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Hepatitis C Coinfection

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

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Background and Epidemiology

General Hepatitis C Epidemiology

Hepatitis C virus (HCV) is a single-stranded RNA virus that is an important cause of cirrhosis, liver failure, and hepatocellular carcinoma. Globally, an estimated 130-150 million people are living with HCV.[1] In the United States, the most recent prevalence data from a National Health and Nutrition Examination Survey (NHANES) estimated 2.4 million persons were HCV RNA positive and 4.1 million were HCV antibody positive.[2] The Centers for Disease Control and Prevention (CDC) estimate that at least two-thirds of all persons with active HCV in the United States were born between 1945 and 1965.[3] Since 2002, however, the number of new HCV cases among younger persons has increased significantly, leading to a bimodal distribution, with peaks at 29 and 59 years of age.[4,5,6] Although the annual number of contemporary new HCV infections in the United States is markedly lower than in the 1980s, the incidence increased significantly from 2010 through 2020 (Figure 1).[6,7] Indeed, compared with 2013, the incidence rate of acute HCV has doubled. The greatest relative increases occurred among adults 20 to 39 years of age, and the burgeoning acute HCV infection rates in the United States in recent years correlate directly with the ongoing major opioid epidemic.[6]

Epidemiology of HIV and HCV Coinfection

In the United States, approximately 15 to 30% of persons with HIV have HCV coinfection.[5,8] The prevalence varies according to the risk factor for HIV and HCV acquisition, with the highest rates among persons with HIV who inject drugs and individuals with hemophilia who were infected through receipt of blood products prior to routine screening of blood products for HCV.[9,10,11] Since 2000, in the United States, Europe, Asia, and Australia, HCV infection has emerged as an important sexually transmitted infection among men with HIV who have sex with men.[12,13,14,15,16] Researchers have identified several risk factors associated with the sexual acquisition of HCV in persons with HIV, including 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.[17,18,19]

Transmission of HCV

The most efficient route of transmission of HCV is through percutaneous exposure to blood or blood products (e.g., via sharing of injection drug equipment, blood transfusion, or organ transplantation), but HCV is also transmitted through sexual contact (especially with condomless receptive anal intercourse), perinatally from mothers to infants, and rarely through environmental exposures.

General Approach to Persons with HIV and HCV Coinfection

With increasing data showing a number of direct-acting antiviral (DAA) agents are highly effective and safe for the treatment of HCV in persons with HIV, all persons with HIV and HCV coinfection should be evaluated for treatment of HCV. Rates of HCV cure with DAA-based therapy have uniformly exceeded 95%, and experts now consider the approach to treatment of HCV in persons with HIV coinfection similar to that in persons with HCV monoinfection, except for needing to consider drug interactions between DAAs and antiretroviral medications.[20,21] A proactive and aggressive approach to HCV is needed in persons with HIV—identify and treat HCV in all persons with HIV and HCV coinfection. This strategy would lead to improved health outcomes and longer survival in persons with HIV, as well as reduced transmission of HCV.[22]

Natural History of HIV-HCV Coinfection

Impact of HIV on the Natural History of HCV Infection

In persons with HCV monoinfection, approximately 20% will spontaneously clear HCV. Preexisting HIV decreases the likelihood of spontaneous HCV clearance to approximately 5 to 15%.[23,24] Compared with individuals who have HCV monoinfection, persons with HIV and HCV coinfection have accelerated rates of liver fibrosis and a more aggressive course of liver disease (Figure 2).[5,25,26] Progression to cirrhosis occurs 12 to 16 years earlier in persons with HIV and HCV coinfection compared with persons who have HCV monoinfection.[27,28] The accelerated liver disease seen in persons with HIV and HCV coinfection is generally more pronounced when HIV infection precedes HCV infection.[28] In persons with HIV-HCV coinfection, more rapid liver fibrosis progression rates have been associated with low CD4 count, higher alcohol consumption rate, and younger age.[26] Compared with persons who have HCV monoinfection, those with HIV-HCV coinfection typically develop hepatocellular carcinoma at a younger age and have more aggressive tumors.[26,29,30] 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.[31,32]

Impact of HCV Infection on the Natural History of HIV

Most studies have reported that HCV does not significantly impact HIV disease progression.[33,34,35] 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.[34,35,36] Achieving a sustained virologic response (SVR) with HCV treatment has not been shown to impact CD4 count or percentage.[37] Chronic HCV infection increases the risk of hepatotoxicity due to antiretroviral therapy in persons with HIV.[38,39] 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.[40,41]

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.[42] Although HIV-related mortality has decreased with the availability of antiretroviral therapy, several large cohort studies in Europe have demonstrated that persons with HIV-HCV coinfection have higher rates of liver-related death compared to persons with HCV monoinfection.[43,44,45,46] 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).[46] 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.[47]

Screening for HCV Infection

Screening for HCV in Persons with HIV

As recommended in the Adult and Adolescent OI Guidelines, 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.[4]

Repeat Screening for HCV Infection

Individuals with HIV who are at risk of acquiring HCV, including persons who inject drugs and men who have sex with men, should have annual HCV antibody testing, or more frequently, if indicated based on exposure to HCV.[4,48] Reinfection with HCV can occur in individuals who achieve an SVR with HCV therapy, as underscored by recent reports showing significant rates of HCV reinfection among men with HIV who have sex with men.[49] Because HCV antibody remains reactive after successful HCV therapy, follow-up HCV antibody testing will not be able to identify new HCV infection in persons previously cured of HCV infection. In this situation, an HCV RNA test should be used to screen for reinfection, at least annually, if indicated based on risk.[50]

HCV Diagnostic Testing

Recommended HCV Diagnostic Testing Sequence

In May 2013, the Centers for Disease Control and Prevention published a recommended testing sequence for diagnosing current (active) HCV infection (Figure 4).[51] The recommended sequence consists of initial testing for HCV antibody (using either a rapid or laboratory-conducted assay), followed by HCV RNA testing for all people who have a positive HCV antibody test.[51] Many laboratories now have a protocol to reflexively perform HCV RNA testing on all positive HCV antibody tests using the same blood sample. Note the diagnostic testing sequence recommended by the CDC is not intended for diagnosing acute HCV infection.[51]

Antibody Tests

Initial testing for the diagnosis of HCV infection utilizes serologic assays that detect human antibodies generated as a response to HCV infection. A positive antibody test indicates infection at some point in time, but it does not differentiate whether the person has resolved HCV infection or chronic (active) HCV infection. Several types of antibody tests are available.[48,52]:

- **Enzyme Immunoassay (EIA):** In the United States, the third-generation EIA test is the preferred serologic assay to use as the initial diagnostic test for HCV infection. The third-generation EIA detects antibodies that bind to recombinant antigens derived from multiple viral regions.[53,54] The EIA test is reported as positive or negative based on an absorbance signal compared with a cutoff value. The third-generation EIA has a sensitivity of approximately 98%. The EIA has a reported specificity of greater than 99%, with false-positive tests occurring more frequently in populations that have a very low HCV prevalence.
- **Chemiluminescence Immunoassay (CIA):** The CIA test is an antibody test similar to the EIA. The CIA is used less frequently than the EIA test. The CIA has similar sensitivity and specificity as the third-generation EIA.
- **Point-of-Care Rapid Immunoassays:** The OraQuick HCV rapid screening antibody test was approved by the FDA in 2010 for use with whole blood samples obtained either by venipuncture or fingerstick (despite the brand name of the test, it is not intended for use on oral samples). The test is read between 20 and 40 minutes after the test device is inserted into the buffer, and the result is either reactive or nonreactive. The specificity and sensitivity of the OraQuick HCV test are similar to laboratory-based HCV antibody assays.[48,55] An individual with a reactive test should be considered to have a preliminary positive test and should undergo supplemental HCV testing.

