

## Special Populations: Hepatitis B Virus/HIV Coinfection

(Last updated December 29, 2020; last reviewed December 29, 2020)

### Panel's Recommendations

- All pregnant women with HIV should be screened during the current pregnancy for:
  - Hepatitis B virus (HBV) infection, unless they are already known to have HBV/HIV coinfection or have 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 with HIV who screen negative for HBV infection and lack HBV immunity (i.e., HBV surface antigen negative, HBV core antibody negative, and HBV surface antibody negative) should promptly 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 antibodies (either IgG or total antibody [IgG and IgM]), they should receive the HAV vaccine series (AIII).
- All pregnant and postpartum women with HBV/HIV coinfection should receive antiretroviral therapy (ART) that includes tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) plus lamivudine or emtricitabine (AII).
- Pregnant women with HBV/HIV coinfection who are receiving ART should be counseled about signs and symptoms of liver toxicity, and liver transaminases should be assessed 1 month after initiating ART and at least every 3 months thereafter during pregnancy (BIII).
- During and after pregnancy, women with chronic HBV should be counseled on the importance of continuing anti-HBV medications indefinitely. If ART that includes medications with anti-HBV activity is 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 is not an indication for cesarean delivery (see [Intrapartum Care for Women with HIV](#)) (AIII).
- Within 12 hours of birth, infants born to women with HBV 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:** = 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 HBV/HIV coinfection in pregnancy is complex, and consultation with an expert in HIV and HBV infection is strongly recommended. For additional information on hepatitis B virus (HBV) and HIV, see [Hepatitis B Virus/HIV Coinfection](#) in the [Adult and Adolescent Antiretroviral Guidelines](#) and [Hepatitis B Virus Infection](#) in the [Adult and Adolescent Opportunistic Infection Guidelines](#).

### Screening and Vaccination

All women with HIV should be screened for HBV and hepatitis C virus (HCV) at entry into general HIV care. All pregnant women with HIV should be screened for HBV during each pregnancy, unless they are known to have HBV/HIV coinfection, or they have serologic documentation of HBV immunity. They also should be screened for HCV during each pregnancy, 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.<sup>1</sup>

To prevent transmission of HIV and HBV from women with HBV/HIV coinfection to their sex partners, their sexual contacts should be counseled and tested for HIV and HBV. All HBV-susceptible contacts should then receive the HBV vaccine series; all sex partners who do not have HIV infection should be counseled about the benefits of condom use, pre-exposure prophylaxis, and having a partner with undetectable HIV (U=U) in preventing HIV transmission, see [Reproductive Options for Couples When One or Both Partners Have HIV](#) and [Let's Stop HIV Together](#) resources from the Centers for Disease Control and Prevention.<sup>1-4</sup> For more information specifically about preventing HBV transmission, see the [CDC guidelines on pre-exposure prophylaxis](#) and the [Hepatitis B Virus Infection](#) section of the [Adult and Adolescent Opportunistic Infection Guidelines](#).

Pregnant women with HIV who screen negative for HBV (i.e., HBsAg negative, anti-HBc negative, and anti-HBs negative) or who lack HBV immunity (i.e., anti-HBs negative) should promptly receive the HBV vaccine series. Women with HIV who have remote HBV infection and who only have current anti-HBc antibody detected (i.e., they test negative for HBV DNA, HBsAg, and anti-HBs) may have lost immunity to HBV and should be vaccinated.<sup>1</sup> Anti-HBs titers should be obtained 1 to 2 months after the vaccine series is completed in patients with HIV; if anti-HBs titers are below 10 IU/mL, a second vaccine series is recommended.<sup>1,5</sup> 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<sup>3</sup> is achieved on ART.<sup>1,5-7</sup> No evidence exists that the HBV vaccine causes adverse effects in developing fetuses or newborns; current vaccines contain noninfectious HBsAg and are recommended for use in pregnancy for women with HIV.<sup>8,9</sup> No consensus exists on how to manage patients whose anti-HBs titers remain below 10 IU/mL following a second HBV vaccine series.<sup>1</sup>

