Hepatitis C Coinfection

Background and Epidemiology

General Hepatitis C Epidemiology

Hepatitis C virus (HCV) is a single-stranded RNA virus is an important global cause of cirrhosis, liver failure, and hepatocellular carcinoma. Globally, an estimated 170 million people living with HCV. In the United States, an estimated 3.2 million persons are living with HCV and approximately two-thirds of those living with HCV are in the “baby boomer generation” and were born between 1945 and 1965.\[1\] Since 2002, however, the number of new HCV cases among younger persons has increased significantly, leading to a bimodal distribution.\[2, 3\] 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 2010 to 2015 (Figure 2), primarily as a result of the opioid epidemic.\[4\] There are seven HCV genotypes, which vary geographically; genotype 1 predominates in North America and accounts for 90% of infections among blacks.\[1, 5\] 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) though HCV is also transmitted through sexual contact, perinatally from mothers to infants, and rarely through environmental exposures.

Epidemiology of Hepatitis C and HIV Coinfection

In the United States, approximately 15 to 30% of persons with HIV infection are coinfected with HCV.\[2, 6\] The prevalence varies according to the risk factor for HIV and HCV acquisition, with the highest among persons with HIV infection who inject drugs and individuals with hemophilia who were infected through receipt of blood products prior to routine screening of blood products for HCV.\[7, 8, 9\] Since 2000, in the United States, Europe, Asia, and Australia, HCV infection has emerged as an important sexually transmitted infection among men with HIV infection who have sex with men.\[10, 11, 12, 13, 14\] One European cohort study that followed a cohort of persons with HIV infection from 1998 to 2011 showed a decrease in HCV incidence in persons who inject drugs, but an 18-fold increase among men who have sex with men.\[15\] 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 diseases, and anal douching.\[16, 17\] In one longitudinal cohort study in persons with HIV, the risk of becoming infected with HCV was inversely proportional to CD4 count.\[18\] The increasing incidence of sexually-transmitted HCV infection in persons with HIV infection correlates with the widespread use of antiretroviral therapy, which has been linked to increased sexual activity and lower use of condoms.\[19, 20\]

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-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 coinfected with HIV similar to that in persons with HCV monoinfection, except for needing to consider drug interactions between DAAs and antiretroviral medications. [21,22] A proactive and aggressive approach for HCV is needed in persons with HIV—identify and treat HCV in all persons with HIV who have HCV coinfection. This strategy would lead to improved health and outcomes in persons with HIV and reduced transmission of HCV.
Natural History of HIV and HCV Coinfection

Impact of HIV on Natural History of HCV Infection

In patients with HCV monoinfection, approximately 80% will develop chronic HCV infection whereas about 20% will spontaneously clear HCV and resolve their infection. Preexisting HIV decreases the likelihood of spontaneous hepatitis C clearance to approximately 5 to 15%.[23,24] Compared with patients who have HCV monoinfection, patients with HCV and HIV coinfection have accelerated rates of liver fibrosis that result in a more aggressive course of liver disease (Figure 3).[2,8,25] Progression to cirrhosis occurs 12 to 16 years earlier in those coinfected with HCV and HIV compared with persons who have HCV monoinfection, and progression to cirrhosis, end-stage liver disease, and death has been documented in as few as 3 years.[26,27] The accelerated liver disease seen in persons with HIV and HCV coinfection is generally more pronounced when HIV infection precedes HCV infection.[27] In persons with HIV and HCV coinfection, more rapid liver fibrosis progression rates have been associated with low CD4 count, higher alcohol consumption rate, and younger age.[25] 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.[28,29] Patients coinfected with HIV and HCV have, on average, higher HCV RNA levels.[25] In addition, patients with HIV-HCV coinfection tend to develop hepatocellular carcinoma at a younger age and have more aggressive tumors compared with patients who have HCV monoinfection.[30,31]

