Special Populations: Hepatitis C Virus/HIV Coinfection

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Panel's Recommendations

• All pregnant people with HIV should be screened during the current pregnancy for hepatitis C virus (HCV) infection, ideally at the initial prenatal visit (AIII).
  o HCV antibody testing, with confirmatory HCV RNA polymerase chain reaction testing if the antibody test is positive, is recommended for screening (AI).
  o HCV screening could be repeated later in pregnancy in people 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).
• For people who are known to be HCV antibody-positive, HCV RNA and liver function tests should be checked at initiation of prenatal care to assess risk of HCV perinatal transmission and severity of liver disease (AIII).
• Pregnant people, including those with HIV/HCV coinfection, should be tested for hepatitis B surface antigen during each pregnancy, preferably in the first trimester, even if vaccinated or tested previously. If they are negative and lack evidence of immunity, they should receive the hepatitis B virus vaccine series (see Hepatitis B Virus/HIV Coinfection) (AIII).
• Pregnant people 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 immunoglobulin G [IgG] or total antibody [IgG and immunoglobulin M]), they should receive the HAV vaccine series (AIII).
• 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 agents in people who are pregnant. If considering initiating HCV treatment in a pregnant person with HCV/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 pregnant people with HIV, including those who have HCV coinfection (AIII).
• Pregnant people 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).
• HCV treatment with direct-acting antiviral agents should be recommended and offered for people with HCV postpartum (AI).
• In people with HCV infection, 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).
• HCV/HIV coinfection is not an independent indication for cesarean delivery (see Intrapartum Care for People with HIV) (AIII).
• Infants born to people 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 hepatitis C virus (HCV)/HIV coinfection in pregnancy is complex, and none of the approved HCV direct-acting antivirals (DAAs) have been evaluated fully for use in people who are pregnant; thus, consultation with an expert in HIV and HCV infection **is strongly recommended** when managing HCV during pregnancy.

For additional information on 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 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

All pregnant people with HIV should be screened for HCV infection at entry into general HIV care and during each pregnancy, ideally at initiation of prenatal care. For individuals who are known to be HCV antibody–positive, HCV RNA and liver function tests should be checked at initiation of prenatal care to assess risk of perinatal transmission of HCV and severity of liver disease. Consultation with an expert is recommended for follow-up testing and/or referral for treatment postpartum, as appropriate.

The primary reasons for HCV testing during pregnancy are—

- To identify pregnant people 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). (If a trial of HCV treatment during pregnancy is available, voluntary enrollment should be offered.)
- To monitor for HCV-related hepatotoxicity, which has been associated with the use of antiretroviral (ARV) drugs in women with HCV/HIV coinfection.[1]
- To monitor for preterm birth, which has been associated with HCV/HIV coinfection in pregnant women.[2-5]
- To ensure appropriate follow-up and evaluation of infants who were exposed to HCV.

The observed prevalence for HCV infection was 2% to 12% in European cohorts of pregnant women with HIV[4] and 3.8% among women with HIV in New York State.[6] 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.[5,7-14]

The Society for Maternal-Fetal Medicine and the American College of Obstetricians and Gynecologists recommend repeating HCV testing later in pregnancy for individuals 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).[15] The partners of all people 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 transmitted infrequently 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 Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV).

Available DAAs have improved HCV therapy dramatically; it is now possible to cure HCV infection in most patients.[16] Current HCV treatment guidelines recommend therapy for nearly all patients with HCV infection. However, the management of HCV/HIV coinfection during pregnancy is complex. A Phase 1 study evaluated the safety and pharmacokinetics (PKs) of sofosbuvir/ledipasvir in pregnancy.[17] Safety data of DAAs in pregnancy are still limited. Ribavirin, although it is no longer commonly used for the treatment of HCV, is contraindicated in pregnancy.[18] If considering HCV treatment for a pregnant person, consultation with an expert in HIV and HCV is strongly recommended.

