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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Initial Postnatal Management of the HIV-Exposed Neonate (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations

- A complete blood count and differential should be performed on newborns as a baseline evaluation **(BIII)**.
- Decisions about the timing of subsequent monitoring of hematologic parameters in infants depend on baseline hematologic values, gestational age at birth, clinical condition of the infants, the zidovudine dose being administered, receipt of other ARV drugs and concomitant medications, and maternal antepartum ARV therapy **(CIII)**.
- If hematologic abnormalities are identified in infants receiving prophylaxis, decisions on whether to continue infant antiretroviral (ARV) prophylaxis need to be individualized. Consultation with an expert in pediatric HIV infection is advised if early discontinuation of prophylaxis is considered **(CIII)**.
- Some experts recommend more intensive monitoring of hematologic and serum chemistry and liver function assays at birth and when diagnostic HIV polymerase chain reaction tests are obtained in infants exposed to combination ARV drug regimens *in utero* or during the neonatal period **(CIII)**.
- A recheck of hemoglobin and neutrophil counts is recommended 4 weeks after initiation of prophylaxis for infants who receive combination zidovudine/lamivudine-containing ARV prophylaxis regimens **(AI)**.
- Routine measurement of serum lactate is not recommended. However, measurement can be considered if an infant develops severe clinical symptoms of unknown etiology (particularly neurologic symptoms) **(CIII)**.
- Virologic tests are required to diagnose HIV infection in infants <18 months of age and should be performed within the first 14 to 21 days of life, at 1 to 2 months, and at 4 to 6 months of age **(AII)**.
- To prevent *Pneumocystis jirovecii* pneumonia (PCP), all infants born to women with HIV infection should begin PCP prophylaxis at ages 4 to 6 weeks, after completing their ARV prophylaxis regimen, unless there is adequate test information to presumptively exclude HIV infection (see USPHS/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and Infected Children) **(AII)**.
- Health care providers should routinely inquire about premastication of foods fed to infants, instruct HIV-infected caregivers to avoid this practice, and advise on safer feeding options **(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*

A complete blood count (CBC) and differential should be performed on HIV-exposed newborns before initiation of infant antiretroviral (ARV) drug prophylaxis. Decisions about the timing of hematologic monitoring of infants after birth depend on a number of factors, including baseline hematologic values, gestational age at birth, clinical condition of the infants, which ARV drugs are being administered, receipt of concomitant medications, and maternal antepartum ARV drug regimen. Anemia is the primary complication seen in neonates given the standard 6-week postnatal zidovudine regimen. In PACTG 076, infants in the zidovudine group had lower hemoglobin at birth than those in the placebo group, with the maximal difference (1 g/dL) occurring at age 3 weeks.[1] The lowest mean value for hemoglobin levels (10 g/dL) occurred at age 6 weeks in the zidovudine group. By age 12 weeks, hemoglobin values in both groups were similar. No significant differences in other laboratory parameters were observed between groups.

Some experts recheck hematologic values in healthy infants receiving zidovudine prophylaxis only if symptoms are present. Hematologic safety data are limited on administration of 4 mg/kg of zidovudine twice

daily in infants. When administering this dosing regimen, some experts recheck hemoglobin and neutrophil counts routinely after 4 weeks of zidovudine prophylaxis and/or when diagnostic HIV polymerase chain reaction (PCR) tests are obtained.

In utero exposure to maternal combination ARV drug regimens may be associated with some increase in anemia and/or neutropenia compared with that seen in infants exposed to zidovudine alone.[2-5] In PACTG 316, where 77% of mothers received antenatal combination therapy, significant Grade 3 or higher anemia was noted in 13% and neutropenia in 12% of infants, respectively. Depending on the combination regimen the mother has received, some experts advise more intensive laboratory monitoring, including serum chemistry and transaminases at birth plus a CBC at the time of diagnostic HIV PCR testing; monitoring of bilirubin levels may be considered for infants exposed antenatally to atazanavir.

In addition, data are limited on infants receiving zidovudine in combination with other ARVs for prophylaxis. However, higher rates of hematologic toxicity have been observed in infants receiving zidovudine/lamivudine combination prophylaxis compared with those receiving zidovudine alone or zidovudine plus nevirapine.[6] A recheck of hemoglobin and neutrophil counts, therefore, is recommended for infants who receive combination zidovudine/lamivudine-containing ARV prophylaxis regimens 4 weeks after initiation of prophylaxis and/or at the time that diagnostic HIV PCR testing is done.[7]

If hematologic abnormalities are found, decisions on whether to continue infant ARV prophylaxis need to be individualized. Considerations include the extent of the abnormality, whether related symptoms are present, duration of infant prophylaxis, risk of HIV infection (as assessed by the mother's history of ARV prophylaxis, viral load near delivery, and mode of delivery), and the availability of alternative interventions such as erythropoietin and transfusion. Consideration can be given to reducing the duration of infant prophylaxis from 6 to 4 weeks, as is the case in many European centers. In a recent prospective, observational study, the 4-week regimen was found to allow earlier recovery from anemia in otherwise healthy infants compared with the 6-week regimen.[8] Consultation with an expert in pediatric HIV infection is advised if discontinuation of prophylaxis is considered.

