Hepatitis C Coinfection

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Module 4: Co-Occurring Conditions
Lesson 6: Hepatitis C Coinfection

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Background

Hepatitis C virus (HCV) is a single-stranded RNA virus (Figure 1) that is an important cause of cirrhosis, liver failure, and hepatocellular carcinoma.[1] Transmission of HCV usually occurs predominantly through percutaneous exposure to blood or through sexual contact, especially with condomless receptive anal intercourse.[2] Infection with HCV is common among people with HIV and liver disease is accelerated by HIV coinfection.[3,4] There are robust data that show modern, pangenotypic, direct-acting antiviral (DAA) agents are highly effective and safe for the treatment of HCV in persons with HIV. Rates of HCV cure with DAA-based therapy have uniformly exceeded 95%, regardless of HIV status.[5,6] Experts now consider the approach to treatment of HCV in persons with HIV coinfection similar to that in persons with HCV monoinfection, except for the need to consider drug interactions between DAAs and antiretroviral medications.[5,6] Therefore, all persons with HIV should undergo screening for HCV, and all persons identified with current (active) HCV infection should receive HCV treatment.[7]

HCV Epidemiology

Hepatitis C Epidemiology in the United States

In the United States, approximately 2.5–4.0 million people are estimated to have current HCV infection, which corresponds to a hepatitis C population prevalence rate of 1.0–1.6%.[8] The hepatitis C prevalence estimates for the United States are based on data from the National Health and Nutrition Examination Survey (NHANES) that was conducted on noninstitutionalized civilian populations during 2017-2020. These NHANES data were supplemented with estimates of HCV in populations not included in the NHANES sampling frame and the expanded estimates are referred to as the NHANES+ HCV prevalence models.[8] In contrast, the Centers for Disease Control and Prevention (CDC) provides annual HCV incidence estimate in the United States. For the year 2023, the CDC estimated 69,000 cases of acute (new) HCV infection occurred during that year.[2] The annual number of contemporary new HCV infections in the United States is significantly higher than in 2013, but this number has leveled off in recent years, remaining slightly below 70,000 cases per year (Figure 2).[2,9] The sustained high number of acute HCV infections in the United States in the past decade correlates directly with the major opioid epidemic.[9]

Epidemiology of HIV and Hepatitis C Coinfection

In the United States, approximately 15 to 30% of persons with HIV have HCV coinfection.[3,4,10,11] The prevalence varies according to the risk factor for HIV and HCV acquisition, with the highest rates among people who inject drugs, followed next by men who have sex with men.[10,12,13,14] In the United States, HCV infection has emerged as an important sexually transmitted infection among men with HIV who have sex with men.[15,16,17,18] Researchers have identified several risk factors associated with the sexual acquisition of HCV in persons with HIV: non-injection recreational drug use, condomless receptive anal intercourse, use of sex toys, concurrent sexually transmitted infections (STIs), anal douching, and low CD4 cell count.[19,20,21]

Hepatitis C-related Deaths in Persons with HIV

Multiple cohort studies have identified shifting patterns of mortality for individuals with HIV as they are living longer with effective antiretroviral therapy. Liver disease, especially due to chronic infection with hepatitis B virus (HBV) or HCV, is now a leading cause of mortality among persons with HIV.[22] Although HIV-related mortality has decreased with the availability of antiretroviral therapy, several large cohort studies in Europe have demonstrated that persons with HIV and HCV coinfection have higher rates of liver-related death compared to persons with HCV monoinfection.[23,24,25,26] In the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) cohort study, analysis of 1,246 deaths in persons with HIV during the years 1999 through 2004 found that 14.5% resulted from liver causes and HCV infection was a predictor of liver-related death (Figure 3).[26] In the follow-up D:A:D cohort study from 1999 through 2011 that included 308,719 person-years of data, the percentage of deaths due to liver disease had decreased over time, but liver disease remained the third leading cause of death (13%) behind AIDS-related causes and non-AIDS-related malignancies.[27]

Natural History

Natural History with HCV Monoinfection

For persons with HCV monoinfection, the outcomes are highly variable and the rate of disease progression is influenced by many factors (Figure 4).[28] Following acute HCV infection, approximately 15 to 45% of individuals mount a robust immune response that spontaneously clears HCV from the liver.[28] Individuals who spontaneously clear HCV will have a reactive HCV antibody test and a negative HCV RNA. The 55 to 85% who do not achieve spontaneous clearance will develop chronic HCV.[28] Among those with chronic HCV monoinfection, approximately 20 to 30% will develop cirrhosis, but this occurs slowly, with a typical range of 20 to 30 years after HCV acquisition. For those with cirrhosis, approximately 1 to 4% per year develop hepatocellular cancer. In addition, for those with cirrhosis, approximately 2 to 5% per year are at risk of developing a complication of end-stage liver disease, which may include ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and/or variceal hemorrhage.

Impact of HIV on the Natural History of HCV Infection

In contrast to the 15–45% of persons with HCV monoinfection who spontaneously clear HCV, individuals with preexisting HIV have lower spontaneous HCV clearance rates (only 5–15%).[29,30] In addition, individuals with HIV and HCV coinfection have accelerated rates of liver fibrosis and a more aggressive course of liver disease (Figure 5).[4,31,32] Progression to cirrhosis occurs 12 to 16 years earlier in persons with HIV and HCV coinfection compared with persons who have HCV monoinfection.[33,34] With HIV and HCV coinfection, more rapid liver fibrosis progression rates have been associated with acquisition of HIV prior to HCV, low CD4 cell counts, higher alcohol consumption, and younger age.[32,34] Further, compared with persons who have HCV monoinfection, those with HIV and HCV coinfection typically develop hepatocellular carcinoma at a younger age and have more aggressive tumors.[32,35,36] The use of effective antiretroviral therapy does not appear to fully neutralize the adverse effect of HIV on the progression of HCV-related liver disease.[37,38]

Impact of HCV Infection on the Natural History of HIV

Most studies have reported HCV does not significantly impact HIV disease progression.[39,40,41] Some studies have shown that coinfection with HCV may blunt increases in CD4 cell counts after initiation of antiretroviral therapy, whereas others have shown no significant impact of HCV on immune reconstitution.[40,41,42] Achieving a sustained virologic response (SVR) with HCV treatment has not been shown to significantly impact CD4 count or percentage.[43] Chronic HCV infection increases the risk of hepatotoxicity due to antiretroviral therapy in persons with HIV.[44,45] Nevertheless, for nearly all individuals with HIV and HCV coinfection, including those with cirrhosis, the benefits of antiretroviral therapy outweigh the risks of liver injury caused by antiretroviral medications, particularly with use of currently recommended antiretroviral regimens in the United States, which rarely are associated with hepatotoxicity when compared to older antiretroviral regimens.[46,47]

Screening and Diagnosis

Screening for HCV in Persons with HIV

All persons with HIV should undergo routine testing for HCV infection at entry to care, primarily because of the high rate of HCV coinfection among persons with HIV and the availability of safe, highly-effective HCV treatment.[1] Individuals with HIV who are at the highest risk of acquiring HCV—persons who inject drugs and men who have sex with men—should have yearly HCV testing, or more frequently, if indicated.[1,48] Reinfection with HCV can occur in individuals who clear HCV either naturally or with treatment.[49] After HCV clearance, the HCV antibody will remain reactive and thus follow-up HCV antibody testing will not be able to identify new HCV infection. In this situation, an HCV RNA test should be used to screen for reinfection.[50]

Hepatitis C Tests

The tests used to make a serologic diagnosis of HCV are HCV antibody tests and HCV RNA tests. Although HCV antigen tests have been developed, they are not widely used and thus will not be discussed.

- **Antibody Tests**: Laboratory HCV antibody tests typically use an enzyme immunoassay (EIA) or a chemiluminescence Immunoassay (CIA).[51,52] A reactive HCV antibody test indicates infection with HCV at some point in time, but it does not differentiate resolved HCV infection from chronic (active) HCV infection. Resolved HCV infection can occur though natural immune clearance of HCV or with successful treatment of HCV. A point-of-care rapid HCV antibody test is approved for use with whole blood samples obtained either by venipuncture or fingerstick.[48,53] A reactive point-of-care HCV antibody test should be considered as a preliminary positive result and supplemental laboratory-based HCV testing should be performed.
- **HCV RNA Tests**: Molecular diagnostic tests for HCV specifically detect HCV RNA and are commonly referred to as a nucleic acid test (NAT) or nucleic acid amplification test (NAAT).[51] The HCV RNA becomes positive approximately 1 to 2 weeks after acquiring HCV. Low HCV RNA levels may be intermittently detectable very early after infection.[54,55] The HCV RNA test has become the gold standard supplemental test following a reactive HCV antibody screening test. The NAT can usually determine whether a person with a positive HCV antibody test has chronic HCV or resolved HCV infection. In addition, the NAT can be used to diagnose individuals with acute HCV infection. More recently, a point-of-care HCV RNA test was approved, and this test requires a fingerstick blood sample. A positive point-of-care HCV RNA test is considered diagnostic for HCV infection.[56]

