HIV/Hepatitis B 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) and 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/Hepatitis C Virus Coinfection) (AII).

- All pregnant women living with HIV who screen negative for HBV (i.e., HBV surface antigen-negative, HBV core antibody-negative, and HBV surface antibody-negative) should receive the HBV vaccine series (AII).

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

- All pregnant and postpartum women with HIV/HBV coinfection should receive antiretroviral therapy (ART). Antepartum ART in pregnant women with HIV/HBV coinfection should include tenofovir disoproxil fumarate (TDF) plus lamivudine or emtricitabine (AI). If women with HIV/HBV are virally suppressed on a tenofovir alafenamide (TAF) plus lamivudine or emtricitabine-based ART and become pregnant, they can be offered the choice of continuing that ART regimen or switching TAF to TDF in their ART regimen (BIII).

- Pregnant women with HIV/HBV coinfection receiving antiretroviral (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).

- Women with chronic HBV should be counseled on the importance of continuing anti-HBV medications indefinitely, both during and after pregnancy. If ARV drugs that include anti-HBV activity are discontinued in women with HIV/HBV coinfection, frequent monitoring of liver function tests for potential exacerbation of HBV infection is recommended, with prompt re-initiation of treatment for HBV if a flare is suspected (BIII).

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

- Within 12 hours of birth, infants born to women with HBV infection should receive hepatitis B immune globulin and the first dose of the HBV vaccine series (AII).

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 B virus (HBV) and HIV, see HIV/Hepatitis B (HBV) Coinfection in the Adult and Adolescent Guidelines and Hepatitis B Virus Infection in the Adult and Adolescent OI Guidelines. The management of HIV/HBV coinfection in pregnancy is complex and consultation with an expert in HIV and HBV infection is strongly recommended.

Screening and Vaccination

All women living with HIV should be screened for HBV and hepatitis C virus (HCV) at entry into general HIV care. All pregnant women living with HIV should be screened during each pregnancy for HBV unless they are known to have HIV/HBV coinfection and for HCV unless they are known to have HIV/HCV coinfection. Screening for HBV should include hepatitis B surface antigen [HBsAg], hepatitis B core antibody [anti-HBc], and hepatitis B surface antibody [anti-HBs]. Women who test positive for HBsAg should have follow-up testing that includes liver function tests, prothrombin time, HB e antigen, HB e antibody, and HBV DNA polymerase chain reaction.

To prevent horizontal transmission of HIV and HBV from women with HIV/HBV coinfection to their male partners, their sexual contacts should be counseled and tested for HIV and HBV. All HBV susceptible contacts should receive the HBV vaccine series, and all partners who do not have HIV infection should be counseled about condom use and the potential benefits and risks of starting pre-exposure prophylaxis.
Pregnant women living with HIV who screen negative for HBV (i.e., HBsAg-negative, anti-HBc-negative, and anti-HBs-negative) should receive the HBV vaccine series. Women living with HIV with remote HBV infection and current isolated anti-HBc antibody (negative HBV DNA, HBsAg, and anti-HBs) may have lost immunity to HBV and should be vaccinated. Women with HIV infection whose anti-HBs titers are below 10 IU/mL despite having received the HBV vaccine series should receive a second HBV vaccine series; some experts advise using a double dose of HBV vaccine (i.e., a 40-mg dose) and delaying revaccination until after a sustained increase in CD4 T lymphocyte (CD4) cell count >350 cells/mm³ is achieved on antiretroviral therapy (ART). There is no evidence of adverse events from hepatitis B vaccine for developing fetuses or newborns, and current vaccines contain noninfectious HBsAg. Anti-HBs titers should be obtained 1 month after completion of the vaccine series in patients with HIV infection; if anti-HBs titers are below 10 IU/mL, a second vaccine series is recommended (some specialists delay revaccination until after a sustained increase in CD4 cell count >350 cells/mm³ is achieved on ART). There is no consensus for management of patients whose anti-HBs titers remain below 10 IU/mL following a second HBV vaccine series.

A positive test for anti-HBc alone can be false-positive; alternatively, it may signify remote infection with subsequent loss of anti-HBs antibody or longstanding chronic HBV infection with loss of surface antigen (“occult” HBV infection, which can be confirmed by detection of HBV DNA). Incidence of HBV viremia in patients with HIV infection with the isolated anti-HBc pattern ranges from 1% to 36%. The clinical significance of isolated anti-HBc is unknown. Some experts recommend that individuals with HIV infection and anti-HBc alone be tested for HBV DNA to inform decisions about vaccination for HBV and treatment with antiretroviral (ARV) drugs. It may also be important to check HBV DNA levels in women with isolated anti-HBc before ARVs are initiated because of the risk of a paradoxical exacerbation of HBV and the occurrence of immune reconstitution inflammatory syndrome (IRIS). Pregnant women with HIV infection with isolated anti-HBc and occult HBV infection typically have very low levels of HBV DNA and are thought to be at extremely low risk of transmitting HBV to their infants.

