


Management of Newborns Exposed to Maternal HIV Infection

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The management of infants whose mothers are infected with the human immunodeficiency virus (HIV) involves minimizing the risk of vertical transmission of HIV, recognizing neonatal HIV infection early, preventing opportunistic infections, and addressing psychosocial issues. Maternal antiretroviral drug therapy during pregnancy and labor, followed by six weeks of neonatal zidovudine therapy, can significantly decrease the risk of vertical transmission. Additional antiretroviral drugs may be needed in some high-risk newborns. Elective cesarean section also may prevent vertical transmission of HIV. Virologic tests allow early diagnosis of HIV infection, facilitating the timely initiation of aggressive treatment and the prevention of opportunistic infections. Even when tests are negative, infants must be closely monitored until age 18 months to completely rule out HIV infection. Prophylaxis for *Pneumocystis carinii* pneumonia should be initiated when HIV-exposed infants are six weeks old and should be continued for at least four months, regardless of negative virologic tests, because *P. carinii* pneumonia is often the initial presentation of HIV infection in infants. Laboratory monitoring, screening for perinatal infections, appropriate social support, and other modifications of standard infant care are also necessary. (Am Fam Physician 2002;65:2049-56,2061. Copyright© 2002 American Academy of Family Physicians.)

 A patient information handout on preventing HIV infection in babies, written by the authors of this article, is provided on page 2061.

Currently, more than 160,000 women of childbearing age in the United States may be infected with the human immunodeficiency virus (HIV).¹ By 1995, 16,000 U.S. infants had become infected with HIV perinatally, and the leading cause of death in young children was the acquired immunodeficiency syndrome (AIDS).² Before 1995, perinatally infected infants had a 50 percent chance of developing AIDS by three years of age and a 90 percent chance of dying by 10 years of age.³ From 1992 to 1997, the number of AIDS cases in children declined by 66 percent, primarily because major advances in management resulted in decreased vertical transmission of HIV during pregnancy.² The risk of perinatal HIV infection can vary from 1 to 33 percent, depending on interventions and maternal disease state.⁴

The early identification of HIV infection, the administration of highly active antiretroviral drug therapy, the suppression of viral loads to undetectable levels, and the prevention of opportunistic infections all have been shown to prolong life and prevent morbidity in adults. In theory, the principle of viral load suppression would apply to infants as well as adults. However, the management of HIV infection in children is a rapidly evolving area with limited data.

Unique considerations in infants born to HIV-infected mothers include in utero exposure to antiretroviral drugs, perinatal exposure to HIV and other infections, differences in diagnosis and disease manifestations compared with older patients, altered antiretroviral pharmacodynamics, and medication adherence issues such as poor palatability.

The management of HIV infection is subject to frequent changes. The basic principles of caring for infants exposed to or infected with HIV have been outlined in guidelines from several organizations and consensus panels.⁴⁻⁷ HIV management guidelines are regularly updated on the HIV/AIDS Treatment Information Service Web site (<http://www.hivatis.org>).

Regularly updated HIV management guidelines can be found on the Web site of the HIV/AIDS Treatment Information Service (<http://www.hivatis.org>).

TABLE 1

Factors Increasing the Risk of Vertical Transmission of HIV

Maternal factors	Intrapartum events
Low CD4+ lymphocyte count	Instrumental delivery
High viral load	Use of fetal scalp monitor
Advanced AIDS	Fetal scalp pH measurement
Preterm delivery	Use of DeLee suctioning
Chorioamnionitis	Artificial rupture of membranes
Presence of p24 core antigen	Rupture of membranes for longer than 4 hours
	Other events increasing fetal exposure to maternal blood

HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome.

Information from Public Health Service Task Force recommendations for the use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. Living document: January 24, 2001. Retrieved February 2001, from <http://www.hivatis.org/trtgdlns.html#Perinatal>.

