Special Populations: Hepatitis C Virus/HIV Coinfection

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Panel's Recommendations
• All pregnant women with HIV should be screened during the current pregnancy for hepatitis C virus (HCV) infection **(AIII)**.   • HCV screening should be repeated later in pregnancy in women who initially screen negative for HCV but who have persistent or new risk factors for HCV (e.g., new or ongoing injection or intranasal substance use) **(AIII)**. • All pregnant women with HIV should also be tested for hepatitis B virus (HBV) infection (see Hepatitis B Virus/HIV Coinfection)**(AIII)**. • Women with HCV infection who have not already received the hepatitis A virus (HAV) vaccine series should be screened for immunity to HAV **(AIII)**. If they screen negative for HAV antibodies (either IgG or total antibody (IgG and IgM)), they should receive the HAV vaccine series **(AIII)**. • All pregnant women with HIV (with or without HCV) who screen negative for HBV infection and lack HBV immunity (i.e., HBV surface antigen negative, HBV core antibody negative, and HBV surface antibody negative) should receive the HBV vaccine series **(AII)**. • Currently, treatment of HCV during pregnancy **is not recommended** (unless part of an approved experimental protocol) because of the lack of safety data on the use of HCV direct-acting antiviral medications in pregnant women. If considering initiating HCV treatment in a pregnant woman with HIV coinfection, consultation with an expert in HIV and HCV is strongly recommended **(AIII)**. • Recommendations for antiretroviral therapy (ART) during pregnancy are the same for all women with HIV, including those who have HCV coinfection **(AIII)**. • Pregnant women with HCV/HIV coinfection who are receiving ART should be counseled about the signs and symptoms of liver toxicity, and hepatic transaminases should be assessed 1 month following initiation of ART and at least every 3 months thereafter during pregnancy **(BIII)**. • Women with HCV should be strongly considered for HCV treatment with direct-acting antiviral agents (DAAs) postpartum **(AI)**. • In women who have tested positive for HCV, HCV RNA should be evaluated after delivery to assess for spontaneous clearance of HCV infection, particularly as they are being considered for initiation of HCV therapy postpartum **(BII)**. • Decisions concerning the mode of infant delivery in pregnant women with HCV/HIV coinfection should be based on standard obstetric and HIV-related indications alone; HCV coinfection does not necessitate cesarean delivery when not otherwise indicated (see Intrapartum Care for Women with HIV) **(AIII)**. • Infants born to women with HCV/HIV coinfection should be evaluated for HCV infection **(AIII)**. Decisions regarding the specific type of assays to use for HCV screening in children and the timing of those assays should be made after consultation with an expert in pediatric HCV infection **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

The management of HCV/HIV coinfection in pregnancy is complex, and none of the approved HCV direct-acting antivirals (DAAs) have yet been fully evaluated in pregnant women; thus, consultation with an expert in HIV and HCV infection **is strongly recommended** when managing HCV during pregnancy.

For additional information on hepatitis C virus (HCV) and HIV (see Hepatitis C Virus in the Pediatric Opportunistic Infection Guidelines, Hepatitis C Virus/HIV Coinfection in the Adult and Adolescent Antiretroviral Guidelines, and Hepatitis C Virus Infection in the Adult and Adolescent Opportunistic Infection Guidelines). The American Association for the Study of Liver Diseases (AASLD), the Infectious Diseases Society of America (IDSA), and the International Antiviral Society–USA maintain updated information about treating patients with HCV/HIV coinfection. The guidelines are available online at HCVguidelines.org.

Screening and Vaccination

All pregnant women with HIV should be screened at entry into general HIV care and during each pregnancy for the following:

- Hepatitis B virus (HBV), unless they are known to have HBV/HIV coinfection or they have serologic documentation of HBV immunity (see Hepatitis B Virus/HIV Coinfection), *and*
- HCV infection, unless they are known to have HCV/HIV coinfection.