Recommended HCV Diagnostic Algorithms

For diagnosing HCV in persons with no history of prior HCV infection, the Centers for Disease Control and Prevention (CDC) has traditionally recommended a 2-step HCV testing algorithm: perform initial testing with an HCV antibody test and follow all reactive HCV antibody tests with an HCV nucleic acid test (HCV RNA) (Figure 6).[57] Many laboratories now have a protocol to reflexively perform HCV RNA testing on all reactive HCV antibody tests (using the same blood sample).[58,59] More recently, a 1-step HCV testing algorithm has been introduced where a point-of-care (rapid) HCV RNA test is used as the initial test, with positive tests considered diagnostic and sufficient for starting HCV treatment. This single-step HCV RNA algorithm may be particularly useful in high prevalence settings (e.g., harm reduction centers and prison settings) but is not standard practice in most primary care settings. Note the diagnostic 2-step sequence recommended by the CDC is not intended for diagnosing acute HCV infection. In addition, for persons with known prior HCV infection, screening for reinfection should start directly with an HCV RNA test.[57]

Interpretation of Test Results

Individuals who have a nonreactive screening HCV antibody test result are considered not infected with HCV, unless a false-negative test result is suspected. False-negative HCV antibody tests occur in up to 3.2% of

persons with HIV, with most occurring when the CD4 count is less than 200 cells/mm^3.[60] Thus, if an individual who has HIV with a low CD4 count and a high risk for HCV infection has a nonreactive HCV antibody test, HCV RNA testing should be considered. In addition, HCV antibody tests can also be falsely negative in the window period (range 2–12 weeks) after HCV acquisition (before the production of anti-HCV antibodies).[1] Persons with a reactive HCV antibody test and a positive HCV RNA assay are considered to have current (active) HCV infection. Individuals who have a reactive HCV antibody test and a negative HCV RNA test are considered to have past (or resolved) HCV infection, which can occur through natural immune clearance of HCV or after successful treatment for HCV.[57]

Evaluation of Persons Diagnosed with HCV Coinfection

A comprehensive evaluation of persons with HIV who are diagnosed with HCV coinfection should include routine laboratory evaluation, HCV-specific tests, hepatitis A and B serologic testing, and an assessment of liver fibrosis. The newer simplified treatment approach in the AASLD-IDSA HCV Guidance recommends using a pangenotypic DAA-based regimen, and this new approach streamlines the baseline laboratory evaluation.[48]

Routine Laboratory Evaluation

With the simplified treatment approach, all individuals diagnosed with HCV should have a complete blood count (CBC) and a comprehensive metabolic panel that includes the following: serum creatinine and estimated glomerular filtration rate (GFR) [GFR]), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin and albumin.

HCV-Specific Tests

All persons with chronic HCV should have quantitative HCV RNA testing (if not done at the time of HCV diagnosis).[46] Although a positive quantitative HCV RNA test provides documentation of chronic HCV infection, it does not correlate with the degree of liver inflammation or fibrosis.[61,62] With the simplified treatment approach of using a pangenotypic regimen, ordering an HCV genotype is not routinely recommended.[58,59] Although the HCV genotype has become less relevant with the simplified approach of using pangenotypic DAAs, it may be indicated in three situations: (1) if required by an insurance company for medication approval, (2) if an individual has cirrhosis and sofosbuvir-velpatasvir is the planned treatment regimen, and (3) an individual does not meet criteria for simplified HCV treatment.

Hepatitis A and Hepatitis B Status and Immunization

For persons with chronic HCV infection, superinfection with hepatitis A virus (HAV) can cause fulminant hepatitis.[63] Thus, all persons with chronic HCV infection should be assessed for immunity to HAV with hepatitis A IgG and evaluated for HBV with the hepatitis B triple screen: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc).[48] Individuals without immunity to HAV should receive hepatitis A immunization. Similarly, those without immunity to HBV should receive HBV immunization.[1] In addition, detecting HBsAg in persons with chronic HCV has taken on increased importance with reports of HBV reactivation and hepatitis flares in persons with chronic HBV when treating HCV with direct-acting antiviral agents.[46,64,65]

Noninvasive Assessment of Liver Fibrosis

Individuals with chronic HCV should be assessed for the presence of advanced fibrosis using noninvasive methods to help with treatment decisions and to determine the need for screening for hepatocellular carcinoma. Advanced fibrosis is the most robust predictor of liver-related clinical outcomes and risk for hepatocellular carcinoma.[33,37] A liver biopsy is no longer recommended for liver fibrosis staging in HIV and HCV coinfection, unless there are other clinical indications to obtain one.[1] Detecting cirrhosis can have a potential impact on HCV treatment and on screening for hepatocellular carcinoma.

- **FIB-4**: The Adult and Adolescent OI Guidelines recommend calculating a FIB-4 blood test for fibrosis staging (FIB-4 Calculator).[1] A FIB-4 score less than 1.45 has a negative predictive value of 90% for advanced fibrosis.[66] In contrast, a FIB-4 greater than 3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis.[66] Therefore, a patient should be presumed to have cirrhosis if the FIB-4 score is greater than 3.25.[58]
- **Transient Elastography (FibroScan)**: Transient elastography is a noninvasive device that estimates liver stiffness and fat content. Transient elastography is generally considered to be the most accurate noninvasive test for liver fibrosis in patients with chronic HCV; a patient should be

presumed to have cirrhosis if they have a transient elastography stiffness score greater than 12.5 kPa.[58] For individuals with an indeterminate FIB-4 (1.45–3.25) score, transient elastography has particularly high value.[1]

Evaluation of Alcohol Use

Numerous studies have found a strong association between the use of alcohol and the development (or progression) of liver fibrosis and hepatocellular carcinoma.[67,68,69] Some studies have demonstrated that the risk of developing cirrhosis and decompensated liver disease in persons with chronic HCV infection is 2- to 3-fold higher for individuals with significant alcohol intake compared with those who have minimal or no alcohol intake.[70] The threshold level above which alcohol potentiates the progression of HCV disease is unknown, but it appears that even moderate levels of alcohol consumption accelerate histological lesions in persons with chronic HCV infection.[69] Individuals who are identified as having an alcohol use disorder or dependence should be referred to an addiction specialist and/or treatment program, but this should not preclude initiation of HCV treatment.[48]

Assessment of Acetaminophen and Iron Intake

Persons with HIV and HCV coinfection should also be counseled to limit ingestion of acetaminophen to 2 grams or less per day and avoid iron supplementation in the absence of documented iron deficiency.[1]

Education to Avoid HCV Transmission to Others

Transmission of HCV primarily occurs via infected blood and persons with HCV infection should receive counseling on how to prevent transmission of HCV to others.[48,71,72,73] In general, the prevention measures are similar to those used to reduce HIV transmission (since HIV and HCV share the same routes of transmission). People who inject drugs should be encouraged to stop their drug use; if they are unable to stop use of injection drugs, they should be counseled to never share injection equipment.[1] Use of condoms should be emphasized in men who have sex with men since sexual transmission of HCV has been increasingly reported in this group. In addition, persons with HCV should avoid sharing any devices that may be contaminated with blood, such as razors or toothbrushes. The prevention of perinatal transmission of HCV is discussed later in this topic review.

Treatment of HIV in Persons with HCV Coinfection

The Adult and Adolescent ARV Guidelines recommend initiating HIV antiretroviral therapy in all persons with HIV, including all persons with HIV and HCV coinfection.[46,74] Ideally, initiation of antiretroviral therapy should occur before HCV treatment. The HIV antiretroviral therapy regimen should account for potential drug interactions with direct-acting antiviral agents to be used for HCV treatment. In general, the use of integrase strand transfer inhibitor (INSTI)-based HIV antiretroviral therapy allows for concomitant treatment of HCV without major concerns for drug interactions.[46] If the patient also has chronic HBV, it is important that the HIV antiretroviral regimen includes agents with activity against HBV, since HBV reactivation can occur during HCV treatment with direct-acting antivirals. Antiretroviral medications may require dose adjustment or may be contraindicated in patients with advanced cirrhosis (Child-Turcotte-Pugh class B or C).

