT], bilirubin, or international normalized ratio [INR]) should also be referred. Those with a positive hepatitis B surface antigen (HBsAg), indicating chronic HBV, should be evaluated if HBV treatment is needed based on HBV DNA levels.

Treatment experienced patients should typically be referred to a specialist. Treatment experienced includes patients who took more than 4 weeks of HCV direct-acting antiviral (DAA) therapy and do not achieve sustained virologic response (SVR) (i.e., treatment failure) or late relapse (HCV RNA reappears after achieving SVR).[4] Reinfection may occur in patients with ongoing risk factors after previously achieving SVR, including ongoing intravenous drug use (IVDU).[4] Those with reinfection after achieving SVR can be retreated like a treatment naïve patient.

Hepatitis C Treatment

Simplified Treatment

Guidelines recommend a streamlined treatment approach for treatment naïve individuals who are not pregnant, without decompensated cirrhosis, hepatitis B coinfection, hepatocellular carcinoma, or liver transplantation. Simplified treatment can be initiated and monitored in the primary care setting.

The recommended regimens for simplified treatment of HCV in those without cirrhosis are included in **Table 3**. Individualized factors including accessibility to medication, medication adherence, loss-to-follow up, drug interactions, and food accessibility should be assessed in each patient, as these factors may influence the choice of treatment. For uncomplicated cases, treatment duration may vary from 8-12 weeks. **(Table 3).**

Table 3: Simplified Treatment Regimens Without Cirrhosis

Treatment Option(s)	Directions	Duration of Treatment
Glecaprevir (300 mg) / pibrentasvir (120 mg) [MAVYRET]	3 tablets once daily with food	8 weeks
Sofosbuvir (400 mg) / velpatasvir (100 mg) [EPCLUSA]	1 tablet once daily	12 weeks

Those with compensated cirrhosis can also be treated with a simplified treatment regimen, with glecaprevir/pibrentasvir as a pangenotypic option. Baseline nonstructural protein 5A (NS5A) resistance testing is recommended only in patients with genotype 3 HCV if sofosbuvir/velpatasvir is indicated.

Patient Education & Monitoring

Patients should be educated on and monitored for adverse reactions, drug-drug interactions, and disease state interactions during HCV treatment **(Table 4,5).** Individuals with diabetes may experience an increase in symptomatic hypoglycemia due to a rapid lowering of HCV viral load and improved glucose metabolism.[5,6] Regimens with a protease inhibitor, including glecaprevir/pibrentasvir, include a warning of hepatic decompensation/failure in patients with advanced liver disease. A regimen without a protease inhibitor (i.e., sofosbuvir/velpatasvir) may be preferred if there are concerns for advanced liver disease (i.e., portal hypertension).

Routine laboratory monitoring during treatment is not necessary for most patients who meet criteria for a simplified treatment regimen. ALT monitoring can be considered in patients with advanced liver disease, with signs or symptoms of hepatic failure, and in patients with evidence of prior HBV infection. Furthermore, patients coinfected with HBV should receive prophylactic antiviral therapy with HBV DNA levels monitored monthly.[4]

Table 4: Warnings and Common Adverse Reactions[5,6]

Warnings	Common Adverse Reactions
• Hepatitis B reactivation • Hepatic failure* • Symptomatic hypoglycemia in patients with diabetes	• Headache • Fatigue • Nausea
*Regimens that include a protease inhibitor (MAVYRET)	

Medication reconciliation should be completed to screen for drug-drug interactions. Select interactions are presented in Table 5. The University of Liverpool interaction checker (https://www.hep-druginteractions.org/) is a widely used resource for a detailed assessment.

