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CLINICAL REPORT

Guidance for the Clinician in Rendering Pediatric Care

Evaluation and Treatment of the Human Immunodeficiency Virus-1–Exposed Infant

ABSTRACT. In developed countries, care and treatment are available for pregnant women and infants that can decrease the rate of perinatal human immunodeficiency virus type 1 (HIV-1) infection to 2% or less. The pediatrician has a key role in prevention of mother-to-child transmission of HIV-1 by identifying HIV-exposed infants whose mothers' HIV infection was not diagnosed before delivery, prescribing antiretroviral prophylaxis for these infants to decrease the risk of acquiring HIV-1 infection, and promoting avoidance of HIV-1 transmission through human milk. In addition, the pediatrician can provide care for HIV-exposed infants by monitoring them for early determination of HIV-1 infection status and for possible short- and long-term toxicities of antiretroviral exposure, providing chemoprophylaxis for *Pneumocystis* pneumonia, and supporting families living with HIV-1 infection by providing counseling to parents or caregivers. *Pediatrics* 2004;114:497–505; *HIV-1, mother-to-child transmission, HIV-exposed infants, antiretroviral, diagnosis.*

ABBREVIATIONS. HIV, human immunodeficiency virus; AAP, American Academy of Pediatrics; EIA, enzyme immunoassay; ZDV, zidovudine; NVP, nevirapine; 3TC, lamivudine; TB, tuberculosis; PCR, polymerase chain reaction; PCP, *Pneumocystis* pneumonia.

INTRODUCTION

The epidemiology of perinatal human immunodeficiency virus type 1 (HIV-1) infection in North America has changed drastically with implementation of strategies to prevent perinatal HIV-1 transmission. Prevention of 98% of perinatal HIV-1 infections is a realizable goal. HIV-1 testing and interventions to decrease the rate of HIV-1 transmission during pregnancy are detailed in an American Academy of Pediatrics (AAP) technical report.[1] Prevention of perinatal HIV infection requires coordinated efforts from health care professionals caring for both the mother and the child. Those caring for infants born to HIV-1–infected mothers should ensure that strategies for prevention are continued after delivery, that infants are followed and tested for early determination of their HIV infection status, and that appropriate steps are taken for treatment or prevention of other congenital and perinatal infections associated with HIV-1 infection. The pediatrician has a key role in counseling parents, identifying families' needs, and linking them with additional support services.

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

Identification of Maternal HIV-1 Infection

Failure to identify HIV-1 infection of the mother before delivery is clearly suboptimal for prevention of perinatal transmission and for care of the mother. Therefore, programs to identify and initiate care for HIV-1 infection before or during pregnancy should be a priority.[2,3] However, identification of HIV-1 exposure even during labor or at birth rather than later allows for improved care of the HIV-exposed infant.

HIV Testing of the Infant if the Mother's HIV-1-Infection Status Is Unknown

If the infant is born to a mother whose HIV-1 infection status is unknown, the mother or the infant should have HIV-1 testing with maternal consent.[1,4–7] Documented consent for maternal and/or newborn HIV testing may be obtained in a variety of ways, including by right of refusal (documented patient education with testing to take place unless rejected in writing by the patient). The AAP supports use of consent procedures that facilitate rapid incorporation of HIV education and testing into routine medical care settings.[1] Some states mandate HIV-1 testing of all infants whose mothers' HIV-1 infection status is unknown. To intervene with postnatal prophylaxis, the neonatal HIV-1 test result should be available as soon as possible after birth and certainly within 24 hours. This is feasible by using "expedited" HIV-1 enzyme immunoassay (EIA) or by using rapid testing kits. An expedited EIA uses the first step of the standard laboratory HIV-1 antibody testing, with both positive and negative test results being available within 24 hours. A rapid test is one using a kit designed to test a single specimen for HIV-1 antibodies, with a result available within minutes to 2 hours.

Two such tests, OraQuick Rapid HIV-1 Antibody Test (OraSure Technologies Inc, Bethlehem, PA) and Single Use Diagnostic System (SUDS) HIV-1 Test (Murex Corporation, Norcross, GA), are licensed in the United States.[8,9] Clinical testing of a comparable kit is underway in Canada.