Treatment of HCV in Persons with HIV Coinfection

Treatment Goals

Treatment of HCV is now recommended for all individuals with HIV and HCV coinfection.[1,5,75] The short-term goal of HCV therapy in persons with HCV and HIV coinfection is to achieve an undetectable HCV RNA level, which is typically evaluated 12 weeks after completion of HCV therapy; this is commonly referred to as a sustained virologic response at post-treatment week 12 (SVR12) (Figure 7). Among persons who attain an SVR12, more than 99% will maintain the SVR years after completion of therapy and thus are deemed to have a virologic cure of HCV. Multiple studies have shown treatment of HCV in persons with HIV coinfection yields SVR12 rates that typically exceed 95%.[76,77,78] The long-term goal of treatment and cure of HCV is to reduce hepatocellular carcinoma and liver-related morbidity and mortality.[48,79,80,81] Although assessing for SVR12 has been the gold standard for determining cure, recent studies have shown a very high concordance (98% to >99%) between SVR12 and SVR4, particularly among patients without cirrhosis.[82] Although most expert guidelines recommend SVR12 as the gold standard for assessing cure, the AASLD-IDSA HCV Guidance offers SVR4 as an acceptable option for patients without cirrhosis or prior treatment experience.[50,58]

Simplified HCV Treatment Approach

The AASLD-IDSA HCV Guidance simplified HCV treatment approach includes recommendations for people without cirrhosis and those with compensated cirrhosis.[58,83] The simplified treatment approach does not exclude persons with HIV.[58,83] The following will address the four main components of the simplified HCV treatment approach in persons with HIV: (1) criteria for the simplified HCV treatment approach, (2) baseline evaluation, (3) pangenotypic regimen options, and (4) treatment-related monitoring.[1,84] For persons with HIV who are not eligible for the simplified treatment approach, expert consultation is recommended.

Criteria for Simplified HCV Treatment Approach in People with HIV

The AASLD-IDSA HCV Guidance simplified HCV treatment approach can be used for most people with HIV. The simplified treatment regimens apply to both chronic HCV and acute HCV.[1,58,83] The following is a list of characteristics of people with HIV for whom the simplified HCV treatment approach is not recommended.[1]

- Prior HCV treatment (reinfection after prior successful therapy is not an exclusion)
- Decompensated cirrhosis (including, but not limited to, current or prior variceal bleeding, ascites, or hepatic encephalopathy)
- Tenofovir DF-containing antiretroviral regimen with an eGFR less than 60 mL/min
- Receiving an antiretroviral regimen that includes efavirenz, etravirine, nevirapine, or a boosted HIV-1 protease inhibitor
- Untreated chronic HBV infection
- Pregnancy

Pretreatment Assessment

The initial evaluation of persons diagnosed with HCV was outlined in detail in the section Evaluation of Persons Diagnosed with HCV Coinfection. The following list summarizes the recommended baseline pretreatment assessment for people with HIV who are candidates for the simplified HCV treatment

approach.[1]

- Complete blood count (including platelet count)
- Liver function tests
- Serum creatinine
- HCV RNA
- Hepatitis B surface antigen
- Initial fibrosis staging using FIB-4 (FIB-4 calculator)
- Review of concomitant medications and drug interactions
- HCV genotype (if cirrhosis is present and treatment planned with sofosbuvir-velpatasvir)

Simplified HCV Treatment Regimens in People with HIV

For persons with HIV who meet the simplified HCV treatment criteria outlined above, the Adult and Adolescent OI Guidelines recommend treatment of HCV with either glecaprevir-pibrentasvir or sofosbuvir-velpatasvir.[1,58,83] These regimens are highly effective in treating HCV in persons with HIV coinfection.[76,78,85] For patients with compensated cirrhosis who are planning to receive treatment with sofosbuvir-velpatasvir, a baseline HCV genotype is recommended.[58,86] If the individual is identified to have HCV genotype 3, then drug-resistance testing (NS5A) is indicated and the presence of a Y93H mutation precludes use of the simplified HCV treatment approach with sofosbuvir-velpatasvir.[58,86]

Table 1. Simplified HCV Treatment Regimens in Adults with HIV: Adult and Adolescent OI Guidelines

Treatment-Naive Patients Without Cirrhosis
• Glecaprevir-pibrentasvir (100 mg/40 mg tablet): three tablets daily for 8 weeks (AI), *or* • Sofosbuvir-velpatasvir (400 mg/100 mg tablet): one tablet daily for 12 weeks (AI)
Treatment-Naive Patients with Compensated Cirrhosis
HCV Genotypes 1, 2, 4, 5, 6
Preferred Therapy • Glecaprevir-pibrentasvir (100 mg/40 mg tablet): three tablets daily for 8 weeks **(AIII)**, *or* • Sofosbuvir-velpatasvir (400 mg/100 mg tablet): one tablet daily for 12 weeks **(AI)** **Alternative Therapy** • Glecaprevir-pibrentasvir (100 mg/40 mg tablet): three tablets daily for 12 weeks **(CI)**
HCV Genotype 3
Preferred Therapy • Glecaprevir-pibrentasvir (100 mg/40 mg tablet): three tablets daily for 8 weeks **(AIII)** **Alternative Therapy** • Glecaprevir-pibrentasvir (100 mg/40 mg tablet): three tablets daily for 12 weeks **(CI)**, *or* • Sofosbuvir-velpatasvir tablet (400 mg/100 mg tablet): one tablet daily, with or without ribavirin for 12 weeks pending results of NS5A resistance testing **(CI)**
Treatment of Acute HCV Infection
• Glecaprevir-pibrentasvir (100 mg/40 mg tablet): three tablets daily for 8 weeks **(AII)**, *or* • Sofosbuvir-velpatasvir (400 mg/100 mg tablet): one tablet daily for 12 weeks **(AII)**
Recommendations for treatment after direct-acting antiviral failure are not provided; see the corresponding

section in AASLD/IDSA HCV Treatment Guidance.

Rating of strength of recommendation for the statement: A = Strong; B = Moderate; C = Weak
Quality of evidence for the recommendation: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Source:

- Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. National Institutes of Health, HIV Medicine Association, and Infectious Diseases Society of America. Hepatitis C virus. Last updated: January 18, 2023 [HIV.gov]

Laboratory Monitoring

With the simplified HCV treatment approach, no laboratory monitoring is required during treatment.[1] Note that some insurance companies and agencies require HCV RNA testing at week 4 of treatment to document an initial response in order to receive the additional refills needed to complete therapy.[1] All persons receiving HCV treatment should have a quantitative HCV RNA level at baseline and 4 or 12 weeks after completing therapy to assess for an SVR4 or SVR12 (Figure 8).[1]

Follow-Up Evaluation for HCV Reinfection

Individuals who have successfully achieved an SVR do not have HCV immunity and thus are at risk of reinfection with HCV.[1] Accordingly, they should receive counseling regarding the potential for reinfection, and efforts should be made to engage individuals who have risk of reinfection in risk-reduction strategies, such as the use of syringe exchange services and medication-assisted therapy for people with opioid use disorder.[1] Furthermore, screening for HCV reinfection with HCV RNA should be done at least annually for individuals who have ongoing risk factors for reinfection.[1]

Monitoring and Management of Chronic Liver Disease

Ongoing monitoring of liver disease is recommended for individuals in whom HCV therapy is deferred and post-treatment in persons with cirrhosis.[48,50] In persons with HIV and HCV coinfection in whom HCV treatment is deferred, routine monitoring should include laboratory assessment of hepatic function every 3 to 6 months; annual evaluation is appropriate to reevaluate hepatic fibrosis stage and to discuss modifiable risk factors for fibrosis (e.g., alcohol use) with more frequent evaluations for those with advanced liver disease.[5,48,50] All persons with chronic HCV should have a body mass index (BMI) calculated since obesity is associated with accelerated progression of HCV-related fibrosis, metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated steatohepatitis (MASH), and insulin resistance.[87,88,89,90]

Management of Persons with Cirrhosis

Individuals with HIV and HCV coinfection who have cirrhosis are at risk of severe complications related to their liver disease. The incidence rate of hepatocellular carcinoma (HCC) is approximately 2% per year in persons with HCV monoinfection and HCV-related cirrhosis; in persons with HIV and HCV coinfection and cirrhosis, the HCC rates appear to be even higher, especially among individuals with low CD4 counts.[91,92] These complications require special monitoring, including surveillance for hepatocellular carcinoma, evaluation for gastroesophageal varices, and consideration of liver transplantation for those with decompensated cirrhosis. Patients with advanced liver disease should be co-managed with practitioners with hepatology expertise.

- **HCC Surveillance Recommendations**: The 2023 AASLD HCC Guidance recommends hepatocellular carcinoma surveillance for all persons with chronic HCV who have cirrhosis, ideally using an abdominal ultrasound and serum alpha-fetoprotein approximately every 6 months.[93] For individuals with HCV infection and cirrhosis who have spontaneous or treatment-related clearance of HCV, the risk of developing HCC declines over time, but the risk reduction is not immediate. Therefore, these individuals should continue to receive HCC surveillance every 6 months.[50,93]
- **Screening for Gastroesophageal Varices**: Persons with HCV and cirrhosis should undergo an assessment for clinically significant portal hypertension using noninvasive markers (e.g., transient plastography). Clinically significant portal hypertension is highly probable if any of the following criteria are met.[94]
    - Liver stiffness is 25 kPa or greater, *or*
    - Liver stiffness is 20-25 kPa and platelet counts are less than 150,000/mm^3, *or*
    - Liver stiffness is 15-20 kPa and platelet counts are less than 100,000/mm^3.

