

# State-of-the-Art Review: Hepatitis C

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Hepatitis C virus (HCV) infection remains a major cause of chronic liver disease and premature mortality worldwide. The World Health Organization and US Department of Health and Human Services have committed to eliminating HCV infection as a major public health threat by 2030, as defined by a 90% reduction in incidence of new HCV infections and 65% reduction in mortality from a 2015 baseline. To help to achieve HCV elimination, it will be necessary to increase HCV screening and increase uptake of HCV treatment, particularly within primary care, correctional, and substance use treatment settings. In this review, we provide strategies for healthcare providers to implement in their practice to enhance patients' completion of the steps of the HCV care cascade. Improving successful completion of each step of the cascade will help alleviate the burden of HCV infection and make the 2030 HCV elimination goals a reality.

**Keywords.** hepatitis C virus; HCV infection; cascade of care; direct-acting antiviral therapy; HCV elimination.

Infection with hepatitis C virus (HCV) remains a major cause of liver disease across the world. It is estimated that there are 50 million people with HCV infection worldwide (prevalence, 0.7%) [1], of whom 4.0 million are in the United States (prevalence, 1.0%) [2]. If left untreated, chronic HCV-related liver inflammation can promote development of hepatic fibrosis, ultimately resulting in cirrhosis, which can lead to hepatic decompensation, hepatocellular carcinoma (HCC), and death [3]. Direct-acting antiviral (DAA) therapy of HCV infection results in a cure in  $\geq 95\%$  of those treated and reduces the risk of these complications [4].

With the availability of DAA treatments, the World Health Organization (WHO) formulated a global plan for HCV elimination [5]. Aligning with the WHO's HCV elimination goals, the US Department of Health and Human Services established 2 key targets to achieve HCV elimination in the country by 2030: (1) 90% reduction in incidence of new HCV infections, and (2) 65% reduction in HCV-related morbidity and mortality rates, both from a 2015 baseline [6]. A modeling analysis that

evaluated the progress that would be needed across each of the steps of the HCV care cascade [7, 8] showed that these goals could be achieved in the United States by diagnosing 1.9 million new infections and treating 2.7 million persons by 2030 [9]. Successfully achieving the 2030 HCV elimination goals could prevent 30 000 cases of HCC and 29 000 HCV-related deaths in the United States [9].

Meeting the target number of persons diagnosed and treated for HCV infection to achieve HCV elimination efforts requires overcoming existing obstacles to HCV diagnosis, linkage to care, and treatment, particularly among priority populations in whom the prevalence and incidence of HCV infection is high, including people who inject drugs (PWID), men who have sex with men, individuals who are incarcerated, and those underserved [2, 10]. To support HCV elimination efforts, this review provides state-of-the-art approaches to promote HCV screening and diagnosis, facilitate linkage to HCV care, and expand access to DAA-based HCV treatment. The article also presents several case vignettes to emphasize important contemporary aspects of the management of HCV infection across the cascade of care.

## CASE VIGNETTE 1

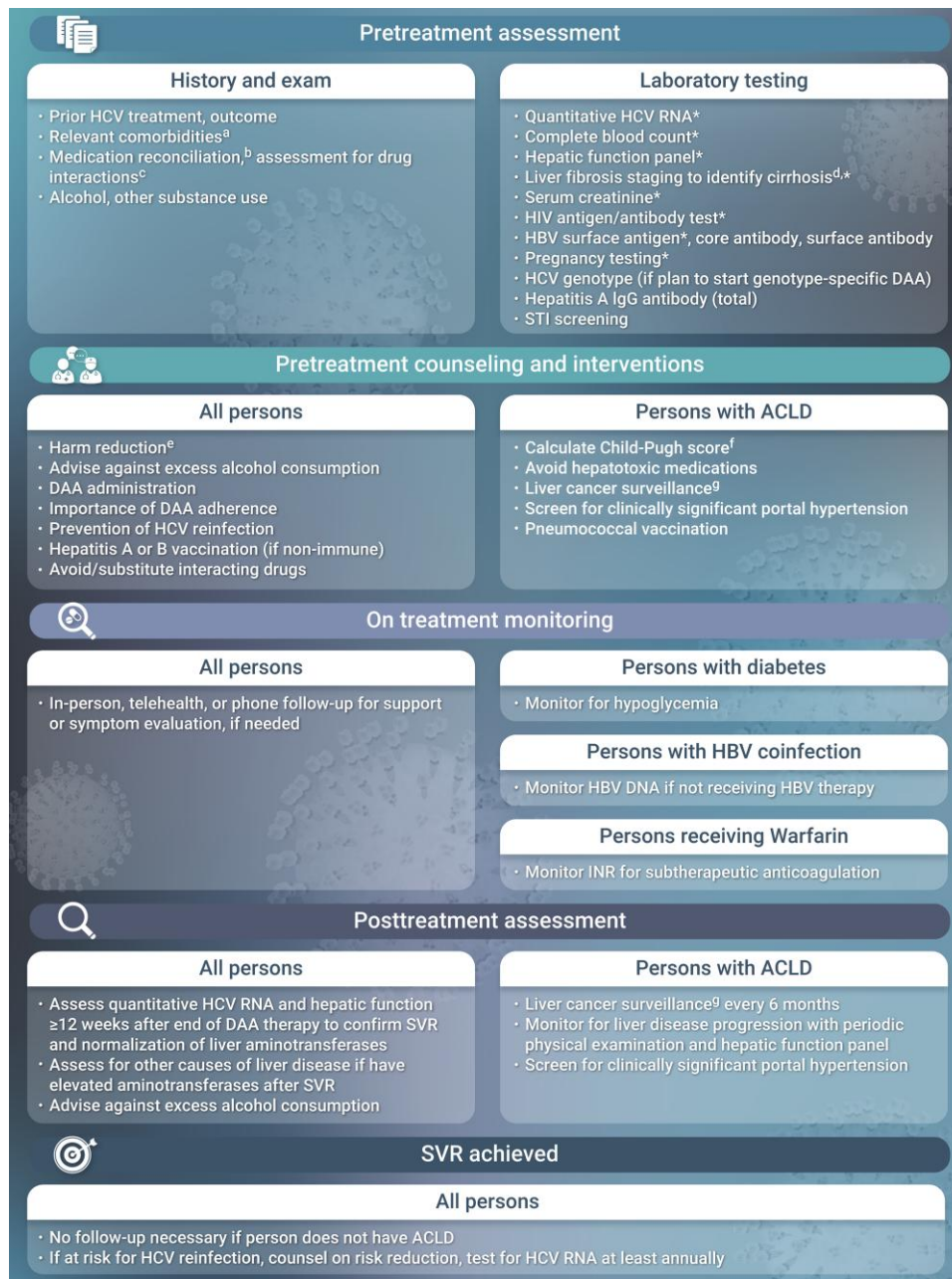
A 31-year-old man with a history of injection opioid use, housing instability, and xylazine-associated skin wounds presented to an outpatient opioid treatment program for an initial visit. He had recently been admitted to a local hospital for wound debridement, and methadone treatment was initiated. He was taking no other medications. As part of his intake visit, he underwent point-of-care (POC) screening for HCV and human