Impact of HCV Infection on Natural History of HIV

Most studies have reported that HCV does not significantly impact HIV disease progression and AIDS-related mortality,[32,33,35] but one large European study noted a significant increase in HIV- and AIDS-related mortality in persons coinfected with HCV.[36] 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.[32,33,37] Achieving a sustained virologic response with hepatitis C treatment has not been shown to impact CD4 count or percentage.[38] Chronic viral hepatitis (caused by either HCV or HBV) increases the risk of hepatotoxicity due to antiretroviral therapy in coinfected patients.[39,40] 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.[41]

Hepatitis C-related Deaths in Persons with HIV Infection

Multiple cohort studies have identified shifting patterns of mortality for individuals with HIV infection as they are living longer with effective antiretroviral therapy. Liver disease, especially due to chronic infection with hepatitis B or hepatitis C, is now a leading cause of mortality among persons with HIV infection.[42] Although HIV-related mortality has decreased with the availability of antiretroviral therapy, several large cohort studies in Europe have demonstrated that persons coinfected with HIV and HCV have higher rates of liver-related death compared to persons with HCV monoinfection.[36,43,44,45] 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 infection during the years 1999-2004 found that 14.5% resulted from liver causes and hepatitis C infection was a predictor of liver-related death (Figure 4).[45] In the follow up D:A:D cohort study from 1999-2011 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-malignancies.[46]
Screening for Hepatitis C Infection

Screening for HCV in Persons with HIV infection

As recommended in the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents, all persons with HIV infection should undergo routine testing for hepatitis C infection at entry to care, primarily because of the high rate of HCV coinfection among persons with HIV infection.[3]

Repeat Screening for HCV Infection

Individuals with HIV infection who are at risk for acquiring HCV infection, including men who have sex with men who have ongoing risk for acquiring HCV, should have annual HCV antibody testing, or more frequently if indicated based on exposure to HCV.[3,47] Patients who achieve a sustained virologic response (SVR) with HCV therapy can become reinfected with HCV, as underscored by recent reports showing significant rates of HCV reinfection in men with HIV infection who have sex with men.[48] Because hepatitis C 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, if indicated based on risk.
HCV Diagnostic Testing

Recommended HCV Diagnostic Testing Sequence

In May 2013, the Centers for Disease Control and Prevention published a new recommended testing sequence for diagnosing current (active) hepatitis C infection (Figure 5).[49] 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.[49] 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 hepatitis C infection utilizes serologic assays that detect human antibodies generated as a response to hepatitis C virus infection. A positive antibody test indicates infection at some point in time, but it does not differentiate whether the person has resolved hepatitis C infection or chronic (active) hepatitis C infection. Several types of antibody tests are available[47,50]:

- **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 hepatitis C. The third-generation EIA detects antibodies that bind to recombinant antigens derived from multiple viral regions.[51,52] 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 hepatitis C 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 FDA approved 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. A patient 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 hepatitis C specifically detect HCV RNA and are commonly referred to as a Nucleic Acid Test (NAT) or Nucleic Acid Amplification Test (NAAT).[50] The HCV NAT becomes positive approximately 1 to 2 weeks after initial HCV infection, but very early after infection the HCV RNA may be detectable intermittently and at low levels.[53,54] 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 this situation, if acute HCV is highly suspected and the HCV RNA is negative, repeating the HCV RNA several months later would be advisable.

- **Quantitative HCV RNA:** The quantitative HCV RNA test is the preferred HCV supplemental test and can determine whether a patient 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, the quantitative HCV RNA assay
report an actual HCV RNA level that may provide useful information as a baseline HCV RNA level; this level can be useful as a baseline or a pretreatment value. The results for the commercially available HCV RNA assay are given in International Units (IU).