Molecular 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).[52] The HCV NAT becomes positive approximately 1 to 2 weeks after acquiring HCV. Low HCV RNA levels may be intermittently detectable very early after infection.[56,57] The NAT test has become the gold standard supplemental test following a positive 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, but unlike with acute HIV, the HCV RNA test can be negative or barely detectable with acute HCV infection. In a clinical scenario where HCV RNA is negative but acute HCV is highly suspected, it is advisable to repeat the HCV RNA test several months later.

- **Quantitative HCV RNA**: The quantitative HCV RNA test is the preferred HCV supplemental test and can determine whether an individual has chronic infection. The ultrasensitive HCV quantitative RNA assays, which detect as few as 5 copies/mL, provide the same level of diagnostic accuracy as the qualitative assay. In addition, if a quantitative HCV RNA assay is used for diagnostic purposes, positive results will include an HCV RNA quantitative value, which provides useful information as a baseline

and pretreatment HCV RNA level. The results for the commercially available HCV RNA assay are given in International Units (IUs).

- **Qualitative HCV RNA**: The qualitative HCV RNA test provides a “yes” or “no” answer to whether detectable HCV RNA is present in the sample. It does not provide a quantitative level of HCV. Because the sensitivity of the quantitative HCV RNA assay has dramatically improved in recent years, the utility of the qualitative HCV RNA has markedly diminished, and it is infrequently used.

Interpretation of Test Results

Individuals who have a negative screening HCV antibody test result are considered not infected with HCV, unless a false-negative test result is suspected. Studies have demonstrated false-negative HCV test rates of up to 3.2% in persons with HIV, with most of the false-negative results occurring in persons who have a CD4 count of less than 200 cells/mm^3.[58] Thus, if an individual is at high risk for HCV infection, HCV RNA testing should be considered if the HCV antibody test is negative. As previously noted, HCV antibody tests can also be falsely negative in the “window period” of acute HCV infection before the production of anti-HCV antibodies. The HCV window period ranges from 2 to 12 weeks, so HCV RNA testing is helpful during this period, especially in persons who have elevated alanine aminotransferase (ALT) levels that suggest acute HCV infection.[4] Persons with a positive HCV antibody test and a positive HCV RNA assay are considered to have current (active) HCV infection. Individuals who have a positive HCV antibody test and a negative HCV RNA test are considered to have no evidence of current HCV infection. Note that the 2013 HCV diagnostic testing sequence recommended by the CDC is not intended for diagnosing acute HCV.[51]

Evaluation of Persons Diagnosed with HCV Coinfection

Due to the rapidly changing landscape of HCV treatment, the AASLD-IDSA HCV Guidance is regularly updated.[48] A comprehensive evaluation of persons with HIV who are diagnosed with HCV coinfection should include routine laboratory evaluation, HCV-specific tests, status of hepatitis A and B, and 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) with differential, comprehensive metabolic panel (CMP) that includes assessment of renal function (creatinine, estimated glomerular filtration rate [GFR]) and hepatic function (ALT, aspartate aminotransferase [AST], total and 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).[40] The quantitative HCV RNA level provides documentation of chronic HCV infection but does not correlate with the degree of liver inflammation or fibrosis.[59,60] With the simplified treatment approach of using a pangenotypic regimen, ordering an HCV genotype is not recommended. 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.[61] Thus, all persons with chronic HCV infection should be assessed for immunity to HAV with total hepatitis A antibody and evaluated for HBV with hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc).[48] The recommendation to screen for hepatitis A and B also applies to all people with HIV. Individuals without immunity to HAV should receive hepatitis A immunization. Similarly, those without immunity to HBV should be vaccinated against HBV.[4] Awareness of hepatitis B status in persons with chronic HCV has taken on increased importance with recent reports of HBV reactivation and hepatitis flares during treatment of HCV with direct-acting antiviral agents.[40,62,63]

Assessment of Stage 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. Fibrosis is the most robust predictor of liver-related clinical outcomes in persons with chronic HCV, and a more rapid progression of hepatic fibrosis occurs in persons with HIV-HCV coinfection.[27,31] 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.[4] Regardless, limited or no access to additional staging modalities should not preclude HCV treatment.[4]

- **Noninvasive Test to Assess Hepatic Fibrosis**: The Adult and Adolescent OI Guidelines recommend using the FIB-4 blood test for fibrosis staging (FIB-4 Calculator).[4] A FIB-4 score less than 1.45 has a negative predictive value of 90% for advanced fibrosis.[64] In contrast, a FIB-4 greater than 3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis.[64] For individuals with an indeterminate FIB-4 (1.45–3.25) score, noninvasive imaging modalities such as transient elastography or magnetic resonance elastography may be indicated, especially if there are

any other clinical or laboratory findings that suggest cirrhosis.[4]

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.[65,66,67] 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.[68] 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.[67] 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 initiating 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 less than 2 grams per day and avoid iron supplementation in the absence of documented iron deficiency.[4]

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.[48,69,70,71] 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.[4] 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 ART Guidelines recommend initiating HIV antiretroviral therapy in all persons with HIV (regardless of CD4 cell count), including all persons with HIV and HCV coinfection.[40,72] Ideally, initiation of antiretroviral therapy should occur before HCV treatment and after suppression of HIV RNA levels, which typically takes less than 3 to 4 months. The choice of the initial HIV antiretroviral therapy regimen should take into account potential drug interactions with the anticipated direct-acting antiviral agents to be used for HCV treatment. In general, the use of unboosted integrase strand transfer inhibitor (INSTI)-based HIV antiretroviral therapy allows for concomitant treatment of HCV without major concerns for drug interactions. The use of tenofovir alafenamide, which has an improved safety profile when compared with tenofovir DF, has also minimized concerns about combined antiretroviral and DAA medication toxicity.[40] For these reasons, persons anticipating DAA treatment of HCV should ideally receive either an antiretroviral regimen that includes an unboosted INSTI but avoids tenofovir DF (e.g., bictegravir-tenofovir alafenamide-emtricitabine or dolutegravir plus tenofovir alafenamide-emtricitabine). Antiretroviral medications may require dose adjustment or may be contraindicated with liver cirrhosis. No dosage adjustment of bictegravir-tenofovir alafenamide-emtricitabine or dolutegravir plus tenofovir alafenamide-emtricitabine is recommended for individuals with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, but these regimens are not recommended for use with severe hepatic impairment (Child-Pugh Class C). In addition, since HBV reactivation can occur during HCV treatment with DAAs, it is important that the HIV antiretroviral regimen includes agents with activity against HBV if indicated.