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immunodeficiency virus (HIV) antibodies and was found to be HCV antibody–positive and HIV antibody–negative. Given the positive POC HCV screening result, he underwent laboratory-based testing for HCV RNA, hepatic function, complete blood cell count, serum creatinine, HIV-1,2 antigen/antibody, and hepatitis B virus (HBV) surface antigen (HBsAg), which revealed the following: HCV RNA, 5.2 log IU/mL; elevated liver aminotransferases (alanine aminotransferase [ALT], 86 U/L; aspartate aminotransferase [AST], 84 U/L) but normal liver function (total bilirubin, 0.9 mg/dL; albumin, 3.2 mg/dL); normal complete blood cell count (platelet count, 255 000/ $\mu$ L);

calculated fibrosis-4 (FIB-4) index, 1.10; estimated glomerular filtration rate, 102 mL/min/1.73 m<sup>2</sup>; and HBsAg, negative. The opioid treatment program’s healthcare provider prescribed glecaprevir-pibrentasvir for 8 weeks, dispensing the medication with daily methadone at the treatment center.

## APPROACHES TO HCV SCREENING AND DIAGNOSIS

### Transmission and Natural History of HCV Infection

HCV is a blood-borne virus transmitted by activities or circumstances that promote percutaneous or parenteral exposure to

**Table 1. Activities, Exposures, and Other Conditions Associated With Hepatitis C Virus Infection**

Condition Associated With HCV Infection	Examples
Risk activities	Injection drug use (ever); intranasal drug use; male engagement in sex with men; recreational drug use during sex
Healthcare exposures	Receipt of a transfusion of blood or blood components or an organ transplant in the United States before July 1992; receipt of clotting factor concentrates produced in the United States before 1987; receipt of blood products in a country outside the United States (risk depends on country-specific HCV prevalence); receipt of long-term hemodialysis (ever); exposure of healthcare, emergency medical, or public safety workers to HCV-infected blood via needlestick, "sharps," or mucosal exposure; birth from a person with HCV infection; any history of incarceration; medical procedures performed in a setting where infection control practices are not followed
Other conditions and circumstances	HIV infection; HBV infection; initiation of preexposure prophylaxis for HIV in a sexually active individual; tattoos obtained outside of licensed parlors

Abbreviation: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

**Table 2. Interpretation of Hepatitis C Virus Antibody and RNA Test Results**

Test Result	Interpretation(s)
HCV antibody negative and HCV RNA not detected	No prior exposure to HCV infection <sup>a</sup>
HCV antibody positive and HCV RNA detected	Current HCV infection (acute or chronic) or HCV reinfection (either spontaneously cleared or cured with treatment)
HCV antibody positive and HCV RNA not detected	Past HCV infection (either spontaneously cleared or cured with treatment) or false-positive HCV antibody result <sup>b</sup>
HCV antibody negative and HCV RNA detected	Current HCV infection (acute or chronic [if immunosuppressed]) or false-negative HCV antibody result

Abbreviation: HCV, hepatitis C virus.

<sup>a</sup>HCV antibodies can be delayed or absent in people who are immunocompromised (eg, due to human immunodeficiency virus infection, hemodialysis, organ transplant, or receipt of immunosuppressive drug therapy); HCV RNA testing may be required in such individuals to rule out current infection.

<sup>b</sup>To determine whether a positive HCV antibody test represents resolved HCV infection or a false-positive result, repeated testing may be performed using a different HCV antibody assay. A biologic false-positive result should not occur with 2 different assays because they target different regions of the virus.

infected blood (Table 1). As demonstrated in case vignette 1, the opioid epidemic has driven an increase in HCV transmission in the United States [11], with unsafe injection practices and limited access to harm reduction services (eg, syringe exchange, substance use treatment) contributing to a rising incidence of HCV infection, particularly among persons aged 20–39 years [12–14]. Injection drug use (IDU) remains the most important risk factor for HCV infection in the United States, accounting for 67% of new infections [15]. Less common modes of HCV acquisition include intranasal drug use, tattoos obtained outside of licensed parlors, unprotected sex, and perinatal transmission [16, 17]. Sexual transmission of HCV among monogamous heterosexual couples is rare (rate, <0.1%/y) [18]. Risk of HCV infection has been increasing among men who have sex with men [19]. HIV infection, receptive condomless anal sex, ≥10 sex partners in the prior 6 months, recreational drug use during sex, and ulcerative sexually transmitted infections (STIs) are factors predisposing to HCV acquisition in this group [20].

