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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Special Situations — HIV/Hepatitis B Virus Coinfection (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations

- Screening for hepatitis B virus (HBV) infection with hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs) is recommended for all pregnant women who have not been screened during the current pregnancy **(AII)**.
- The HBV vaccine series should be administered to pregnant women who screen negative for hepatitis B (that is, HBsAg negative, anti-HBc negative, and anti-HBs negative) **(AII)**.
- Pregnant women with chronic HBV infection should be screened for antibodies to hepatitis A virus (HAV), and those who screen negative should receive the HAV vaccine series **(AII)**.
- Interferon alfa and pegylated interferon alfa are not recommended during pregnancy **(AIII)**.
- The management of HIV/HBV coinfection in pregnancy is complex and consultation with an expert in HIV and HBV is strongly recommended **(AIII)**.
- All pregnant women with HIV/HBV coinfection should receive antiretroviral therapy (ART), including a dual nucleoside reverse transcriptase inhibitor (NRTI)/nucleotide analogue reverse transcriptase inhibitor (NtRTI) backbone with two drugs active against both HIV and HBV **(AII)**. Tenofovir plus lamivudine or emtricitabine is the preferred dual NRTI/NtRTI backbone of antepartum ART in HIV/HBV-coinfected pregnant women **(AI)**.
- If antiretroviral (ARV) drugs are discontinued postpartum in women with HIV/HBV coinfection, frequent monitoring of liver function tests for potential exacerbation of HBV infection is recommended, with prompt reinitiation of treatment for both HIV and HBV if a flare is suspected **(BIII)**.
- Pregnant women with HIV/HBV coinfection receiving ARV drugs should be counseled about the 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 **(BIII)**.
- 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. The second and third doses of vaccine should be administered at ages 1 and 6 months, respectively **(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 and HIV, see *HIV/Hepatitis B (HBV) Coinfection* in *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* (http://AIDSinfo.nih.gov)[1] and *Hepatitis B Virus Infection* in the *Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents, Recommendations from the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the HIV Medicine Association of the Infectious Diseases Society of America*.[2]

All HIV-infected pregnant women should be screened for hepatitis A, B, and C. The management of HIV/hepatitis B virus (HBV) coinfection in pregnancy is complex and consultation with an expert in HIV and HBV infection is strongly recommended. HIV-infected women who are found to have chronic HBV infection on the basis of persistent hepatitis B surface antigenemia for at least 6 months and who are hepatitis A immunoglobulin G negative should receive the hepatitis A virus (HAV) vaccine series because of the

added risk of acute hepatitis A in persons with chronic viral hepatitis. 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.[3]

HIV-infected pregnant women who test negative for hepatitis B surface antibody (anti-HBs) and hepatitis B surface antigen (HBsAg) should receive the HBV vaccine series. Limited data indicate no apparent risk to developing fetuses of adverse events from hepatitis B vaccine, and current vaccines contain noninfectious HBsAg and should cause no risk to fetuses.[3] A positive test for hepatitis B core antibody (anti-HBc) alone can be a false-positive result, or it may signify past exposure with subsequent loss of anti-HBs or "occult" HBV infection, which can be confirmed by detection of HBV DNA.[4, 5] The clinical significance of isolated anti-HBc is unknown.[6, 7] Some experts recommend that HIV-infected individuals with anti-HBc alone be tested for HBV DNA before vaccination for HBV or before treatment or prophylaxis with antiretroviral (ARV) drugs is initiated because of the risk of a paradoxical exacerbation of HBV and the occurrence of immune reconstitution inflammatory syndrome (IRIS).[2]