Natural Course of HIV Infection in Infants

Vertical transmission of HIV can occur in utero, during labor or after delivery. It is estimated that in 65 percent of HIV-infected infants, transmission occurred during labor.⁸ Multiple factors increase the risk of vertical transmission of HIV (*Table 1*).⁹

HIV infection in infants appears to have two forms. The first form, which is similar to HIV infection in adults, has a prolonged course, with HIV infection progressing to AIDS over eight to 10 years. The second and more aggressive form is characterized by early conversion to AIDS and an increased risk of opportunistic infections and mortality.

Early HIV infection increases the risk of rapid progression to AIDS. Defined as a positive virologic test fewer than 48 hours after delivery, early infection is the result of in utero

HIV transmission, as opposed to intrapartum or postpartum transmission.¹⁰ In a French study¹¹ of HIV infection in children, newborns with hepatosplenomegaly, lymphadenopathy, fewer than 30 percent CD4+ lymphocytes or a positive HIV DNA polymerase chain reaction (PCR) test within the first week after birth were found to be at increased risk for rapid progression of HIV infection. A retrospective study from the Intravenous Immunoglobulin Prophylaxis Clinical Trial¹² found that increased viral loads and decreased CD4+ lymphocyte counts increased the relative risk of mortality in HIV-infected infants.

Antiretroviral Drug Therapy

Zidovudine (Retrovir) prophylaxis is recommended for most infants exposed to HIV in utero to decrease the risk of vertical transmission.⁵ Beginning eight hours after birth, these neonates should receive zidovudine in a dosage of 2 mg per kg every six hours for at least six weeks.

The landmark study proving the benefits of zidovudine prophylaxis was the Pediatric AIDS Clinical Trials Group Protocol 076 (ACTG 076).¹³ Maternal zidovudine treatment during pregnancy and labor, and neonatal zidovudine therapy for the first six weeks of life, reduced the relative risk of vertical transmission of HIV by 66 percent (*Table 2*).¹³ Mothers and infants who did not receive zidovudine had a 25.5 percent chance of vertical transmission, whereas those who received the antiretroviral drug had an 8.3 percent chance (number needed to treat is 5.8). Ideally, HIV-infected mothers receive zidovudine during pregnancy and labor. Even if the mothers have not received antiretroviral drug therapy, their infants should be given zidovudine, with treatment started before eight hours after birth and continuing for six weeks.

Mild anemia is the primary side effect of zidovudine prophylaxis in infants. The anemia is maximal at six weeks of life and resolves spontaneously by 12 weeks without treatment.¹³ Comorbid illnesses such as Rh or ABO incompatibility can exacerbate the anemia.

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Infants born to HIV-infected mothers should receive zidovudine in a dosage of 2 mg per kg every six hours, beginning eight hours after birth and continuing for at least six weeks.

Follow-up data from the ACTG 076 study have shown no long-term adverse effects or delays in diagnosing infants who are HIV positive if the mothers were treated with zidovudine during pregnancy.¹⁴

A recent study¹⁵ evaluated the use of nevirapine, a nonnucleoside reverse transcription inhibitor, during labor and after birth. HIV-infected mothers were given a single 200-mg dose of nevirapine orally at the onset of labor; their infants were given 2 mg per kg in a single dose administered orally within 72 hours after delivery. These measures were found to decrease vertical transmission of HIV by 47 percent. However, this study was conducted in Africa (Uganda), where 98 percent of infants are breastfed, and all patients in the study were antiretroviral-naïve.

Given the benefits of nevirapine as shown in the study done in Africa,¹⁵ there are recommendations for the use of antiretroviral drugs instead of or in addition to zidovudine, based on several clinical scenarios (*Table 3*).⁹ Subspecialty consultation should be considered for infants of mothers who have more complicated or advanced HIV disease, because these infants may benefit from alterations in the standard ACTG 076 treatment protocol.

Maternal Care Before Delivery

In 1998, an expert panel from the National Institutes of Health¹⁶ recommended that pregnant HIV-infected women be managed in the same way as nonpregnant HIV-positive women. In both situations, multiple antiretroviral drugs, including protease inhibitors, are used to reduce viral loads to undetectable levels. However, decisions regarding antiretroviral drug therapy during pregnancy are complex and should be made only after patients have been informed of the benefits and risks.