Treatment of HCV in Persons with HIV Coinfection

Rationale for Treatment

The long-term goal of treatment of HCV infection is to reduce liver-related morbidity and all-cause mortality through the achievement of virologic cure.[48,73] Multiple studies have shown treatment of HCV in persons with HIV is highly successful, with SVR12 rates typically exceeding 95%.[74,75,76] Treatment of HCV is now recommended for all individuals with HIV and HCV coinfection.[4,20,77]

Goals of HCV Therapy

The short-term goal of HCV therapy in persons with HCV and HIV coinfection is to achieve an undetectable HCV RNA level 12 weeks after completion of HCV therapy, a goal commonly referred to as a sustained virologic response at posttreatment week 12 (SVR12) (Figure 5). 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 hepatitis C infection.[78] Overall long-term health outcome goals with HCV treatment include reduced risk for hepatocellular carcinoma and lower liver-related mortality.[79,80]

Simplified HCV Treatment Approach

Many DAAs are now available for treatment of HCV, and most are safe, highly effective, and convenient.[20,21] Numerous studies with all-oral DAA regimens have demonstrated comparable sustained virologic response (SVR) rates when treating persons with HIV and HCV coinfection as with those who have HCV monoinfection.[37,81,82,83,84] The excellent safety and high efficacy of pangenotypic DAAs (glecaprevir-pibrentasvir and sofosbuvir-velpatasvir) have greatly streamlined the HCV treatment process.[74,85,86,87] The AASLD-IDSA HCV Guidance now includes recommendations for a simplified HCV treatment approach that applies to most people with chronic HCV, including people with HIV coinfection.[4,88] The following will address the four main components of the implified 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.[4,88]

Criteria for Simplified HCV Treatment Approach in People with HIV

The simplified HCV treatment approach can be used for most people with HIV. The simplified treatment regimens apply to both chronic HCV and acute HCV.[4] The following is a list of exclusions for the simplified HCV treatment approach in persons with HIV.[4]

- 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 regimen with an eGFR less than 60 mL/min
- On an antiretroviral regimen that includes efavirenz, etravirine, nevirapine, or boosted HIV-1 protease inhibitors
- Untreated chronic HBV infection
- Pregnancy

Baseline evaluation with Simplified HCV Treatment Approach in People with HIV

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 evaluation for persons who are candidates for the simplified HCV treatment approach.[4]

- 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)

Simplified HCV Treatment Regimens in People with HIV

In persons with HIV and chronic HCV infection, who meet the simplified treatment criteria outlined above, the Adult and Adolescent OI Guidelines recommend using either of the following pangenotypic DAA regimens, based on whether the person does not have cirrhosis or they have compensated cirrhosis.[4,89,90] Note that glecaprevir-pibrentasvir and sofosbuvir-velpatasvir can be taken with or without food. The one situation with the simplified treatment approach that requires additional baseline evaluation is the person with compensated cirrhosis who is planning to receive treatment with sofosbuvir-velpatasvir.[90,91] In this situation, obtaining a baseline HCV genotype is recommended; if the person is identified with HCV genotype 3, then drug-resistance testing (NS5A) is indicated.[90,91] If a Y93H mutation is identified, then the simplified HCV treatment approach with a 12-week treatment course of sofosbuvir-velpatasvir is not recommended.[90,91]

Table 1. **Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV**

Simplified HCV Treatment Regimens in People with HIV

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, 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 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-velpatasvi (400 mg/100 mg tablet): one tablet daily for 12 weeks **(AII)**
Recommendations for treatment after DAA failure are not provided; see the corresponding section in AASLD/IDSA HCV Treatment Guidance

Source:

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

Laboratory Monitoring and PostTreatment Follow-up

With the simplified HCV treatment approach, no laboratory monitoring is required during treatment.[4] 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.[4] All persons receiving HCV treatment should have a quantitative HCV RNA level at baseline and at least 12 weeks after completing therapy (Figure 6) .[4] An undetectable HCV RNA level 12 weeks after completing therapy is referred to as SVR12 and indicates clearance and cure of HCV infection. Nevertheless, individuals who have successfully achieved an SVR12 do not have HCV immunity and thus are at risk of reinfection with HCV. Accordingly, patients 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. Furthermore, screening for HCV reinfection with HCV RNA should be done at least annually for individuals who have ongoing risk factors for reinfection or more frequently based on clinical circumstances. As outlined in the following section, persons who met criteria for hepatocellular carcinoma screening should continue to have every 6-month screening.

Treatment of HCV in Persons who are Not Eligible for Simplified HCV Treatment

For persons with HIV who are not eligible for the simplified treatment approach, expert consultation is recommended. In addition, data on retreatment of HCV in persons with HIV is very limited. More advanced expanded treatment recommendations are available in the AASLD-IDSA HCV Guidance.[20,92,93] In general, for those individuals who do not meet simplified treatment criteria, the choice of regimen and duration of therapy is based on cirrhosis status, HCV genotype, prior treatment regimen, and in some instances, HCV resistance testing.[20,92,93]

HCV Treatment Data in Persons with HIV Coinfection

The following information summarizes key phase 3 studies involving DAA-based therapy for HCV in persons with HIV coinfection.

- **Glecaprevir-Pibrentasvir** (**EXPEDITION-2**): This open-label, dual-arm, phase 3 trial examined the efficacy of glecaprevir-pibrentasvir in adults with HCV genotype 1, 2, 3, 4, 5, or 6 and HIV coinfection.[74] The 137 participants without cirrhosis received 8 weeks of glecaprevir-pibrentasvir, and the 16 with compensated cirrhosis received 12 weeks of glecaprevir-pibrentasvir.[74] Most (63%)

of the participants had HCV genotype 1 infection; 19% were treatment experienced. All but 10 of the participants were taking either raltegravir, dolutegravir, or rilpivirine as the HIV antiretroviral therapy anchor drug. The overall SVR12 rate was 98%; one person with HCV genotype 3 and cirrhosis had an on-treatment virologic breakthrough.[74]