Table 5: Drug-Drug Interaction with Simplified Regimens[5–7]

Medication Class	Possible Effect	Management
Statins	↑ statin concentration	Monitor for myopathies; may increase risk of rhabdomyolysis. Can hold statin if used for primary prevention.
Acid Reducing agents	↓ antiviral concentration	Sof/Vel: coadministration with PPIs is not recommended
Antiepileptics	↓ antiviral concentration	Sof/Vel: coadministration with carbamazepine, phenytoin, or phenobarbital is not recommended. Gle/Pib: coadministration with carbamazepine is not recommended
Amiodarone	Sofosbuvir-containing regimens	Sof/Vel coadministration of amiodarone is not recommended

Anticoagulants and Antiplatelets	↑ anticoagulant and antiplatelet concentration	Sof/Vel: monitor for signs of bleeding and anemia Gle/Pib: coadministration with dabigatran is not recommended; for other agents, monitor for signs of bleeding and anemia
HIV Protease Inhibitors	May ↑ or ↓ HCV antiviral levels	Sof/Vel: coadministration with tipranavir/ritonavir is not recommended. Gle/Pib: coadministration with atazanavir is contraindicated; coadministration with darunavir, lopinavir, and ritonavir is not recommended

↑ = increase; ↓ = decrease; H2RAs, histamine-2 receptor antagonists; PPIs, proton-pump inhibitors
Mavyret: glecaprevir/pibrentasvir (gle/pib)r; Epclusa: sofosbuvir/velpatasvir (sof/vel)

Adherence

Individuals should be educated on preventing HCV transmission to others, including avoiding sharing or reusing needles, using barrier precautions to prevent sexual transmission, refraining from donating blood, avoiding sharing toothbrushes or shaving equipment, and keeping any bleeding wounds covered.

Although patients should be counseled on the importance of adherence, missed doses of DAAs are common. Despite imperfect adherence, sustained virologic response (SVR) rates remain high.[8] For patients who have missed ≤ 7 consecutive days of therapy, it is recommended to restart immediately and finish the originally prescribed treatment duration. If patients miss ≥ 21 consecutive days, it is recommended to stop DAA treatment and assess for SVR after 12 weeks. Re-treat according to guidelines if SVR is not achieved. For patients who have missed 8-20 consecutive days, DAA treatment should be restarted immediately, and HCV RNA should be obtained to assess if extending the DAA course is needed. Details on how to manage incomplete adherence are included in Figure 1 and in the AASLD HCV guidelines.[4]

Harm Reduction Strategies

Individuals with an active HCV infection should be advised to abstain from alcohol, and interventions to assist with alcohol cessation should be provided when indicated.[4] Hepatitis A and hepatitis B vaccinations are recommended for all susceptible individuals with an HCV infection. Additionally, the pneumococcal vaccine is advised in patients with cirrhosis.

Post-Treatment Patient Evaluation

Patients started on treatment should be tested for HCV RNA 12 weeks after treatment completion.[4] Sustained virologic response is defined as an undetectable or unquantifiable HCV RNA at 12 weeks or longer after treatment completion. For those who achieve SVR, there is no HCV-specific recommended monitoring needed other than education on risks of reinfection, harm reduction strategies, and periodic screening if indicated. If SVR is not achieved, a disease progression assessment is recommended every 6-12 months, and patients should be referred for retreatment. Patients with cirrhosis should be referred for ongoing liver care, including biannual screening for hepatocellular carcinoma.

Current Policies

In January 2023, prior authorization criteria and required case management was removed for preferred DAA regimens for treatment -naïve patients in Oregon Medicaid with HCV. Currently, both glecaprevir/pibrentasvir and sofosbuvir/velpatasvir are preferred regimens in the Oregon Health Plan. Prior authorization is required for the retreatment of HCV and for non-preferred regimens.

Conclusion

Despite the rising rates of hepatitis C, a growing number of resources and treatment options exist for those at risk or affected by the virus, and policies are being implemented to increase treatment accessibility. Interventions including performing hepatitis C screening when indicated and informing at-risk patients of harm reduction strategies have the potential to make a profound impact on the wellbeing of individuals in the greater community. When indicated, providers can tailor treatment options to each individual patient, taking into consideration drug-drug interactions and lifestyle factors, to further support their patients. Increasing awareness and education, both for those in the healthcare field and for patients, is a crucial step in achieving hepatitis C eradication.