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 people in the United States should be screened for HCV at each pregnancy, except in settings where the prevalence of HCV infection is <0.1%.[19,20] 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.[21,22] Individuals who have a positive HCV antibody test should undergo confirmatory testing with a quantitative plasma HCV RNA assay. Many laboratories now perform reflex RNA testing for individuals who test positive for HCV antibodies. Pregnant people also should 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).[23] At the initial prenatal visit, pregnant people who are known to be HCV antibody–positive should have a quantitative plasma HCV RNA assay and liver function tests performed to assess the risk of transmission of HCV to the infant and severity of liver disease.[16]

Because of the added risk of hepatic decompensation from acute infection with any viral hepatitis, people with HCV infection also should be screened for both hepatitis A virus (HAV) and hepatitis B virus (HBV). People with chronic HCV infection who have not already received the HAV vaccine series should be screened for immunity to HAV (either immunoglobulin G [IgG] alone or IgG and immunoglobulin M together). If they screen negative for HAV antibodies, they should receive the HAV vaccine series. Antibody responses to the HAV vaccine should be assessed 1 month after vaccination is complete. If anti-HAV IgG is negative, people should be revaccinated[24] when the CD4 T lymphocyte (CD4) cell count is >200 cells/mm^3. People with HCV/HIV coinfection who screen negative for HBV and lack HBV immunity (i.e., they are hepatitis B surface antigen negative, hepatitis B core antibody negative, and hepatitis B surface antibody [HBsAb] negative) should receive the appropriate HBV vaccine series. People with HCV/HIV coinfection who are HBsAb negative despite receiving the HBV vaccine series may benefit from revaccination (see Hepatitis B Virus/HIV Coinfection).[25]

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

Although the HCV viral load tends to rise in the third trimester, pregnancy does not appear to influence the course of HCV infection clinically. People with chronic HCV generally do well during pregnancy, provided that they have not progressed to decompensated cirrhosis.[26,27]

HCV Transmission to the Infant

About 6% of infants born to women with HCV acquire HCV infection.[22] 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 (7% to 20% transmission risk) than among women with HCV mono-infection.[28-32] The 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.[3,33,34] Early and sustained control of HIV viremia with antiretroviral therapy (ART), however, could reduce the risk of HCV transmission to infants.[27,35-37] A European study of perinatal HCV transmission found that the use of effective ART for HIV was associated with a trend toward reduced rates of HCV transmission (odds ratio [OR] 0.26; 95% confidence interval [CI], 0.07–1.01).[35] In an Italian cohort, [3] 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. In a re-analysis of data from three prospective European cohorts conducted between 1994 and 2004, HCV transmission rates were estimated as about 24% higher than previously thought, but rates of spontaneous HCV clearance in the children were also higher, resulting in clearance–net transmission rates of 2.4% (1.1% to 4.1%) in women with HCV mono-infection and 4.1% (1.7% to 7.3%) in women with HIV/HCV coinfection.[38]

HIV Transmission to the Infant

In the absence of ART, maternal HCV/HIV coinfection can increase the risk of perinatal HIV transmission.[39,40] The risk of perinatal HIV transmission can be reduced in pregnant people with HCV/HIV coinfection by following the standard recommendations for ART that are in place for all people with HIV.

Impact of HCV on HIV Management

Data are limited on the optimal management of pregnant people with HCV/HIV coinfection. Recommendations on the use of ART during pregnancy for treating HIV and preventing perinatal HIV transmission are the same for people with HCV/HIV coinfection as for those with HIV mono-infection (see Antepartum Care of Individuals with HIV). In one Canadian study, HCV/HIV coinfection was associated with an increased risk of HIV viral load increases near delivery among women who were on previously effective ART. Although the authors suggest that additional factors (e.g., adherence) may have played a role, these findings support the need to follow recommendations for HIV RNA monitoring during pregnancy.[41]

HCV-Specific Therapy in Pregnancy

Several DAA regimens have been approved for the treatment of HCV. At present, all currently available DAAs lack sufficient safety data to be recommended for use during pregnancy, but general considerations for treatment are presented in this section.