The rapid test result should be confirmed by standard HIV-1 testing. If the expedited EIA or the rapid test result is positive, then a confirmatory supplemental test is required to diagnose HIV-1 seropositivity definitively. Starting antiretroviral infant prophylaxis as soon as possible after birth (before 24 hours of age) is critical to prevent perinatal transmission. Therefore, if antiretroviral prophylaxis is given to an infant born to a mother with a positive EIA or rapid test result, it should be initiated pending results of her confirmatory test. The decision whether to start antiretroviral prophylaxis would take into consideration the positive predictive value of the screening test and the potential benefits and risks of the prophylactic agents.[10]

INTERVENTIONS FOR PREVENTION OF PERINATAL HIV-1 TRANSMISSION

Antiretroviral Prophylaxis When Initiated During Pregnancy

In North America, most HIV-1–infected pregnant women receive care for HIV infection during the prenatal period, in which case most receive combination antiretroviral therapy with 3 or more drugs, have a low viral load, have access to obstetric interventions such as scheduled cesarean section at 38 weeks' gestation, and plan not to breastfeed. Perinatal HIV-1 transmission rates as low as 1% have been observed in such circumstances.[11,12] When prenatal and intrapartum maternal antiretroviral therapy have been received, administration of zidovudine (ZDV) for 6 weeks to the infant remains the preferred prophylactic regimen for most infants.[1,13] Two studies conducted in developing countries have suggested that a single maternal intrapartum dose and a single neonatal dose of nevirapine (NVP) in addition to short-course maternal ZDV (with oral ZDV during labor and either no infant prophylaxis or 1 week of infant ZDV prophylaxis) may provide increased efficacy in decreasing perinatal transmission compared with short-course maternal ZDV alone.[14,15] In contrast to these studies, a clinical trial in the United States, Europe, Brazil, and the Bahamas (PACTG 316) evaluated whether the addition of a single dose of NVP to the regimens of both the mother and infant compared with placebo added to standard antiretroviral therapy for both would provide additional benefits in lowering transmission; at a minimum, women received prenatal and intrapartum ZDV, and 75% of women received combination therapy. All infants received standard 6-week ZDV prophylaxis. In this study, transmission rates were very low in both groups (1.5%), and the addition of NVP did not demonstrate any additional protection against perinatal transmission but was associated with the development of NVP-resistance mutations 6 weeks after birth in 15% of the women who received NVP.[16,17] Thus, currently, addition of NVP as a single maternal intrapartum dose with a single neonatal dose is not recommended for women who have received highly active antiretroviral therapy during pregnancy.[11]

Antiretroviral Prophylaxis When Initiated During Labor

If the woman's HIV-1 infection status is determined only at the time of labor and delivery, several effective regimens for prevention of perinatal transmission are available (Table 1). These regimens include:

TABLE 1. Maternal Intrapartum and Infant Prophylactic Antiretroviral Drug Regimens When an HIV-1—Infected Mother Has Not Received Prenatal Antiretroviral Therapy

Drug	Maternal Dosing, Intrapartum	Infant Dosing	Infant Schedule
NVP	Single 200-mg dose PO at onset of labor	2 mg/kg PO single dose	Single dose at 48–72 h
ZDV with 3TC	ZDV, 600 mg PO at onset of labor followed by 300 mg PO every 3 h until delivery; and 3TC, 150 mg PO at onset of labor followed by 150 mg PO every 12 h until delivery	ZDV, 4 mg/kg PO every 12 h; and 3TC, 2 mg/kg PO every 12 h	For 1 wk
ZDV	2 mg/kg, IV bolus followed by continuous infusion of 1 mg/kg per h until delivery	2 mg/kg PO 4 times per day If unable to tolerate oral therapy, 1.5 mg/kg IV every 6 h If infant is preterm, 1.5 mg/kg every 12 hours for 2 weeks and then increase to 2 mg/kg every 8 h	Beginning 8–12 h after birth and continuing through 6 wk of age
ZDV with NVP	ZDV, 2 mg/kg IV bolus followed by continuous infusion of 1 mg/kg per h until delivery; and NVP, single 200-mg dose, PO, at onset of labor	ZDV, 2 mg/kg PO 4 times per day; and NVP, 2 mg/kg PO single dose	Start ZDV beginning 8–12 h after birth and continuing through 6 wk of age; and single dose of NVP at 48–72 h of age

IV indicates intravenous; PO, oral.