When clinically significant portal hypertension is highly probable, a non-selective beta-blocker (typically carvedilol) should be started to decrease the risk of hepatic decompensation.[94] Patients with clinically significant portal hypertension who have a contraindication to nonselective beta-blockers should undergo screening esophagogastroduodenoscopy (EGD) to evaluate for the presence of gastroesophageal varices.[94] If transient elastography or imaging surrogates of clinically significant portal hypertension are not available and empiric use of a nonselective beta-blocker is contraindicated, patients with compensated cirrhosis should undergo EGD.[94] Screening EGD is not necessary in patients taking a nonselective beta-blocker. Among individuals with a contraindication to beta-blockade, who require EGD, if no substantial varices are observed, then EGD should be repeated every 2–3 years, or sooner if liver decompensation occurs (progression from Child-Turcotte-Pugh class A to Child-Turcotte-Pugh class B/C cirrhosis).[94]

Special Considerations During Pregnancy

All pregnant women should have testing for HCV during each pregnancy, regardless of HIV status.[95] Repeat HCV screening should ideally be performed late in the pregnancy if the initial test is negative but persistent or new risk factors for HCV are identified. All pregnant women with HIV and HCV coinfection should be screened for hepatitis A and B infection and receive vaccination during pregnancy if they are not already immune. For pregnant women diagnosed with HIV and HCV coinfection, expert consultation is recommended.

Risk of Perinatal HCV Transmission

In pregnant women with HCV monoinfection, the risk of perinatal HCV transmission is 4 to 7%; coinfection with HIV increases the risk of perinatal HCV transmission to approximately 10 to 14%.[1,13,96,97,98] Maternal HIV and HCV coinfection may also increase the risk of perinatal HIV transmission. Similar to the risk of perinatal HIV transmission, the risk of perinatal HCV transmission increases with high HCV RNA levels, particularly near the time of delivery.[97] Intrapartum HCV transmission is more common than in utero transmission.[97]

Management of HCV in Pregnant Women with HIV Coinfection

The currently recommended DAA treatments for HCV have limited data for use in pregnancy, even for women without HIV. Note that ribavirin is absolutely contraindicated for use during any time of pregnancy. Effective combination antiretroviral therapy with at least three drugs is recommended to treat HIV for all pregnant women with HIV and HCV coinfection, regardless of CD4 cell count or HIV RNA levels.[86] Suppressive antiretroviral therapy for pregnant women, which markedly lowers the risk of perinatal HIV transmission, may also reduce the risk of perinatal HCV transmission.[86,99]

- **AASLD-IDSA Guidance and Pediatric Opportunistic Infections Guidelines**: These guidelines indicate that treatment of HCV with DAAs can be considered during pregnancy on an individual basis after shared decision-making regarding the potential risks and benefits.[100,101]
- **HIV Perinatal Guidelines**: These guidelines do not recommend treatment of HCV in pregnant women who have HIV due to the lack of safety data on the use of DAAs in pregnancy.[102] If treatment of HCV is considered during pregnancy, expert consultation is recommended. If HCV treatment is not administered during the pregnancy, it should be recommended and offered postpartum. In addition, pregnant women with HIV and HCV coinfection should have an HCV RNA checked postpartum to evaluate for spontaneous clearance of HCV prior to initiating DAA therapy.[100,102]
- **Mode of Delivery**: For pregnant women with HIV and HCV coinfection, the mode of delivery should be based on standard obstetrical and HIV-related indications; specific intrapartum factors that may increase the risk of HIV transmission include emergent cesarean section, prolonged rupture of membranes (longer than 6 hours), and invasive fetal monitoring. These same intrapartum factors increase the risk of perinatal HCV transmission and thus should be avoided in pregnant women with HIV monoinfection, HCV monoinfection, or HIV and HCV coinfection.[1,13,86]
- **Breastfeeding**: Although HCV can be detected in breast milk, most studies have not shown an increase in transmission in breastfed infants.

Summary Points

- An estimated 15 to 30% of persons with HIV have HCV coinfection, with the highest rates among people with HIV who inject drugs and men with HIV who have sex with men.
- Compared with individuals who have HCV monoinfection, persons with HIV and HCV coinfection have accelerated rates of liver fibrosis that result in a more aggressive course of liver disease and higher rates of liver-related mortality.
- All persons with HIV should be tested for HCV at entry to care with an HCV antibody test, and if positive, should have HCV RNA testing to confirm active infection.
- Individuals diagnosed with HCV coinfection require an initial evaluation that includes a cirrhosis assessment.
- All persons with HIV and HCV coinfection should undergo treatment for HCV with the goal of achieving sustained virologic response and cure of HCV. Multiple studies have demonstrated comparable rates of sustained virologic response in persons with HCV monoinfection and HCV-HIV coinfection.
- Most people with HIV can receive the simplified HCV treatment approach with either an 8-week course of glecaprevir-pibrentasvir or a 12-week course with sofosbuvir-velpatasvir. Expert consultation is recommended to manage individuals who are not eligible for the simplified HCV treatment approach.
- Individuals with HCV and cirrhosis should undergo HCC screening every 6 months using abdominal ultrasound and serum alpha-fetoprotein.
- In pregnant women with HCV monoinfection, the risk of perinatal HCV transmission is 4 to 7%, and coinfection with HIV increases the risk of perinatal HCV transmission by approximately 2-fold.

Citations

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Figures

Figure 1 Hepatitis C Virus: Cross-Section

This cross-sectional view of the HCV particle shows all of the viral elements: the envelope glycoproteins (E1 and E2 heterodimers), a lipid membrane, the nucleocapsid, and the single-stranded RNA genome.

Illustration credit: Cognition Studio, Inc.

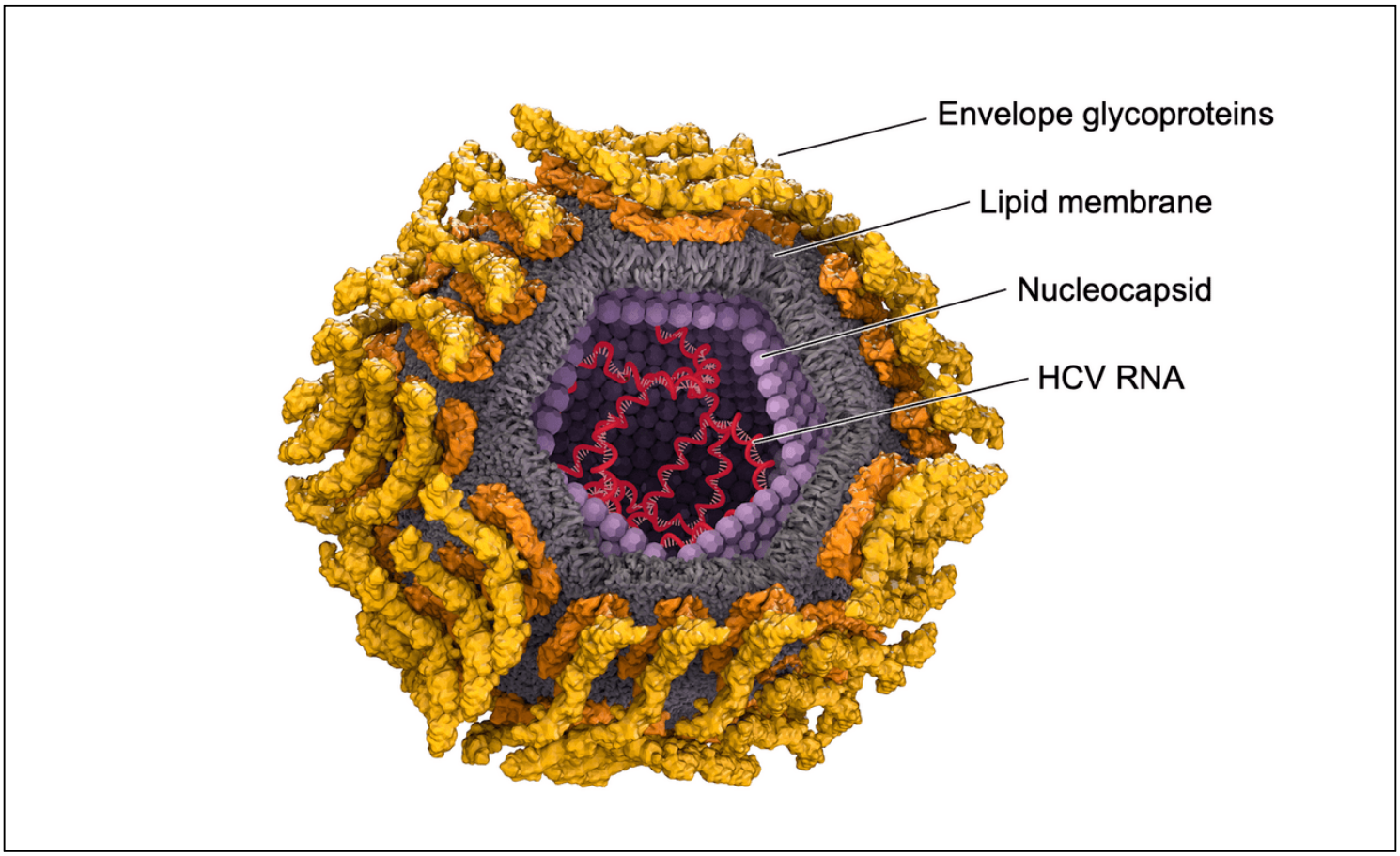


Figure 2 Estimated Number of New Annual HCV Infections—United States, 2013 through 2023

Source: Centers for Disease Control and Prevention. Viral Hepatitis Surveillance—United States, 2023. Published April 2025.

