INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Hepatitis C Virus Elimination***
-April 2025-

Background:

A pharmacotherapeutic review of the Direct-Acting Antiviral agents (DAA) used to treat chronic Hepatitis C Virus infection was provided at the Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) meeting in April 2025. Medications listed on the IHS National Core Formulary (NCF) relevant to this review includes glecaprevir/pibrentasvir (Mavyret®), ledipasvir/sofosbuvir (Harvoni®), and sofosbuvir/velpatasvir (Epclusa®). This topic was initially and most recently reviewed by the NPTC in November 2018. Following review and deliberation during the April 2025 meeting, the NPTC voted to **remove ledipasvir/sofosbuvir (Harvoni®)** from the NCF.

Discussion:

The prevalence of hepatitis C virus (HCV) infection is an estimate because among those who develop HCV infection, approximately one third of patients will spontaneously clear the HCV infection, those who have symptoms of HCV infection may not seek medical treatment, and not all of those who seek medical treatment will have their case reported. As a result, acute HCV infections in the United States (U.S.) are approximately 14 times greater than the reported cases in 2023.[1] HCV disproportionately affects American Indian/Alaska Native (AI/AN) communities. In 2023, AI/ANs had the highest rate of newly-reported chronic HCV cases (99.4 per 100,000) compared to other racial/ethnic groups. This has increased from 68.9 per 100,000 in 2021. This rate was more than 3 times the next highest group, which was white, non-Hispanic (30.0 per 100,000).[3] In 2023, chronic liver disease was the 4th leading cause of death in the AI/AN population, compared to the 9th leading cause in the U.S.[4,5] In 2023, the age-adjusted HCV-related death rate for AI/AN was 7.75 per 100,000, compared to the national rate of 2.52 per 100,000.[6] Although this was close to the 2023 annual target of 7.17 per 100,000, observed rates have been above annual targets since 2020. Consistent with other populations in the U.S., the group with the highest risk are people who inject drugs (PWID). In the U.S., it is estimated that up to 20% of new injectors contract HCV within one year, and 80% of new HCV infections are linked to injection drug use.[2]

The U.S. Centers for Disease Control and Prevention (CDC) recommend a one-time universal hepatitis C screening for all adults ≥18 years of age and all pregnant women during each pregnancy. Additionally, the CDC recommends testing people in certain high-risk groups more frequently. Examples of high-risk groups include PWID or those who have previously injected drugs and shared needles, syringes, or other drug preparation equipment; people with human immunodeficiency virus (HIV); and health care personnel after needle stick, sharps, or mucosal exposure to HCV positive blood. Screening should utilize the HCV antibody test with reflex to analyze for HCV RNA if antibodies are positive. Patients who test positive for both should be evaluated for DAA treatment.[7] Both HCV antibody and RNA tests should be drawn for those with known HCV exposure and further follow up should be determined according to the American Association for the Study of Liver Diseases-Infectious Diseases Society of America (AASLD-IDSA) guidelines.[8]

Consistent with AASLD-IDSA and World Health Organization (WHO) recommendations, treatment-naïve adults without cirrhosis or with compensated cirrhosis should receive DAA according to simplified treatment protocols. Initiation, monitoring, and follow up of simplified treatment protocols can all be completed in the primary care setting, without the need to consult specialty services. This is intended to decrease any delays from positive test results and treatment.[8,10]

Current treatment regimens for treatment-naïve adults without cirrhosis or with compensated cirrhosis include:

- Glecaprevir/pibrentasvir (Mavyret®): Fixed-dose combination (300 mg glecaprevir, 120 mg pibrentasvir), 3 tablets once daily with food for 8 weeks.
- Sofosbuvir/velpatasvir (Epclusa®): Fixed-dose combination (400 mg sofosbuvir, 100 mg velpatasvir), 1 tablet once daily for 12 weeks, with or without food. Genotyping is required for patients with compensated cirrhosis.
- These regimens achieve SVR rates above 95% with minimal side effects.[9]

Monitoring for HCV treatment involves baseline and ongoing assessments to ensure efficacy and safety. Before initiating DAA therapy, patients should be assessed for cirrhosis. They require the following; a hepatic function panel, complete blood count, calculated eGFR, medication reconciliation, assessment for drug-drug interactions, quantitative HCV RNA, testing for HIV and HepB, and pregnancy test as indicated (as well as counseling about risks of DAA's if needed). Patients should also receive counseling on the importance of adherence, prevention of reinfection, and avoidance of alcohol. In addition, patients with compensated cirrhosis should receive a liver ultrasound and the HCV should be genotyped if treating with sofosbuvir/ velpatasvir. During treatment, only patients with diabetes who are receiving warfarin require additional monitoring for hypoglycemia and subtherapeutic INR, respectively. Patients with compensated cirrhosis should

also be monitored for liver injury. Follow up appointments can be conducted if needed to support the patient or to assess symptoms.

Post-treatment, sustained virologic response at 12 weeks (SVR12) is assessed via HCV RNA testing to confirm virologic cure (undetectable viral load) and adequate liver function testing. For patients achieving SVR12, those without advanced fibrosis or cirrhosis require no further routine monitoring unless new risk factors emerge. Patients with advanced fibrosis or cirrhosis should receive a liver ultrasound every 6 month for hepatocellular carcinoma surveillance. Patients who have confirmed virologic cure, but are at risk for reinfection, should receive counseling on mitigation strategies and have an HCV RNA tested annually.[8]

Managing missed doses and treatment Interruptions depends on duration of therapy received and length of interruption:[8]

- Interruptions *Before* Receiving 28 Days of DAA Therapy:
  - Missed ≤7 Days: Restart DAAs immediately and complete the originally planned duration (8 or 12 weeks).
  - Missed ≥8 Days: Restart DAAs immediately, prioritizing resumption over obtaining HCV RNA levels. Obtain an HCV RNA test as soon as possible, preferably the same day. If HCV RNA is negative (undetectable), complete the original course (8 or 12 weeks), with an additional 4 weeks recommended for genotype 3 or compensated cirrhosis. If HCV RNA is positive (>25 IU/L) or not obtained, extend treatment by 4 weeks.

- Interruptions *After* Receiving ≥28 Days of DAA Therapy:
  - Missed ≤7 Days: Restart immediately and complete the original duration (8 or 12 weeks).
  - Missed 8–20 Consecutive Days: Restart immediately and obtain an HCV RNA test. If negative, complete the original course, with an additional 4 weeks for genotype 3 or compensated cirrhosis. If positive or not obtained, stop treatment and retreat per retreatment guidelines.
  - Missed ≥21 Consecutive Days: Stop DAA treatment, assess for SVR12, and retreat if SVR12 is not achieved, following retreatment recommendations. These protocols aim to maximize treatment success while addressing adherence challenges, particularly in populations with barriers to consistent care.

Findings:

Chronic Hepatitis C Virus infection causes high morbidity and mortality among AI/AN patients, at rates much higher than the rest of the U.S. population. Significant efforts are being made across the Agency to address this health disparity. Updated guidelines highlight the importance of treatment and monitoring taking place in a primary care setting, thus making treatment regimens more accessible to patients. Ledipasvir/sofosbuvir (Harvoni®) is still included in guidelines for the treatment of hepatitis C, but is not available as a simplified treatment regimen and warrants less consideration as an initial treatment. As such, the NPTC voted to remove ledipasvir/sofosbuvir (Harvoni®) from the NCF.

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If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

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