1. One oral dose of NVP at the onset of labor followed by 1 oral dose of NVP for the infant 48 to 72 hours after birth
2. Intrapartum oral ZDV and lamivudine (3TC) followed by 1 week of oral ZDV and 3TC for the infant
3. Intrapartum intravenous ZDV followed by 6 weeks of ZDV for the infant
4. The ZDV with NVP regimen, 1 oral dose of NVP at the onset of labor, followed by 1 oral dose of NVP for the infant, combined with intrapartum intravenous ZDV, followed by 6 weeks of ZDV for the infant

In randomized, clinical trials among breastfeeding populations, the NVP regimen and the ZDV-with-3TC regimen have been shown to decrease the rate of perinatal transmission by 38% to 47%.[1,13,18–21] Observational data from populations of HIV-1–infected women in which breastfeeding is uncommon suggest that the third regimen, maternal intrapartum and infant ZDV alone, is associated with lower transmission rates when compared with no intervention (10% vs 27%, respectively, in New York state and 11% vs 31%, respectively, in North Carolina).[22,23] The fourth regimen of ZDV with NVP is theoretically appealing, but limited data are available to address whether the combination regimen offers added benefit to either drug alone.[13] Conflicting data are available from a study conducted in Malawi of women first identified as HIV-1 infected during labor, in which the effect of a single maternal intrapartum and single neonatal dose of NVP was compared with the same NVP regimens plus 1 week of ZDV for the infant.[24] When the mother received intrapartum NVP, there was no difference between the NVP and NVP-plus-ZDV groups; however, when the woman did not receive intrapartum NVP, the combination regimen seemed to have greater efficacy.[24] Thus, at the present time, any of the 4 potential intrapartum/postnatal regimens are reasonable to consider in the circumstance in which the woman had not received antiretroviral therapy during pregnancy.

Postnatal Antiretroviral Prophylaxis

When the mother's or infant's HIV-1 infection status is known only after the infant's birth and, thus, maternal prenatal and intrapartum antiretroviral therapy is not received, observational data suggest that 6 weeks of antiretroviral prophylaxis with ZDV given to the infant may provide some protection against transmission if initiated within 24 hours of birth.[13,22] This 6-week ZDV regimen is considered standard for prophylaxis in this circumstance in developed countries.[13] Results from the Malawi study comparing single-dose infant NVP to single-dose infant NVP plus 1 week of infant ZDV to infants whose mothers did not receive antiretroviral therapy during pregnancy suggest that the combination regimen is more effective than single-dose infant NVP alone, but only if the mother did not receive intrapartum NVP.[24] However, whether this combination would be more effective than the standard 6-week course of ZDV prophylaxis used in developed countries is unknown. Although data to demonstrate superior efficacy of combination regimens are lacking, when only infant prophylaxis can be provided, some clinicians combine the 6-week infant ZDV prophylaxis regimen with 1 or more additional antiretroviral drugs, viewing the situation as analogous to postexposure prophylaxis in other circumstances.

Data from studies of animals indicate that the longer the delay in institution of prophylaxis, the less likely that infection will be prevented. In most studies of animals, antiretroviral prophylaxis initiated 24 to 36 hours after exposure usually is not effective for preventing infection.[25–27] HIV-1 infection is established in most perinatally infected infants by 1 to 2 weeks of age. Initiation of postexposure prophylaxis after 2 days of age is not likely to be efficacious in preventing transmission, and by 14 days of age infection would be established in most infants.

Avoidance of HIV-1 Infection From Human Milk

Postnatal HIV-1 transmission can occur from ingestion of human milk from HIV-1–infected women. The literature on breastfeeding and HIV-1 transmission is detailed in the AAP technical report "Human Milk, Breastfeeding, and Transmission of Human Immunodeficiency Virus-1 Infection in the United States."[28] In the United States and Canada, where infant formulas are safe and readily available, an HIV-1–infected mother should be advised not to breastfeed even if she is receiving antiretroviral therapy.[1,13] Complete avoidance of breastfeeding (and milk donation) by HIV-1–infected women remains the only mechanism by which prevention of human milk transmission of HIV-1 can be ensured.

CARE OF THE HIV-1–EXPOSED INFANT

Assessment at Birth

At the time of the initial assessment of the infant (see Table 2), maternal health information should be reviewed to determine if the infant may have been exposed to maternal coinfections such as tuberculosis (TB), syphilis, toxoplasmosis, hepatitis B or C, cytomegalovirus, or herpes simplex virus.[29] Although there is little information as to the relative transmission or infection rates of these agents in infants of mothers with and without HIV-1 infection, there is theoretic concern that latent infections may reactivate in immunocompromised pregnant women and be transmitted to their infants. Diagnostic testing and treatment of the infant are based on maternal findings.