- **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 infection, with most of the false-negative results occurring in patients who have a CD4 count less than 200 cells/mm³.\(^{[55]}\) Thus, if a patient is at high risk for HCV infection, HCV RNA testing should be considered if the HCV antibody test is negative. As previously discussed, HCV antibody tests can also be falsely negative in the “window period” of acute HCV infection before the production of anti-HCV antibodies (this window period prior to seroconversion ranges from 2 to 12 weeks), so HCV RNA testing is similarly helpful in this scenario, especially if elevated ALT levels suggest acute HCV infection.\(^{[3]}\) Individuals who have 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.
Evaluation of Persons Diagnosed with HCV Coinfection

Due to the rapidly changing landscape of hepatitis C treatment, the American Association for the Study of Liver Diseases and the Infectious Disease Society of America (AASLD-IDSA) has developed an evidence-based, regularly updated guidelines for the management of hepatitis C—HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C.[47] According to the AASLD-IDSA HCV Guidance, persons with current (active) HCV infection should be evaluated by a practitioner who is prepared to provide comprehensive management, including treatment of hepatitis C, education and interventions aimed at reducing progression of liver disease, and preventing transmission of HCV.[47] 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 hepatitis C 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, 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 patients with chronic HCV should have testing for HCV genotype and quantitative HCV RNA (if not done at time of HCV diagnosis).[41] 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.[56,57]

Hepatitis A and Hepatitis B Status and Immunization

In persons with chronic HCV infection, superinfection with hepatitis A virus can cause fulminant hepatitis.[58] Thus, all patients with chronic HCV infection should be assessed for immunity to hepatitis A with total hepatitis A antibody and those without immunity to hepatitis A should receive hepatitis A vaccine. All patients with chronic HCV and HIV coinfection should also be screened for HBV by checking hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody.[47] Patients without immunity to HBV should be vaccinated against HBV.[3] Awareness of hepatitis B status in persons with chronic HCV has taken on increased importance with recent reports of hepatitis B reactivation and hepatitis flares during treatment of hepatitis C.[59,60]

Evaluation for Nonalcoholic Fatty Liver Disease

All patients 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.[47,61,62,63] Prevalence of hepatic steatosis among persons coinfected with HIV and HCV in cross-sectional studies has ranged from 30% to 70%.[64] Patients who are overweight or obese (defined by a body mass index 25 kg/m² or higher or 30 kg/m² or higher, respectively) should receive counseling regarding strategies to reduce weight.[47] Patients 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 patients with chronic liver disease and statins have been shown to be safe and effective in patients with chronic HCV and other chronic liver disease.[65,66]
Assessment of Stage of Liver Fibrosis

Patients 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 coinfected with HIV.\[26,28\] 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, requires experienced medical provider to obtain an appropriate histological sample, and can lead to complications. Thus, 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.\[67\] No single method has high accuracy when used alone, and the HCV Guidance suggests that the most efficient approach to fibrosis assessment is to use both direct biomarkers and liver elastography; a liver biopsy can be considered for any patient 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.\[67,68\] It is important to keep in mind that tests that use the platelet count in the score may overestimate fibrosis since some patients with HIV infection may have thrombocytopenia related to HIV, rather than to liver disease alone.\[42\]

Frequency of Reassessment of Liver Disease

Ongoing assessment of liver disease is recommended for patients in whom HCV therapy is deferred.\[67\] Routine HCV-related monitoring for all patients with HIV infection 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).\[67\]

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.\[69,70,71\] 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.\[72\] 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.\[71\] The exact mechanisms underlying the interaction between alcohol and viral hepatitis are not fully understood though they may include immune dysfunction, increased viral replication, emergence of HCV quasi-species, apoptosis, steatosis, and hepatic iron overload.\[71\] Patients who are identified as having alcohol use disorder or dependence should be referred to an addiction specialist and/or treatment program.\[47\]

Acetaminophen and Iron Intake

Patients 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.\[3\]

Screening for Gastroesophageal Varices

Patients 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.\[73\] Patients 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.[47, 74, 75, 76] 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.[3] 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 hepatitis C is discussed later in this lesson.
Treatment of HIV in Persons Coinfected with HCV

The Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV recommend initiating HIV antiretroviral therapy in all persons with HIV infection (regardless of CD4 cell count) to reduce the risk of HIV disease progression and to prevent transmission of HIV; this applies to persons with HIV and HCV coinfection.\[77\] For selected antiretroviral-naïve patients with HIV-HCV coinfection and with CD4 counts greater than 500 cells/mm\(^3\), a clinician could choose to defer antiretroviral therapy temporarily until HCV treatment is completed to avoid the challenges of concurrent HIV and HCV therapy. Note that in the current HIV treatment era, the scenario of deferring antiretroviral therapy to first administer HCV therapy is very unlikely to occur. In patients with lower CD4 counts (especially below 200 cells/mm\(^3\)), antiretroviral therapy initiation should take precedence and HCV treatment can be delayed until the patient is stable on HIV treatment.\[41\] Recommended initial antiretroviral combination regimens are the same for persons with HIV and HCV coinfection as for those without HCV. When treatment for both HIV and HCV are given concurrently, it is important to consider potential drug interactions.\[41\] The initiation of antiretroviral therapy in patients with cirrhosis or advanced liver disease should take into account that some antiretroviral medications may require dose adjustment or may be contraindicated in advanced stages of liver disease.
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.[47,78] Treatment is now recommended for all individuals with chronic HCV and HIV coinfection; the highest priority for immediate treatment includes individuals with advanced fibrosis or compensated cirrhosis, liver transplant recipients, patients with severe extrahepatic hepatitis C.[3,67] A complicating factor that lends additional urgency for HCV treatment in persons with HIV coinfection is the decreased access to liver transplantation in patients coinfected with HCV and HIV compared to patients with HCV monoinfection.[29] This differential in transplant access has been attributed, in part, to higher HCV recurrence rates after transplant in patients coinfected with HIV, but this may change in the current era of more effective and safer pre- and post-transplant HCV therapies.

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 6). Among persons who attain an SVR at week 12, 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.[80] Overall long-term health outcome goals with HCV treatment include reduced risk for hepatocellular carcinoma, and lower liver-related mortality.[81,82]

Approach to Treatment

Many DAAs are now available for treatment of HCV and most are safe, highly effective, and convenient.[21,22] Numerous studies with all-oral DAA regimens have demonstrated comparable rates of sustained virologic response in patients with HCV-HIV coinfection and HCV monoinfection, indicating that HCV-HIV coinfection does not negatively affect the HCV outcomes of patients treated with DAAs.[38,83,84,85] These trials of patients coinfected with HIV and HCV have primarily included individuals with high CD4 counts and often those without cirrhosis.

Phase 3 HCV Treatment Data in Persons with HIV Coinfection

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

- **Daclatasvir and Sofosbuvir (ALLY-2):** In this phase 3, open-label trial, patients with HCV genotype 1 through 4 and HIV coinfection were treated with daclatasvir and sofosbuvir.[86] Previously untreated patients received either an 8-week or 12-week course, whereas treatment-experienced patients were treated with a 12-week course. Patients with cirrhosis comprised 10% and 29% of treatment-naïve and treatment-experienced groups, respectively. Overall, 168 (83%) of 203 patients had genotype 1 infection. Among treatment-naïve patients, the SVR12 rates were 97% in the 12-week treatment group and 76% in the 8-week group. For the treatment-experienced patients, all of whom received therapy for 12 weeks, the SVR12 rate was 98%.[86]

- **Elbasvir-Grazoprevir (C-EDGE Coinfection):** In this prospective, single-arm, open-label, phase 3 clinical trial, 218 patients with chronic hepatitis C genotype 1, 4, or 6 and HIV coinfection received the fixed-dose combination of elbasvir-grazoprevir once daily for 12 weeks.[87] Nearly all (97%) participants were taking antiretroviral therapy and had suppression of HIV RNA levels; the median CD4 cell count was 568 cells/mm³. Overall, 86% had HCV genotype 1a or 1b infection and 35 (16%) had compensated cirrhosis. The overall
SVR12 rate was 96% by primary analysis, with the breakdown by genotype showing 96.5% SVR12 for genotype 1a, 95.5% for genotype 1b and 96.4% for genotype 4. All the cirrhotic patients achieved an SVR12. When excluding participants who did not achieve an SVR12 due to treatment discontinuation or reinfection, the overall SVR12 rate was 97%.[87]

