HIV/Hepatitis C Virus Coinfection  (Last updated November 14, 2017; last reviewed November 14, 2017)

Panel’s Recommendations

- All pregnant women living with HIV should be screened during the current pregnancy for hepatitis B virus (HBV) unless they are known to have HIV/HBV coinfection and for hepatitis C virus (HCV) infection unless they are known to have HIV/HCV coinfection (see HIV/HBV Coinfection section) (AIII).

- All pregnant women living 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).

- Women with chronic 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 antibody, they should receive HAV vaccine, which is safe to use in pregnancy (AIII).

- If considering initiation or continuation of HCV treatment in a pregnant woman with HIV coinfection, consultation with an expert in HIV and HCV is strongly recommended (AIII).

- Recommendations for antiretroviral (ARV) drug use during pregnancy are the same for women living with HIV whether they have chronic HCV or not (AIII).

- Pregnant women with HIV/HCV coinfection receiving ARV drugs should be counseled about signs and symptoms of liver toxicity, and liver transaminases should be assessed 1 month following initiation of ARV drugs and at least every 3 months thereafter during pregnancy (BIII).

- Decisions concerning mode of delivery in pregnant women with HIV/HCV coinfection should be based on standard obstetric and HIV-related indications alone; HCV coinfection does not necessitate cesarean delivery, if not otherwise indicated (see Intrapartum Care) (AIII).

- Infants born to women with HIV/HCV coinfection should be evaluated for HCV infection (AIII). The specific type and timing of assays for HCV in children should be performed 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 Infections Guidelines, HIV/Hepatitis C Coinfection in the Adult and Adolescent Antiretroviral Guidelines and Hepatitis C Virus Infection in the Adult and Adolescent Opportunistic Infections Guidelines. The American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, and International Antiviral Society-USA maintains updated information about treating patients with HIV/HCV coinfection. The guidelines are available online at HCVguidelines.org. The management of HIV/HCV coinfection in pregnancy is complex and none of the approved HCV oral medications/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 if treatment of HCV infection during pregnancy is being considered.

Screening and Vaccination

All pregnant women living with HIV should be screened for HCV at entry into general HIV care and during each pregnancy for hepatitis B virus (HBV) unless they are known to have HIV/HBV coinfection, and for hepatitis C virus (HCV) infection unless they are known to have HIV/HCV coinfection. Among women with HIV, the observed HCV seroprevalence rate was 12% in a European cohort 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 U.S., the prevalence of HCV among women of childbearing age in the general population has increased substantially in recent years. The male partners of all patients with HIV/HCV coinfection should be referred for both HIV and hepatitis counseling and testing to prevent horizontal transmission of HIV as well as HCV from women to their male partners. All 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 HIV/HCV coinfection in pregnancy is complex, however. Although one study is now evaluating HCV treatment in pregnancy, none of the approved DAAs have been fully evaluated in pregnant women; the use of ribavirin, although rarely required with DAAs, is also contraindicated in pregnancy. If considering initiation or continuation of treatment of HCV in a pregnant woman with HIV/HCV coinfection, 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 many 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, therefore, are:

• To identify women with HIV/HCV 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 potential for increased risk of preterm birth with HCV infection in women with HIV/HCV coinfection;
• To ensure vaccination against other viral hepatitis (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 antibody is recommended for all individuals living with HIV, including pregnant women. 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. 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.11

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; if they screen negative for HAV antibody, they should receive the HAV vaccine series. Although the safety of HAV vaccination during pregnancy has not been directly evaluated, HAV vaccine is produced from inactivated HAV and the theoretical risk to the developing fetus is expected to be low.12 In women with CD4 T lymphocyte (CD4) count <200 cells/mm$^3$, 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/mm$^3$.13 Women with HIV/HCV coinfection who screen negative for HBV (i.e., hepatitis B surface antigen [HBsAg]-negative, hepatitis B core antibody-negative, and hepatitis B surface antibody-negative) should receive the HBV vaccine series. Women with HIV/HCV coinfection who are HBsAb negative despite having received the HBV vaccine series may benefit from revaccination (see HIV/HBV).14 There is no apparent risk to developing fetuses from hepatitis B vaccination, as current vaccines contain noninfectious HBsAg.12

Impact of HIV/HCV 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. Women with chronic HCV generally do well during pregnancy, provided that
they have not progressed to decompensated cirrhosis.\textsuperscript{15,16} \textbf{HCV infection may increase the risk of intrahepatic cholestasis of pregnancy},\textsuperscript{15} there are no data about the risk among women with HIV/HCV coinfection.

