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 170 million people are living with HCV. 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.[1] The CDC estimates that at least two-thirds of all persons with active HCV in the United States were born between 1945 and 1965.[2] Since 2002, however, the number of new HCV cases among younger persons has increased significantly, leading to a bimodal distribution.[3,4]

Although the annual number of contemporary new HCV infections in the United States is markedly lower than in the 1980's (Figure 1), the incidence increased significantly from 2011 through 2016 (Figure 2), primarily as a result of the opioid epidemic.[5] There are seven HCV genotypes, which vary geographically; genotype 1 predominates in North America and accounts for 90% of infections among blacks.[2,6] The most efficient route of transmission of the hepatitis C virus 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.

Epidemiology of HIV-HCV Coinfection

In the United States, approximately 15 to 30% of persons with HIV are coinfected with HCV.[3,7] 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.[8,9,10] 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.[11,12,13,14,15] Researchers have identified several risk factors associated with the sexual acquisition of HCV in persons with HIV, including noninjection recreational drug use, condomless receptive anal intercourse, use of sex toys, concurrent sexually transmitted diseases, anal douching, and low CD4 cell count.[16,17,18]

The increasing incidence of sexually-transmitted HCV infection in persons with HIV correlates with the widespread use of antiretroviral therapy, which has been linked to increased sexual activity and lower use of condoms.[19,20] More recently, there is an evolving body of literature regarding higher rates of sexually transmitted infections, including HCV, in HIV-negative men who have sex with men who access HIV
preexposure prophylaxis; the expanding use of preexposure prophylaxis has the potential to impact the sexual networks of HCV transmission between HIV-positive and HIV-negative men who have sex with men.[21,22]

General Approach to Persons with HIV-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-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.[23,24] A proactive and aggressive approach for HCV is needed in persons with HIV—identify and treat HCV in all persons with HIV-HCV coinfection. This strategy would lead to improved health outcomes and longer survival in persons with HIV, as well as reduced transmission of HCV.[25]


**Natural History of HIV-HCV Coinfection**

**Impact of HIV on 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%.\[26,27\] Compared with individuals who have HCV monoinfection, persons with HIV-HCV coinfection have accelerated rates of liver fibrosis and a more aggressive course of liver disease (Figure 3).\[3,28,29\] Progression to cirrhosis occurs 12 to 16 years earlier in persons with HIV-HCV coinfection compared with persons who have HCV monoinfection.\[30,31\] The accelerated liver disease seen in persons with HIV-HCV coinfection is generally more pronounced when HIV infection precedes HCV infection.\[31\] 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.\[29\] 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.\[29,32,33\] 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.\[34,35\]

**Impact of HCV Infection on Natural History of HIV**

Most studies have reported that HCV does not significantly impact HIV disease progression.\[36,37,38\] 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.\[37,38,39\] Achieving a sustained virologic response (SVR) with HCV treatment has not been shown to impact CD4 count or percentage.\[40\] Chronic HCV infection increases the risk of hepatotoxicity due to antiretroviral therapy in persons with HIV.\[41,42\] Nevertheless, for nearly all individuals with HIV-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.\[43,44\]

**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.\[45\] 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.\[46,47,48,49\] 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 4).\[49\] 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 has decreased over time, but liver disease remained the third leading cause of death (13%) behind AIDS-related causes and non-AIDS-related malignancies.\[50\]
Screening for HCV Infection

Screening for HCV in Persons with HIV

As recommended in the Adult and Adolescent Opportunistic Infection 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 for acquiring HCV infection, 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, 51] Individuals who achieve an SVR with HCV therapy can become reinfected with HCV, as underscored by recent reports showing significant rates of HCV reinfection among men with HIV who have sex with men.[52] 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.[53]
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 5).[54] 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 patients with positive HCV antibody tests.[54] Some laboratories now have protocols 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.