- **Glecaprevir-Pibrentasvir (EXPEDITION-2):** In this open-label, dual-arm phase 3 trial, 137 noncirrhotic adults with HCV (genotype 1-6) and HIV coinfection received 8 weeks of glecaprevir-pibrentasvir and 16 coinfected patients with compensated cirrhosis received 12 weeks of glecaprevir-pibrentasvir.[88] The majority (63%) of participants had genotype 1 infection; 19% were treatment-experienced (16% with interferon and 2% sofosbuvir based). All but 10 patients were taking either raltegravir, dolutegravir, or rilpivirine as the anchor drug for HIV antiretroviral therapy. The overall SVR12 rate was 98%; one patient with genotype 3 HCV and cirrhosis experienced on-treatment virologic breakthrough.[88]

- **Ledipasvir-Sofosbuvir (ION-4):** In this phase 3, open-label, multicenter study, investigators enrolled 335 patients with hepatitis C and HIV coinfection to receive a 12-week course of ledipasvir-sofosbuvir.[89] 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-emtricitabine plus either efavirenz, rilpivirine, or raltegravir. Most (98%) of the patients enrolled had genotype 1 HCV infection and 55% were treatment experienced. Overall, 321 (96%) of 335 treated patients achieved an SVR12. The results were similar regardless of prior treatment status or presence of cirrhosis.[89]

- **Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir (TURQUOISE-I):** This multicenter, multipart, randomized, open-label, phase 2/3 trial evaluated the safety and efficacy of ombitasvir-paritaprevir-ritonavir and dasabuvir plus ribavirin for 12 or 24 weeks in treatment-naïve and experienced patients with chronic hepatitis C genotype 1 and HIV coinfection.[90] Patients were required to have a CD4 count of at least 200 cells/mm$^3$ (or a CD4 percentage of at least 14%) and an HIV RNA level less than 40 copies/mL while receiving atazanavir- or raltegravir-based HIV antiretroviral therapy. Enrollment included participants with compensated cirrhosis (Child-Turcotte-Pugh class A) and patients with prior treatment with peginterferon plus ribavirin. In the 12-week arm, SVR12 was achieved in 29 (93.5%) of 31 patients; in the 24-week arm, 29 (90.6%) of 32 achieved an SVR12. Among the five patients who did not achieve an SVR12, one withdrew from the study prematurely, one relapsed with resistance, one had virologic breakthrough with resistance, and two appeared to have been reinfected after completing treatment.[90]

- **Sofosbuvir plus Ribavirin (PHOTON-1):** This open label, nonrandomized, uncontrolled, phase 3 trial evaluated sofosbuvir plus ribavirin (weight-based dosing) in 223 patients with chronic hepatitis C genotypes 1, 2, or 3 and HIV coinfection.[38] Enrollment included HCV treatment-naïve and treatment-experienced patients. All participants were required to be on stable antiretroviral therapy with an undetectable HIV RNA level and CD4 count greater than 200 cells/mm$^3$, or if they were not taking HIV antiretroviral medications, they were required to have a CD4 count greater than 500 cells/mm$^3$. Patients with cirrhosis were included in the trial, but could not comprise more than 20% of the total number of subjects enrolled. The trial included treatment-naïve patients with HCV genotype 1, 2, or 3 and treatment-experienced patients with genotype 2 or 3. A 24-week treatment course was given to all patients with HCV genotype 1 and to treatment-experienced patients with HCV genotype 2 or 3; treatment-naïve patients with HCV genotype 2 or 3 received a 12-week treatment course. For treatment-naïve patients, the SVR12 rates were 76% with genotype 1, 88% with genotype 2, and 67% with genotype 3. Treatment-experienced patients with genotype 2 had a 92% SVR12 rate and those with genotype 3 had a 94% SVR12 rate.[38]

