Special Populations: Hepatitis C Virus/HIV Coinfection (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel’s Recommendations

- All pregnant women with HIV should be screened during the current pregnancy for
  1. Hepatitis B virus (HBV) infection, unless they are known to have HBV/HIV coinfection or serologic documentation of HBV immunity coinfection (see Hepatitis B Virus/HIV Coinfection), and
  2. Hepatitis C virus (HCV) infection unless they are known to have HCV/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, because they are at increased risk of complications from coinfection with other viral hepatitis infections (AIII). If they screen negative for HAV antibodies (IgG or IgG plus IgM), they should receive the HAV vaccine series (AIII).
- All pregnant women with HIV and/or HCV who screen negative for HBV infection (i.e., HBV surface antigen negative and HBV core antibody negative) and lack HBV immunity (i.e., HBV surface antibody negative) should receive the HBV vaccine series (AIII).
- When considering 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 living with HIV, whether they have HCV or not (AIII).
- Pregnant women with HCV/HIV coinfection who are receiving ART should be counseled about 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).
- 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 it is not otherwise indicated (see Transmission and Mode of Delivery) (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

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 Guidelines, and Hepatitis C Virus Infection in the Adult and Adolescent Opportunistic Infection Guidelines. The American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, and the International Antiviral Society-USA maintain updated information about treating patients with HCV/HIV coinfection. The guidelines are available online at HCVguidelines.org. 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, particularly when HCV treatment during pregnancy is being considered.

Screening and Vaccination

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

1. Hepatitis B virus (HBV), unless they are known to have HBV/HIV coinfection or serologic documentation of HBV immunity, and
2. HCV infection, unless they are known to have HCV/HIV coinfection.
Among women with HIV, the observed risks for HCV infection were 2% to 12% in European cohorts of pregnant women with HIV and 3.8% among women with HIV in New York State. Although data about secular trends in HCV risk among women living with HIV are limited in the United States, the prevalence of HCV among women of childbearing age and children aged <2 years in the general population has increased substantially in recent years. The male partners of all patients with HCV/HIV coinfection should be referred for both HIV and hepatitis counseling and testing to prevent the sexual transmission of HIV and HCV from women to their male partners; however, 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 potential benefits and risks of starting oral pre-exposure prophylaxis to prevent HIV acquisition (see Preconception Counseling).

Newly available DAAs have dramatically improved HCV therapy; it is now possible to cure HCV infection in most patients. Current HCV treatment guidelines recommend therapy for nearly all patients with HCV infection. The management of HCV/HIV coinfection during pregnancy is complex, however. Although a single Phase 1 study is now evaluating the safety and pharmacokinetics (PKs) of HCV treatment in pregnancy, with data expected in late 2018, none of the approved DAAs have been fully evaluated in pregnant women. The use of ribavirin, although rarely needed now with DAAs, is also contraindicated in pregnancy. When considering HCV treatment in a pregnant person, consultation with an expert in HIV and HCV is strongly recommended. In addition, the risks of perinatal HCV transmission are much lower than those of perinatal HIV transmission, and some children will clear HCV infection spontaneously, making the balance of risks and benefits for treating HCV in pregnancy different from that for treating HIV.

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 system, so that HCV treatment can be offered after delivery (ideally before a subsequent pregnancy);
- To monitor for the increased risk of HCV-related hepatotoxicity related to antiretroviral (ARV) use and the potential increased risk of preterm birth with HCV infection in women with HCV/HIV coinfection;
- To ensure vaccination against other viral hepatitis infections (hepatitis A virus [HAV] and HBV) if needed; and
- To ensure appropriate follow-up and evaluation of infants 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. False-negative anti-HCV immunoassay results can occur in individuals with HIV, but it is uncommon with the more sensitive immunoassays. If HCV infection is suspected despite a negative HCV antibody screen, a quantitative HCV RNA assay can be performed. Individuals who have a positive HCV antibody test should undergo confirmatory testing for plasma HCV RNA using a commercially available quantitative diagnostic assay. Many laboratories now perform reflex RNA testing for individuals who test positive for HCV antibodies. Testing for HCV RNA also should be performed during pregnancy on individuals whose serologic test results are indeterminate or negative but in whom HCV infection is suspected because of elevated aminotransaminase levels or risk factors such as a history of injection drug use.

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/mm³, antibody responses to HAV vaccine should be assessed 1 month after completion of vaccination series; those who are HAV Ab IgG negative should be revaccinated when the CD4 count is >200 cells/mm³. Women with HCV/
HIV coinfection who screen negative for HBV (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 having received the HBV vaccine series may benefit from revaccination (see Hepatitis B Virus/HIV Coinfection). The hepatitis B vaccination poses no apparent risk to developing fetuses, as current vaccines contain noninfectious HBsAg.

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

Although the HCV viral load appears 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.