In most studies of women with HIV/HCV coinfection who are not receiving treatment for either infection, the incidence of perinatal HCV transmission is approximately 2-fold higher among women with HIV/HCV coinfection (10% to 20% transmission risk), compared to HCV mono-infection.\textsuperscript{18-21} These higher transmission rates are likely related to an increase in HCV viremia and/or other HIV-related impact on HCV disease activity.\textsuperscript{10,22} However, early and sustained control of HIV viremia with ART may reduce HCV transmission to infants.\textsuperscript{16,23,24} A European study of perinatal transmission of HCV found that use of effective ART for HIV was associated with a strong trend toward reduced HCV transmission (odds ratio 0.26, 95% CI, 0.07–1.01).\textsuperscript{23} In an Italian cohort, HCV transmission in infants of mostly ART-treated HIV/HCV-coinfected women occurred in 9%, but no HCV transmissions occurred among women with HCV viral loads <5 log IU/mL.\textsuperscript{10}

In the absence of ART, maternal HIV/HCV coinfection also may increase the risk of perinatal transmission of HIV.\textsuperscript{25,26} Perinatal HIV transmission will likely be reduced in pregnant women with HIV/HCV coinfection by following standard recommendations for ART for all women living with HIV.

\textbf{Impact of Hepatitis C Virus on HIV Management}

Few data exist on the optimal management of pregnant women with HIV/HCV coinfection. Recommendations for ARV drug use during pregnancy for treatment of HIV and prevention of perinatal transmission are the same for women who have HIV/HCV coinfection as for those with HIV monoinfection (see \href{https://aidsinfo.nih.gov/guidelines/}{HIV/Hepatitis C Coinfection} in the \href{https://aidsinfo.nih.gov/guidelines/}{Adult and Adolescent Antiretroviral Guidelines}).

\textbf{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.\textsuperscript{27} Some DAA regimens are approved for use with ribavirin in specific non-pregnant populations, due to suboptimal treatment response with DAAs alone. Combination regimens of DAAs plus ribavirin are \textbf{contraindicated} in pregnant women due to 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. Concerns have also been raised about potential mutagenic effects of ribavirin in the offspring of men taking ribavirin before conception because of possible accumulation of ribavirin in spermatzoa. However, in a small number of inadvertent pregnancies occurring in partners of men receiving ribavirin therapy, no adverse outcomes were reported.\textsuperscript{28} Pregnancies that occur in women taking ribavirin should be reported to the Ribavirin Pregnancy Registry (800-593-2214 or \texttt{http://www.ribavirinpregnancyregistry.com}).

There are many interferon-free DAA regimens approved for the treatment of HCV. Determination of the optimal regimen for an individual patient is based on many factors, including HCV genotype (GT), prior treatment experience, and stage of liver disease (e.g., compensated or decompensated cirrhosis). There are three main classes of DAAs:\textsuperscript{29,30}

- \textbf{NS5A inhibitors:} Daclatasvir, elbasvir, ledipasvir, ombitasvir, pribrentasvir, and velpatasvir
- \textbf{NS5B polymerase inhibitors:} Dasabuvir and sofosbuvir
- \textbf{NS3/4A protease inhibitors:} Glecaprevir, grazoprevir, paritaprevir, simeprevir, and voxilaprevir

DAAs are not yet recommended for use in pregnancy because of the lack of pharmacokinetic and safety data, although at least one study of ledipasvir/sofosbuvir in pregnancy is ongoing (see \texttt{https://clinicaltrials.gov/ct2/show/NCT02683003}). 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 ARVs and anti-HCV...
medications. For detailed information on HIV/HCV drug interactions, see Adult and Adolescent Guidelines, Adult and Adolescent Opportunistic Infections Guidelines and the HCV treatment guidelines (http://www.hcvguidelines.org) or http://www.hep-druginteractions.org/.

Monitoring of Women with HIV/HCV Coinfection during Pregnancy
An elevation in hepatic enzymes following initiation of ART can occur in women with HIV/HCV 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. HCV infection may increase the hepatotoxic risk of certain ARV agents, specifically PIs and nevirapine. Pregnant women with HIV/HCV coinfection should be counseled about signs and symptoms of liver toxicity, and transaminase levels should be assessed 1 month after initiation of ARV drugs and then every 3 months thereafter. If hepatic toxicity occurs, consideration may need to be given to substituting 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, consultation with an expert in HIV and HCV coinfection is strongly recommended.

Rates of preterm delivery are also high among HIV/HCV-coinfected women. In an Italian cohort of mostly ART-treated women with HIV/HCV coinfection, preterm delivery occurred in 41% of women overall (29% of women with HCV RNA <5 log IU/ml and 43% of women with HCV RNA >5 log IU/ml; the difference between the two groups was not statistically significant, although women with preterm delivery had statistically significantly higher levels of HCV RNA than those who delivered at term).

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 HIV/HCV coinfection as in those with HIV infection alone (see Intrapartum Care).

Evaluation of Infants Exposed to HCV
Infants born to women with HIV/HCV coinfection should be assessed for HCV infection. Testing with anti-HCV antibody should be performed after age 18 months, when maternal anti-HCV antibody has waned. Sensitivity of HCV RNA testing is low at birth and viremia can be intermittent; 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. The Pediatric Opportunistic Infections Guidelines provide further details about diagnostic evaluation of HCV-exposed infants.

References


23. European Paediatric Hepatitis C Virus Network. A significant sex--but not elective cesarean section--effect on mother-