Determination of the Infant's HIV-1 Infection Status

Determining as soon as possible whether the HIV-1–exposed infant is infected is important to allow early initiation of antiretroviral therapy and adjunctive therapies as needed. The types of virologic assays that detect the virus include the following.

- HIV-1 DNA polymerase chain reaction (PCR): these PCR assays detect HIV-1 DNA within the peripheral blood mononuclear cells. For HIV-1 subtype B, the most common subtype in North America, the sensitivity and specificity of HIV-1

TABLE 2. Care of the HIV-1–Exposed Infant (Birth to 6 Months of Age)

	Infant Age						
	Birth	4 wk	6 wk	2 mo	3 mo	4 mo	6 mo
History and physical examination	X	X		X			X
Assess risk of other infections*	X						
Antiretroviral prophylactic regimen†	⟵	———	⟶				
CBC and differential leukocyte counts	X	X		X			
HIV-1 DNA PCR or other virologic assays for HIV-1‡	X	⟵	———	⟵	———	———	⟶
Initiate prophylaxis for PCP§			⟵	———	⟶		

If during this period the infant is diagnosed as HIV-1 infected, then laboratory monitoring and immunizations should follow the guidelines for treatment of pediatric HIV-1 infection.[27] CBC indicates complete blood cell; arrows indicate the time intervals over which the procedure may be performed.

* Review maternal health information to assess for possible exposure to coinfections (see text).

† ZDV is usually the preferred prophylactic agent, although alternatives are: 1) ZDV with 3TC; 2) NVP; or 3) ZDV with NVP when the mother did not receive prenatal antiretroviral therapy (see Table 1). The arrow indicates treatment spanning from birth to 6 weeks of age.

‡ See text for discussion of HIV-1 virologic assays. If a test result is positive, repeat HIV-1 DNA PCR assay immediately to confirm infection. Some HIV-1 specialists suggest an additional HIV-1 DNA PCR test at 2 weeks of age. If clinical status or other laboratory parameters suggest HIV-1 infection, repeat testing as soon as possible. If by 4 months of age the test results are all negative for infection, testing for HIV-1 seroreversion at 12 to 18 months of age is indicated to definitively exclude HIV-1 infection.

§ The preferred prophylactic agent is trimethoprim-sulfamethoxazole; alternatives are dapsone, pentamidine, and atovaquone (Table 3). The arrow indicates the time interval over which the procedure may be performed.

DNA PCR assays approach 96% and 99%, respectively, by 28 days of age.[30] However, the currently available HIV-1 DNA PCR assays have less sensitivity for detection of non-B subtype, and false-negative DNA PCR assay results have been reported for infants infected with non-B subtype virus infection.[31–33]

- HIV-1 RNA assays: these assays detect viral RNA in the plasma by using a variety of methodologies including PCR, in vitro signal amplification nucleic probes (branched DNA, also known as bDNA), and nucleic acid sequence-based amplification (NASBA). RNA assays may be at least as sensitive or more sensitive than HIV-1 DNA PCR assays and are as specific.[34–37] Some HIV-1 RNA assays may be more sensitive than HIV-1 DNA PCR assays for detection of non-B subtype.[37] Although the sensitivity of HIV-1 RNA assays has been shown not to be affected by the use of ZDV alone as prophylaxis,[37,38] it is not known if it would be affected by the use of additional antiretroviral agents.
- HIV-1 peripheral blood cell culture: HIV-1 culture has largely been replaced by HIV-1 DNA PCR assays. HIV-1 culture is expensive, is available in only a few laboratories, and may require up to 28 days for positive results.
- HIV-1 immune complex-dissociated p24 antigen: HIV-1 p24 antigen is not recommended for diagnosis in infants because of its low sensitivity.

In general, HIV-1 DNA PCR assay is the preferred diagnostic test in North America.[1,3] However, women who acquired their HIV-1 infection outside North America or Western Europe may be infected with an HIV-1 non-B subtype.[39] For infants born to women known or suspected to be infected with non-B subtypes, consultation with an HIV-1 specialist is recommended for advice on diagnostic investigations. The birth specimen must be a neonatal, not cord blood, sample. Cord-blood sampling is associated with an unacceptably high rate of false-positive test results. For infants born in North America who have not been breastfed, if the HIV-1 DNA PCR assay results (obtained at birth, at 4–7 weeks of age, and at 8–16 weeks of age) are negative, then HIV-1 infection has been reasonably excluded.[40]

If the mother is HIV-2 infected, then the laboratory HIV antibody tests, but not all rapid tests, will detect both HIV-1 and HIV-2. In these circumstances, a specific request must be made for HIV-2 PCR testing for diagnosis of HIV-2 infection in the infant.