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[51,55]:

- **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.[56,57] 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 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 is similar to laboratory based HCV antibody assays.[51,58] 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).[55] The HCV NAT becomes positive approximately 1 to 2 weeks after initial HCV infection. Low HCV RNA levels may be intermittently detectable very early after infection.[59,60] The NAT test has become the gold standard supplemental test for patients who have positive HCV antibody screening tests. The NAT can usually determine whether a patient 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 very 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 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

Persons 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 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 less than 200 cells/mm$^3$.\[^{61}\] 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 infection.\[^{54}\]
Evaluation of Persons Diagnosed with HCV Coinfection

Due to the rapidly changing landscape of HCV treatment, the AASLD-IDSA HCV Guidance are regularly updated.[51] These guidelines recommend that persons with current (active) HCV infection should be evaluated by a practitioner who is prepared to provide comprehensive HIV management.[51] 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.

Routine Laboratory Evaluation

All individuals diagnosed with HCV infection should have a complete blood count (CBC) with differential, prothrombin time (PT) with international normalized ratio (INR), 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, albumin), and a thyroid-stimulating hormone (TSH). Cryoglobulin levels should be obtained in patients with signs or symptoms of cryoglobulinemia (palpable purpura, arthralgias, renal disease, or peripheral neuropathy).

HCV-Specific Tests

All persons with chronic HCV should have testing for HCV genotype and quantitative HCV RNA (if not done at time of HCV diagnosis).[43] The genotype provides valuable information regarding genotype-specific treatment options. The quantitative HCV RNA level provides documentation of chronic HCV infection, but does not correlate with the degree of liver inflammation or fibrosis.[62, 63]

Hepatitis A and Hepatitis B Status and Immunization

In persons with chronic HCV infection, superinfection with hepatitis A virus (HAV) can cause fulminant hepatitis.[64] Thus, all persons with chronic HCV infection should be assessed for immunity to HAV with total hepatitis A antibody and those without immunity to HAV should receive hepatitis A vaccine. All persons with HIV-HCV coinfection should also be screened for HBV by checking hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (anti-HBs).[51] Individuals 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.[43, 65, 66]

Evaluation for Nonalcoholic Fatty 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, nonalcoholic fatty liver disease and hepatic steatosis, and insulin resistance.[51, 67, 68, 69] Prevalence of hepatic steatosis among persons with HIV-HCV coinfection in cross-sectional studies has ranged from 30 to 70%.[70] Persons who are overweight or obese (defined by a body mass index 25 kg/m$^2$ or higher or 30 kg/m$^2$ or higher, respectively) should receive counseling regarding strategies to reduce weight.[51] Individuals with HCV infection who have nonalcoholic fatty liver disease, 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 disease.[71, 72]

Assessment of Stage of Liver Fibrosis

Individuals with chronic HCV should be assessed for the presence of advanced fibrosis using noninvasive methods or liver biopsy 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.[30,34]

- **Liver Biopsy**: Liver biopsy is the diagnostic gold standard for assessing fibrosis (and can also assess
  liver inflammation and exclude competing causes of liver injury), but it is an invasive test that
  requires an experienced medical provider to obtain an appropriate histological sample, and it has
  potential complications.
- **Noninvasive Test to Assess Hepatic Fibrosis**: Noninvasive tests are commonly used instead of
  liver biopsy to estimate hepatic fibrosis. These noninvasive tests include the AST-Platelet Ratio Index
  (APRI), FibroTest, and transient elastography.[73] It is important to keep in mind that tests that use
  the platelet count in the score may overestimate fibrosis since some individuals with HIV may have
  thrombocytopenia related to HIV, rather than to liver disease alone.[45]
- **AASLD-IDSA Recommendations**: No single method has high accuracy when used alone, and the
  AASLD-IDSA HCV Guidance suggests that the most efficient approach to fibrosis assessment is to use
  both direct biomarkers and transinet elastography; a liver biopsy can be considered for any person
  who has discordant results between the two testing modalities, but in the current DAA treatment era
  the role of liver biopsy in this setting has steadily declined.[73,74]

**Frequency of Reassessment of Liver Disease**

Ongoing assessment of liver disease is recommended for individuals in whom HCV therapy is deferred.[73]
Routine HCV-related monitoring for all persons with HIV should include laboratory assessment of hepatic
function every 3 to 6 months, at a minimum; annual evaluation is appropriate to reevaluate hepatic fibrosis
stage and to discuss modifiable risk factors for fibrosis (e.g. alcohol use).[73]

**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.[75,76,77] 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.[78] 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.[77] Individuals who are identified as having alcohol use disorder or
dependence should be referred to an addiction specialist and/or treatment program.[51]

**Acetaminophen and Iron Intake**

Persons with HIV-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]

**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.[79] 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 when liver decompensation occurs (progression
from Child-Turcotte-Pugh Class A to Child-Turcotte-Pugh Class B/C cirrhosis).