- **Sofosbuvir-Velpatasvir** (**ASTRAL-5**): The ASTRAL-5 study was a single-arm, open-label, phase 3 trial of treatment of HCV with sofosbuvir-velpatasvir for 12 weeks in adults with HIV-HCV coinfection.[94] The study enrolled 106 participants with HCV genotype 1, 2, 3, 4, or 6. Eighteen percent had compensated cirrhosis, and 29% were treatment experienced. The mean CD4 count was 583 cells/mm^3, and all participants had suppressed HIV RNA levels. A variety of antiretroviral regimens, including tenofovir DF and pharmacokinetic boosting agents (cobicistat or ritonavir), were permitted. The overall SVR12 rate was 95%; two viral relapses occurred, both in the genotype 1a subgroup. The presence of cirrhosis or treatment experience did not appear to influence treatment response. Creatinine clearance was lower among those taking a boosting agent and tenofovir DF, but it remained relatively stable over time in all groups.[94]

Monitoring and Management of Chronic Liver Disease

Ongoing monitoring of liver disease is recommended for individuals in whom HCV therapy is deferred and posttreatment 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.[20,48,50]

Management of Metabolic Dysfunction-Associated Steatotic Liver Disease

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.[95,96,97,98] The prevalence of MASLD among persons with HIV and HCV coinfection in cross-sectional studies has ranged from 30 to 70%.[99] Individuals with HCV infection who have MASLD, hyperlipidemia, or other cardiovascular comorbidities should also be considered candidates for lipid-lowering therapy, ideally with a statin medication. Prospective studies have demonstrated increased cardiovascular morbidity in persons with chronic liver disease, and statins have been shown to be safe and effective in persons with chronic HCV and other chronic liver diseases.[100,101]

Management of Persons with Cirrhosis

Individuals with HIV and HCV coinfection who have cirrhosis are at risk for severe complications related to their liver disease. The incidence rate of hepatocellular carcinoma (HCC) is 2 to 8% per year in persons with HCV-related cirrhosis; in persons with HIV and HCV coinfection, the HCC rates appear to be even higher, especially among patients with low CD4 counts.[102,103] 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 recommend 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.[104] 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.[50,104]
- **Screening for Gastroesophageal Varices**: Persons with HCV and cirrhosis should undergo screening with an esophagogastroduodenoscopy (EGD) to determine whether they have gastroesophageal varices large enough to warrant variceal bleed prophylactic therapy.[105] Individuals with varices should undergo evaluation by a medical provider or specialist experienced with management of cirrhosis and prevention of variceal bleeding. If no substantial varices are observed, then EGD should be repeated every 2 years, or sooner if liver decompensation occurs (progression from Child-Turcotte-Pugh Class A to Child-Turcotte-Pugh Class B/C cirrhosis).

Special Considerations During Pregnancy

Risk of Perinatal HCV Transmission

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 to approximately 10 to 14%.[4,10,106,107,108] Maternal HIV and HCV coinfection may also increase the risk of perinatal HIV transmission. As with HIV (and HBV), the risk of perinatal transmission of hepatitis C during pregnancy is correlated with higher HCV RNA levels, particularly near the time of delivery. Intrapartum HCV transmission is more common than in utero transmission.[107]

Management of HCV in Pregnant Women who Have HIV Coinfection

Expert consultation is recommended for the management of pregnant women with HCV who have HIV coinfection. Current recommended DAA treatments for HCV have limited data for use in pregnancy. 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.[91] Suppressive antiretroviral therapy for pregnant women, which markedly lowers the risk of perinatal HIV transmission, may also reduce the risk of perinatal HCV transmission.[91,109]

- **AASLD-IDSA Guidance and Pediatric Opportunistic Infections Guidelines**: These guidelines indicate that treatment for hepatitis C with DAAs can be considered during pregnancy on an individual basis after shared decision-making regarding the potential risks and benefits.[110,111]
- **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.[112] Instead, these individuals should be considered for HCV treatment with DAAs postpartum. Hence, 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.[110,112]
- **Immunizations for Hepatitis A and B**: 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, and should be counseled about the signs and symptoms of liver toxicity.
- **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.[4,10,91]
- **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% percent 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.
- End-stage liver disease (ESLD), predominantly due to HCV infection, is now a leading cause of mortality in persons with HIV.
- 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 with HIV and 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.
- All persons with HIV and HCV coinfection who are not eligible for the simplified HCV treatment strategy can be treated using the standard approach as outlined in the AASLD/IDSA treatment guidelines.
- 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.
- Individuals with HCV and cirrhosis should undergo HCC screening every 6 months using abdominal ultrasound and serum alpha-fetoprotein.

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Figures

Figure 1 Estimated Number of New Annual HCV Infections—United States, 2010 through 2020

Source: Centers for Disease Control and Prevention. Viral Hepatitis Surveillance—United States, 2020.