Women who have HBV infection and who have not already received the HAV vaccine series should also be screened for hepatitis A virus (HAV) using antibody testing for immunoglobulin G (IgG) because of the added risk of hepatic decompensation from acute infection with HAV in individuals with chronic HBV (note that some labs only provide a combined IgG and IgM HAV titer, which is acceptable). Women with chronic HBV infection who have not already received the HAV vaccine series and are HAV IgG antibody-negative should receive the HAV vaccine series, which is safe in pregnancy. Responses to the HAV vaccine are reduced in patients living with HIV with CD4 counts <200 cells/mm³. Antibody response should be assessed in such patients 1 month after HAV vaccine series is complete. If HAV antibody immunoglobulin (HAV Ab IgG) is negative, patients should be revaccinated when the CD4 cell count is >200 cells/mm³. Women who have already received the HAV vaccine series when their CD4 cell count was ≥200 cells/mm³ do not need to be revaccinated for HAV because they are likely protected (even if they have undetectable HAV IgG levels using commercially available assays). 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.

**Therapy for HIV and Hepatitis B Virus in Pregnancy**

An ART regimen that includes drugs active against both HIV and HBV is recommended for all individuals with HIV/HBV coinfection, including all pregnant women. Initiation of ART may be associated with reactivation of HBV and development of IRIS, particularly in patients with high HBV DNA levels and more severe liver disease. Risk of miscarriage and preterm labor and delivery may be increased with acute HBV infection (see Hepatitis B Infection in the Adult and Adolescent OI Guidelines).

In addition, use of ARV drugs with anti-HBV activity during pregnancy lowers HBV viremia, potentially further reducing the risk of HBV transmission beyond the reduction seen with neonatal prophylaxis with hepatitis B immune globulin (HBIG) and hepatitis B vaccine. High maternal HBV DNA levels are strongly correlated with perinatal HBV transmission and with failures of HBV passive-active immunoprophylaxis.
Several studies and a meta-analysis suggest that lamivudine or telbivudine may reduce the risk of perinatal transmission of HBV if given during the third trimester to HIV-seronegative women with HBV infection and high HBV DNA levels. In addition to HBV viral load, the presence of certain HBV variants is also a risk factor for failure of HBV prophylaxis. In a study of 2,048 pregnant women living with HIV in Malawi, 103 women (5%) were HBsAg-positive, 70 of whom also had HBV viremia. Nearly 10% of infants born to mothers with HIV/HBV coinfection had HBV DNA detected by age 48 weeks despite being immunized according to national recommendations at ages 6, 10, and 14 weeks.

Lamivudine, TDF, TAF (a prodrug of TDF), and emtricitabine have activity against both HIV and HBV. TDF or TAF with emtricitabine or lamivudine is the preferred dual nucleoside reverse transcriptase inhibitor backbone in women with HIV/HBV coinfection. However, only lamivudine, TDF, and emtricitabine are recommended for use in pregnancy (see Table 6). There is no pharmacokinetic information and there are few reports of use of TAF in human pregnancy. In animal studies, there were no developmental effects when TAF was administered during the period of organogenesis at exposure equal to or 51 times the usual therapeutic dosage (rats and rabbits, respectively).

Cases of exposure during pregnancy to any of the ARV drugs and HBV drugs listed should be reported to the Antiretroviral Pregnancy Registry (800-258-4263; http://www.apregistry.com).

Some pregnant women may already be receiving TAF-containing ART prior to pregnancy. TAF is effective against HBV in non-pregnant adults but has not been studied in pregnancy. In this case, the woman can be offered a choice of continuing that ART regimen or switching TAF to TDF in their ART regimen. Please see individual drug sections for TDF, TAF, emtricitabine, and lamivudine for detailed review of safety, pharmacologic, and other clinical data for use in pregnancy.

Consultation with an expert in HIV and HBV is strongly recommended for a pregnant woman with HIV/HBV coinfection who continues to have detectable HBV DNA viremia despite receiving an ART regimen with 2 anti-HBV nucleos(t)ides.

Several other antivirals with activity against HBV, including entecavir, adefovir, and telbivudine, have not been well evaluated in pregnancy. Entecavir is associated with skeletal anomalies in rats and rabbits but only at doses high enough to cause toxicity to the mother. Seventy-nine cases of exposure to entecavir, 77 during the first trimester and 2 in the second trimester, have been reported to the Antiretroviral Pregnancy Registry with no birth defects noted, but this number of exposures is too few to assess overall risk. Seventy-nine cases of exposure to telbivudine have been reported to the Antiretroviral Pregnancy Registry, with 68 during the first trimester, 7 in the second trimester, and 4 in the third trimester. Telbivudine was given during the third trimester to 135 women with HBV infection and without HIV infection; it was well tolerated, and perinatal transmission of HBV was lower in telbivudine-treated mothers than in the comparison group not on telbivudine (0% vs. 8%; P = 0.002). In a recent systematic review and meta-analysis of single-drug anti-HBV therapy during pregnancy in chronic HBV monoinfection, antiviral therapy reduced perinatal transmission with no significant differences in congenital malformation rate, prematurity rate, and Apgar scores. TDF, lamivudine, or telbivudine all improved maternal HBV viral suppression at delivery with no significant difference in postpartum hemorrhage, cesarean section or creatinine kinases levels.