The observed prevalence for HCV infection was 2% to 12% in European cohorts of pregnant women with HIV[1] and 3.8% among women with HIV in New York State.[2] Although data about secular trends in HCV among women with HIV in the United States are limited, the prevalence of HCV among women of childbearing age and children aged <2 years in the general population has increased substantially in recent years, partly because of the ongoing opioid epidemic.[3-9]

The Society for Maternal–Fetal Medicine and the American College of Obstetricians and Gynecologists recommend repeating HCV testing later in pregnancy for women who initially screen negative for HCV but who have persistent risk factors for HCV or who develop new risk factors for HCV infection (e.g., new or ongoing use of injected or intranasal substance use).[10] The male partners of all women with HCV/HIV coinfection should be referred for both HIV and hepatitis counseling and testing to prevent the sexual transmission of HIV and HCV; however, HCV is infrequently transmitted via heterosexual sex. People who do not share injection equipment have a very low risk of horizontal transmission of HCV. Partners who do not have HIV infection should be counseled about the benefits of starting oral pre exposure prophylaxis (PrEP) to prevent HIV acquisition (see Preconception Counseling and Care for Women of Childbearing Age Living with HIV).

Newly available DAAs have dramatically improved HCV therapy; it is now possible to cure HCV infection in most patients.[11] Current HCV treatment guidelines recommend therapy for nearly all patients with HCV infection.[11] However, the management of HCV/HIV coinfection during pregnancy is complex. A Phase 1 study is now evaluating the safety and pharmacokinetics (PKs) of ledipasvir/sofosbuvir in pregnancy.[12] Ribavirin is also contraindicated in pregnancy, although it is no longer commonly used for the treatment of HCV.[13] If considering HCV treatment for a pregnant person, consultation with an expert in HIV and HCV is strongly recommended.

The primary reasons for HCV testing during pregnancy are—

- To identify women with HCV/HIV coinfection at a time when they are engaged with the health care system, so that HCV treatment can be offered after delivery (ideally before a subsequent pregnancy);
- To monitor for HCV-related hepatotoxicity, which has been associated with the use of antiretroviral (ARV) drugs in women with HCV/HIV coinfection;[14]
- To monitor for preterm birth, which has been associated with HCV/HIV coinfection in pregnant women;[1,8,15,16]
- To ensure vaccination against other viral hepatitis infections (HAV and HBV) when needed; *and*
- To ensure appropriate follow-up and evaluation of infants who were exposed to HCV.

Screening for chronic HCV infection using a sensitive immunoassay for HCV antibodies is recommended for all individuals with HIV, including those who are pregnant. All pregnant women in the United States should be screened for HCV at each pregnancy, except in settings where the prevalence of HCV infection is <0.1%.[11,17,18] False-negative anti-HCV immunoassay results can occur in individuals with HIV, but this is uncommon with the more sensitive immunoassays. If HCV infection is suspected despite a negative HCV antibody screen, a commercially available diagnostic quantitative plasma HCV RNA assay can be performed.[19,20] Individuals who have a positive HCV antibody test should undergo confirmatory testing for HCV RNA with this quantitative assay. Many laboratories now perform reflex RNA testing for individuals who test positive for HCV antibodies.

Pregnant women should also be tested for HCV RNA when they have indeterminate or negative serologic test results for HCV but are suspected of having HCV infection because of elevated aminotransaminase levels or risk behaviors (e.g., a history of injection drug use).[21]

Because of the added risk of hepatic decompensation from acute infection with any viral hepatitis, women with HCV infection should also be screened for both HAV and HBV. Women with chronic HCV infection who have not already received the HAV vaccine series should be screened for immunity to HAV (either IgG alone or IgG and IgM together). If they screen negative for HAV antibodies, they should receive the HAV vaccine series. In women with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3, antibody responses to the HAV vaccine should be assessed 1 month after the patient completes the vaccination series; those who are HAV antibody IgG negative should be revaccinated when the CD4 count is >200 cells/mm^3.[22] Women with HCV/HIV coinfection who screen negative for HBV and lack HBV immunity (i.e., they are hepatitis B surface antigen [HBsAg] negative, hepatitis B core antibody negative, and hepatitis B surface antibody negative [HBsAb]) should receive the HBV vaccine series. Women with HCV/HIV coinfection who are HBsAb negative despite receiving the HBV vaccine series may benefit from revaccination (see Hepatitis B Virus/HIV Coinfection).[23] The hepatitis B vaccination poses no apparent risk to developing fetuses, because current vaccines contain noninfectious HBsAg.[24]

Impact of HCV/HIV Coinfection on Progression and Perinatal Transmission of Both Viruses