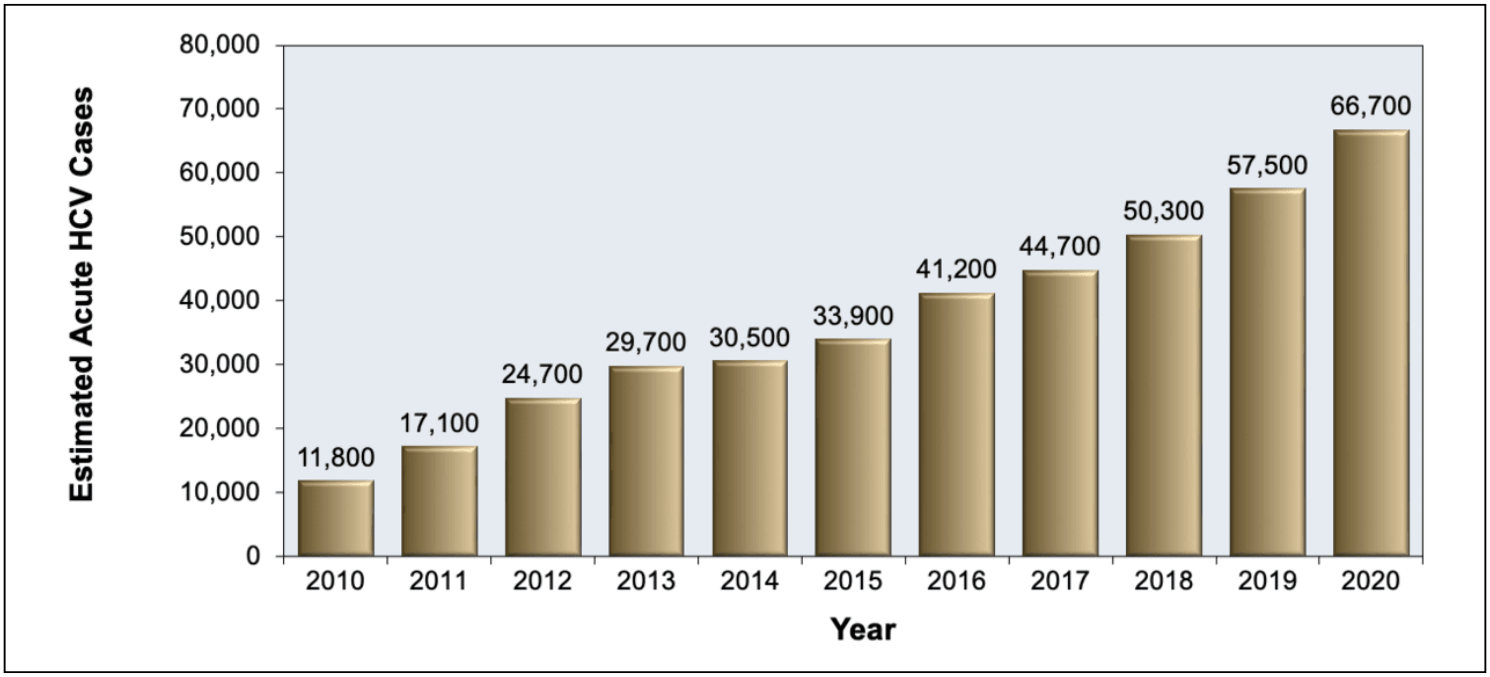

Figure 2 Progression to Cirrhosis in Persons with HIV and HCV Coinfection and HCV Monoinfection

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.

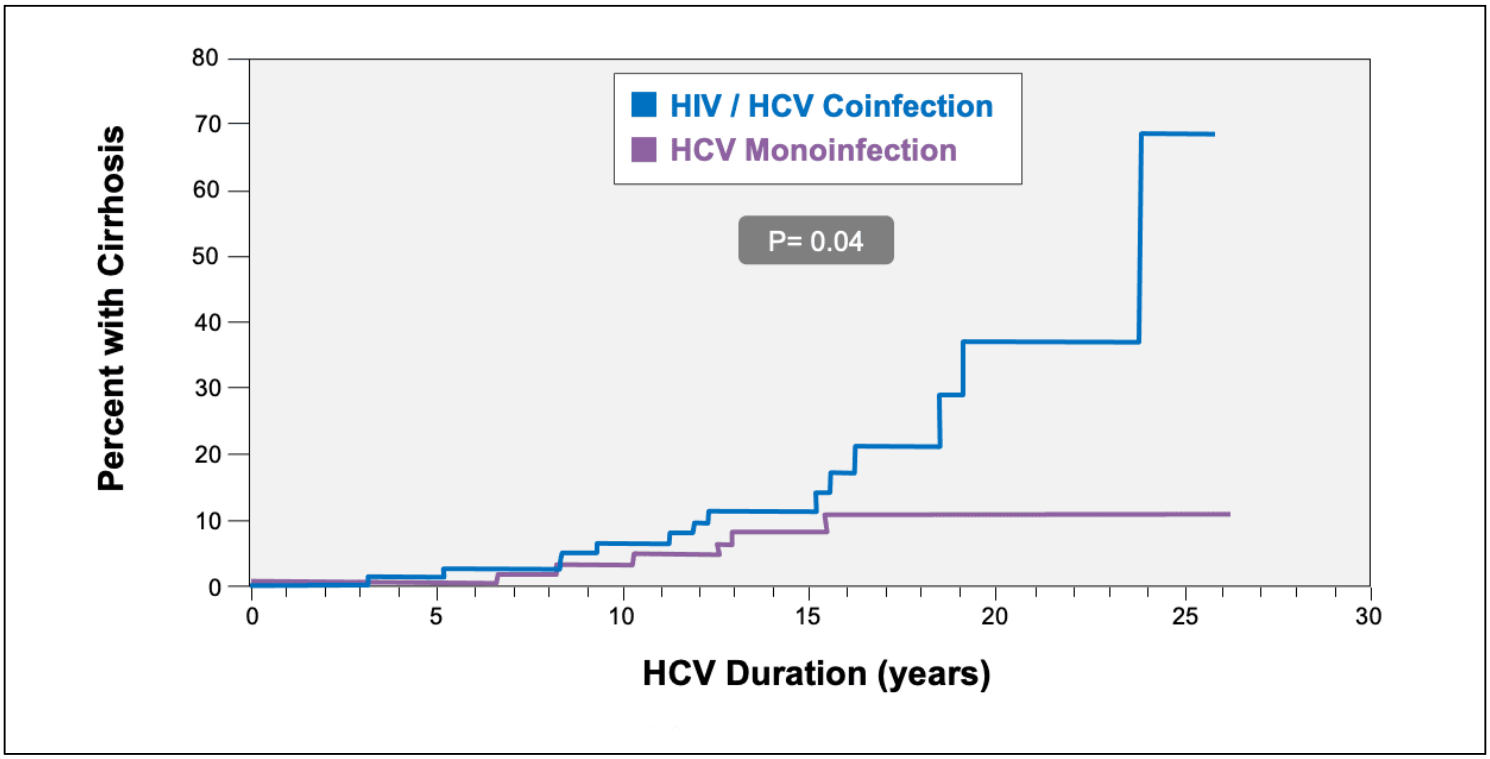

Figure 3 Risk Factors for Liver-Related Deaths in Persons with HIV Infection

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.