Hyperlactatemia has been reported in infants with *in utero* exposure to ARVs, but it appears to be transient and, in most cases, asymptomatic.[9, 10] Routine measurement of serum lactate is not recommended in asymptomatic neonates to assess for potential mitochondrial toxicity because the clinical relevance is unknown and the predictive value for toxicity appears poor.[9, 10] Serum lactate measurement should be considered, however, for infants who develop severe clinical symptoms of unknown etiology, particularly neurologic symptoms. In infants with symptoms, if the levels are significantly abnormal (>5 mmol/L), ARV prophylaxis should be discontinued and an expert in pediatric HIV infection should be consulted regarding potential alternate prophylaxis.

To prevent *Pneumocystis jirovecii* pneumonia, all infants born to women with HIV infection should begin trimethoprim-sulfamethoxazole prophylaxis at age 6 weeks, after completion of the infant ARV prophylaxis regimen, unless there is adequate virologic test information to presumptively exclude HIV infection (see *USPHS/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and Infected Children*).[11]

HIV infection in infants should be diagnosed using HIV DNA PCR or RNA virologic assays. Maternal HIV antibody crosses the placenta and will be detectable in all HIV-exposed infants up to age 18 months; therefore, standard antibody tests should not be used for HIV diagnosis in newborns. HIV virologic testing should be performed within the first 14 to 21 days of life, at 1 to 2 months, and at 4 to 6 months of age.[12] Some experts also perform a virologic test at birth, especially in women who have not had good virologic control during pregnancy or if adequate follow-up of the infant may not be assured. A positive HIV virologic test should be confirmed as soon as possible with a second HIV virologic test on a different specimen. Two

positive HIV tests constitute a diagnosis of HIV infection. Data do not indicate any delay in HIV diagnosis with HIV DNA PCR assays in infants who have received the zidovudine regimen.[1, 13] However, the effect of maternal or infant exposure to combination ARV drug regimens on the sensitivity of infant virologic diagnostic testing—particularly using HIV RNA assays—is unknown. Therefore, although HIV RNA assays may be acceptable for diagnosis (particularly in older infants), HIV DNA PCR assays may be optimal for diagnosing infection in the neonatal period. Any newly diagnosed infant should undergo viral resistance testing by genotype and/or phenotype to assess for susceptibility to combination antiretroviral therapy.

HIV may be presumptively excluded with two or more negative tests, one at age 14 days or older and the other at age 1 month or older. Definitive exclusion of HIV in non-breastfed infants can be based on two negative virologic tests at age 1 month or older and at age 4 months or older. Many experts confirm HIV-negative status with an HIV antibody test at ages 12 to 18 months. Alternative algorithms exist for presumptive and definitive HIV exclusion.[12] This testing algorithm applies mainly to exposure to HIV subtype B, which is the predominant viral subtype found in the United States. Non-subtype B viruses predominate in some other parts of the world. Non-subtype B infection may not be detected by many commercially available nucleic acid tests, particularly HIV DNA PCR. Many of the newer HIV RNA assays have improved detection of non-subtype B HIV, but there are still variants that are either poorly detected or undetectable. If non-subtype B HIV infection is suspected based on maternal origins, then newer HIV RNA assays that have improved ability to detect non-subtype B HIV should be used as part of the initial diagnostic algorithm. Exposed infants also should be closely monitored and undergo definitive HIV serologic testing at age 18 months (see the *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, Issues Related to Diagnosis of Non-Subtype B HIV Infection* for additional information).

Following birth, HIV-exposed infants should have a detailed physical examination, and a thorough maternal history should be obtained. HIV-infected mothers may be coinfected with other pathogens that can be transmitted from mother to child, such as cytomegalovirus, herpes simplex virus, hepatitis B, hepatitis C, syphilis, toxoplasmosis, or tuberculosis. Infants born to mothers with such coinfections should undergo appropriate evaluation, as indicated by maternal CD4 T-lymphocyte count and evidence of disease activity, to rule out transmission of additional infectious agents. The routine primary immunization schedule should be followed for HIV-exposed infants born to HIV-infected mothers. Modifications in the schedule for live virus vaccines may be required for infants with known HIV infection (see *USPHS/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and Infected Children*).

Infant Feeding Practices and Risk of HIV Transmission

In the United States, where safe infant feeding alternatives are available and free for women in need, HIV-infected women should not breastfeed their infants. Maternal receipt of combination ARV regimens is likely to reduce free virus in the breast milk, but the presence of cell-associated virus (intracellular HIV DNA) remains unaffected and, therefore, may continue to pose a transmission risk.[14]

Late HIV transmission events in infancy have been reported in HIV-infected children suspected of acquiring HIV infection as a result of consuming premasticated food given to them by their caregivers. Phylogenetic comparisons of virus from cases and suspected sources and supporting clinical history and investigations identified the practice of feeding premasticated foods to infants as a potential risk factor for HIV transmission. Health care providers should routinely inquire about premastication, instruct HIV-infected caregivers against this feeding practice, and advise on safer feeding options.[15, 16]

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