**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.\[51,80,81,82\] 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 never to 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 ARV Guidelines recommend initiating HIV antiretroviral therapy in all persons with HIV (regardless of CD4 cell count) and this recommendation applies to all persons with HIV-HCV coinfection.[43,83] In general, initiation of antiretroviral therapy should occur before HCV treatment, with deferral of HCV treatment until HIV virologic suppression has been achieved. Recommended initial antiretroviral regimens are the same for persons with HIV-HCV coinfection as for those with HIV monoinfection.[43]

When treatment for both HIV and HCV are given concurrently, it is important to consider potential drug interactions.[43] The initiation of antiretroviral therapy for individuals with cirrhosis or advanced fibrosis should take into account that some antiretroviral medications may require dose adjustment or may be contraindicated. In addition, since HBV reactivation can occur during HCV treatment with DAAs, it is important that the HIV antiretroviral regimen include agents with activity against HBV if indicated.
Treatment of HCV Infection in Persons Coinfected with HIV

Rationale for Treatment

The long-term goal of treatment of HCV infection is to reduce liver-related morbidity and all-cause mortality by the achievement of virologic cure.[51,84] Multiple studies have shown treatment of HCV in persons with HIV is highly successful, with SVR12 rates typically exceeding 95%.[85,86,87] Treatment of HCV is now recommended for all individuals with HIV-HCV coinfection; the highest priority for immediate treatment are individuals with advanced fibrosis or compensated cirrhosis, liver transplant recipients, and individuals with severe extrahepatic HCV-related manifestations.[4,73] In addition, it is very important to treat HCV before severe cirrhosis-related complications occur, since persons with HIV-HCV coinfection have less access to liver transplantation than individuals with HCV monoinfection.[88] This differential in transplant access has been attributed, in part, to higher HCV recurrence rates after transplant in persons with HIV-HCV coinfection, but this is changing in the current era of more effective and safer pre- and post-transplant HCV therapies.[89,90]

Goals of HCV Therapy

The short-term goal of HCV therapy in persons coinfected with HIV 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 week 12 (SVR12) (Figure 7) and (Figure 7). Among persons who attain an SVR12, more than 99% will maintain an SVR years after completion of therapy and thus are deemed to have a virologic cure of hepatitis C infection.[91] Overall long-term health outcome goals with HCV treatment include reduced risk for hepatocellular carcinoma, and lower liver-related mortality.[92,93]

Approach to Treatment

Many DAAs are now available for treatment of HCV and most are safe, highly effective, and convenient.[23,24] Numerous studies with all-oral DAA regimens have demonstrated comparable sustained virologic response (SVR) rates when treating persons with HIV-HCV coinfection as with those who have HCV monoinfection, indicating that HIV-HCV coinfection does not negatively affect the HCV outcomes of treatment when using DAAs.[40,94,95,96,97] Clinical trials involving persons with HIV-HCV coinfection have primarily enrolled individuals with high CD4 counts and often excluded those with cirrhosis.

Phase 3 HCV Treatment Data in Persons with HIV-HCV Coinfection

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

- **Elbasvir-Grazoprevir** *(C-EDGE Coinfection)*: In this prospective, single-arm, open-label, phase 3 clinical trial, 218 adults with chronic HCV genotype 1, 4, or 6 and HIV coinfection received the fixed-dose combination of elbasvir-grazoprevir once daily for 12 weeks.[86] Nearly all (97%) participants were taking antiretroviral therapy and had suppression of HIV RNA levels; the median CD4 cell count was 568 cells/mm$^3$. Overall, 86% of those enrolled had HCV genotype 1a or 1b infection and 16% had compensated cirrhosis. The overall SVR12 rate was 96% by primary analysis, with the SVR12 breakdowns by genotype showing 96.5% for genotype 1a, 95.5% for genotype 1b, and 96.4% for genotype 4. All participants with cirrhosis achieved an SVR12. When excluding participants who did not achieve an SVR12 due to treatment discontinuation or reinfection, the overall SVR12 rate was 97%.[86]

