



**Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States**

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### Panel's Recommendations

- All HIV-infected pregnant women should be screened during the current pregnancy for hepatitis B virus (HBV) and hepatitis C virus, unless they are known to be coinfecting (see [HIV/Hepatitis C Virus Coinfection](#)) (AIII).
- All HIV-infected pregnant women 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 (AIII). Women with chronic HBV infection who are hepatitis A immunoglobulin G antibody-negative should receive the HAV vaccine series if they have never received it (AII).
- All pregnant and postpartum women with HIV/HBV coinfection should receive antiretroviral therapy (ART). Antepartum ART in HIV/HBV-coinfecting pregnant women should include tenofovir disoproxil fumarate plus lamivudine or emtricitabine (AI).
- 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 both HIV and HBV if a flare is suspected (BIII).
- Decisions concerning mode of delivery in HIV/HBV-coinfecting pregnant women should be based on standard obstetric and HIV-related indications alone; HBV coinfection does not necessitate cesarean delivery, if not otherwise indicated (see [Intrapartum Care](#)) (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 [HIV/Hepatitis B \(HBV\) Coinfection](#) in the [Adult and Adolescent Guidelines](#)<sup>1</sup> and [Hepatitis B Virus Infection](#) in the [Adult and Adolescent OI Guidelines](#).<sup>2</sup> 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 HIV-infected women should be screened for HBV and hepatitis C virus (HCV) at entry into general HIV care. All HIV-infected pregnant women should be screened for HBV and HCV during each pregnancy, unless they are known to be coinfecting. 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.<sup>1</sup> To prevent horizontal transmission of HIV as well as HBV from HIV/HBV-infected women to their male partners, their sexual contacts should be counseled and tested for HIV, HBV and hepatitis A (HAV). All HAV/HBV susceptible contacts should receive both HAV and HBV vaccines and all HIV-uninfected partners of HIV/HBV-coinfecting women should be counseled about the potential benefits and risks of starting pre-exposure prophylaxis (PrEP).<sup>2,3</sup>

HIV-infected pregnant women who screen negative for HBV (i.e., HBsAg-negative, anti-HBc-negative, and anti-HBs-negative) should receive the HBV vaccine series. HIV-infected women 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.<sup>2</sup> HIV-infected women whose anti-HBs titers are below 10 IU/mL despite

having received the HBV vaccine series should receive a second vaccine series; some experts advise using a double dose of HBV vaccine (e.g. 40 mg dose) and delaying revaccination until after a sustained increase in CD4 T lymphocyte (CD4) cell count is achieved on antiretroviral therapy (ART).<sup>2</sup> Data indicate no apparent risk to developing fetuses of adverse events from hepatitis B vaccine, and current vaccines contain noninfectious HBsAg.<sup>4</sup> Anti-HBs titers should be obtained 1 month after completion of the vaccine series in HIV-infected patients; 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 is achieved on ART). There is no consensus for management of patients whose anti-HBs titers remain below 10 IU/mL following a second vaccine series.<sup>2</sup>

A positive test for anti-HBc alone can be false-positive; alternatively, it may signify remote exposure 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).<sup>5,6</sup> **Incidence of HBV viremia in HIV-infected patients with the isolated anti-HBc pattern ranges from 1% to 36%.** The clinical significance of isolated anti-HBc is unknown.<sup>7,8</sup> Some experts recommend that HIV-infected individuals with 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 ARV drugs are initiated because of the risk of a paradoxical exacerbation of HBV and the occurrence of immune reconstitution inflammatory syndrome (IRIS). HIV-infected pregnant women 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.<sup>2,9</sup>

Women who are found to have HBV infection should also be **screened for 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 or HCV. If HAV IgG is negative, and if the HAV vaccine was not given previously, HIV/HBV-coinfected women should receive the HAV vaccine series. Responses to the HAV vaccine were reduced in HIV-infected patients with CD4 counts <200 cells/mm<sup>3</sup>. Antibody response should be assessed 1 month after vaccination is complete. If HAV antibody immunoglobulin (HAV Ab IgG) is negative, patients should be revaccinated when the CD4 cell count is >200 cells/mm<sup>3</sup>.<sup>2</sup> Women who have already received the HAV vaccine series when their CD4 cell count was ≥200 cells/mm<sup>3</sup> do not need to repeat it 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 determined, HAV vaccine is produced from inactivated HAV and the theoretical risk to the developing fetus is expected to be low.<sup>4</sup>

### ***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 who require HBV treatment or who are starting ARV drugs, 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.<sup>2,10</sup> Risk of preterm labor and delivery may be increased with acute HBV infection (see [Hepatitis B Infection](#) in the [Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents](#)).