A positive test for anti-HBc alone can be a false positive, especially in regions of low HBV prevalence; alternatively, it may signify remote infection with subsequent loss of anti-HBs antibodies or longstanding chronic HBV infection with loss of surface antigen (this is known as “occult” HBV infection, which can be confirmed by detection of HBV DNA).<sup>10,11</sup> Incidence of HBV viremia with the isolated anti-HBc pattern ranges from 1% to 30% in patients with HIV, depending on the population sampled.<sup>12</sup> The clinical significance of isolated anti-HBc is unknown.<sup>13,14</sup> 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 that have specific activity against HBV.<sup>5</sup> In areas where the prevalence of HBV is low, patients with isolated anti-HBc should be vaccinated with one standard dose of HBV vaccine, and anti-HBs titers should be checked 1 to 2 months after vaccination. If the anti-HBs titer is >100 IU/mL, no further vaccination is needed. If the titer is <100 IU/mL, the patient should receive a complete HBV vaccine series, followed by anti-HBs testing. The cut-off of 100 IU/mL is used in this situation because one study demonstrated that 100% of patients with isolated anti-HBc who achieved a titer of 100 IU/mL after a booster dose maintained an anti-HBs response for >18 months, compared to only 23% of those who achieved a titer of 10 IU/mL to 100 IU/mL.<sup>1</sup> Pregnant women with HIV who have 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.<sup>1,15</sup>

Women who have HBV infection and who have not already received the hepatitis A virus (HAV) vaccine series also should be screened for HAV using antibody testing for immunoglobulin G (IgG) (note that some laboratories provide only a combined IgG and immunoglobulin M [IgM] HAV titer, which is acceptable). Individuals with chronic HBV have an added risk of hepatic decompensation from acute infection with HAV. Women with chronic HBV infection who have not already received the HAV vaccine series and who are not immune to HAV should receive the HAV vaccine series. Responses to the HAV vaccine are reduced in patients with HIV who have CD4 counts <200 cells/mm<sup>3</sup>. Antibody response should be assessed in such patients 1 month after the HAV vaccine series is complete. If HAV antibody immunoglobulin (HAV Ab IgG) is negative, patients should be revaccinated when the CD4 count is >200 cells/mm<sup>3</sup>.<sup>1</sup> Women who received the HAV vaccine

series when their CD4 count was  $\geq 200$  cells/mm<sup>3</sup> 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, the HAV vaccine contains inactivated HAV, and the theoretical risk to the developing fetus is expected to be low.<sup>8</sup>

### ***HBV/HIV Coinfection in Pregnancy***

A study of 4,236 pregnant women with HIV in France who were followed between 2005 and 2013 found that the prevalence of HBV (HBsAg positive) was 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.<sup>16</sup> HBV/HIV coinfection was not associated with preterm delivery, lower CD4 counts, or detectable HIV viral load in this cohort.<sup>16</sup> In a retrospective analysis of response to ART among Italian women with HIV during 1,462 pregnancies, 12% of women had HBV/HIV coinfection.<sup>17</sup> In a multivariable analysis, women with only HIV had better CD4 responses on ART during pregnancy than women with HBV/HIV coinfection. However, no differences in maternal and infant outcomes were observed between women with HBV/HIV coinfection and women with HIV alone.

### ***Therapy for HIV and HBV 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 immune reconstitution inflammatory syndrome, particularly in patients with high HBV DNA levels and severe liver disease.<sup>1,18</sup> Risk of miscarriage<sup>19</sup> and preterm labor and delivery may increase in people with acute HBV infection;<sup>20</sup> see [Hepatitis B Virus Infection](#) in the [Adult and Adolescent Opportunistic Infection Guidelines](#).

The use of ARV drugs with anti-HBV activity during pregnancy in women with HBV mono-infection 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 HBV vaccine (known as passive-active immunoprophylaxis).<sup>21</sup> High maternal HBV DNA levels are strongly correlated with perinatal HBV transmission and with failures of HBV passive-active immunoprophylaxis.<sup>22–25</sup> Several studies and a meta-analysis of women with HBV mono-infection suggest that lamivudine (3TC) and tenofovir 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.<sup>26–36</sup> In addition to HBV viral load, the presence of certain HBV variants is also a risk factor for failure of HBV prophylaxis.<sup>15,37</sup>

3TC, emtricitabine (FTC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF, a prodrug of tenofovir) have activity against both HIV and HBV. All these drugs are preferred nucleoside reverse transcriptase inhibitors (NRTIs) for use during pregnancy in women with HBV/HIV coinfection, except TAF, which is an alternative NRTI, because data about use in pregnancy are more limited (see [Table 4](#)). Please see individual drug sections for [TDF](#), [TAF](#), [FTC](#), and [3TC](#) 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 when providing care 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 nucleotide or nucleoside analogues (NAs).