- **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.[85] The 137 participants without cirrhosis received 8 weeks of glecaprevir-pibrentasvir and the 16 with compensated cirrhosis received 12 weeks of glecaprevir-pibrentasvir.[85] 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.[85]

- **Ledipasvir-Sofosbuvir (ION-4):** In this phase 3, open-label, multicenter study, investigators enrolled 335 adults with hepatitis C and HIV coinfection to receive a 12-week course of ledipasvir-sofosbuvir.[87] Participants had genotype 1 or 4 HCV and were treatment-naïve or treatment-experienced; enrollment included those without cirrhosis or with compensated cirrhosis. At enrollment, participants were required to have an HIV RNA level less than 50 copies/mL and a CD4 count greater than 100 cells/mm$^3$. The antiretroviral regimens that were allowed consisted of tenofovir DF-emtricitabine plus either efavirenz, rilpivirine, or raltegravir. Most (98%) of the patients enrolled had genotype 1 HCV infection and 55% were treatment experienced. Overall, 96% (321 of 335) of the participants achieved an SVR12. The results were similar regardless of prior treatment status or presence of cirrhosis.[87]

- **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.[98] 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.[98]

### Choice of HCV Regimen and Duration

As a result of the above studies that have demonstrated equal efficacy of DAAs in persons with HCV-HIV coinfection and those with HCV monoinfection, the AASLD-IDSA HCV Guidance recommends using the same regimens to treat HCV in persons with HIV coinfection as when treating HCV monoinfection, even though some regimens may not have specifically been studied in persons with HCV-HIV coinfection.[23,99] There are, however, two specific differences in treatment duration that is different in persons with HIV-HCV coinfection than in persons with HCV monoinfection. First, for initial treatment of HCV (all genotypes) in persons with compensated cirrhosis, the duration of glecaprevir-pibrentasvir is 12 weeks with HIV-HCV coinfection versus 8 weeks with monoinfection; this also pertains to persons with HCV genotype 5 or 6 who do not have cirrhosis. Second, the ledipasvir-sofosbuvir 8-week regimen that is an option in certain circumstances for initial treatment in HCV monoinfection is not an option in persons with HIV-HCV coinfection (12-week regimen required).[23] When choosing an HCV treatment regimen in persons with HIV-HCV coinfection, it is important to consider any potential drug interaction between DAAs and antiretroviral medications.[43] The following links are to recommended regimens in the AASLD-IDSA HCV Guidance based on the HCV genotype:

#### Initial Treatment for Chronic HCV Infection

- **Genotype 1a: No cirrhosis**
- **Genotype 1a: Compensated cirrhosis**
- **Genotype 1b: No cirrhosis**
- **Genotype 1b: Compensated cirrhosis**
- **Genotype 2: No cirrhosis**
- **Genotype 2: Compensated cirrhosis**
- **Genotype 3: No cirrhosis**
- **Genotype 3: Compensated cirrhosis**
- **Genotype 4: No cirrhosis**
- **Genotype 4: Compensated cirrhosis**
- **Genotype 5 or 6**
Retreatment of Persons in Whom Prior Therapy Failed

- **Genotype 1a: PEG + RIB Experienced**: No Cirrhosis
- **Genotype 1a: PEG + RIB Experienced**: Compensated Cirrhosis
- **Genotype 1b: PEG + RIB Experienced**: No Cirrhosis
- **Genotype 1b: PEG + RIB Experienced**: Compensated Cirrhosis
- **Genotype 1: NS3 PI + PEG + RIB Experienced**: No Cirrhosis
- **Genotype 1: NS3 PI + PEG + RIB Experienced**: Compensated Cirrhosis
- **Genotype 1: Non-NS5a Inhibitor, SOF-Containing Regimen-Experienced**: No Cirrhosis
- **Genotype 1: Non-NS5a Inhibitor, SOF-Containing Regimen-Experienced**: Compensated Cirrhosis
- **Genotype 1: NS5A Inhibitor DAA-Experienced
- **Genotype 2: PEG + RIB Experienced**: No cirrhosis
- **Genotype 2: PEG + RIB Experienced**: Compensated cirrhosis
- **Genotype 2: DAA-Experienced (Including NS5A Inhibitors) With or Without Compensated Cirrhosis
- **Genotype 3: PEG + RIB Experienced**: No cirrhosis
- **Genotype 3: PEG + RIB Experienced**: Compensated cirrhosis
- **Genotype 3: DAA-Experienced (Including NS5A Inhibitors)
- **Genotype 4: PEG + RIB Experienced**: No cirrhosis
- **Genotype 4: PEG + RIB Experienced**: Compensated cirrhosis
- **Genotype 4: DAA Experienced (Including NS5A Inhibitors
- **Genotype 5 or 6: PEG + RIB Experienced
- **Genotype 5 or 6: DAA Experienced (Including NS5A Inhibitors