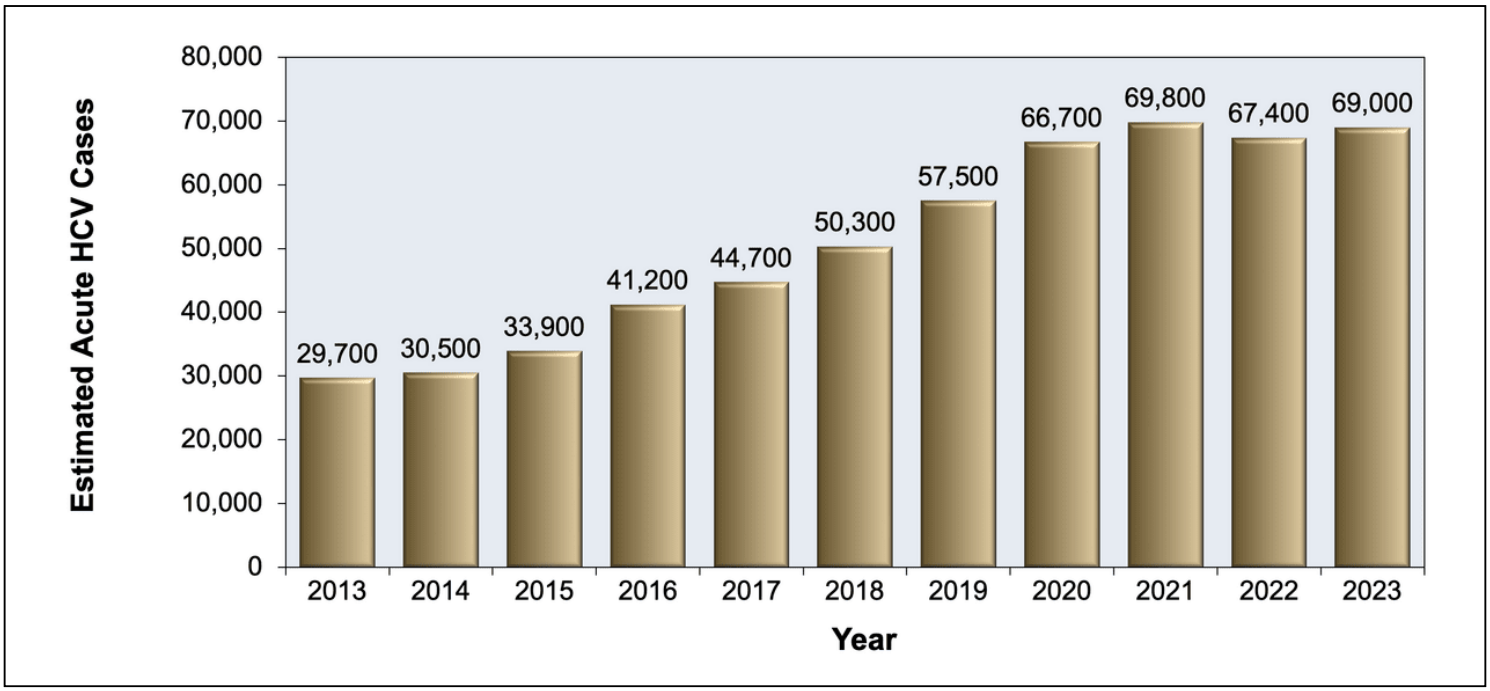


Figure 3 Risk Factors for Liver-Related Deaths in Persons with HIV Infection

Abbreviations: HBV = hepatitis B viurs; HCV = hepatitis C virus

Source: Weber R, Sabin CA, Friis-Møller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med. 2006;166:1632-41.