Current recommendations for maternal and neonatal antiretroviral drug therapy are based on four main clinical scenarios (*Table 3*).⁹ Recommendations for mode of delivery to decrease the risk of vertical HIV transmission are also given. Elective cesarean section at 38 weeks of

gestation (with a first- or second-trimester ultrasound examination to confirm dates when possible) may decrease the risk of HIV transmission. Surgery carries increased risks for mothers; thus, as with antiretroviral drug therapy, benefits and risks should be discussed to allow an informed decision.

Monitoring of Newborns

Early detection of HIV infection is important. Before 1994, the only widely available tests for HIV were an enzyme-linked immunosorbent assay (ELISA) and a Western blot test that detected HIV-specific IgG. Reliance on these tests delayed definitive diagnosis of HIV infection in infants because maternal IgG antibody crosses the placenta and remains detectable in the newborn's blood up to 18 months.⁶

A number of tests that directly detect HIV are now available. Compared with antibody-dependent tests, the HIV DNA PCR test, HIV culture, p24 core antigen level, and HIV RNA viral level all allow earlier detection of neonatal HIV infection. The HIV DNA PCR test is the recommended initial screening tool in infants born to HIV-positive mothers. The test has a sensitivity of 93.2 percent and a speci-

TABLE 2
Zidovudine Protocol Used in the Pediatric AIDS Clinical Trials Group Protocol 076

Maternal zidovudine (Retrovir) during pregnancy: 100 mg orally five times daily from 14 weeks of gestation to delivery*
Maternal zidovudine during labor: 2 mg per kg by intravenous load over 1 hour, then 1 mg per kg per hour until delivery
Neonatal zidovudine: 2 mg per kg orally every 6 hours from 8 hours after delivery until 6 weeks of age

AIDS = acquired immunodeficiency syndrome.

*—Commonly used alternative regimens include 300 mg twice daily and 200 mg three times daily.

Information from Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994;331:1173-80.

TABLE 3

Reduction of Perinatal HIV Transmission: Clinical Scenarios and Management Recommendations

<i>Clinical scenario</i>	<i>Management recommendations</i>
Antiretroviral therapy	
Scenario 1: HIV-infected pregnant woman not previously exposed to antiretroviral drugs	Antiretroviral drug therapy is selected based on the same parameters used in nonpregnant HIV-infected women. The regimen should include orally administered zidovudine (Retrovir) during pregnancy and intravenously administered zidovudine during labor.
Scenario 2: HIV-infected woman receiving antiretroviral drugs during current pregnancy	Continuation of antiretroviral drug therapy should be considered. Zidovudine should be incorporated into the regimen and should be given intravenously during labor.
Scenario 3: HIV-infected woman in labor with no previous antiretroviral drug therapy	Consider one of four regimens: <ol style="list-style-type: none"> 1. Single dose of orally administered nevirapine (Viramune) given to the mother at the onset of labor, and single dose given to the newborn by 48 hours after birth 2. Orally administered lamivudine-zidovudine (Combivir) given to the mother during labor and to the newborn for 1 week after birth 3. Intravenously administered zidovudine given to the mother during labor, and orally administered zidovudine given to the newborn for 6 weeks after birth 4. Two doses of orally administered nevirapine and intravenously administered zidovudine given to the mother during labor, and orally administered zidovudine given to the newborn for 6 weeks after birth
Scenario 4: Infant of an HIV-infected mother who did not receive antiretroviral drugs during pregnancy or labor	Give orally administered zidovudine to the newborn for 6 weeks after birth. Consider use of additional antiretroviral drugs.
Mode of delivery	
Scenario A: HIV-infected woman presenting late in pregnancy, not receiving antiretroviral drug therapy and unlikely to have laboratory evaluations before delivery	Begin antiretroviral drug therapy. Consider elective cesarean section at 38 weeks of gestation.
Scenario B: HIV-infected woman initiating prenatal care in third trimester, receiving highly active antiretroviral drug therapy but with a viral load of >1,000 copies per mL	Continue antiretroviral drug therapy as long as the viral load is dropping appropriately. Consider elective cesarean section at 38 weeks of gestation.
Scenario C: HIV-infected woman on highly active antiretroviral drug therapy with an undetectable viral load	Whether elective cesarean section has any additional benefit is unclear. The risk of vertical transmission of HIV is less than 2 percent with vaginal delivery.
Scenario D: HIV-infected woman who has elected cesarean section for delivery but presents in labor	Begin intravenous administration of zidovudine. If delivery is imminent, vaginal delivery may be used, with oxytocin (Pitocin) augmentation considered. If a long labor is anticipated, consider proceeding with cesarean section. The risk of vertical transmission of HIV is increased with rupture of membranes for longer than 4 hours.