- **Sofosbuvir plus Ribavirin (PHOTON-2):** In this open-label, phase 3 trial, 274 participants with HIV who were coinfected with HCV genotype 1, 2, 3, or 4 received treatment with the all-oral regimen of sofosbuvir plus weight-based ribavirin.[91] The study enrolled treatment-naïve patients with genotypes 1, 2, 3, or 4 and treatment-experienced patients with genotype 2 or 3. A 24-week treatment course was given to all patients with HCV genotype 1,
3, or 4 and treatment-experienced patients with genotype 2, whereas treatment-naïve patients with HCV genotype 2 received 12 weeks of therapy. Among those enrolled, 81% of the patients were HCV treatment naïve and 20% had cirrhosis. The mean CD4 count was 588 cells/mm$^3$ and 97% were on antiretroviral therapy (tenofovir-emtricitabine plus one of the following: efavirenz, atazanavir plus ritonavir, darunavir plus ritonavir, rilpivirine, or raltegravir). The SVR12 rates were greater than 80% with all HCV genotypes: GT1 (85%), GT2 (88%), GT3 (89%), and GT4 (84%). In addition, the treatment responses were similar in the treatment-naïve and treatment-experienced patients.[91]

- **Sofosbuvir-Velpatasvir** (ASTRAL-5): The ASTRAL-5 study was a single-arm, open-label phase 3 trial of sofosbuvir-velpatasvir for 12 weeks in patients with HIV and HCV coinfection.[92] The study enrolled 106 patients with genotype 1, 2, 3, 4 or 6 HCV infection; 18% had compensated cirrhosis and 29% were treatment-experienced. The mean CD4 count was 583 cells/mm$^3$ and all patients had suppressed HIV RNA levels. A variety of antiretroviral regimens, including tenofovir DF and 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 people taking a boosting agent and tenofovir DF, but it remained relatively stable over time in all groups.[92]

**Choice of HCV Regimen**

The AASLD-IDSA HCV Guidance recommends using the same regimens to treat HCV in persons coinfected with HIV as those in persons with HCV monoinfection.[21] The following links are to recommended regimens in the AASLD-IDSA HCV Guidance based on 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: SOF + RIB Experienced
- 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)
Screening for Hepatocellular Carcinoma

Risk of Hepatocellular Carcinoma in Person with HCV-HIV 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.[93,94] 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 HCV coinfection dramatically promotes the development both of HCC (5-fold increase) and of cirrhosis (10- to 20-fold increase).[95]

HCC Surveillance Recommendations

The 2011 Guidelines from the American Association for the Study of Liver Disease (AASLD) recommend hepatocellular carcinoma screening for patients with hepatitis C infection and cirrhosis.[93] The more recent AASLD/IDSA HCV Guidance recommends HCC surveillance in all patients with chronic HCV infection who have advanced fibrosis (Metavir stage F3) or cirrhosis (Metavir stage F4).[93,96] Both of these guidelines recommend performing hepatic ultrasound every 6 months as the hepatocellular carcinoma screening method. The use of alpha-fetoprotein (AFP) for HCC surveillance increases cost and has limited sensitivity and specificity, and is no longer recommended by the AASLD. Use of AFP screening does not replace ultrasound and should not be used alone. The criteria for performing HCC surveillance and the surveillance method are the same for persons with HIV-HCV coinfection as with HCV monoinfection. In general, patients diagnosed with HCC have a poor prognosis, but the best chance for survival is with detection of the cancer at a very early stage. One retrospective analysis found that tumor staging and survival are similar for patients with HCC in the setting of HIV-HCV coinfection compared with HCV monoinfection.[97] For patients 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 patients 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 4-7%, and coinfection with HIV increases the risk of perinatal HCV transmission by approximately 2-fold. 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.