**HCV Transmission**

Approximately six of every 100 infants born to women with HCV acquire HCV infection. 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 two-fold higher among women with HCV/HIV coinfection (10% to 20% transmission risk) than among women with HCV monoinfection. These higher transmission rates are likely related to an increase in HCV viremia and/or other HIV-related impacts on HCV disease activity. However, early and sustained control of HIV viremia with antiretroviral therapy (ART) may reduce the risk of HCV transmission to infants. A European study of perinatal transmission of HCV found that use of effective ART for HIV was associated with a strong trend toward reduced rates of HCV transmission (odds ratio 0.26; 95% CI, 0.07–1.01). In an Italian cohort, HCV transmission occurred in 9% of infants born to HCV/HIV-coinfected women, most of whom were on ART. No HCV transmissions occurred in infants born to women with HCV viral loads of <5 log IU/mL.

**HIV Transmission**

In the absence of ART, maternal HCV/HIV coinfection also may increase the risk of perinatal transmission of HIV. The risk of perinatal HIV transmission can likely 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**

Few data exist on the optimal management of pregnant women with HCV/HIV coinfection. Recommendations for ART use during pregnancy for treatment of HIV and prevention of perinatal transmission are the same for women who have HCV/HIV coinfection as for those with HIV monoinfection (see Hepatitis C Virus/HIV Coinfection in the Adult and Adolescent Guidelines). 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 recommended HIV RNA monitoring during pregnancy.

**Hepatitis C Virus-Specific Therapy in Pregnancy**

All currently available DAAs lack sufficient safety data to be recommended 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. Some DAA regimens are approved for use with ribavirin in specific nonpregnant populations, due to the suboptimal treatment responses observed with the use of DAAs alone. Any treatment regimens that include ribavirin are contraindicated in pregnant women due to 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. Pregnancies that
occur in women taking ribavirin should be reported to the Ribavirin Pregnancy Registry (online or by phone at 800-593-2214)

There are many interferon-free DAA regimens that have been approved for the treatment of HCV. Determining the optimal regimen for an individual patient is based on many factors, including HCV genotype, prior treatment experience, and stage of liver disease (e.g., compensated or decompensated cirrhosis). There are three main classes of DAAs:

- **NS5A inhibitors**: daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, velpatasvir
- **NS5B polymerase inhibitors**: dasabuvir, sofosbuvir
- **NS3/4A protease inhibitors**: glecaprevir, grazoprevir, paritaprevir, simeprevir, voxilaprevir.

DAAs are not yet recommended for use in pregnancy because of the lack of PK and safety data; at least one small PK study that is investigating the use of ledipasvir/sofosbuvir in pregnancy is ongoing. In addition, potential drug interactions exist between these 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 HCV/HIV drug interactions, see the Adult and Adolescent Guidelines, the Adult and Adolescent Opportunistic Infection Guidelines, HCVGuidelines.org, and the HEP Drug Interaction Checker.

**Monitoring of Women with HCV/HIV Coinfection during Pregnancy**

An elevation in hepatic enzymes following initiation of ART can occur in women with HCV/HIV coinfection—particularly in those with low CD4 cell 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 infection may increase the hepatotoxic risk of certain ARV agents, specifically protease inhibitors and nevirapine. HCV monoinfection may increase the risk of intrahepatic cholestasis of pregnancy; there are no data about the risk among women with HCV/HIV coinfection. Pregnant women with HCV/HIV coinfection should be counseled about signs and symptoms of liver toxicity, and transaminase levels should be assessed 1 month after initiation of ART and then every 3 months thereafter. 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 temporarily discontinued. Differentiating between a flare of HCV disease associated with immune reconstitution and drug toxicity often can be difficult; therefore, consulting an expert in HCV/HIV coinfection is strongly recommended.

Rates of preterm delivery are also high among HCV/HIV-coinfected women. 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 29% among women with HCV RNA <5 log IU/mL and 43% among women with HCV RNA >5 log IU/mL; the difference in rates of preterm delivery was not statistically significant between the two groups. Women with preterm delivery had significantly higher levels of HCV RNA than those who delivered at term. HCV infection in pregnancy may also be associated with increased risks for gestational diabetes, small-for-gestational-age infants, and low birth weight infants. Although no obstetric guidelines suggest increased monitoring among women with HCV infection for diabetes or infant growth, knowledge of these increased risks may inform clinical care.

**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 transmission of HCV. Thus, the general recommendations for mode of delivery are the same in women with HCV/HIV coinfection as in those with HIV infection alone (see Transmission and Mode of Delivery).

**Evaluation of Infants Exposed to HCV**

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.\textsuperscript{42} Sensitivity of HCV RNA testing is low at birth, and viremia can be intermittent or infection may resolve spontaneously; 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.\textsuperscript{43} Uptake of HCV testing is very low for HCV-exposed infants; therefore, it is important for providers to counsel patients about the need for pediatric follow-up and testing during the first few years of life.\textsuperscript{44,45} The Pediatric Opportunistic Infection Guidelines provide further details about diagnostic evaluation of HCV-exposed infants.

References