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.**<sup>12-14</sup> Several small studies and a recent meta-analysis suggest that lamivudine or telbivudine may reduce the risk of perinatal transmission of HBV if given during the third trimester to HBV-infected, HIV-seronegative women with high HBV DNA viremia.<sup>15-23</sup> Although a high HBV viral load clearly is important, it is not the only factor predisposing to failure of HBV prophylaxis.<sup>9,24</sup> In a study of 2,048 HIV-infected pregnant women in Malawi, 5% (103 women) were HBsAg-positive, 70 of whom were also HBV DNA-positive. Nearly 10%

of infants born to HBV/HIV co-infected mothers had HBV DNA detected by age 48 weeks despite being immunized at ages 6, 10, and 14 weeks per standard-of-care health practices in this population.<sup>25</sup>

Lamivudine, tenofovir disoproxil fumarate (TDF), and emtricitabine have activity against both HIV and HBV. TDF with emtricitabine or lamivudine is the preferred dual nucleoside reverse transcriptase inhibitor backbone in women who are HIV/HBV-coinfected (see [Table 6](#)). These agents are recommended for use in pregnancy (see [Table 6](#)). Please see individual drug sections for [TDF](#), [emtricitabine](#), and [lamivudine](#) for detailed review of safety, pharmacologic, and other clinical data for use in pregnancy.

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. Fewer than 68 cases of exposure to each of these drugs during the first trimester have been reported to the Antiretroviral Pregnancy Registry prospectively, with no increased risk of birth defects being reported.<sup>26</sup> Telbivudine was given to 135 HBV-positive, HIV-seronegative women during the third trimester; it was well tolerated, and perinatal transmission of HBV was lower in telbivudine-treated mothers than in the controls not on telbivudine (0% vs. 8%;  $P = 0.002$ ).<sup>18,27</sup> In two separate meta-analyses of the effects of telbivudine in late pregnancy in women infected with HBV alone, telbivudine was effective in interrupting intrauterine HBV infection without significant adverse effects or complications.<sup>19,28</sup> In a recent systematic review and meta-analysis of single-drug anti-hepatitis B antiviral therapy during pregnancy in chronic HBV mono-infection, Brown et al. found that antiviral therapy reduced perinatal transmission with no significant differences in congenital malformation rate, prematurity rate, and Apgar scores. Compared to the use of HBIG and vaccination alone, 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.<sup>29</sup> For HIV/HBV coinfecting pregnant women, 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, they may select for anti-HIV drug resistance in the absence of fully suppressive ART regimen as well as confer the potential for developing 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.<sup>2</sup> 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>). If a pregnant woman coinfecting with HIV/HBV treated with ART with 2 anti-HBV nucleos(t)ides continues to have detectable HBV DNA viremia, consultation with an expert in HIV and HBV is strongly recommended.

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.<sup>30</sup>

### ***Monitoring of HIV/Hepatitis B Virus-Infected Women 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 OI Guidelines](#)).

Following initiation of ARV drugs, an elevation in hepatic enzymes can occur in HIV/HBV-coinfected women—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, treatment is recommended to be continued indefinitely.<sup>1,2</sup> Discontinuation of anti-HIV agents that also have anti-HBV activity may be associated with hepatocellular damage resulting from reactivation of HBV. If ART with anti-HBV-active drugs must be discontinued, serum transaminase levels should be monitored every 6 weeks for 3 months, then every 3 to 6 months thereafter, with prompt reinitiation of treatment for both HIV and HBV if a flare is suspected.<sup>2</sup>

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

Decisions concerning mode of delivery in HIV/HBV-coinfected pregnant women 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 HIV/HBV-coinfected women or when HBV-infected women receive antiviral therapy active against HBV. Current guidelines for HBV-monoinfected women advise that cesarean delivery is not indicated to prevent perinatal transmission of HBV.<sup>31-33</sup>

Treatment of HIV/HBV-coinfected pregnant women with ART that includes TDF and emtricitabine and/or lamivudine will result in low or suppressed HBV viral loads near delivery, which should further reduce risk of HBV perinatal transmission

### ***Evaluation and Management of Hepatitis B Virus-Exposed Infants***

Within 12 hours of birth, all infants born to mothers with chronic HBV infection should receive HBIG and the first dose of the HBV vaccination series. For infants weighing  $\geq 2,000$  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 three additional doses at ages 1, 2–3, and 6 months.<sup>34,35</sup> This regimen is  $>95\%$  effective in preventing HBV infection in these infants.

Post-vaccination testing for anti-HBs and HBsAg should be performed after completion of the vaccine series, at age 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 HBV-infected mothers 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.

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