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

Panel's Recommendations

- All pregnant women living with HIV should be screened during the current pregnancy for
  - Hepatitis B virus (HBV) infection, unless they are known to have HBV/HIV coinfection or serologic documentation of HBV immunity, and
  - Hepatitis C virus (HCV) infection, unless they are already known to have HCV/HIV coinfection (see Hepatitis C Virus/HIV Coinfection) (AIII).

- 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. If they screen negative for HAV immunoglobulin G antibody, they should receive the HAV vaccine series (AIII).

- All pregnant and postpartum women with HBV/HIV coinfection should receive antiretroviral therapy (ART). Antepartum ART in pregnant women with HBV/HIV coinfection should include tenofovir disoproxil fumarate (TDF) plus lamivudine or emtricitabine (AI). If a woman with HBV/HIV coinfection becomes pregnant while virally suppressed on an antiretroviral (ARV) regimen that includes tenofovir alafenamide (TAF) plus lamivudine or emtricitabine, she can be offered the choice of continuing that ART regimen or switching TAF to TDF in her ART regimen (BIII).

- Pregnant women with HBV/HIV coinfection who are receiving ARV drugs should be counseled about signs and symptoms of liver toxicity, and liver transaminases should be assessed 1 month following initiation of ART 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 HBV/HIV coinfection, frequent monitoring of liver function tests for potential exacerbation of HBV infection is recommended, with prompt re-initiation of treatment for HBV when a flare is suspected (BIII).

- Decisions concerning mode of delivery of the infant in a pregnant woman with HBV/HIV coinfection should be based on standard obstetric and HIV-related indications alone; HBV/HIV coinfection does not necessitate a cesarean delivery if not otherwise indicated (see Transmission and Mode of Delivery) (AIII).

- 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 (AI).

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 Hepatitis B Virus/HIV Coinfection in the Adult and Adolescent Guidelines and Hepatitis B Virus Infection in the Adult and Adolescent Opportunistic Infections Guidelines. The management of HBV/HIV 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 HBV/HIV coinfection or serologic documentation of HBV immunity, and for HCV, unless they are known to have HCV/HIV 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 to evaluate liver function, prothrombin time, and levels of HBV DNA, HB e antigen, and HB e antibody.

To prevent horizontal transmission of HIV and HBV from women with HBV/HIV 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.\textsuperscript{2,3}

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 who have remote HBV infection and current isolated anti-HBc antibody (they test negative for HBV DNA, HBsAg, and anti-HBs) may have lost immunity to HBV and should be vaccinated.\textsuperscript{2} 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/mm\textsuperscript{3} is achieved on antiretroviral therapy (ART).\textsuperscript{2} There is no evidence that the hepatitis B vaccine causes adverse effects in developing fetuses or newborns, and current vaccines contain noninfectious HBsAg.\textsuperscript{4} 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/mm\textsuperscript{3} is achieved on ART). There is no consensus on how to manage patients whose anti-HBs titers remain below 10 IU/mL following a second HBV vaccine series.\textsuperscript{2}

A positive test for anti-HBc alone can be a 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).\textsuperscript{5,6} Incidence of HBV viremia with the isolated anti-HBc pattern ranges from 1\% to 36\% in patients with HIV. The clinical significance of isolated anti-HBc is unknown.\textsuperscript{7,8} 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 test for HIV DNA levels in women with isolated anti-HBc, since those with detectable HBV DNA levels are at risk for developing 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.\textsuperscript{2,9}

Women who have HBV infection and who have not already received the hepatitis A virus (HAV) vaccine series should also be screened for HAV using antibody testing for immunoglobulin G (IgG), because there is an 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 immunoglobulin M [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 who have CD4 cell counts <200 cells/mm\textsuperscript{3}. 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/mm\textsuperscript{3}.\textsuperscript{2} Women who have already received the HAV vaccine series when their CD4 cell count was ≥200 cells/mm\textsuperscript{3} do not need to be revaccinated for HAV, because they are likely protected (even if their HAV IgG levels are undetectable 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.\textsuperscript{4}

**Outcomes of HIV/Hepatitis B Virus Coinfection in Pregnancy**

A study of 4,236 pregnant women with HIV-1 in France who were followed between 2005 and 2013 found the prevalence of HBV (HBsAg positive) to be 6.2\%; HBV/HIV coinfection was six times more frequent in pregnant women who were born in sub-Saharan Africa than in those who were born in France.\textsuperscript{10} HBV/HIV coinfection was not associated with preterm delivery, lower CD4 cell counts, or HIV viral load in this cohort.\textsuperscript{10} In a retrospective analysis of response to ART among 1,462 pregnant women with HIV, 12\% of women had contracted both HIV/HBV.\textsuperscript{11} In a multivariable analysis, women with HIV had better CD4 cell responses on ART during pregnancy than women with both HBV/HIV coinfection. However, no differences in maternal and infant outcomes were observed between women with HBV/HIV and women with HIV alone.\textsuperscript{10}
Therapy for HIV and Hepatitis B Virus in Pregnancy

An ART regimen that includes drugs that are active against both HIV and HBV is recommended for all individuals with HBV/HIV 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 severe liver disease.\(^2\)\(^{12}\) Risk of miscarriage\(^13\) and preterm labor and delivery may increase\(^14\) in people with acute HBV infection (see Hepatitis B Virus Infection in the Adult and Adolescent Opportunistic Infections Guidelines).