HIV = human immunodeficiency virus.

Adapted from Public Health Service Task Force recommendations for the use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. Living document: January 24, 2001. Retrieved February 2001, from <http://www.hivatis.org/trtgdlns.html#Perinatal>.

ficity of 94.9 percent; however, it is less accurate in neonates. In infants with a low risk of transmission, the positive predictive value of the HIV DNA PCR test is 55.8 percent during the first month after birth and 83.2 percent after the first month.¹⁷

Although the HIV culture is as sensitive as the HIV DNA PCR test, culture is more expensive, and results are not available for two weeks.¹⁸ Of the direct detection tests, the p24 antigen level is the least sensitive and has a high false-positive rate.¹⁹⁻²¹ The HIV RNA viral level is a useful measure of disease pro-

gression in patients with known HIV infection. However, the HIV RNA viral level is generally not recommended for use in screening infants for HIV infection, because commercially available assays have a lower sensitivity and specificity than the HIV DNA test.²²

The HIV DNA PCR test should be performed before the newborn of an HIV-positive mother is 48 hours old. The test should be repeated when the infant is one to two months old, and again at age four to six months⁶ (Table 4).^{4,7,23} The first PCR test should not be performed on cord blood because of an

All newborns of HIV-infected mothers should receive *Pneumocystis carinii* pneumonia prophylaxis starting at age six weeks and continuing until HIV infection is excluded.

increased risk for a false-positive result. HIV infection is definitively diagnosed by two positive virologic tests performed on separate blood samples.

If three virologic tests are negative (at birth, one month of age and four months of age), there is a 95 percent chance that the infant is not infected with HIV.⁷ A negative HIV-specific IgG assay (ELISA) at 18 months of age definitively rules out HIV infection in exposed infants.

The CD4⁺ lymphocyte level should be monitored to assess the infant's immune status, and the complete blood cell count should be followed to monitor for medication side effects. The absolute number of CD4⁺ lymphocytes varies with age, but the percentage of CD4⁺ lymphocytes does not; hence, the CD4⁺ percentage is a better marker for assessing an infant's immune status.

***Pneumocystis carinii* Pneumonia Prophylaxis**

Pneumocystis carinii pneumonia in infants can have an acute onset and a high mortality rate. It is often the first indicator of perinatal HIV infection.²⁴ In HIV-infected infants, the peak incidence of *P. carinii* pneumonia is at three to six months of age. This pneumonia can occur in HIV-infected children younger than one year, regardless of the CD4⁺ lymphocyte count (unlike in HIV-infected adults). Therefore, all newborns of HIV-infected mothers should receive *P. carinii* pneumonia prophylaxis starting at six weeks of age and continuing until HIV infection is excluded.²⁵

The recommended agent for *P. carinii* pneumonia prophylaxis is trimethoprim-sulfamethoxazole (Bactrim, Septra).²⁶ Dapsone and atovaquone (Mepron) are possible alternatives (Table 5).²⁵ Because of the side effects of these medications, the complete blood count should be evaluated at the initiation of therapy and monthly thereafter.¹⁶

P. carinii pneumonia prophylaxis should be started after completion of six weeks of zidovudine therapy. Prophylaxis is not recommended

before four weeks of age because of the low incidence of this pneumonia in neonates. Also, trimethoprim-sulfamethoxazole can exacerbate the anemia caused by zidovudine and increase adverse effects on the newborn's immature bilirubin metabolism.