Although the HCV viral load tends to peak in the third trimester, pregnancy does not appear to influence the course of HCV infection clinically. Women with chronic HCV generally do well during pregnancy, provided that they have not progressed to decompensated cirrhosis.[25,26]

Hepatitis C Virus Transmission

About 6% of infants born to women with HCV acquire HCV infection.[20] In most studies of women with HCV/HIV coinfection who are not receiving treatment for either infection, the incidence of perinatal HCV transmission is approximately twofold higher among women with HCV/HIV coinfection (10% to 20% transmission risk) than among women with HCV monoinfection.[27-30] These higher transmission rates likely are related to the higher levels of HCV viremia observed in patients with HCV/HIV coinfection and/or other HIV-related impacts on HCV disease activity.[16,31] Early and sustained control of HIV viremia with ART, however, could reduce the risk of HCV transmission to infants.[26,32-34] A European study of perinatal HCV transmission found that the use of effective ART for HIV was associated with a strong trend toward reduced rates of HCV transmission (odds ratio [OR] 0.26; 95% confidence interval [CI], 0.07–1.01).[32] In an Italian cohort, HCV transmission occurred in 9% of infants born to women with HCV/HIV coinfection, most of whom were on ART. No HCV transmissions occurred in infants born to women with HCV viral loads of <5 log IU/mL.[16]

HIV Transmission

In the absence of ART, maternal HCV/HIV coinfection can increase the risk of perinatal HIV transmission.[35,36] The risk of perinatal HIV transmission can be reduced in pregnant women with HCV/HIV coinfection by following the standard recommendations for ART for all women with HIV.

Impact of Hepatitis C Virus on HIV Management

Data are limited on the optimal management of pregnant women with HCV/HIV coinfection. Recommendations on the use of ART during pregnancy for treating HIV and preventing perinatal HIV transmission are the same for women who have HCV/HIV coinfection as for those with HIV monoinfection (see General Principles Regarding Use of Antiretroviral Drugs during Pregnancy). In one Canadian study, HCV/HIV coinfection was associated with an increased risk of HIV viral rebound among women who were on previously effective ART. Although the authors suggest that additional factors (e.g., adherence) may have varied between the groups, these findings support the need to follow recommendations for HIV RNA monitoring during pregnancy.[37]

Hepatitis C Virus–Specific Therapy in Pregnancy

All currently available DAAs lack sufficient safety data to be recommended for use during pregnancy. In the past, most anti-HCV therapy included both interferon and ribavirin. Interferons are not recommended for use in pregnancy because they are abortifacient at high doses in monkeys and have direct antigrowth and antiproliferative effects.[38] Some DAA regimens are approved for use with ribavirin in specific nonpregnant populations, because of the suboptimal treatment responses observed with the use of DAAs alone. Any treatment regimens that include ribavirin are **contraindicated** in pregnant women because of the teratogenic and embryocidal effects observed in all animal species exposed to ribavirin. Ribavirin-associated defects in animals include limb abnormalities, craniofacial defects, anencephaly, and anophthalmia. The risk of teratogenicity persists for up to 6 months following ribavirin cessation and applies also to female partners of men taking ribavirin.[11] Pregnancies that occur in women taking ribavirin should be reported to the Ribavirin Pregnancy Registry (online or by phone at 1-800-593-2214)

Many interferon-free DAA regimens have been approved for the treatment of HCV. When determining the optimal regimen for an individual patient, clinicians must consider many factors, including HCV genotype, prior treatment experience, and stage of liver disease (e.g., compensated or decompensated cirrhosis). The following main classes of DAAs are currently available in the United States:[11,39]

- NS5A inhibitors: elbasvir, ledipasvir, pibrentasvir, velpatasvir
- NS5B nucleoside polymerase inhibitors: sofosbuvir
- NS3/4A protease inhibitors (PIs): glecaprevir, grazoprevir, voxilaprevir

DAAs are not yet recommended for use in pregnancy because of the lack of PKs and safety data; one small PK study that is investigating the use of ledipasvir/sofosbuvir in pregnant women with HCV alone demonstrated 100% virologic suppression and no safety concerns. Similarly, a small case series of 15 pregnant women treated with ledipasvir/sofosbuvir reported 100% virologic suppression at 12 weeks and no early safety concerns in the women or their infants.[40] Women with HCV/HIV coinfection should be strongly considered for HCV treatment with DAAs postpartum.[41] Potential drug interactions exist between the newer anti-HCV drugs and ARV drugs that may produce clinically significant changes in serum levels of both ARV drugs and anti-HCV medications. For detailed information on the interactions between ARV drugs and anti-HCV drugs, see the Adult and Adolescent Antiretroviral Guidelines, the Adult and Adolescent Opportunistic Infection Guidelines, HCVGuidelines.org, and the HEP Drug Interaction Checker.