An ARV 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 pregnant women. Initiation of an ARV regimen that does not include anti-HBV drugs may be associated with reactivation of HBV and development of IRIS; IRIS-related flare of HBV activity during pregnancy can occur even in women with relatively high CD4 T-lymphocyte (CD4-cell) counts at the time of ARV initiation. In addition, use of ARV drugs with anti-HBV activity during pregnancy lowers HBV viremia, potentially increasing the efficacy of neonatal hepatitis B immune globulin (HBIG) and hepatitis B vaccine in prevention of perinatal transmission of HBV. High maternal HBV DNA levels are strongly correlated with perinatal HBV transmission and with failures of HBV passive-active immunoprophylaxis.[8-10] Several small studies 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.[11-14] Although a high HBV viral load clearly is important, it is not the only factor predisposing to failure of prophylaxis.[15]

Because lamivudine, tenofovir, and emtricitabine have activity against both HIV and HBV, the recommended dual-nucleoside reverse transcriptase (NRTI)/nucleotide analogue reverse transcriptase inhibitor (NtRTI) backbone for HIV/HBV-coinfected individuals, including pregnant women, is tenofovir/emtricitabine or tenofovir/lamivudine. Lamivudine has been extensively studied and is recommended for use in pregnancy (Table 5). The Antiretroviral Pregnancy Registry includes reports on the outcomes of 4,088 pregnancies that involved administration of lamivudine in the first trimester and there is no indication that the exposure was associated with an increased risk of birth defects.[16] Similarly, no increase in birth defects has been noted in 899 cases of first-trimester exposure to emtricitabine, which is an alternative NRTI for use in pregnancy (Table 5). Tenofovir is not teratogenic in animals, but reversible bone changes at high doses have been seen in multiple animal species. A total of 1,370 cases of first-trimester exposure have been reported to the Antiretroviral Pregnancy Registry, with no increase in birth defects noted.[16] Although tenofovir is recommended as an alternative NtRTI during pregnancy for ARV-naive women, it is a preferred NtRTI in women with HIV/HBV coinfection (Table 5).

Several other antivirals with activity against HBV, including entecavir, adefovir, and telbivudine, have had minimal evaluation 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 70 cases of exposure to each of these drugs during pregnancy have been reported to the Antiretroviral Pregnancy Registry.[16] Telbivudine was given to 135 HBV-positive, HIV-negative women during the third trimester and was well tolerated, and perinatal transmission of HBV was lower in telbivudine-treated mothers (0% vs. 8%; P = 0.002).[14, 17] Each of these anti-HBV drugs should be administered only in addition to a fully suppressive 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 a fully suppressive ARV regimen as well as potential cross resistance to other ARV drugs. (Entecavir, for example, can select for the M184V mutation, which confers HIV resistance to lamivudine and emtricitabine.) These drugs should be used during pregnancy only if the preferred drugs are not appropriate in specific cases. 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).

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 the direct antigrowth and antiproliferative effects of these agents.[18]

Following initiation of ARV drugs, an elevation in hepatic enzymes can occur in HIV/HBV-coinfected women—particularly those with low CD-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 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 tenofovir has potential to cause renal toxicity, kidney function also should be monitored regularly in women receiving this drug, based on toxicity seen in non-pregnant adults.

Following delivery, considerations regarding continuation of the ARV drug regimen are the same as for other non-pregnant individuals (see General Principles Regarding Use of Antiretroviral Drugs During Pregnancy). Discontinuation of agents with anti-HBV activity may be associated with hepatocellular damage resulting from reactivation of HBV. Frequent monitoring of liver function tests for potential HBV flare is recommended in women with HIV/HBV coinfection whose ARV drugs are discontinued postpartum, with prompt reinitiation of treatment for both HIV and HBV if a flare is suspected.

Within 12 hours of birth, all infants who weigh >2,000 g born to mothers with chronic HBV infection should receive HBIG and the first dose of the HBV vaccination series. The second and third doses of vaccine should be administered at ages 1 and 6 months, respectively. This regimen is >95% effective in preventing HBV infection in these infants. Consult the CDC MMWR recommendations for similar infants with birth weights <2,000 g at birth.[19]

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