Prophylactic medication can be discontinued when two HIV DNA PCR tests are negative (one after the infant is one month old and the other after the infant is four months old). Prophylaxis in an HIV-infected infant should be continued until the age of 12 months, regardless of the CD4⁺ lymphocyte count. After the age of 12 months, the need for prophylaxis is determined by the CD4⁺ lymphocyte count.

Screening for Tuberculosis

The reemergence of tuberculosis has coincided with the spread of HIV.²⁷ Infants infected with HIV and all children living with an HIV-positive person are at increased risk for tuberculosis. HIV-infected pregnant women should be screened for tuberculosis before delivery. Infants should be kept away from any person with active pulmonary disease until that person is no longer considered to be contagious.⁷

Infants and young children exposed to a person with active tuberculosis should have a purified protein derivative (PPD) skin test and a chest radiograph. A positive PPD test in HIV-exposed or HIV-infected children is 5 mm of induration. Even if the PPD test is negative, infants who have been exposed to tuberculosis should be given isoniazid (INH) for three months.⁷ Then, the PPD test should be repeated. If the test is negative, isoniazid may be discontinued. If the test is positive, prophylaxis is continued.²⁸ All HIV-infected children should have a screening PPD test annually, starting at 12 months of age.

Modifications of Standard Infant Care

Although perinatal exposure to HIV generally does not result in prematurity or low birth weight, newborns need to be monitored closely for appropriate growth and neuro-

TABLE 4
Overall Management and Monitoring of Infants Exposed to HIV

Tests, treatments, vaccines	Birth	1 mo.	6 wks	2 mo.	3 mo.	4 mo.	6 mo.	9 mo.	12 mo.	15 mo.	18 mo.
HIV DNA PCR test	X		X				X				
HIV-specific IgG assay: ELISA											X
Complete blood cell count	X	X	X	X	X	X					
CD4 ⁺ lymphocyte count and percentage		X			X						
Zidovudine (Retrovir)	Start [—————] Stop										
<i>Pneumocystis carinii</i> pneumonia prophylaxis	Start [—————] Stop*										
Hepatitis B vaccine†	[————— First dose —————] [————— Second dose —————]										
Diphtheria and tetanus toxoids and acellular pertussis vaccine				X		X	X				X
Inactivated poliovirus vaccine				X		X			X		
Haemophilus influenzae b conjugate vaccine				X		X	X			X	
Pneumococcal 7-valent conjugate vaccine				X		X	X			X	
MMR vaccine‡										X	
Varicella vaccine§											X
Influenza vaccine							X				

HIV DNA PCR = human immunodeficiency virus DNA polymerase chain reaction; ELISA = enzyme-linked immunosorbent assay; HBsAg = hepatitis B surface antigen; MMR = measles, mumps and rubella; CDC = Centers for Disease Control and Prevention.

*—Prophylaxis is stopped if HIV DNA PCR testing is negative at birth, age 6 weeks and age 4 to 6 months.

†—If the mother is HBsAg-negative, the infant is given the first dose of hepatitis B vaccine by age 2 months, the second dose 1 month after the first dose, and the third dose 2 months after the second dose but not before age 6 months. If the mother is HBsAg-positive, the infant is given the first dose of hepatitis B vaccine at birth along with hepatitis B immunoglobulin; the second dose of vaccine is given at age 1 to 2 months, and the third dose is given at age 6 months.

‡—Combination MMR vaccine is safe for HIV-negative infants and for HIV-positive infants with a minimally to moderately compromised immune system (CDC immune category I or II).

§—Varicella vaccine is safe for HIV-negative infants and for HIV-positive infants with a minimally compromised immune system (CDC immune category I).

||—Influenza vaccine may be given after age 6 months during the appropriate season.

Information from Public Health Service Task Force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing perinatal HIV-1 transmission in the United States. *MMWR Morb Mortal Wkly Rep* 1998;47(RR-2):1-30; Evaluation and medical treatment of the HIV-exposed infant. *Pediatrics* 1997;99:909-17; and Immunization in special circumstances. In: Pickering LK, ed. 2000 Red book: report of the Committee of Infectious Diseases. 25th ed. Elk Grove Village, Ill.: American Academy of Pediatrics, 2000:54-69.

development, as well as signs of perinatal exposure to other infectious diseases.²⁹

The HIV-exposed newborn should be tested for syphilis, hepatitis B, and hepatitis C if the mother has not been screened. If the mother is hepatitis B surface antigen-positive, the infant should receive hepatitis B immunoglobulin and hepatitis B vaccine at birth, and hepatitis vaccine again at one to two months of age and six months of age.