Monitoring Women with HCV/HIV Coinfection During Pregnancy

Hepatic enzyme levels can increase after ART is initiated in women with HCV/HIV coinfection—particularly in those with low CD4 counts at treatment initiation—as a result of an immune-mediated flare in HCV disease triggered by immune reconstitution with ART. In patients with HIV, HCV coinfection may increase the hepatotoxic risk of certain ARV agents, specifically PIs and nevirapine. HCV monoinfection may increase the risk of intrahepatic cholestasis of pregnancy;[42] this risk also is higher among women with HCV/HIV coinfection than among women with HIV infection alone.[1] Pregnant women with HCV/HIV coinfection should be counseled about the signs and symptoms of liver toxicity, and transaminase levels should be assessed 1 month after initiating ART and then every 3 months. If hepatic toxicity occurs, a clinician may need to consider initiating a less hepatotoxic drug regimen, and, if clinical symptoms or significant elevations of transaminases occur, drugs may need to be discontinued temporarily. Differentiating between drug toxicity and a flare of HCV disease that is associated with immune reconstitution can be difficult; therefore, consulting an expert in HCV/HIV coinfection is recommended.

HCV RNA levels can fluctuate during pregnancy and postpartum, with frequent increases in HCV RNA levels

during pregnancy followed by a drop in the postpartum period.[43] Spontaneous clearance of HCV can occur postpartum. [43-46] As a result, the AASLD and the IDSA recommend that women have their HCV RNA re-evaluated after delivery, particularly if they are being assessed for initiation of therapy with DAA.[41]

Rates of preterm delivery also are high among women with HCV/HIV coinfection. In an Italian cohort of mostly ART-treated women with HCV/HIV coinfection, preterm delivery occurred in 41% of women overall. The rate of preterm delivery was not significantly different among women with lower or higher HCV RNA levels: 29% among women with HCV RNA <5 log IU/mL and 43% among women with HCV RNA >5 log IU/mL. Women with preterm delivery had significantly higher levels of HCV RNA than those who delivered at term.[16] A study of 4,236 pregnant women with HIV reported a higher risk of preterm delivery in women with HCV coinfection (OR 3.0; 95% CI, 1.6–5.7) than in women with HIV alone.[1] Infants born to women with HCV also were more likely to have low birth weights (defined as weighing <2,500 g) than those born to women without HCV (23 vs. 8%, $P < 0.01$).[8]

HCV infection in pregnancy may also be associated with increased risks for gestational diabetes, small for-gestational-age infants, and low birth weight infants.[5,47] Although currently no obstetric guidelines suggest that women with HCV infection should be monitored more frequently for diabetes or for fetal growth,[48] knowledge of these increased risks may inform clinical care.[10]

Mode of Delivery

The majority of studies of scheduled cesarean delivery in women with HCV infection (with or without HIV coinfection) have found that the procedure does not reduce the risk of perinatal HCV transmission.[32,49-51] Thus, the general recommendations for mode of delivery are the same for women with HCV/HIV coinfection as for those with HIV infection alone (see Intrapartum Care for Women with HIV).

Evaluation of Infants Exposed to Hepatitis C Virus

Infants born to women with HCV/HIV coinfection should be assessed for chronic HCV infection. An HCV antibody test should be performed after age 18 months, when the maternal anti-HCV antibody level has waned.[52] Sensitivity of HCV RNA testing is low at birth, and viremia can be intermittent or infection may resolve spontaneously; [5,53,54] thus, HCV RNA testing should not be performed before age 2 months, and a single negative test is not conclusive evidence of lack of infection.[55] Uptake of HCV testing is very low for infants who were exposed to HCV;[56] therefore, it is important for providers to counsel women about the need for pediatric follow-up and testing during the first few years of life.[8,57-59] The Pediatric Opportunistic Infection Guidelines provide further details about the diagnostic evaluation of infants who were exposed to HCV.

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