After exposure, acute HCV infection is typically asymptomatic. If symptoms are present, they may manifest as malaise, headaches, anorexia, nausea, vomiting, diarrhea, abdominal pain, fever, and/or jaundice [21]. HCV RNA levels often

fluctuate during acute infection and may even become transiently undetectable [22]. Liver aminotransferase levels may be transiently elevated. In the absence of antiviral therapy, patients acutely infected with HCV either spontaneously clear the virus or go on to develop chronic infection. In approximately 25% of acutely infected individuals, infection spontaneously clears by 1 year [23]. Chronic infection develops in those without spontaneous clearance of acute HCV and is defined by persistence of HCV RNA for ≥6 months. Chronic HCV infection can promote liver inflammation and fibrosis and ultimately lead to cirrhosis [3]. Once cirrhosis develops, the risk of hepatic decompensation is 3%/y [24], and risk of HCC is 2%/y [25]. Chronic HCV infection is also associated with extrahepatic diseases, including mixed cryoglobulinemic vasculitis, B-cell lymphoma, cardiovascular disease, type 2 diabetes mellitus, and renal dysfunction [26].

#### Who to Screen

Approximately 40% of people with HCV infection in the United States remain unaware of their infection [8]. In 2020, to address this issue, the US Centers for Disease Control and Prevention and US Preventive Services Task Force recommended one-time, routine, opt-out HCV testing for all

individuals aged  $\geq 18$  years and HCV screening of all pregnant women during each pregnancy [27, 28]. One-time HCV testing is recommended for all persons  $< 18$  years of age with risk factors for HCV infection (Table 1) [29]. Annual HCV testing is recommended for all persons with activities or exposures associated with HCV infection (Table 1), particularly men who have sex with men and those with active IDU. Despite these recommendations, HCV screening has still not fully penetrated into hard-to-reach populations, particularly people who are incarcerated or underserved or those with former or current IDU [30–32].

### HCV Testing

All persons for whom HCV screening is recommended should initially be tested for HCV antibodies, which become detectable 6–12 weeks after exposure [33]. Antibodies may be delayed or absent in immunocompromised persons [34]. Once infection occurs, HCV antibodies are typically persistently detectable, even after successful cure or spontaneous clearance of viremia [33].

Laboratory-based enzyme immunoassays or POC indirect immunoassays (ie, OraQuick HCV rapid antibody test; OraSure Technologies) can be used to detect HCV antibodies [35]. POC assays have diagnostic performance similar to that of laboratory-based assays; use finger-stick blood, whole blood, or oral fluid rather than venipuncture; and provide results within 20 minutes [36]. As shown in case vignette 1, these tests are increasingly being used in community settings and can improve HCV screening uptake and enable decentralization of HCV care [37]. A positive laboratory-based or POC HCV antibody test might indicate current HCV infection (acute or chronic), past infection that has resolved, or a rare false-positive and should be followed up with immediate quantitative or qualitative HCV RNA confirmatory testing rather than referring the person to another clinician or setting to have the test performed [38]. Many laboratories now perform reflex HCV RNA testing if HCV antibodies are detected [39], avoiding the need to bring people back for confirmatory HCV RNA testing [40].

POC HCV RNA testing for HCV diagnosis (ie, the Xpert HCV test) was approved for use in the United States in June 2024 [41]. Since this test screens for HCV RNA, confirmatory testing is unnecessary. POC HCV RNA testing can be performed on site in primary care, emergency department, correctional, or substance use treatment settings and can help increase HCV screening in these venues. It uses capillary blood from a finger stick, provides qualitative results within 1 hour, and has excellent accuracy [42]. Implementation of POC HCV RNA testing increases diagnosis, linkage to care, and same-day treatment initiation [43–45], and it is a key component of “test-and-treat” plans to support HCV elimination [46]. The American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA)

developed simplified “test and treat” algorithms using POC HCV RNA assays (available at <https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/HCV%20Test%20and%20Treat%20Final%20011725.pdf>) to enable safe initiation of antiviral treatment once the diagnosis is made [47].

Table 2 summarizes the interpretation of HCV antibody and RNA test results. Individuals with HCV antibodies and detectable HCV RNA have current HCV infection. Those with HCV antibodies but negative HCV RNA results should be informed that they do not have current HCV infection, though they may have had previous infection [48]. They should be told that the presence of HCV antibodies does not protect them from reinfection. HCV antibody–negative persons who were exposed to HCV in the prior 6 months may have acute infection and should undergo HCV RNA testing. Those identified with acute HCV with quantifiable viremia should receive antiviral treatment on initial diagnosis without awaiting spontaneous resolution [49, 50], since delay introduced by waiting for spontaneous clearance can lead to loss to follow-up [40]. Immediate treatment of acute HCV infection also decreases the risk of HCV transmission [51]. HCV RNA testing should also be considered in HCV antibody–negative persons who are immunocompromised and potentially unable to produce antibodies [35].

Annual HCV antibody testing is recommended for PWID, men with HIV who have unprotected sex with men, and men who have sex with men who are receiving preexposure prophylaxis [47]. For individuals who cleared a previous HCV infection (spontaneously or with treatment) but who have activities, exposures, or conditions associated with increased risk of HCV exposure, assessment for reinfection should be done with HCV RNA testing instead of antibody testing.