**Monitoring for Treatment Efficacy**

The optimal and standard approach to monitoring for treatment efficacy consists of measurement of quantitative HCV RNA levels. Monitoring requires use of a highly sensitive quantitative HCV RNA assay, typically with a lower limit of quantification in the range of 12-25 IU/mL.[100] For persons receiving HCV therapy, the American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD-IDSA) HCV Guidance recommends obtaining a quantitative HCV RNA level at baseline and at 12 weeks after completing therapy (Figure 8) and (Figure 9).[53] An undetectable HCV RNA level 12 weeks after completing therapy is referred to as SVR12 and this generally translates into a long-term cure of HCV infection.[101,102,103] In addition, the AASLD-IDSA HCV Guidance now advises against routine testing for HCV RNA level during treatment unless: (1) ALT fails to decline from baseline, or (2) there is concern regarding patient adherence with DAA therapy.[53] The panel also notes there are no data to support HCV treatment cessation or modification based on a detectable level at week 4 of treatment. The significance of on-treatment persistent low-level viremia (that does not increase) is not known and there is no clear indication this represents lack of adherence or likelihood of virologic relapse.
Screening for Hepatocellular Carcinoma

Risk of Hepatocellular Carcinoma with HIV-HCV Coinfection

The incidence rate of hepatocellular carcinoma (HCC) is 2 to 8% per year in persons with HCV-related cirrhosis; in those with HIV-HCV coinfection, the HCC rates appear to be even higher, especially among patients with low CD4 counts.\textsuperscript{104, 105} In a large retrospective Veterans Health Administration cohort study, investigators compared the risk of cirrhosis and HCC in persons with HIV monoinfection and HIV-HCV coinfection and demonstrated that HIV-HCV coinfection dramatically promotes the development both of HCC (5-fold increase) and of cirrhosis (10- to 20-fold increase).\textsuperscript{106}

HCC Surveillance Recommendations

The AASLD-IDSA HCV Guidance recommends hepatocellular carcinoma screening for all persons with chronic HCV infection who have advanced fibrosis (Metavir stage F3) or cirrhosis (Metavir stage F4), ideally using every 6 month abdominal ultrasound as the primary HCC screening method.\textsuperscript{53} The AASLD 2018 guidelines for the Treatment of Hepatocellular Carcinoma recommend using an abdominal ultrasound with or without serum alpha-fetoprotein every 6 months as the HCC surveillance method.\textsuperscript{107} The criteria for performing HCC surveillance and the surveillance method are the same for persons with HIV-HCV coinfection as with HCV monoinfection. 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.
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 by approximately 2-fold.[4, 9, 108, 109, 110] Maternal HIV-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.[109]

Management of Pregnant Women with HIV-HCV Coinfection

Expert consultation is recommended for the management of pregnant women with HIV-HCV 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 persons with HIV-HCV coinfection, regardless of CD4 cell count or HIV RNA levels.[111] Suppressive antiretroviral therapy for pregnant persons, which markedly lowers the risk of perinatal HIV transmission, may also reduce the risk of perinatal HCV transmission.[111, 112]

- **AASLD-IDSA Recommendations**: The AASLD-IDSA HCV Guidance indicate that treatment for hepatitis C with DAAs can be considered during pregnancy on an individual basis after a patient-physician discussion about the potential risks and benefits.[113]
- **Immunizations for Hepatitis A and B**: Pregnant individuals with HIV-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 persons with HIV-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 HCV transmission from mother to infant and so should be avoided in pregnant women with HIV, HCV, or HIV-HCV coinfection.[4, 9, 111]
- **Breastfeeding**: Although HCV can be detected in breast milk, most studies have not shown an increase in transmission in breastfed infants (note that mothers with HIV coinfection should avoid breastfeeding to prevent HIV transmission).