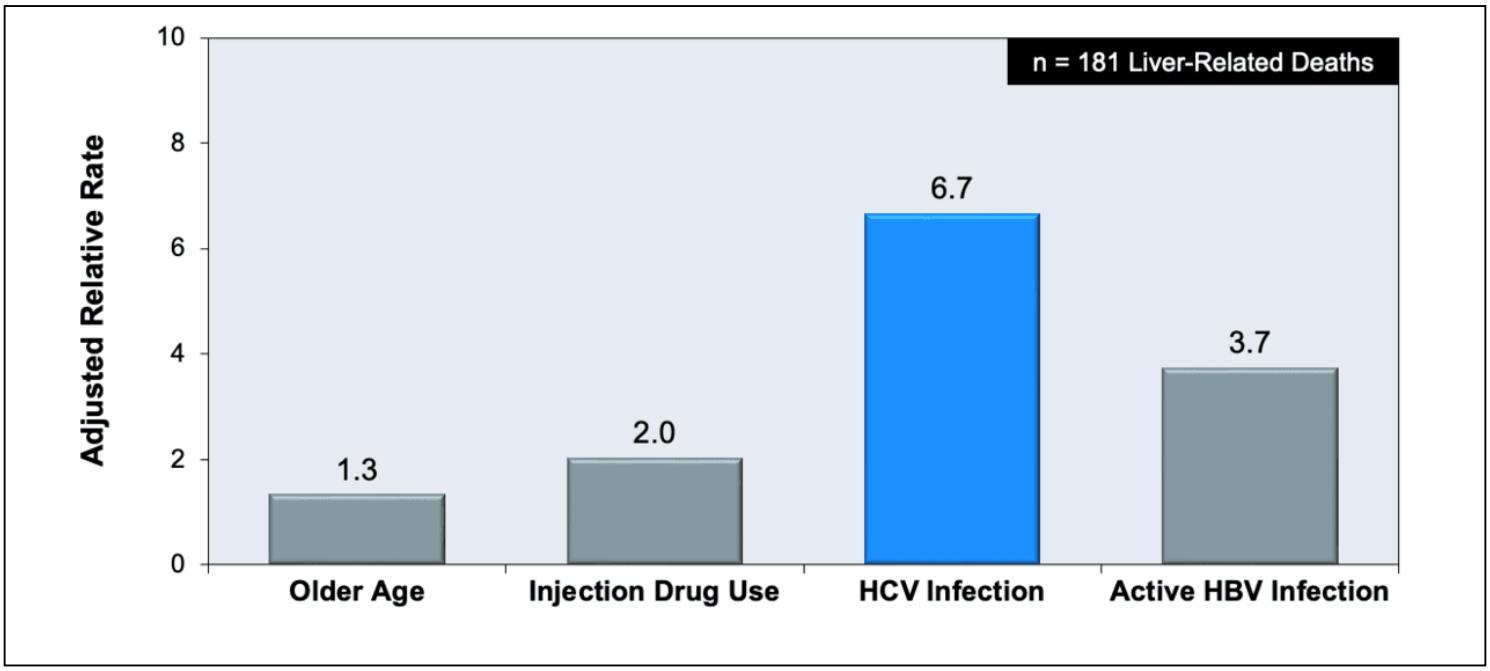

Figure 4 HCV Testing Algorithm to Identify Current HCV Infection*

*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.

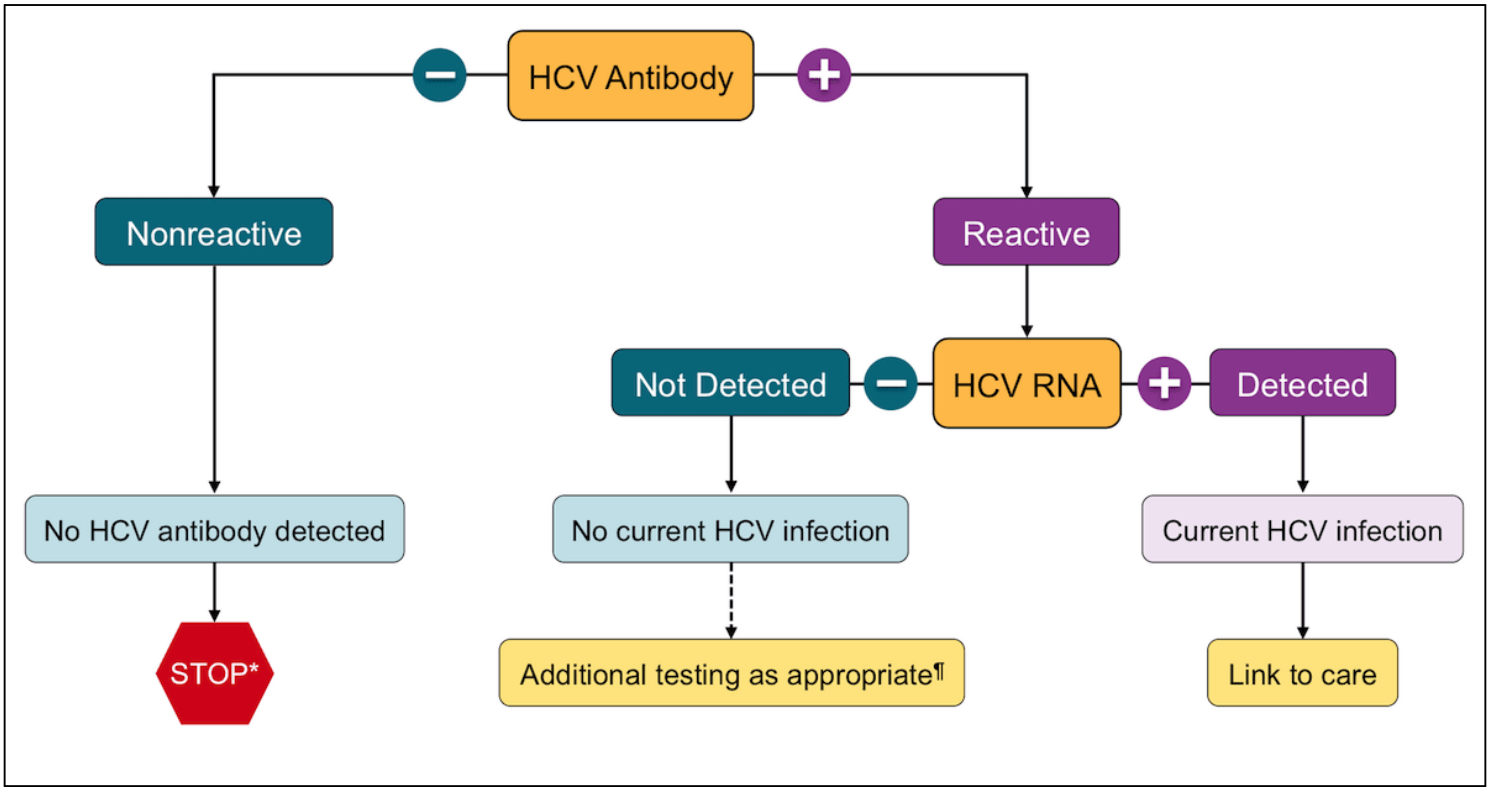

Figure 5 (Image Series) - Sustained Virologic Response 12 (SVR12) after HCV Treatment (Image Series) - Figure 5 (Image Series) - Sustained Virologic Response 12 (SVR12) after HCV Treatment

Image 5A: Sustained Virologic Response 12 (SVR12) after 8 Weeks of Treatment

This example shows virologic response to an 8-week HCV treatment course. As shown, a sustained virologic response 12 (SVR12) is defined as an undetectable HCV RNA level 12 weeks after stopping HCV therapy.