### CASE VIGNETTE 2

A 23-year-old woman with active injection opioid use was admitted to the hospital with intermittent fevers, fatigue, dyspnea on exertion, and a 10-lb weight loss over the prior 2 weeks. Methicillin-susceptible *Staphylococcus aureus* grew in blood cultures obtained on admission. Transesophageal echocardiography demonstrated a large, mobile vegetation on the mitral valve with a perivalvular abscess. The infectious diseases team was consulted and, as part of their recommendations, suggested laboratory testing that revealed a reactive HCV antibody with an HCV RNA level of 6.1 log IU/mL on reflex testing, normal liver aminotransferase levels and hepatic function, normal blood cell count and renal function, negative HBsAg and HIV antibody test results, and negative urine/serum pregnancy test results. The patient underwent surgical intervention with mitral valve replacement on hospital day 5 and received intravenous cefazolin for a planned 6-week course.

She was unable to be discharged home for outpatient antimicrobial therapy, and transfer to a skilled nursing facility was not

possible. The infectious diseases team completed a pretreatment evaluation for HCV therapy, recommended noninvasive hepatic fibrosis assessment, and submitted an outpatient prescription for glecaprevir-pibrentasvir. A FibroSure test revealed a score of 0.15, consistent with no cirrhosis. The prescription underwent prior authorization by her insurer, and the DAA regimen was dispensed to the patient by a local specialty pharmacy. The first 28-day supply of glecaprevir-pibrentasvir was brought to the patient for inpatient initiation on hospital day 25 as a nonformulary medication. All remaining glecaprevir-pibrentasvir, including the refill, was given to the patient at the time of discharge on hospital day 47, after completion of her intravenous cefazolin course. She had repeat HCV RNA testing from a local commercial laboratory 12 weeks after completing her glecaprevir-pibrentasvir regimen, and this showed no detectable viremia, consistent with cure. She attended a telemedicine visit with the infectious diseases clinician to review the result.

## LINKAGE TO HCV CARE

Novel strategies to promote linkage to HCV care and DAA uptake have been developed and evaluated, particularly for priority populations. These strategies have been patient-based (eg, care coordination, accelerated DAA initiation, and patient education), healthcare provider-based (eg, provider education, telemedicine, multidisciplinary teams, and general practitioner-led care), and system-based (universal DAA access and availability of HCV services in multiple care settings) [52]. Several of these strategies are highlighted below.

### HCV Treatment Among PWID Admitted for Inpatient Care

Studies evaluating the cascade of HCV care among PWID have demonstrated treatment initiation rates <15% [53, 54], predominantly due to stigma, lack of health insurance, difficulty obtaining laboratory studies, and lack of transportation [55]. However, when PWID have access to DAA treatment, they achieve HCV cure at similar rates as the general population in clinical trial and real-world settings [56, 57]. Given that PWID are at increased risk of hospitalization due to IDU-related skin/soft-tissue, bloodstream, and bone/joint infections [58, 59], hospital admissions offer a prime opportunity to engage PWID in HCV care, as demonstrated by case vignette 2.

Opportunistic treatment of HCV infection among hospitalized PWID was examined in a trial to evaluate its effect on DAA uptake in this population [60]. A pragmatic, stepped wedge cluster-randomized trial recruited HCV viremic individuals admitted for inpatient care in departments of internal medicine, addiction medicine, and psychiatry at 3 hospitals in Oslo, Norway. Departments were sequentially randomized to change from control conditions (standard-of-care referral to outpatient HCV care) to intervention conditions (immediate inpatient HCV treatment initiation). DAA treatment initiation and

completion was accomplished by 68.4% of patients during intervention conditions versus 35.3% during control conditions. Cure was documented in 61.2% during intervention and in 64.7% during control conditions. The study showed that an opportunistic test-and-treat approach to HCV infection could promote HCV treatment uptake and be considered for broader implementation. Other programs that initiate HCV treatment among PWID during hospitalization have similarly demonstrated superior outcomes compared with outpatient referral to treatment [61, 62].

### Accelerated DAA Treatment Initiation

Programs have been developed that offer a single-day assessment for HCV followed by on-site DAA initiation either on the same day as the medical evaluation or at a subsequent visit [52]. Such an accelerated model of care was evaluated in a randomized pilot trial for curing HCV infection in young PWID [63]. Participants aged 18–29 years who were HCV antibody-positive, treatment-naïve and used injection drugs in the past 30 days were recruited from the community and randomized 1:1 to “rapid treatment” (same-day medical evaluation, confirmatory HCV RNA, baseline laboratory testing, and a 7-day starter pack of sofosbuvir-velpatasvir at a syringe service program) or “usual care” (same-day evaluation/HCV RNA confirmatory testing and, if the result was positive, facilitated referral to local providers). A total of 9 of 14 (64%) in the rapid treatment arm, compared with 1 of 11 (9.1%) in the usual care arm, achieved HCV cure ( $P = .01$ ). The study showed that providing easy access to DAAs for young PWID and initiating treatment quickly is a promising treatment strategy.

### Telementoring of Primary Care Providers

A telementoring model links specialists in HCV care together with primary care providers in a knowledge network to discuss the management of individual patients. People with HCV infection managed by primary care providers in the Extension for Community Healthcare Outcomes project had HCV cure rates that were comparable to those in specialty care [64]. Such networks can address gaps in availability of specialty care for people with HCV infection in rural and underserved settings. To promote accessibility of this model, prerecorded workshops to help providers treat patients with HCV infection and “e-consults” to facilitate prompt input on clinical care questions are also being incorporated [65, 66]. In San Francisco, in-person training followed by e-consult support resulted in a >100% increase in the number of patients treated for HCV infection [67].