Diagnosis of HCV Infection in Infants

Because maternal antibodies cross the placenta and can be detected in infants until 18 months of age, the diagnosis of hepatitis C in an infant can be challenging. In addition, false-positive and false-negative HCV PCR results may occur during the first 3 months of life. Current Perinatal Guidelines recommend postponing HCV antibody testing in newborns until 18 months of age.[111] Children are considered to have chronic HCV infection if they have two or more positive HCV RNA results or are HCV antibody-positive beyond age 18 months (with a confirmatory positive HCV RNA test). To make an earlier diagnosis, HCV RNA virologic testing can be performed after 2 months of age; because HCV viremia can be intermittent, two negative HCV RNA tests at or after age 2 months of age, including one at or after age 12 months, are needed to definitively exclude HCV infection.[111]
Summary Points

- An estimated 15 to 30% percent of persons with HIV have HCV coinfection. The prevalence of HIV-HCV coinfection is highest among persons with HIV who inject drugs, although rising rates of sexually transmitted HCV infection have recently been documented in men with HIV who have sex with men.
- Compared with individuals who have HCV monoinfection, persons with HIV-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-HCV coinfection require evaluation and staging of HCV-related liver disease, which should include laboratory testing and assessment of fibrosis as well as identification of other risk factors for fibrosis (e.g. alcohol use disorder, obesity, hepatitis B coinfection).
- All persons with HIV-HCV coinfection should be treated for HCV, if possible, 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.
- Individuals with HIV-HBV-HCV coinfection should be on a fully suppressive HIV and HBV regimen prior to initiating HCV DAA treatment, to avoid HBV reactivation.
- In mothers 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. Expert consultation is recommended for the management of these individuals. Currently, no DAAs are indicated for the treatment of HCV in pregnancy.
- In persons with HIV-HCV coinfection, HCC occurs at a higher rate, usually develops at an earlier age, and progresses more aggressively than in persons with HCV monoinfection. Individuals with HCV and cirrhosis should undergo HCC screening every 6 months using abdominal ultrasound, with or without serum alpha-fetoprotein.
Citations


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- AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection. [AASLD/IDSA Hepatitis C Guidance]

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Figures

Figure 1 Estimated Number of New Annual HCV Infections—United States, 1982 through 2016

Figure 2 Estimated Number of New Annual HCV Infections—United States, 2010 through 2016

This graph shows a retrospective analysis of 160 persons who inject drugs and the impact of HIV infection on the progression of HCV-related cirrhosis. Persons with HIV-HCV coinfection had significantly more rapid progression to cirrhosis than persons with HCV monoinfection.

Figure 4 Risk Factors for Liver-Related Deaths in Persons with HIV Infection

Figure 5 HCV Testing Algorithm to Identify Current HCV Infection*

*For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered. †To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Figure 6 Sustained Virologic Response 12 (SVR12) after 8 Weeks of Treatment

This example shows virologic response to a 8-week HCV treatment course. As shown in this example, a sustained virologic response 12 (SVR12) is defined as an undetectable HCV RNA level 12 weeks after stopping HCV therapy. The timing of recommended HCV RNA monitoring is shown in red dash circles.

Illustration by David H. Spach, MD
Figure 7 Sustained Virologic Response 12 (SVR12) after 12 Weeks of Treatment

This example shows virologic response to a 12-week HCV treatment course. As shown in this example, a sustained virologic response 12 (SVR12) is defined as an undetectable HCV RNA level 12 weeks after stopping HCV therapy. The timing of recommended HCV RNA monitoring is shown in red dash circles.

Illustration by David H. Spach, MD
Figure 8 Virologic Monitoring with 8-Week HCV Treatment Course

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

Illustration by David H. Spach, MD
Figure 9 Virologic Monitoring with 8-Week HCV Treatment Course

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

Illustration by David H. Spach, MD