HIV-exposed infants need the appropriate standard immunizations: diphtheria and tetanus toxoids and acellular pertussis vaccine, *Haemophilus influenzae* b conjugate vaccine, inacti-

vated poliovirus vaccine, pneumococcal seven-valent conjugate vaccine, and hepatitis B vaccine^{23,30} (Table 4).^{4,7,23}

Live virus vaccines should be used with caution in HIV-exposed infants, both for their safety and the safety of HIV-infected family members. The combination measles-mumps-rubella vaccine can be given to the HIV-positive infant who has only a minimally to moderately compromised immune system (Centers for Disease Control and Prevention [CDC] immune category I or II).²³ Varicella vaccine can be given to the HIV-positive infant who has a minimally compromised immune

system (CDC immune category I) after parents have been informed about the benefits and risks of immunization.²³ Influenza vaccine should be given annually starting at six months of age until HIV infection has been ruled out.²⁹

Immunizations may not be effective in immunocompromised persons. The ability to respond to vaccines is likely to be related to overall immune status at the time of immunization. As a result, infants of HIV-infected mothers who are exposed to vaccine-preventable diseases (e.g., varicella, measles, tetanus) should be considered for passive immunoprophylaxis or chemoprophylaxis, regardless of immunization status, unless recent serologic tests demonstrate adequate antibody concentrations.²³

At each routine examination, parents and other caregivers should be educated about warning signs of HIV and opportunistic infections. HIV-infected infants are at increased risk for serious bacterial infections. Fever warrants early evaluation and presumptive treatment, pending further clarification of its cause.

Parents and other caregivers also should be educated about preventing exposure to opportunistic infections. Appropriate measures include avoiding undercooked foods (salmonellosis), cat litter boxes (toxoplasmosis), and potentially contaminated water (giardiasis and cryptosporidiosis).⁷

Psychosocial Issues

HIV-infected mothers may have multiple physical, emotional, and social concerns, including coming to terms with the reality of their own infection while facing uncertainty about the HIV status of their infant. Physicians should help these women obtain necessary social services, access to appropriate subspecialist care, and guidance in providing long-term care for their children in the event of their incapacitation or death.

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TABLE 5

Regimens for *Pneumocystis carinii* Pneumonia Prophylaxis in Infants

Recommended drug: trimethoprim-sulfamethoxazole suspension (Bactrim, Septra). All dosing regimens use trimethoprim at 150 mg per m² daily (or 5 mg per kg daily) with sulfamethoxazole at 750 mg per m² daily (or 25 mg per kg daily).

Recommended dosing regimen: trimethoprim-sulfamethoxazole taken orally twice daily three times a week on three consecutive days (e.g., Monday, Tuesday, Wednesday)

Acceptable alternative dosing regimens for trimethoprim-sulfamethoxazole:

Orally once daily three times a week on three consecutive days

Orally twice daily for one week

Orally twice daily three times a week on alternate days (e.g., Monday, Wednesday, Friday)

Alternative drugs and regimens*:

Dapsone: in infants 1 month of age and older, the dosage is 2 mg per kg taken orally once daily (maximum of 100 mg per dose)

Atovaquone (Mepron): in infants 1 to 3 months of age and young children older than 24 months of age, the dosage is 30 mg per kg daily taken orally; in infants and young children 4 to 24 months of age, the dosage is 45 mg per kg daily taken orally.

*—Only if trimethoprim-sulfamethoxazole is not tolerated.

Adapted with permission from 1995 revised guidelines for prophylaxis against Pneumocystis carinii pneumonia for children infected with or perinatally exposed to human immunodeficiency virus. MMWR Morb Mortal Wkly Rep 1995;(RR-4):1-11.

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