### Colocalization of HCV Care in Syringe Service and Substance Use Treatment Programs

Colocalization of HCV care in syringe service and substance use treatment programs promotes HCV treatment uptake and cure among PWID compared with referral-based models

<b>Pretreatment assessment</b>	<p><u>Medical history</u></p> <ul style="list-style-type: none"> <li>• Prior HCV treatment, outcome</li> <li>• Relevant comorbid conditions</li> <li>• Medication reconciliation, assessment for drug interactions<sup>c</sup></li> <li>• Alcohol, other substance use</li> </ul>	<p><u>Laboratory testing</u></p> <ul style="list-style-type: none"> <li>• Quantitative HCV RNA*</li> <li>• Complete blood count*</li> <li>• Hepatic function panel*</li> <li>• Liver fibrosis staging to identify cirrhosis*</li> <li>• Serum creatinine*</li> <li>• HIV antigen/antibody test*</li> <li>• HBV surface antigen*, core antibody, surface antibody</li> <li>• Pregnancy testing*</li> <li>• HCV genotype (if planning to start genotype-specific DAA)</li> <li>• Hepatitis A IgG antibody (total)</li> <li>• STI screening (if HCV may have been acquired sexually)</li> </ul>
	<p><u>All persons</u></p> <ul style="list-style-type: none"> <li>• Harm reduction</li> <li>• Advise against excess alcohol consumption</li> <li>• DAA administration</li> <li>• Importance of DAA adherence</li> <li>• Prevention of HCV reinfection</li> <li>• Hepatitis A or B vaccination (if nonimmune)</li> <li>• Avoid/substitute interacting drugs</li> </ul>	<p><u>Persons with ACLD</u></p> <ul style="list-style-type: none"> <li>• Calculate Child-Pugh score</li> <li>• Avoid hepatotoxic medications</li> <li>• Liver cancer surveillance</li> <li>• Screening for clinically significant portal hypertension (or varices)</li> <li>• Pneumococcal vaccination</li> </ul>
<b>On-treatment monitoring</b>	<p><u>All persons</u></p> <ul style="list-style-type: none"> <li>• In-person, telehealth, or phone follow-up for support or symptom evaluation, if needed</li> </ul>	<p><u>Persons with diabetes</u></p> <ul style="list-style-type: none"> <li>• Monitor for hypoglycemia</li> </ul> <p><u>Persons with HBV coinfection</u></p> <ul style="list-style-type: none"> <li>• Monitor HBV DNA if not receiving HBV therapy</li> </ul> <p><u>Persons receiving warfarin</u></p> <ul style="list-style-type: none"> <li>• Monitor INR for subtherapeutic anticoagulation</li> </ul>
	<p><u>All persons</u></p> <ul style="list-style-type: none"> <li>• Assess quantitative HCV RNA and hepatic function <math>\geq 12</math> after end of DAA therapy to confirm SVR and normalization of liver aminotransferases</li> <li>• Assess for other causes of liver disease if aminotransferases are elevated after SVR</li> <li>• Advise against excess alcohol consumption</li> </ul>	<p><u>Persons with ACLD</u></p> <ul style="list-style-type: none"> <li>• Liver cancer surveillance every 6</li> <li>• Monitor for liver disease progression with periodic physical examination and liver function tests</li> <li>• Screening for clinically significant portal hypertension (or varices)</li> </ul>
<b>SVR achieved</b>	<p><u>All persons</u></p> <ul style="list-style-type: none"> <li>• No follow-up necessary if person does not have ACLD</li> <li>• In those at risk for HCV reinfection, counsel on risk reduction, test for HCV RNA at least annually</li> </ul>	

**Figure 1.** Overview of approach to management of persons diagnosed with hepatitis C virus (HCV) infection. Abbreviations: ACLD, advanced chronic liver disease; DAA, direct-acting antiviral; IgG, immunoglobulin G; INR, international normalized ratio; STI, sexually transmitted infection; SVR, sustained virologic response.

of care [68, 69]. This strategy aims to decentralize HCV care by placing it as close to persons with HCV as possible. These programs have varied in provider locations (on site vs telehealth), pharmacy access, and availability of support services (eg, care navigators, case managers, and enrollment assistance). One major approach has involved training pharmacists to manage HCV care and treatment at these sites. A study in Scotland showed that pharmacist-led HCV care resulted in a 2-fold increase in HCV treatment initiation among patients in a substance use treatment program [70]. A second key approach involves colocalization through telemedicine. Biweekly telehealth sessions between HCV care specialists and patients receiving substance use treatment in a New York City-based

program resulted in 73% being evaluated for HCV care, with 93% of those evaluated receiving DAA treatment and achieving cure [71].

#### Outreach Services for Priority Populations

Innovative programs have recently been designed to implement HCV testing and treatment on the streets to reach populations experiencing homelessness and unstable housing. Mobile clinic and community-based screening can reach people who are not engaged in care [72, 73]. In San Francisco, a mobile van provided HCV screening and treatment with the assistance of telehealth with a specialist in HCV care [72]. In Adelaide, Australia, individuals experiencing homelessness were offered POC HCV antibody

testing, and those who were HCV antibody–positive underwent POC HCV RNA testing [74]. HCV RNA–positive individuals were linked to a viral hepatitis nurse for treatment.

## HCV PRETREATMENT EVALUATION

### Support and Education

HCV infection can be a source of social stigma [75]. Patients may benefit from support and education as a component of HCV care. Providers should review how HCV is transmitted, natural history and factors that accelerate liver disease progression, and the benefits of DAA therapy. Harm reduction (eg, syringe service programs to support safe injections, education on safe drug consumption, and medication-assisted therapy for substance use), STI screening, HIV preexposure prophylaxis, and pregnancy testing (for women of childbearing age) should also be addressed. Providers should consider providing educational materials and offer referral to support groups to those experiencing anxiety or stigma from their diagnosis.

### Who to Treat and Goals of Therapy

All individuals with acute or chronic HCV infection should be considered for treatment, except those with a short life expectancy that cannot be improved by HCV treatment, liver transplantation, or other directed therapy [47]. DAA treatment is indicated for all adults and children aged  $\geq 3$  years.