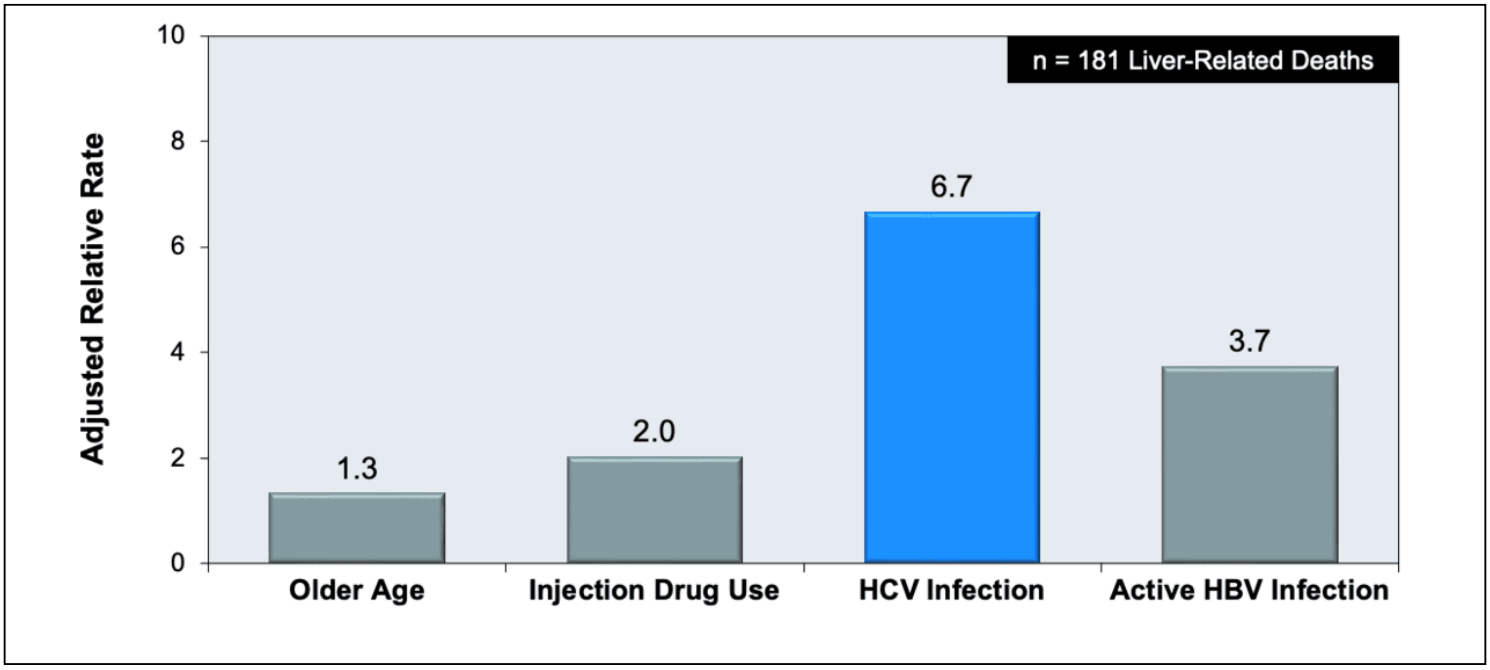


Figure 4 Natural History of Untreated Hepatitis C Monoinfection

Illustration: David H. Spach, MD

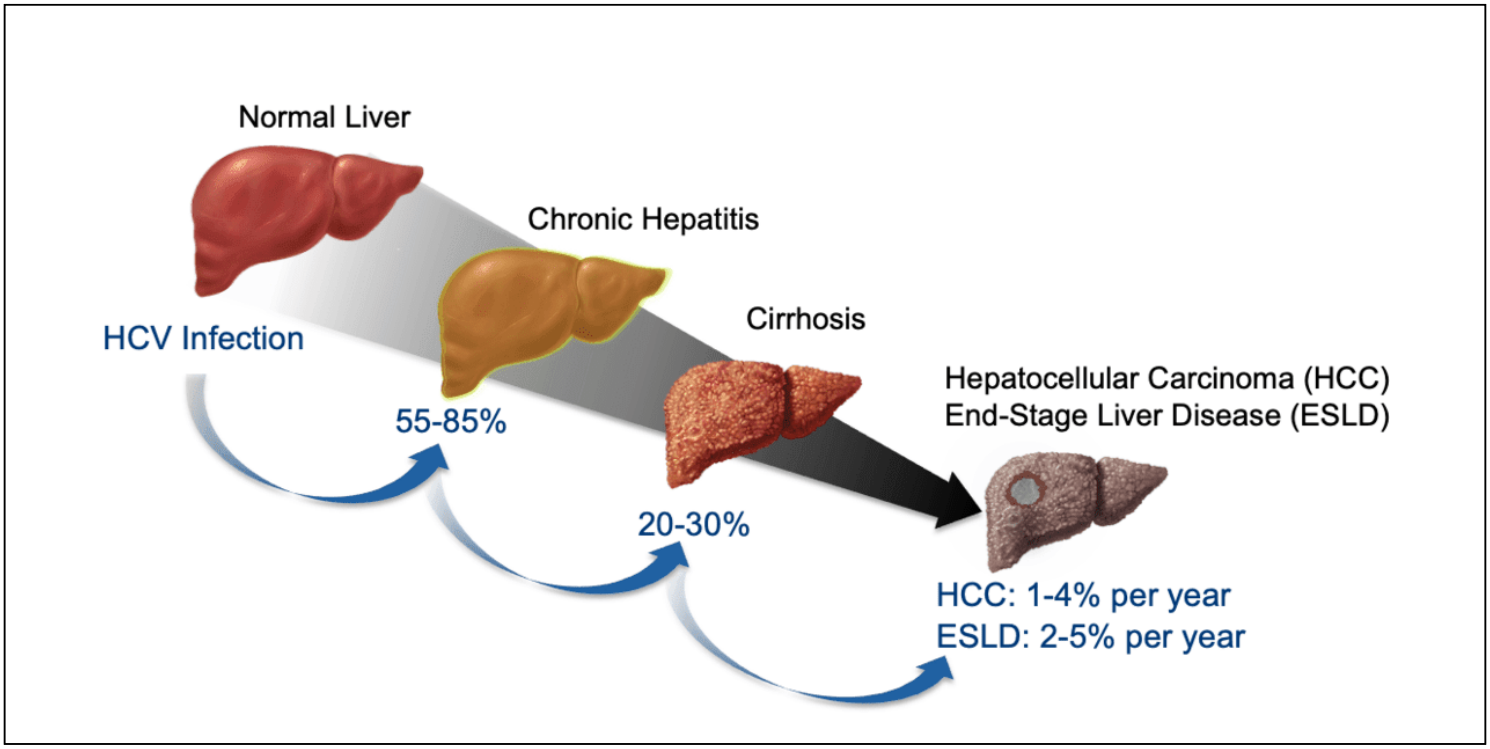


Figure 5 Progression to Cirrhosis in Persons with HIV and HCV Coinfection and HCV Monoinfection

This graph shows a retrospective analysis of 160 persons with HCV and the impact of HIV on the progression of HCV-related cirrhosis.

Source: Di Martino V, Rufat P, Boyer N, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. Hepatology. 2001;34:1193-9.

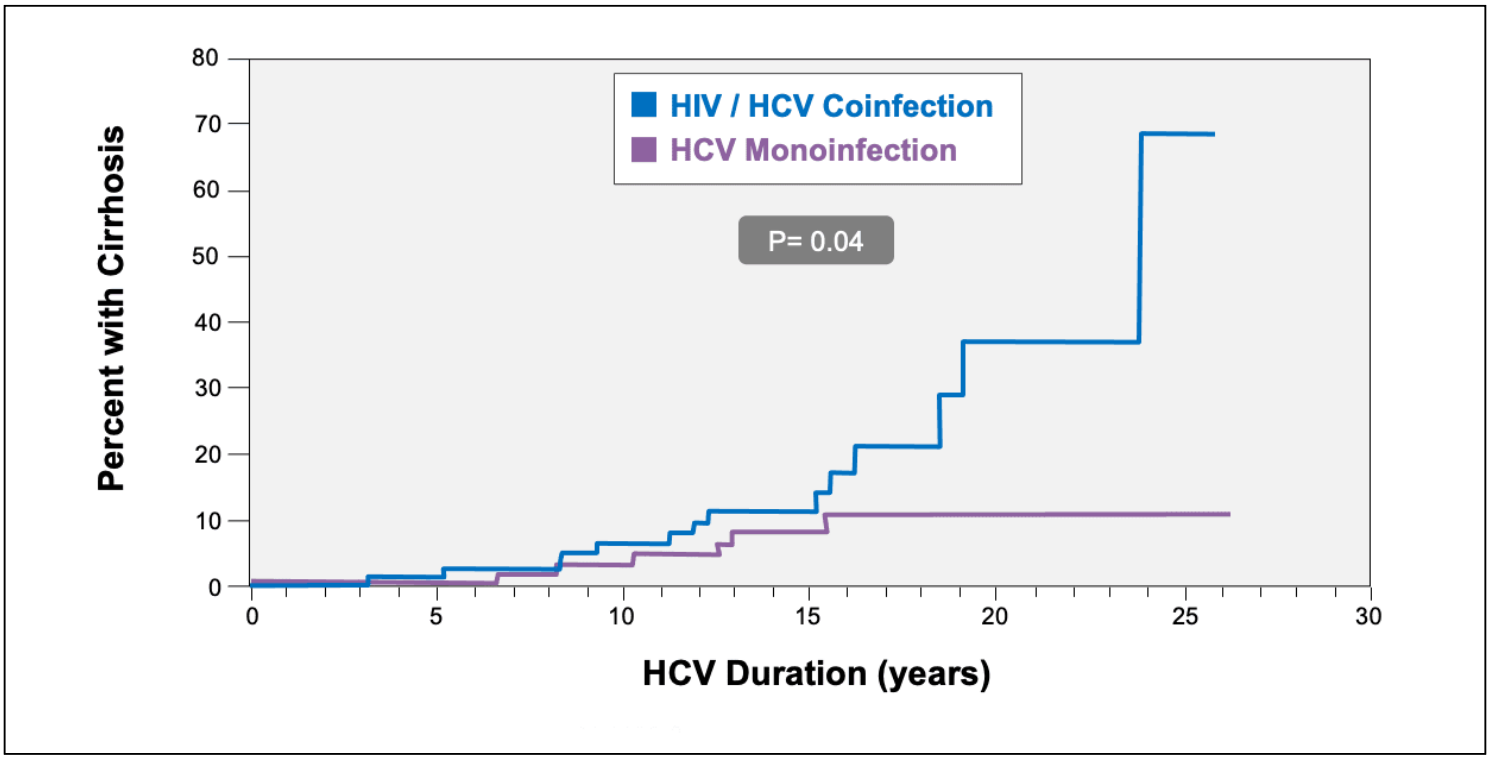


Figure 6 HCV Testing 2-Step Algorithm to Identify Current HCV Infection*

*For persons exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For immunocompromised persons, testing for HCV RNA can be considered.
¶To differentiate past resolved HCV infection from biologic false positivity for HCV antibody, consider testing with another HCV antibody assay. Repeat HCV RNA testing if the person had HCV exposure within the past 6 months or has clinical evidence of HCV disease.

Source: Centers for Disease Control and Prevention (CDC). Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal Wkly Rep. 2013;62:362-5.