In addition, the use of ARV drugs with anti-HBV activity during pregnancy lowers HBV viremia and lowers the risk of HBV transmission to the infant. Lowering HBV viremia may reduce the risk of HBV transmission to an even greater extent than neonatal prophylaxis with hepatitis B immune globulin (HBIG) and hepatitis B vaccine.\(^15\) High maternal HBV DNA levels are strongly correlated with perinatal HBV transmission and with failures of HBV passive-active immunoprophylaxis.\(^16\)\(^-\)\(^19\) 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.\(^20\)\(^-\)\(^28\) In addition to HBV viral load, the presence of certain HBV variants is also a risk factor for failure of HBV prophylaxis.\(^9\)\(^,\)\(^29\)

In a study of 2,048 pregnant women living with HIV in Malawi, 103 women (5%) were HBsAg positive, and 70 of those women also had HBV viremia. Nearly 10% of infants born to mothers with HBV/HIV coinfection had HBV DNA that was detected by age 48 weeks, despite being immunized according to national recommendations at ages 6, 10, and 14 weeks.\(^30\)

Lamivudine, tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (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 HBV/HIV coinfection. However, only lamivudine, TDF, and emtricitabine are recommended for use in pregnancy (see Table 6). There is no pharmacokinetic information for TAF use in pregnancy, and there are few reports of TAF being used during pregnancy. In animal studies, however, there were no developmental effects when TAF was administered during the period of organogenesis at exposures that were either equal to or 51 times the usual therapeutic dosage (in rats and rabbits, respectively).\(^31\)\(^,\)\(^32\) Cases of exposure during pregnancy to any of the ARV drugs and HBV drugs listed should be reported to the Antiretroviral Pregnancy Registry (online or by telephone at 1-800-258-4263).

Some pregnant women may already be receiving TAF-containing ART prior to pregnancy. TAF is effective against HBV in nonpregnant adults,\(^33\)\(^-\)\(^35\) 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 reviews 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 HBV/HIV coinfection who continues to have detectable HBV DNA viremia despite receiving an ART regimen that includes two 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 two during the second trimester, have been reported to the Antiretroviral Pregnancy Registry with no birth defects noted, but this number of exposures is too low to assess overall risk.\(^31\) Seventy-nine cases of exposure to telbivudine have been reported to the Antiretroviral Pregnancy Registry, with 68 cases occurring during the first trimester, seven during the second trimester, and four during 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 the incidence of perinatal transmission of HBV was lower in telbivudine-treated mothers than in the comparison group that did not receive telbivudine (0% vs. 8%; \(P = 0.002\)).\(^23\)\(^,\)\(^36\) In a recent systematic review and meta-analysis of single-drug anti-HBV therapy during pregnancy in cases of
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 differences in postpartum hemorrhage, cesarean section or creatinine kinases levels. For pregnant women with HBV/HIV coinfection, both entecavir and telbivudine should be administered only in addition to a fully suppressive ART regimen for HIV. Because these 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). The Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents does not currently recommend the use of adefovir or telbivudine for patients with HBV/HIV coinfection, because these agents have lower potency than the preferred agents and are associated with certain adverse events—renal disease with adefovir-containing regimens, and myopathy and neuropathy with telbivudine-containing regimens.

Interferon alfa and pegylated interferon alfa are not recommended for use during 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.

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

Prior to initiating ARV drugs that are 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 Hepatitis B Virus Infection in the Adult and Adolescent Opportunistic Infections Guidelines).

Following initiation of ART, an elevation in hepatic enzymes can occur in women with HBV/HIV coinfection—particularly those with low CD4 cell 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 HBV/HIV 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 the effects of drug toxicity and a flare in HBV disease caused by immune reconstitution often can be difficult, and consultation with an expert in HIV and HBV coinfection is strongly recommended. Because TDF can potentially cause renal toxicity, kidney function also should be monitored regularly in pregnant women as in nonpregnant adults.

Once HBV therapy with anti-HBV nucleos(t)ide analogs is initiated, lifelong treatment is recommended. Discontinuing anti-HBV agents may lead to reactivation of HBV, resulting in hepatocellular damage. 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.

**Mode of Delivery**

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

**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 to prevent perinatal transmission.
of HBV. For infants weighing ≥2,000 g at birth, the second and final doses of the vaccine series should be administered at ages 1 month and 6 months, respectively. For infants with birth weights <2,000 g, do not count the birth dose as part of the vaccine series and administer three additional doses at ages 1, 2 to 3, and 6 months. 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 the risk of HBV perinatal transmission in women with HBV/HIV coinfection.

Infant postvaccination 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 three-dose series and retested 1 to 2 months after the final dose of vaccine.

References