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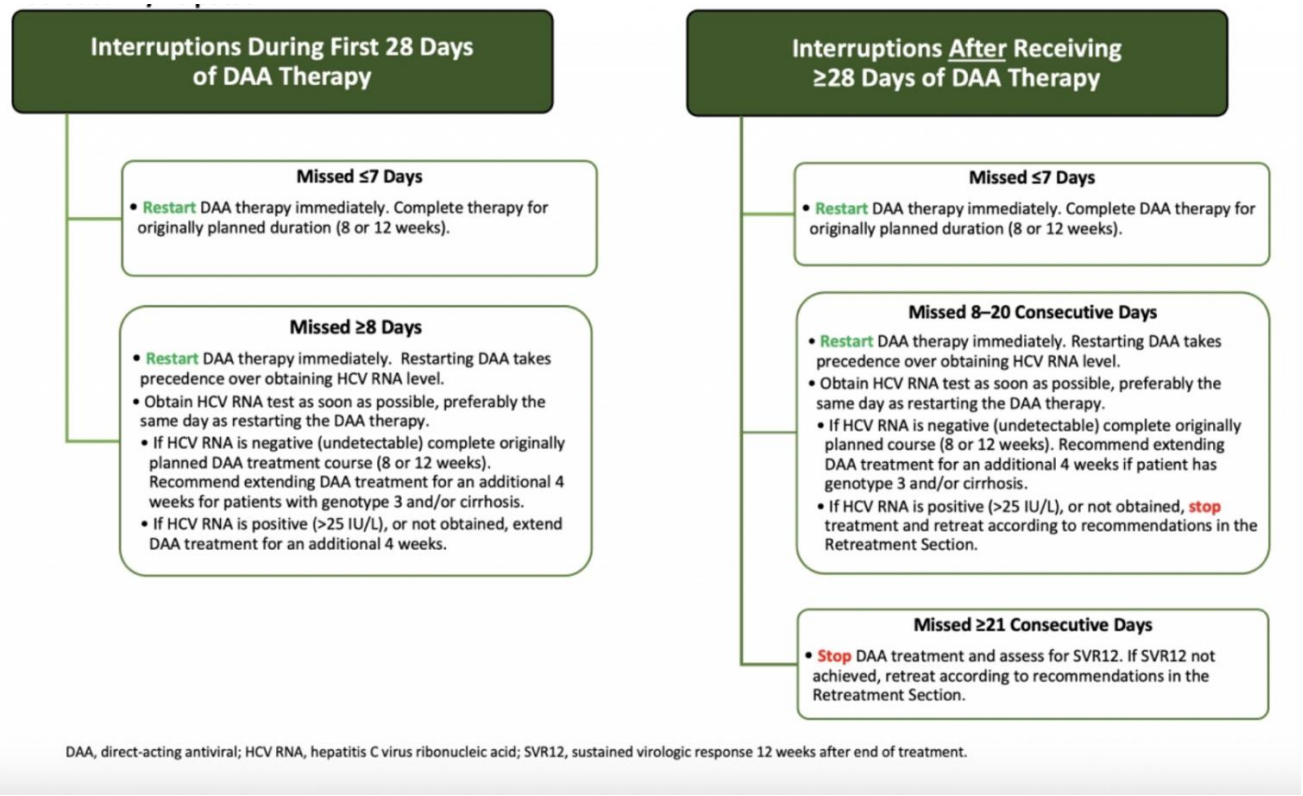
Appendix 1

Figure 1: Recommended Management of DAA Treatment Interruptions [4]



DAA, direct-acting antiviral; HCV RNA, hepatitis C virus ribonucleic acid; SVR12, sustained virologic response 12 weeks after end of treatment.