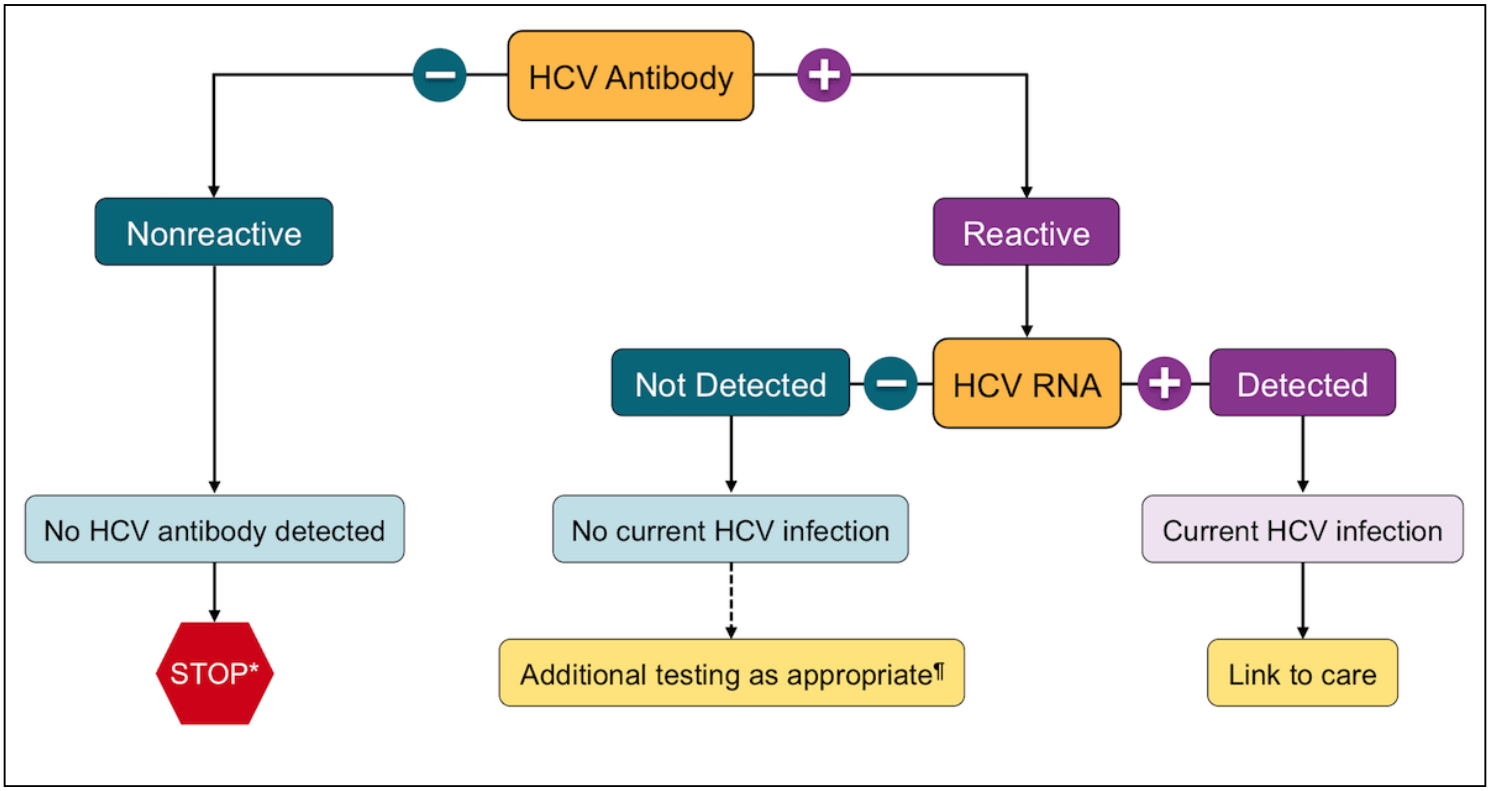


Figure 7 (Image Series) - Sustained Virologic Response (SVR) after HCV Treatment (Image Series) - Figure 7 (Image Series) - Sustained Virologic Response (SVR) after HCV Treatment
Image 7A: SVR4 and SVR 12 after a Treatment Duration of 8 Weeks

This example shows virologic response to an 8-week HCV treatment course.

Illustration by David H. Spach, MD

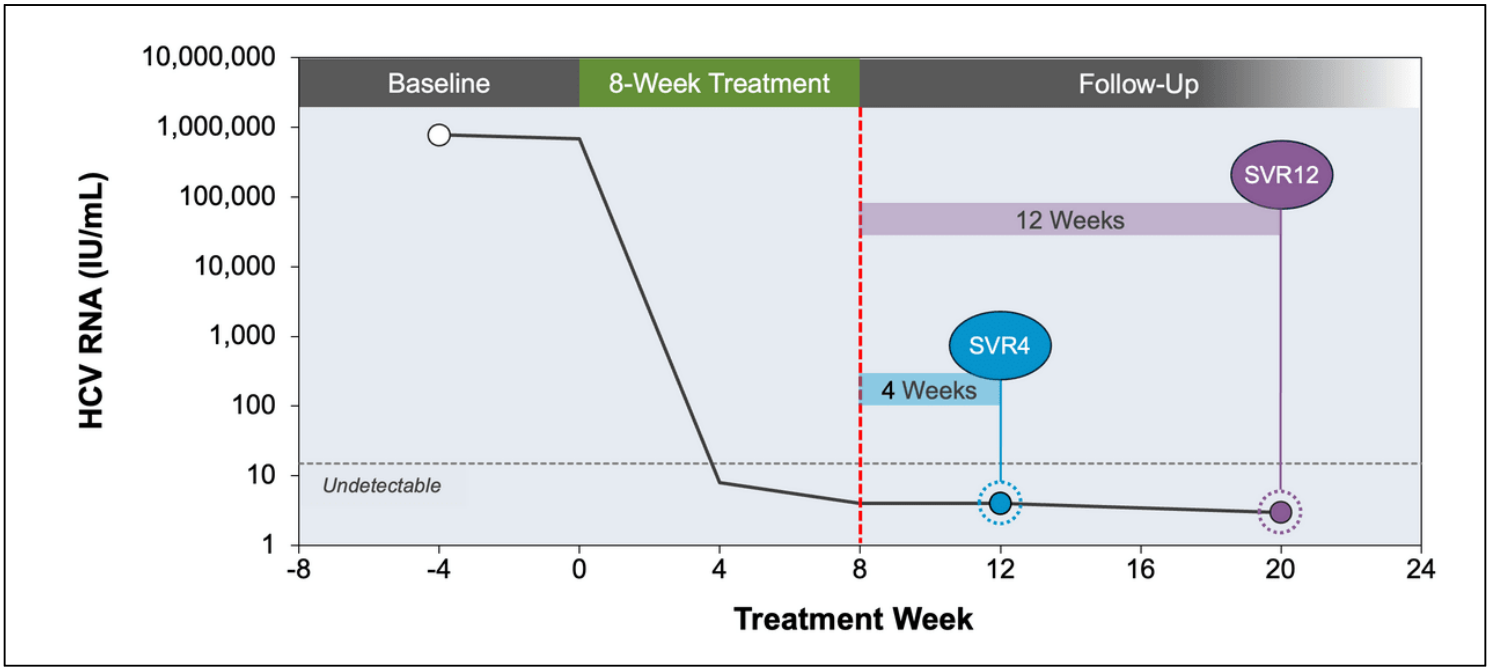


Figure 7 (Image Series) - Sustained Virologic Response (SVR) after HCV Treatment
Image 7B: SVR4 and SVR 12 after a Treatment Duration of 12 Weeks

This example shows virologic response to a 12-week HCV treatment course.

Illustration by David H. Spach, MD

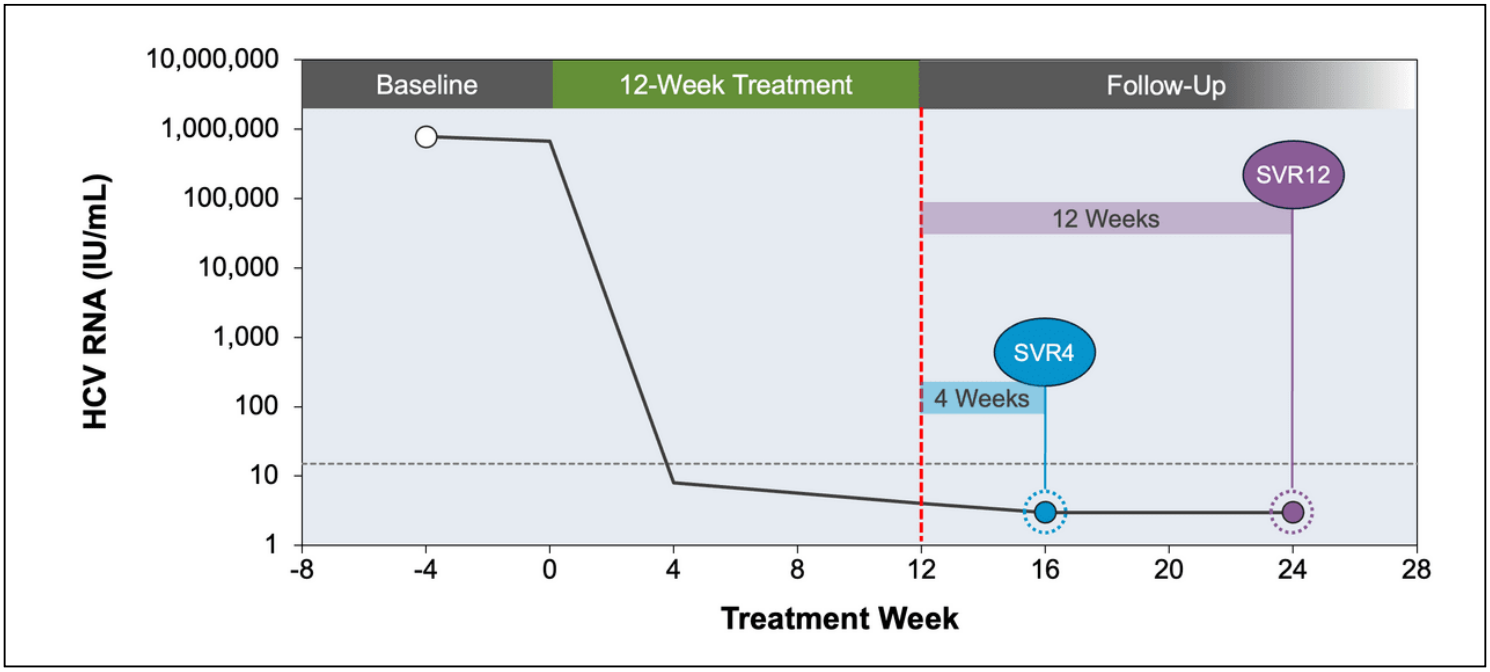


Figure 8 (Image Series) - Virologic Monitoring HCV Treatment (Image Series) - Figure 8 (Image Series) - Virologic Monitoring HCV Treatment
Image 8A: Virologic Monitoring with 8-Week HCV Treatment Course

With this 8-week hepatitis C treatment course, the recommended HCV RNA monitoring consists of a baseline level and repeated at 4 or 12 weeks post-treatment.