The main goal of antiviral therapy is cure of infection, referred to as sustained virologic response (SVR) and defined as undetectable HCV RNA in whole blood or plasma  $\geq 12$  weeks after treatment completion (SVR12) [47]. Achievement of SVR4, defined as undetectable HCV RNA 4 weeks after treatment cessation, can also be considered as a measure of HCV cure among people without cirrhosis or prior DAA exposure for whom there may be potential barriers to completion of SVR12 [47]. Data from randomized trials of first-line DAA therapy among people without cirrhosis or with compensated cirrhosis showed a high correlation between SVR4 and SVR12, such that  $>99\%$  of people who achieve SVR4 also achieve SVR12 [76]. Other goals of therapy are to: (1) reduce HCV transmission, (2) decrease the risk of progression of liver fibrosis, and (3) prolong survival.

### Simplified Algorithms for Treatment-Naive Adults

To increase HCV screening and treatment uptake in high HCV prevalence settings and outside of traditional specialty practice venues, the AASLD/IDSA HCV guidance panel developed simplified HCV treatment algorithms that make treatment by non-specialist providers feasible and accessible (Figure 1) [47]. As highlighted in case vignettes 1 and 2, these simplified treatment pathways limit the pretreatment workup and on-treatment monitoring, substantially reducing barriers to HCV care, and are available for HCV treatment-naive adults without cirrhosis or with compensated cirrhosis. Given the safety of DAAs, for most patients, the entire course can be provided at initiation

without on-treatment monitoring [77]. People with prior DAA treatment failure, active HBV infection, decompensated cirrhosis, organ transplant, or HCC are ineligible for this approach because of additional management considerations and should receive DAA therapy from a specialist in HCV care.

### Relevant History to Ascertain Before HCV Treatment

Evaluation should include assessment of prior HCV treatment, adherence, and outcome; relevant comorbid conditions (HIV, HBV, and other liver diseases [eg, metabolic dysfunction–associated fatty liver disease and alcohol-related liver disease]); substance use; alcohol use; pregnancy status for women of childbearing age; and current medications (Figure 1) [47]. Ongoing substance or alcohol use, including active IDU, should not preclude DAA therapy.

For PWID, use of harm reduction services should be assessed, because these are essential to HCV prevention [13]. A meta-analysis showed that HCV cure rates with DAA therapy among those who actively inject drugs or receive substance use treatment are comparable to those in people without IDU [78]. As noted earlier, colocalizing HCV care in syringe service and substance use treatment programs facilitates HCV treatment and prevention [68–71].

Current and past alcohol consumption should be evaluated. Consumption of  $\geq 30$  g/d of alcohol increases liver fibrosis [79], but lesser amount of alcohol in the setting of HCV infection may also promote liver disease progression [80]. Individuals with excessive alcohol use may benefit from alcohol use disorder treatment. A cohort study of 69 229 adults with HCV infection treated with DAAs showed no difference in cure rates across alcohol use categories, even with high-risk consumption or alcohol use disorder [81]. Thus, restricting access to DAA therapy on the basis of alcohol use creates an unnecessary barrier for patients and challenges HCV elimination goals.

Medication reconciliation should be performed to elicit use of prescribed drugs, over-the-counter therapies, and herbal/dietary supplements [82]. Potential interactions between concomitantly used products and DAA regimens should be identified by consulting prescribing information and using online resources (eg, <http://www.hep-druginteractions.org/checker>). When possible, interacting medications should be stopped or switched to an alternative with less risk for potential interactions [47].

### Pretreatment Laboratory Testing

As highlighted in case vignettes 1 and 2, under the simplified HCV treatment algorithms [47], the following laboratory tests are needed within 6 months before starting DAA therapy (Figure 1): hepatic function panel (ALT, AST, total/direct bilirubin, and albumin), blood cell count, and serum creatinine level [47]. HCV RNA and assessment for active HBV coinfection with HBsAg are recommended any time before DAA therapy [47]. All people with HCV infection should undergo HIV-1,2 antigen/antibody testing with appropriate pretest/posttest

**Table 3. Direct-Acting Antivirals for the Treatment of Hepatitis C Virus Infection**

Dose per Tablet	Administration <sup>a</sup>	Duration, wk	HCV Genotypes Treated
Regimens for treatment-naïve patients			
Pangenotypic			
Glecaprevir (100 mg)–pibrentasvir (40 mg)	3 Tablets daily with food	8	All
Sofosbuvir (400 mg)–velpatasvir (100 mg)	1 Tablet daily with or without food	12	All
Genotype-specific			
Elbasvir (50 mg)–grazoprevir (100 mg)	1 Tablet daily with or without food	12	1, 4
Sofosbuvir (400 mg)–ledipasvir (90 mg)	1 Tablet daily with or without food	12 <sup>b</sup>	1, 4–6
Regimen for treatment-experienced patients			
Sofosbuvir (400 mg)–velpatasvir (100 mg)–voxilaprevir (100 mg)	1 Tablet daily with food	12	All

Abbreviation: HCV, hepatitis C virus.  
<sup>a</sup>Administration for adult dosing.  
<sup>b</sup>An 8-week course can be considered in people without human immunodeficiency virus or advanced chronic liver disease and in those with an HCV RNA level <6 million IU/mL.

counseling, since risk factors for HCV transmission are shared with HIV infection [48]. Pregnancy testing should be performed for women of childbearing potential. STI screening should be done in all people with HCV infection [48].

Additional laboratory tests are not required before HCV treatment, but several may be considered. HCV genotype testing is not mandatory before pangenotypic DAA therapy but should be done before initiating genotype-specific therapy [47]. Testing for hepatitis A virus IgG antibody should be considered for men who have sex with men and individuals who report substance use or homelessness among whom hepatitis A infection has increased more than 10-fold since 2014 [83]. Hepatitis A vaccination should be offered to individuals who are hepatitis A nonimmune. Providers could also assess for presence of HBV core and surface antibodies [47]. Hepatitis B immunization should be offered to individuals who are HBV nonimmune.