Illustration by David H. Spach, MD

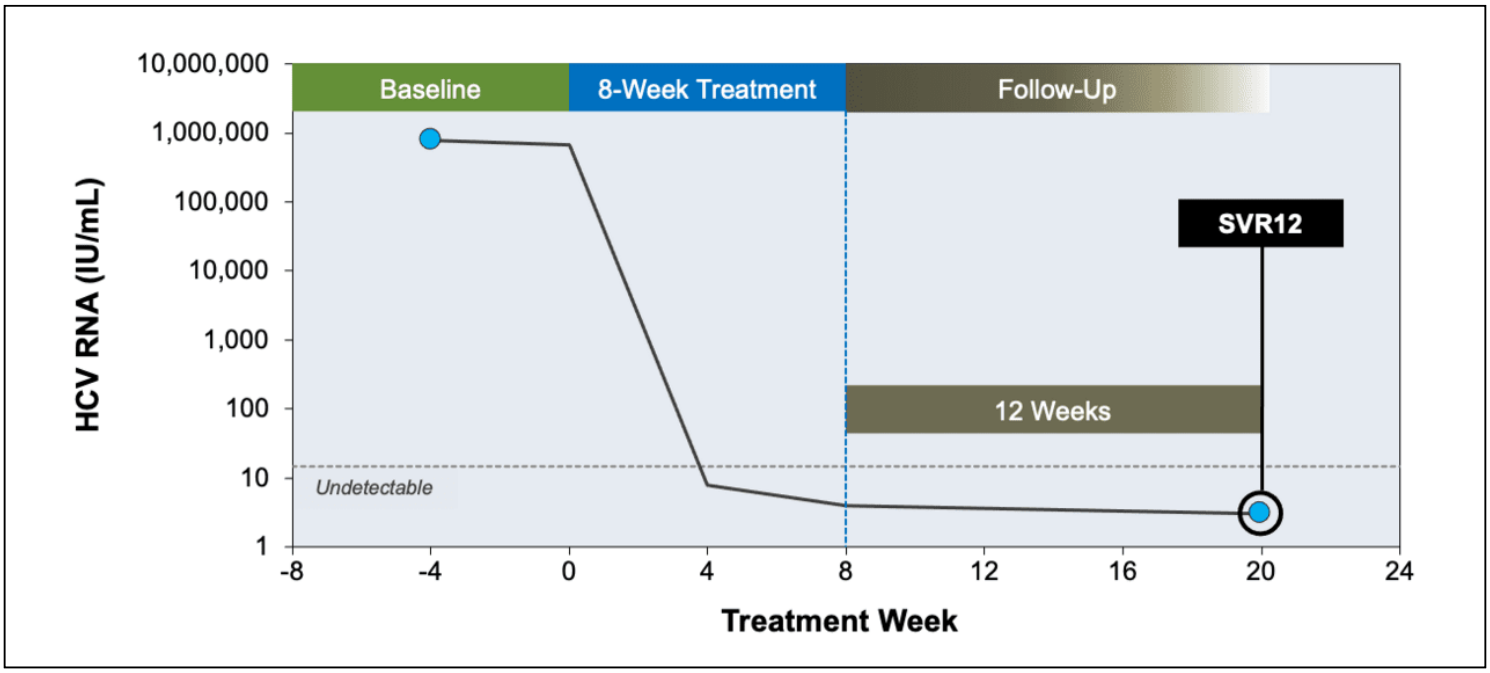

Figure 5 (Image Series) - Sustained Virologic Response 12 (SVR12) after HCV Treatment
Image 5B: Sustained Virologic Response 12 (SVR12) after 12 Weeks of Treatment

This example shows virologic response to a 12-week HCV treatment course. As shown, a sustained virologic response 12 (SVR12) is defined as an undetectable HCV RNA level 12 weeks after stopping HCV therapy.

Illustration by David H. Spach, MD

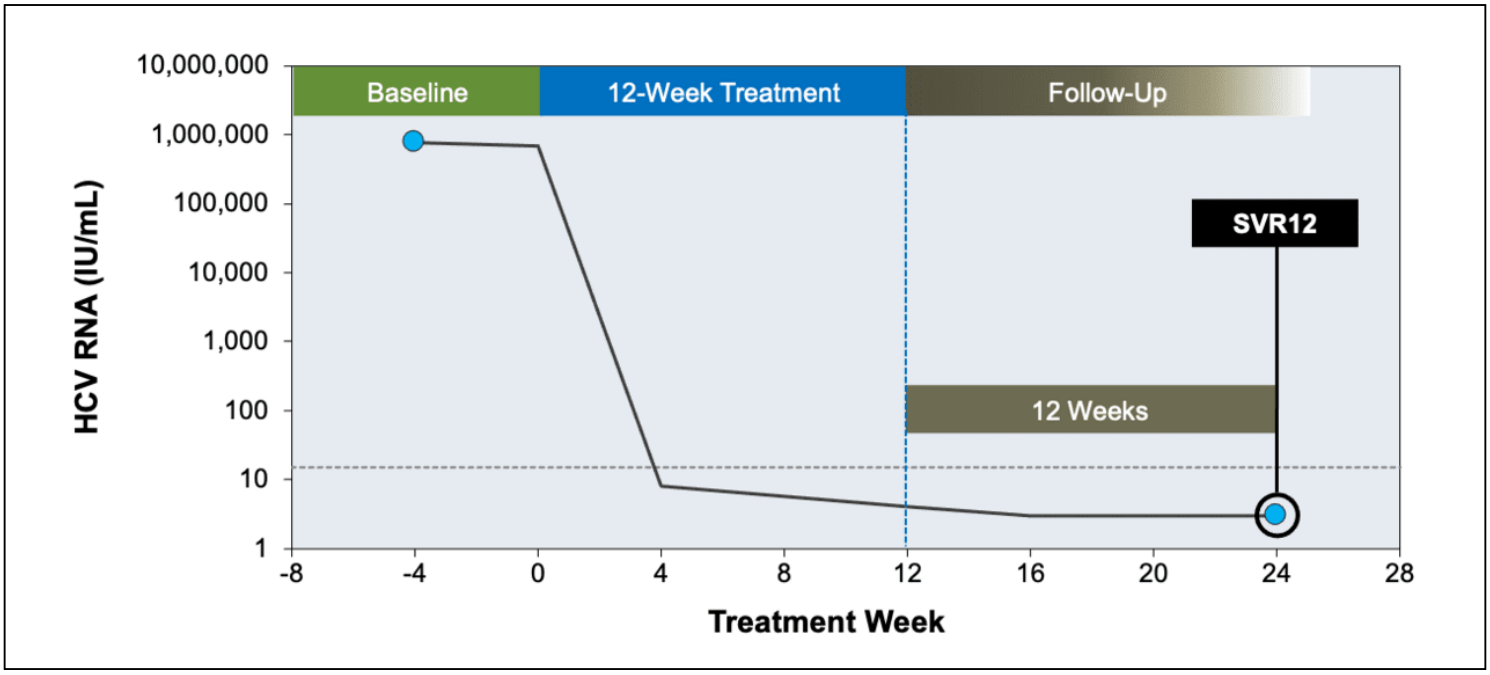

Figure 6 (Image Series) - Virologic Monitoring HCV Treatment (Image Series) - Figure 6 (Image Series) - Virologic Monitoring HCV Treatment
Image 6A: Virologic Monitoring with 8-Week HCV Treatment Course

With this 8-week hepatitis C treatment course, the recommended virologic monitoring consists of baseline and 12-week posttreatment HCV RNA levels as shown in red dash circles.