Illustration by David H. Spach, MD

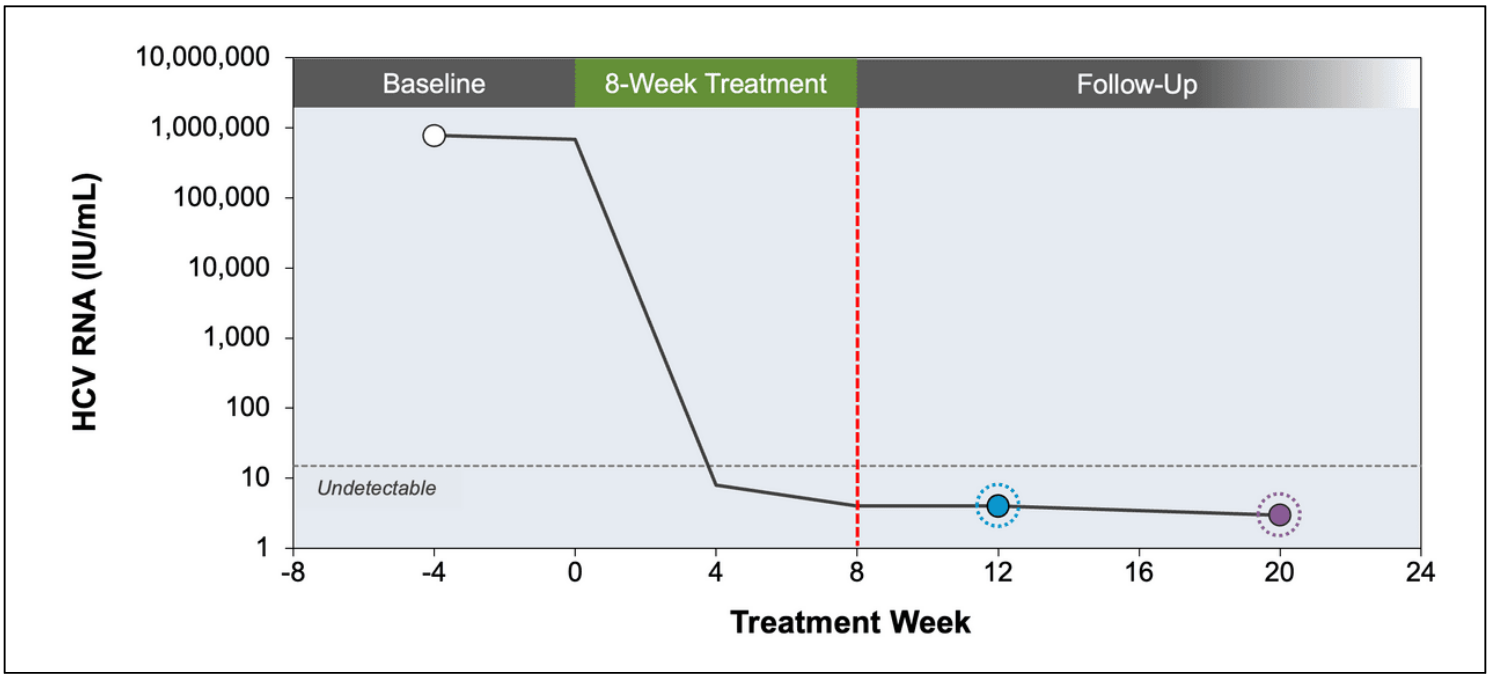


Figure 8 (Image Series) - Virologic Monitoring HCV Treatment
Image 8B: Virologic Monitoring with 12-Week HCV Treatment Course

With this 12-week hepatitis C treatment course, the recommended HCV RNA monitoring consists of a baseline level and repeated at 4 or 12 weeks post-treatment.

Illustration by David H. Spach, MD

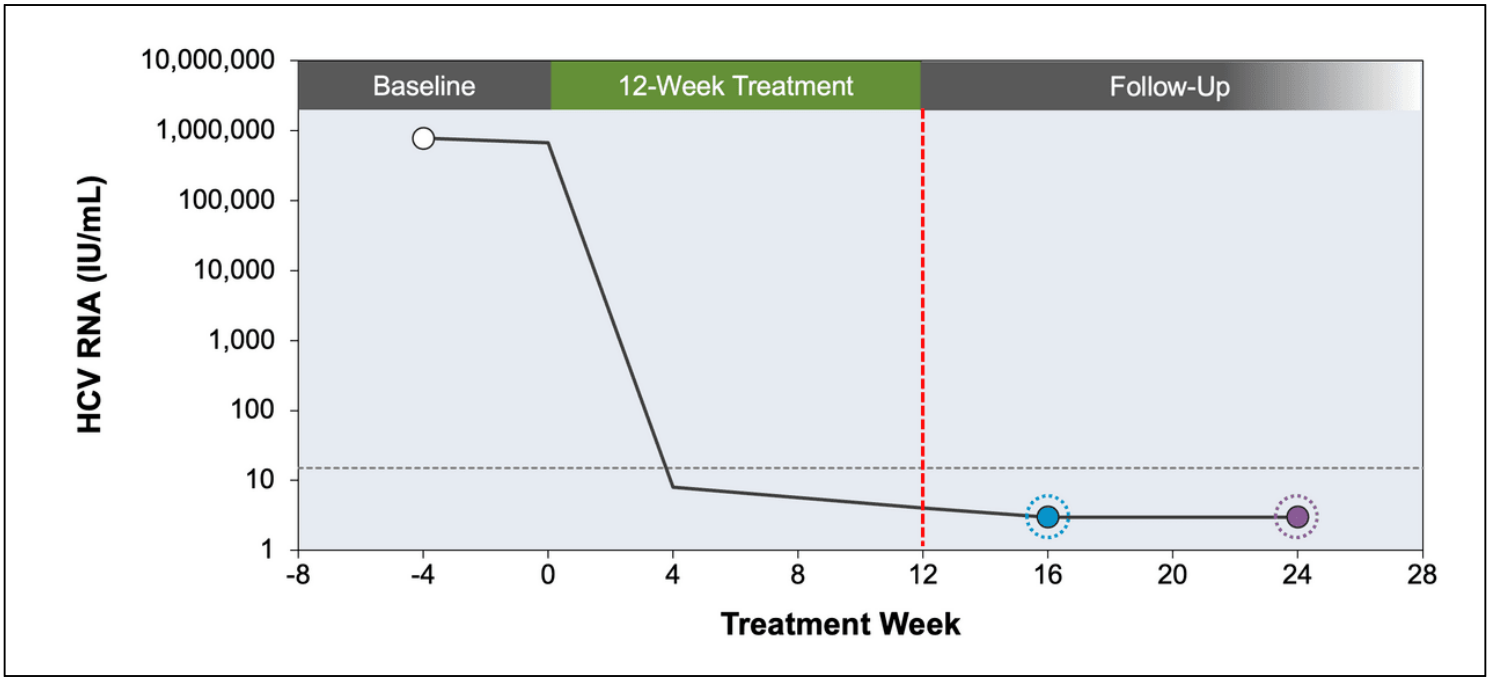


Table 1. Simplified HCV Treatment Regimens in Adults with HIV: Adult and Adolescent OI Guidelines

Treatment-Naive Patients Without Cirrhosis

- Glecaprevir-pibrentasvir (100 mg/40 mg tablet): three tablets daily for 8 weeks (AI), *or*
- Sofosbuvir-velpatasvir (400 mg/100 mg tablet): one tablet daily for 12 weeks (AI)

Treatment-Naive Patients with Compensated Cirrhosis

HCV Genotypes 1, 2, 4, 5, 6

Preferred Therapy

- Glecaprevir-pibrentasvir (100 mg/40 mg tablet): three tablets daily for 8 weeks **(AIII)**, *or*
- Sofosbuvir-velpatasvir (400 mg/100 mg tablet): one tablet daily for 12 weeks **(AI)**

Alternative Therapy

- Glecaprevir-pibrentasvir (100 mg/40 mg tablet): three tablets daily for 12 weeks **(CI)**

HCV Genotype 3

Preferred Therapy

- Glecaprevir-pibrentasvir (100 mg/40 mg tablet): three tablets daily for 8 weeks **(AIII)**

Alternative Therapy

- Glecaprevir-pibrentasvir (100 mg/40 mg tablet): three tablets daily for 12 weeks **(CI)**, *or*
- Sofosbuvir-velpatasvir tablet (400 mg/100 mg tablet): one tablet daily, with or without ribavirin for 12 weeks pending results of NS5A resistance testing **(CI)**

Treatment of Acute HCV Infection

- Glecaprevir-pibrentasvir (100 mg/40 mg tablet): three tablets daily for 8 weeks **(AII)**, *or*
- Sofosbuvir-velpatasvir (400 mg/100 mg tablet): one tablet daily for 12 weeks **(AII)**

Recommendations for treatment after direct-acting antiviral failure are not provided; see the corresponding section in AASLD/IDSA HCV Treatment Guidance.

Rating of strength of recommendation for the statement: A = Strong; B = Moderate; C = Weak
Quality of evidence for the recommendation: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Source:

- Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. National Institutes of Health, HIV Medicine Association, and Infectious Diseases Society of America. Hepatitis C virus. Last updated: January 18, 2023 [HIV.gov]