#### Pretreatment Assessment for Advanced Chronic Liver Disease

Chronic HCV infection leads to advanced hepatic fibrosis/cirrhosis, now referred to as advanced chronic liver disease (ACLD), in approximately 16% of individuals >20 years of age [84]. ACLD denotes the patient who, without a liver biopsy confirming it, is likely to have cirrhosis based on noninvasive testing and presence of thrombocytopenia [85]. Because HCV-related cirrhosis increases risk of hepatic decompensation and HCC, it is important for clinicians to identify patients who have ACLD before antiviral treatment, since they will require surveillance for liver complications [86, 87].

Noninvasive tests have replaced liver biopsy to identify ACLD because of biopsy risks, cost, and sampling error [88]. As highlighted in case vignette 1, the FIB-4 index is frequently used before HCV treatment to identify ACLD, particularly outside traditional care settings, and it can be calculated as follows:  $(\text{age [years]} \times \text{AST [U/L]}) / (\text{platelets [10}^9\text{/L]} \times (\text{ALT [U/L]}))^{1/2}$ ; FIB-4 index >3.25 indicates ACLD [89]. Alternative tests used to identify ACLD in routine practice settings may include serum biochemical markers (eg, FibroSure or FibroTest), as was

used in case vignette 2, vibration-controlled transient elastography, magnetic resonance elastography, and shear wave elastography [89]. In the absence of clinical findings of hepatic decompensation, HCV treatment should not be delayed awaiting hepatic fibrosis assessment, since this may compromise retention in care [90].

If ACLD is identified, the provider should calculate the Child-Pugh score, which classifies the severity of liver disease based on total bilirubin, albumin, prothrombin time, and degree of ascites and encephalopathy [91]. Scores  $\geq 7$  identify decompensated ACLD. DAA regimens that include a protease inhibitor (ie, glecaprevir-pibrentasvir or elbasvir-grazoprevir) are contraindicated in people with decompensated ACLD [92]. Patients with compensated ACLD (ie, Child-Pugh score  $\leq 6$ ) should be regularly monitored for symptoms of hepatic decompensation (eg, increased abdominal girth or confusion) and undergo surveillance for HCC every 6 months with liver ultrasonography and serum  $\alpha$ -fetoprotein testing [87]. Individuals with ACLD are susceptible to invasive pneumococcal infection [93] and septicemia due to *Vibrio vulnificus* [94]. They should receive pneumococcal vaccination [95] and be counseled to avoid consumption of raw/undercooked shellfish and prevent exposure of open wounds to seawater.

#### DAA THERAPY

##### Treatment for DAA-Naïve Adults and Children

DAAs inhibit HCV nonstructural (NS) viral proteins and are classified by their mechanism of action and targets: (1) NS3/4A protease inhibitors (medications ending in -previr), (2) NS5B RNA-dependent RNA polymerase inhibitors (medications ending in -buvir), and (3) NS5A replication complex inhibitors (medications ending in -asvir). Two pangenotypic DAA regimens (glecaprevir-pibrentasvir and sofosbuvir-velpatasvir) and 2 genotype-specific regimens (elbasvir-grazoprevir for HCV genotypes 1 or 4; sofosbuvir-ledipasvir for HCV genotypes 1, 4, 5, or 6) are available in the United States (Table 3) [47]. These regimens are all-oral, administered once daily, cure HCV infection in  $\geq 95\%$  of persons with 8 or 12 weeks of therapy, and have

few treatment-limiting adverse effects. They are safe and effective in people who are incarcerated, inject drugs, or have HIV coinfection or chronic kidney disease [96]. Treatment can be considered during pregnancy after shared decision making about potential risks and benefits [97]. Important considerations in selecting a DAA regimen include the presence of ACLD, comorbid conditions, potential for drug interactions, and availability on the insurer's formulary. Patients with decompensated ACLD should be referred to a gastroenterologist or hepatologist, preferably at a liver transplant center.

#### Initial Treatment of HBsAg-Positive Patients

People with HCV infection who are positive for HBsAg should be tested for HBV DNA [98]. Among those planning to initiate DAA therapy who are HBsAg-positive but not receiving HBV treatment because their HBV DNA level does not meet treatment criteria, there is the risk for reactivation of HBV infection during DAA treatment and early after the end of their treatment course [98]. In a meta-analysis of observational studies of 242 DAA-treated patients who were HBsAg-positive, the pooled proportion with HBV reactivation was 24% (95% confidence interval, 19%–30%) [98]. To mitigate the risk of HBV reactivation in these individuals, prophylactic HBV therapy can be started at DAA initiation and continued until 12 weeks after the completion of treatment [99]. If there is reluctance to initiate HBV therapy, HBV DNA levels should be monitored monthly during DAA therapy through 12 weeks after treatment completion [99]. If HBV DNA increases >10-fold above baseline, or to >1000 IU/mL in those with previously undetectable HBV DNA, HBV treatment should be initiated.

#### ON-TREATMENT MONITORING

Routine testing for HCV RNA or hepatic function during DAA treatment is not recommended unless there are concerns regarding incomplete adherence or certain special circumstances (highlighted in Figure 1). A multinational phase 4 single-arm trial suggested that a minimal monitoring approach during HCV treatment was safe and could lead to cure at a rate comparable to that seen with standard monitoring [77], and it informed the simplified treatment algorithms for treatment-naive adults without ACLD and with compensated ACLD [47].