For pregnant women with HIV/HBV coinfection, both entecavir and telbivudine should be administered only in addition to a fully suppressive ART regimen for HIV. Because these other anti-HBV drugs also have weak activity against HIV, their use in the absence of a fully suppressive ART regimen may lead to development of cross-resistance to other ARV drugs (e.g., entecavir can select for the M184V mutation, which confers HIV resistance to lamivudine and emtricitabine). Although adefovir does not have significant anti-HIV activity, it is not recommended for treatment of HBV because it is less potent and has a higher risk of selecting for resistance mutations than the preferred HBV nucleos(t)ides.

Interferon alfa and PEGylated interferon alfa are not recommended for use in pregnancy and should be used only if the potential benefits outweigh the potential risks. Although interferons are not teratogenic, they are abortifacient at high doses in monkeys and should not be used in pregnant women because of their direct...
antigrowth and antiproliferative effects.\textsuperscript{34}

**Monitoring Women With HIV/Hepatitis B Virus Coinfection During Pregnancy**

Prior to initiation of ARV drugs active against HBV, a baseline HBV DNA level should be measured. After initiation of therapy, HBV DNA should be monitored every 12 weeks to ensure adequate response to therapy (see Adult and Adolescent OI Guidelines).

Following initiation of ART, an elevation in hepatic enzymes can occur in women with HIV/HBV coinfection—particularly those with low CD4 counts at the time of treatment initiation—as a result of an immune-mediated flare in HBV disease triggered by immune reconstitution with effective HIV therapy. HBV infection also can increase hepatotoxic risk of certain ARV drugs, specifically protease inhibitors and nevirapine. Pregnant women with HIV/HBV coinfection should be counseled about signs and symptoms of liver toxicity, and transaminases should be assessed 1 month following initiation of ARV drugs and at least every 3 months thereafter. If hepatic toxicity occurs, it may be necessary to consider substituting a less hepatotoxic regimen or, if clinical symptoms or significant elevations of transaminases occur, drugs may need to be temporarily discontinued. Differentiating between a flare in HBV disease due to immune reconstitution and drug toxicity often can be difficult, and consultation with an expert in HIV and HBV coinfection is strongly recommended. Because TDF has potential to cause renal toxicity, kidney function also should be monitored regularly in pregnant women as in non-pregnant adults.

Once HBV therapy with anti-HBV nucleos(t)ide analogs is initiated, lifelong treatment is recommended.\textsuperscript{1,2} Discontinuation of anti-HBV agents may be associated with hepatocellular damage resulting from reactivation of HBV. If anti-HBV-active drugs are discontinued, serum transaminase levels should be monitored every 6 weeks for 3 months, then every 3 to 6 months thereafter, with prompt re-initiation of HBV treatment if a flare is suspected.\textsuperscript{2}

**Mode of Delivery**

Decisions concerning mode of delivery in pregnant women with HIV/HBV coinfection should be based on standard obstetric and HIV-related indications alone (see Intrapartum Care). There are no data on the role of cesarean delivery in reducing perinatal transmission of HBV in women with HIV/HBV coinfection. Current guidelines for women with HBV monoinfection advise that cesarean delivery is not indicated to prevent perinatal transmission of HBV.\textsuperscript{35-37}

**Evaluating and Managing Infants Exposed to Hepatitis B Virus**

Within 12 hours of birth, all infants born to mothers with chronic HBV infection, including those with HIV, should receive HBIG and the first dose of the HBV vaccination series. For infants weighing ≥2,000 g at birth, the second and final doses of the vaccine series should be administered at ages 1 and 6 months, respectively. For infants with birth weights <2,000 g at birth, do not count the birth dose as part of the vaccine series and administer 3 additional doses at ages 1, 2–3, and 6 months.\textsuperscript{38,39} This regimen is >95% effective in preventing HBV infection in these infants. ART that includes nucleos(t)ides with anti-HBV activity will result in low or suppressed HBV viral loads near delivery, which should further reduce risk of HBV perinatal transmission in women with HIV/HBV coinfection.

Infant post-vaccination testing for anti-HBs and HBsAg should be performed after completion of the vaccine series, at ages 9 months to 18 months. Testing should not be performed before age 9 months to avoid detection of anti-HBs from HBIG administered during infancy and to maximize the likelihood of detecting late HBV infection. Anti-HBc testing of infants is not recommended because passively acquired maternal anti-HBc might be detected in infants born to mothers with HBV infection up to age 24 months. HBsAg-negative infants with anti-HBs levels >10 mIU/mL are protected and need no further medical management. HBsAg-negative infants with anti-HBs levels <10 mIU/mL should be revaccinated with a second 3-dose series and retested 1 to 2 months after the final dose of vaccine.
References