Illustration by David H. Spach, MD

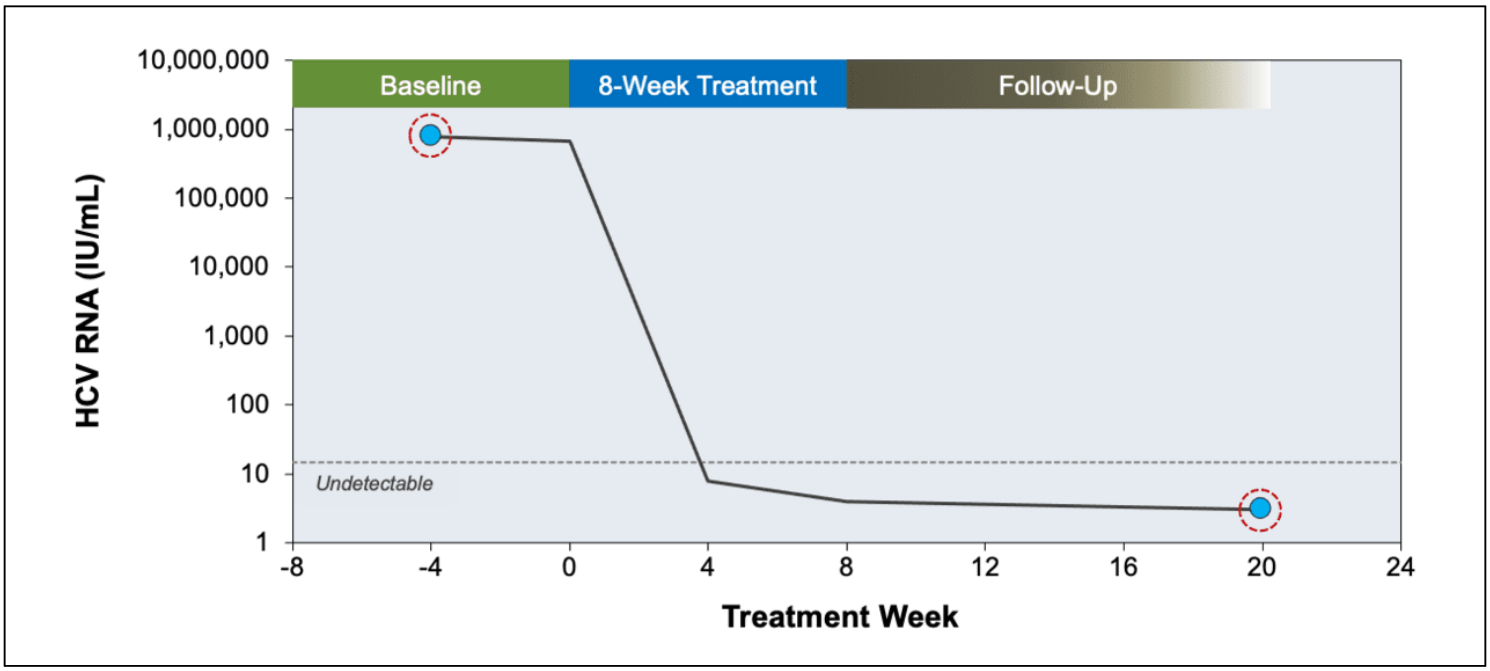

Figure 6 (Image Series) - Virologic Monitoring HCV Treatment
Image 6B: Virologic Monitoring with 12-Week HCV Treatment Course

With this 12-week hepatitis C treatment course, the recommended virologic monitoring consists of baseline and 12-week posttreatment HCV RNA levels as shown in red dash circles.

Illustration by David H. Spach, MD

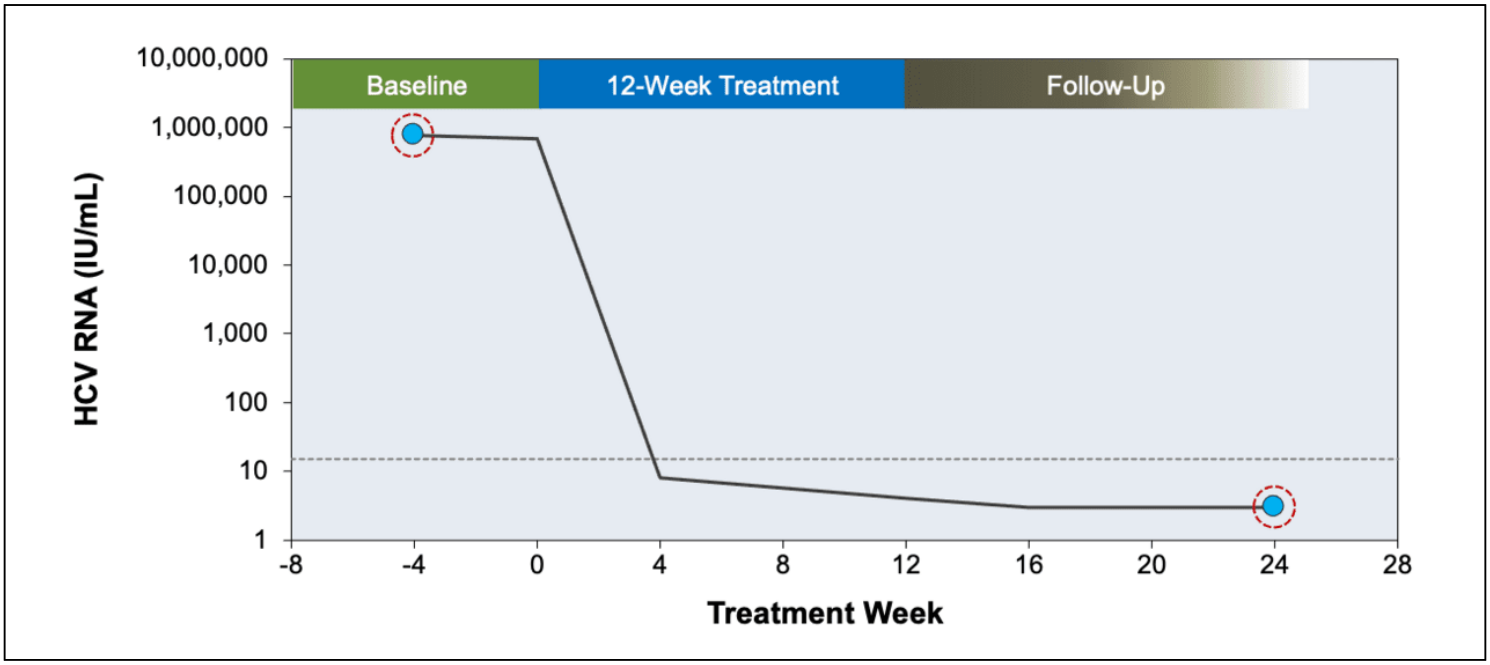

Table 1. **Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV**

Simplified HCV Treatment Regimens in People with HIV

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, 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 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-velpatasvi (400 mg/100 mg tablet): one tablet daily for 12 weeks **(AII)**
Recommendations for treatment after DAA failure are not provided; see the corresponding section in AASLD/IDSA HCV Treatment Guidance

Source:

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