#### Incomplete Adherence to DAA Treatment

DAA adherence may be limited by lack of social support, housing, literacy, or transportation. There are few data examining the outcomes of incomplete adherence to DAA therapy. One open-label, single-arm multicenter study that recruited participants with recent IDU (within 6 months) from 7 countries measured adherence to 12 weeks of sofosbuvir-velpatasvir using electronic blister packs and assessed the incidence of SVR12 [100]. Among 103 participants, median adherence to therapy was 94%, and 33 (32%) had <90% adherence (ie,

were nonadherent). SVR12 was similar for adherent and nonadherent participants (94% in both;  $P = .9$ ). Nonadherence of <7 consecutive days did not affect SVR12. A second randomized trial of 496 PWID in the United States similarly measured adherence to 12 weeks of sofosbuvir-velpatasvir using electronic blister packs and assessed the SVR12 incidence [101]. Participants with  $\geq 50\%$  adherence to sofosbuvir-velpatasvir achieved an SVR12 rate of >90%. These studies show that HCV infection can be cured even with suboptimal levels of DAA adherence. Strategies to promote DAA adherence will be patient-specific but can include telemedicine, in-person visits, and/or outreach/support by peers.

#### CONFIRMING HCV CURE AND POSTCURE MONITORING

##### Assessment for Cure

It is essential to test for HCV RNA after treatment completion (Figure 1). Undetectable HCV RNA  $\geq 12$  weeks after DAA completion defines SVR12 and is consistent with cure of HCV infection. Virologic relapse is rare  $\geq 12$  weeks after treatment completion [102]. As previously noted, SVR4 can be considered an alternative measure of cure among DAA-naive individuals without ACLD or individuals with compensated ACLD who have barriers to SVR12 assessment.

Cure of HCV infection is associated with improvement in liver function, liver fibrosis regression, and decreased rates of decompensated ACLD, HCC, and death [4]. Cure also leads to improvements in extrahepatic manifestations [103] and quality of life [104] and prevents HCV transmission [51]. People without ACLD who achieve cure do not require further monitoring of liver fibrosis progression unless they have non-HCV-related liver disease (eg, metabolic dysfunction-associated steatotic or alcohol-related liver disease).

#### CASE VIGNETTE 3

A 52-year-old man presented to his primary care clinic for ongoing HIV preexposure prophylaxis. He had a history of hypertension, tobacco use disorder, and HCV infection in 2023, which was treated with sofosbuvir-velpatasvir, achieving cure. His medications included lisinopril (20 mg), atorvastatin (10 mg), and tenofovir alafenamide (25 mg)–emtricitabine (200 mg) daily. He was taking doxycycline as needed after sexual encounters for postexposure prophylaxis. He acknowledged smoking methamphetamine occasionally and reported 3 male sexual partners in the past month, with intermittent use of barrier protection. STI screening showed an HCV RNA level of 6.2 log IU/mL, consistent with HCV reinfection. Additional laboratory testing showed elevated liver aminotransferase levels (ALT, 125 U/L; AST, 118 U/L), normal liver function, a normal complete blood cell count with a platelet count of 310 000/ $\mu$ L, a calculated FIB-4 index of 1.77, an estimated glomerular

filtration rate of 97 mL/min/1.73 m<sup>2</sup>, and negative results of rapid plasma reagent test and nucleic acid amplification tests of urine, pharyngeal, and rectal samples for chlamydial and gonococcal infections. He was previously hepatitis A and B immune following prior vaccination. His primary care provider prescribed a 12-week course of sofosbuvir-velpatasvir.

#### Postcure Assessment for HCV Reinfection

As highlighted in case vignette 3, HCV reinfection risk is increased among people with IDU or sexual activities associated with transmission [105, 106]. People at risk for reinfection should be counseled about transmission risks, harm reduction measures, and need for posttreatment surveillance. Testing of HCV RNA and liver aminotransferases should be performed at least annually in those at risk for HCV reinfection [47]. DAA treatment in those with HCV reinfection should be selected as recommended for people who are treatment-naïve.

#### Post-cure Monitoring of People With Compensated ACLD

People with compensated ACLD who achieve SVR should be monitored with periodic physical examination and liver function tests. They remain at risk for HCC and should undergo surveillance every 6 months with liver ultrasonography and serum  $\alpha$ -fetoprotein testing [87]. Those with other causes of liver disease should be counseled on the risk of liver fibrosis progression and undergo monitoring by a gastroenterologist or hepatologist. People with decompensated ACLD should also be monitored by a gastroenterologist or hepatologist.

#### Approach to HCV Treatment Failure

Although the efficacy of DAA regimens is high, virologic failure may occur after initial DAA therapy. These patients should be considered for retreatment by a specialist in HCV care. Retreatments are typically effective (SVR12 in >90%) with few adverse effects. For those who did not respond to sofosbuvir-velpatasvir or sofosbuvir-ledipasvir, retreatment with 12 weeks of sofosbuvir-velpatasvir-voxilaprevir is efficacious and safe [107]. For people with compensated ACLD, HCV genotype 3, or prior sofosbuvir-velpatasvir therapy, addition of ribavirin or treatment extension to 24 weeks should be considered [108, 109]. An alternative regimen is glecaprevir-pibrentasvir for 16 weeks [110]. For those with virologic failure after glecaprevir-pibrentasvir treatment, retreatment can be undertaken with sofosbuvir-velpatasvir-voxilaprevir for 12 weeks or sofosbuvir plus glecaprevir-pibrentasvir plus ribavirin for 12 or 16 weeks [111].

## CONCLUSIONS

HCV infection remains a major cause of chronic liver disease and premature death. The WHO has committed to eliminating HCV infection as a major public health threat by 2030.

Improving completion of each step along the HCV care cascade, including screening and diagnosis, linkage to care, DAA treatment, and management of concomitant substance use and ACLD, will require concerted and sustained effort on the part of all to make the 2030 HCV elimination goals a reality. We possess the necessary tools to effectively combat HCV infection on a global scale. The remaining challenge is determining the most effective implementation strategies to maximize benefits for the greatest number of individuals.

## Notes

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