Management of Pregnant Women with HIV-HCV Coinfection

Currently available treatments for HCV are not recommended for use during pregnancy. Note that ribavirin is absolutely contraindicated for use during any time of pregnancy. Suppressive antiretroviral therapy for the pregnant woman, which markedly lowers the risk of perinatal HIV transmission, may also reduce the risk of perinatal HCV transmission. Women 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. For women 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. Although hepatitis C virus can be detected in breast milk, most studies have not shown an increase in transmission in breastfed infants (note that mothers coinfected with HIV should avoiding breastfeeding to prevent HIV transmission). Expert consultation is recommended for the management of pregnant women with HIV-HCV coinfection.

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 guidelines recommend postponing HCV antibody testing in newborns until 18 months of age. 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). If earlier diagnosis is desired, 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. Among children with HCV monoinfection, spontaneous clearance of HCV occurs in up to 20% by 3 years of age; HCV clearance appears to be lower in children with HIV-HCV coinfection.
Summary Points

- An estimated 15-30% percent of persons with HIV infection are coinfected with HCV.
- The prevalence of HIV-HCV coinfection is highest among persons with HIV infection who inject drugs although rising rates of sexually transmitted hepatitis C infection have recently been documented in men with HIV infection who have sex with men.
- Compared with individuals who have HCV mono-infection, 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 infection.
- All persons with HIV infection should be tested for hepatitis C infection 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.
- Treatment for hepatitis C has evolved rapidly following the introduction of DAAs, and multiple studies have demonstrated comparable rates of sustained virologic response in persons with HCV mono-infection and HCV-HIV coinfection.
- In mothers with HCV mono-infection, the risk of perinatal HCV transmission is 4-7%, 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.
- In persons with HIV-HCV coinfection, hepatocellular carcinoma occurs at a higher rate, usually develops at an earlier age, and progresses more aggressively than in persons with HCV mono-infection; individuals with HIV infection who have cirrhosis should undergo ultrasound screening for HCC every 6 months.
Citations


13. van der Helm JJ, Prins M, del Amo J, et al. The hepatitis C epidemic among HIV-positive MSM:
[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

21. AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Unique patient populations: patients with HIV/HCV coinfection. [AASLD/IDSA Hepatitis C Guidance]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]


38. Sulkowski MS, Mehta SH, Chaisson RE, Thomas DL, Moore RD. Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir. AIDS.


46. AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. HCV testing and linkage to care. [AASLD/IDSA Hepatitis C Guidance]


52. Glynn SA, Wright DJ, Kleinman SH, et al. Dynamics of viremia in early hepatitis C virus infection. Transfusion. 2005;45:994-1002. [PubMed Abstract]


66. AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. When and in whom to initiate HCV therapy.


76. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. Initiation of antiretroviral therapy. October 17, 2017. [AIDSinfo] -


95. AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Monitoring Patients Who Are Starting HCV Treatment, Are on Treatment, or Have Completed Therapy. [AASLD/IDSA Hepatitis C Guidance]


References

- AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection. [AASLD/IDSA Hepatitis C Guidance]
- AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed. [AASLD/IDSA Hepatitis C Guidance]


• Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Baseline evaluation. May 1, 2014. [AIDSinfo]


• Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon Alfa-2a plus ribavirin for


Figures

Figure 1 Estimated Number of New Annual HCV Infections—United States, 1982-2015

Figure 2 Estimated Number of New Annual HCV Infections—United States, 2005-2015

Figure 3 Comparison of Progression to Cirrhosis in Persons with HIV-HCV Coinfection and HCV Monoinfection

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.


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**Recommended Testing Sequence for Identifying Current HCV Infection**

- **HCV Antibody**
  - **Nonreactive**: No HCV antibody detected
    - **STOP**
  - **Reactive**: HCV RNA
    - **Not Detected**: No current HCV infection
    - **Detected**: Current HCV infection
      - **Link to care**
    - Additional testing as appropriate†
**Figure 6 Sustained Virologic Response 12 (SVR12)**

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.

Illustration by David H. Spach, MD