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:

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

In the past, most anti-HCV therapy regimens 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.[42] Pegylated interferon is now used rarely for treatment of HCV. DAA regimens with ribavirin are indicated for certain patient populations. Any treatment regimens that include ribavirin are **contraindicated** for use during pregnancy 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 also applies to pregnancies of partners of men taking ribavirin.[16]

DAAs are not yet recommended for use in pregnancy because of the lack of PK and safety data; one small PK study investigating the use of sofosbuvir/ledipasvir in eight pregnant women with HCV alone demonstrated 100% virologic suppression and no safety concerns.[17] This open-label, Phase 1 study of sofosbuvir/ledipasvir started between 23 and 24 weeks' gestation in eight women with genotype 1 HCV infection showed that ledipasvir and sofosbuvir exposures were similar in the pregnant women and the nonpregnant reference group and the drug combination was safe.[17] Similarly, a small case series of 15 pregnant women treated with sofosbuvir/ledipasvir reported 100% virologic suppression at 12 weeks and no early safety concerns in the women or their infants.[43] An open-label, Phase 1 study of the pharmacokinetics of sofosbuvir/velpatasvir started between 23 and 25 weeks' gestation reported results in 11 HIV-negative pregnant women with chronic HCV infection. All 10 participants that completed treatment had undetectable HCV RNA at delivery, and all the infants that followed up (n = 7) had undetectable HCV RNA. Nine mothers experienced adverse events related to sofosbuvir/velpatasvir; however, only one adverse event was greater than grade 2 (vomiting) and resulted in discontinuation of sofosbuvir/velpatasvir.[44] A multicenter study (NCT05140941) to evaluate sofosbuvir/velpatasvir safety and efficacy in pregnancy is underway. Another small case series reported results of two pregnant women and one child with severe chronic HCV started on a 12-week course of sofosbuvir/ledipasvir initiated at 31 weeks' gestation, sofosbuvir/velpatasvir initiated at 26 weeks' gestation, and sofosbuvir/ledipasvir initiated at 1.2 years of life, respectively. All three patients were safely cured of HCV with favorable tolerance, and the two newborns were breastfeeding and consistently negative for anti-HCV antibody during the 1-year follow-up after birth.[45]

Pregnant people with HCV/HIV coinfection should be started on HCV treatment with DAAs postpartum.[16] Drug interactions exist between the DAA 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 People with HCV/HIV Coinfection During Pregnancy

Hepatic enzyme levels can increase after ART is initiated in people 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 mono-infection may increase the risk of intrahepatic cholestasis of pregnancy[46]; this risk also is higher among people with HCV/HIV coinfection than among individuals with HIV infection alone.[4] Pregnant patients 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.[47] Spontaneous clearance of HCV can occur postpartum.[47-50] As a result, the AASLD and the IDSA recommend that women have their HCV RNA reevaluated after delivery, particularly if they are being assessed for initiation of therapy with DAA.[16]

Rates of preterm delivery are high among individuals 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). However, women with preterm delivery had significantly higher levels of HCV RNA than those who delivered at term.[3] 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.[4] A study of 339 HIV/HCV coinfected pregnant women from Spain demonstrated a 50% rate of preterm delivery.[32]

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%, $P < 0.01$).[5]

HCV infection in pregnancy may be associated with increased risks for gestational diabetes, small-for-gestational-age infants, and low birth weight infants.[9,51] Although no obstetric guidelines currently suggest that persons with HCV infection should be monitored more frequently for diabetes, preterm birth, or fetal growth during pregnancy,[52] knowledge of these increased risks may inform clinical care.[15]

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.[35,53-55] Thus, the general recommendations for mode of delivery are the same for people with HCV/HIV coinfection as for those with HIV infection alone (see Intrapartum Care for People with HIV).

Evaluation of Infants Exposed to HCV

Infants born to people 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.[56] Sensitivity of HCV RNA testing is low at birth, and viremia can be intermittent or

infection may resolve spontaneously[9,38,57,58]; 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.[59] Rate of HCV testing is very low for infants who were exposed to HCV[60]; 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.[5,61-64] The Pediatric Opportunistic Infection Guidelines and these new CDC Guidelines provide further details about the diagnostic evaluation of infants who were exposed to HCV.

Transmission of HCV to the infant is not increased with breastfeeding.[65] For guidance about infant feeding for people with HIV, see Infant Feeding for Individuals with HIV in the United States.

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