Several other antiviral agents have activity against HBV, including entecavir, adefovir, and telbivudine. However, these drugs have not been well evaluated in pregnancy, with too few exposures to assess overall risk. They **are currently not recommended** for pregnant women with HBV/HIV coinfection.<sup>38</sup>

In a systematic review and meta-analysis of single-drug anti-HBV therapy during pregnancy in women with chronic HBV mono-infection, antiviral therapy reduced perinatal transmission with no significant differences in congenital malformation rate, prematurity rate, and Apgar scores. TDF, 3TC, or telbivudine all improved maternal HBV viral suppression at delivery with no significant increase in the incidence of postpartum hemorrhage or cesarean section, and no significant increase in creatinine kinase levels.<sup>39</sup> For pregnant women with HBV/HIV coinfection, entecavir and telbivudine should be administered only in addition to a fully suppressive ART regimen for HIV and only if the potential benefits outweigh the potential risks. 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 resistance to 3TC and FTC). The Panel on Opportunistic Infections in Adults and Adolescents with HIV 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.<sup>1</sup> (See the [Adult and Adolescent Opportunistic Infection Guidelines](#).)

Interferon alfa and pegylated interferon alfa are also **not recommended** for use during pregnancy, and they 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.<sup>40</sup>

Cases of exposure during pregnancy to any of the ARV drugs and HBV drugs listed above should be reported to the [Antiretroviral Pregnancy Registry](#) (online or by telephone at 1-800-258-4263).

### ***Monitoring Women With HBV/HIV Coinfection During Pregnancy***

Prior to initiating ARV drugs that are active against HBV, a baseline HBV DNA level should be measured. After initiating 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 Infection Guidelines](#)).

Following initiation of ART, an elevation in hepatic enzymes can occur in women with HBV/HIV 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 can also increase the 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 transaminase levels should be assessed 1 month after initiating ARV drugs and at least every 3 months thereafter. If hepatotoxicity 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 should be monitored in pregnant women using the same monitoring schedule as the one recommended for nonpregnant adults.

Once HBV therapy with anti-HBV NAs is initiated, lifelong treatment is recommended.<sup>1,41</sup> Discontinuing anti-HBV agents may lead to reactivation of HBV, resulting in hepatocellular damage. If anti-HBV 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.<sup>1</sup>

### ***Mode of Delivery***

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 (see [Intrapartum Care for Women with HIV](#)). No data have been published on the role of cesarean delivery in reducing the risk of perinatal transmission of HBV in women with HBV/HIV coinfection. Currently, the guidelines for women with HBV mono-infection do not recommend performing a cesarean delivery to prevent perinatal transmission of HBV.<sup>42–44</sup>

### ***Evaluating and Managing Infants Who Were Exposed to HBV***

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  $\geq 2,000$  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 month, 2 to 3 months, and 6 months.<sup>45,46</sup> This regimen is  $>95\%$  effective in preventing HBV infection in these infants. Maternal ART that includes NAs with anti-HBV activity will result in low or suppressed HBV viral loads near delivery, which should further reduce the risk of perinatal HBV transmission in women with HBV/HIV coinfection.<sup>35,36</sup>

Infant postvaccination testing for anti-HBs and HBsAg should be performed after completing the vaccine series, between the ages of 9 months and 18 months. Serologic testing should not be performed before age 9 months; this delay helps avoid detecting anti-HBs from HBIG that was administered during infancy and maximizes 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 aged  $\leq 24$  months who were born to mothers with HBV. 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 single dose of HBV vaccine and receive postvaccination serologic testing 1 to 2 months later. Infants whose anti-HBs levels remain  $<10$  mIU/mL following single-dose re-vaccination should receive two additional doses of HBV vaccine to complete the second series, followed by post-vaccination serologic testing at 1 to 2 months after the final dose.<sup>47</sup>

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