Management if an HIV-1 Virologic Assay Result Is Positive

A positive HIV-1 virologic assay result should be repeated immediately for confirmation. If infection is confirmed, an HIV-1 specialist should be consulted for advice regarding antiretroviral therapy. It is currently recommended that treatment be initiated in all HIV-infected infants younger than 12 months who have HIV-associated clinical or immunologic abnormalities regardless of HIV-1 RNA level, and that therapy be considered for HIV-infected infants younger than 12 months who are asymptomatic and have normal immune parameters.[41] This recommendation is based on the substantial risk of rapid disease progression in infants and the inability to predict those at risk of rapid disease progression.[42–44]

Role of HIV-1 Antibody Testing in HIV-1–Exposed Infants

Serologic testing after 12 months of age is used to confirm that maternal HIV-1 antibodies transferred

to the infant in utero have disappeared. If the child is still antibody positive at 12 months of age, then testing should be repeated at 18 months of age.[3,40] Loss of HIV-1 antibody in a child with previously negative HIV-1 DNA PCR test results definitively confirms that the child is HIV-1 uninfected. Positive HIV-1 antibodies at ≥18 months of age indicates HIV-1 infection. Repeat HIV-1 antibody testing at 24 months of age is no longer recommended.

Prevention of *Pneumocystis* Pneumonia

Pneumocystis pneumonia (PCP) is the most common serious opportunistic infection in HIV-1–infected children. This condition is caused by *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*). It is recommended that PCP prophylaxis be started at or near the completion of ZDV prophylaxis (4–6 weeks of age) but discontinued when HIV-1 infection is reasonably excluded. PCP prophylaxis would be discontinued, therefore, when results of 2 virologic assays performed on 2 separate samples, 1 after 1 month of age and the other after 2 to 4 months of age, are known to be negative (see Table 2). Drugs and dosing regimens for PCP prophylaxis in the infant are listed in Table 3. Infants who are HIV-1 infected should remain on PCP prophylaxis until 12 months of age, at which time they should receive PCP prophylaxis according to guidelines from the US Public Health Service/Infectious Diseases Society of America for prevention of opportunistic infections.[45]

Prevention of TB

The populations at risk of infection with HIV-1 and TB overlap. Therefore, for the infant born to an HIV-1–infected mother, information should be obtained regarding the TB infection status of the mother and other household members. If the mother has hematogenous dissemination of TB, the infant should be evaluated for congenital TB as outlined in US or Canadian TB guidelines.[46–48] If the mother or a household member has active TB that is of a contagious form, the infant should be separated from that person, if possible, until the person is considered noncontagious. If the infant is exposed to TB, the infant should be managed as outlined in US or Canadian TB guidelines.[46–48] Although the BCG vaccine is widely used in infants around the world for prevention of TB, it is rarely used in most of North America and is contraindicated in infants who are HIV-1 infected or are of unknown HIV-1 status.[49]

Immunizations

All routine infant immunizations should be given to HIV-1–exposed infants.[50,51] However, if HIV-1 infection is confirmed, then guidelines for the HIV-1–infected child should be followed.[50–54]

Monitoring for Toxicity From Exposure to Antiretroviral Drugs in Utero and During Infancy

Infants born to HIV-1–infected mothers who have received prenatal care and are receiving therapy according to the US Public Health Service guidelines for treatment of HIV-1 infection will be exposed to antiretroviral agents in utero and as infants.[1,13,55,56] Some studies suggest that combination antiretroviral therapy during pregnancy increases the risk of preterm birth and other adverse outcomes of pregnancy.[57] However, a review of outcomes in 7 studies in which 3266 HIV-1–infected pregnant women were enrolled suggests that combination therapy is not associated with increased rates of preterm birth, low birth weight, low Apgar scores, or stillbirth.[58]

The data available on the short- and long-term toxicity for the infant exposed to combinations of antiretroviral drugs in utero are limited.[10,59] The most common short-term adverse consequence with ZDV prophylaxis is anemia.[10,59] Therefore, infants receiving ZDV should have a complete blood cell count at birth, 1 month of age, and 2 months of age (Tables 1 and 2). Transient lactatemia also has been observed, but the significance of this is not known.[60,61] Mitochondrial dysfunction was described in 8 of 1754 (0.46%) uninfected infants in a French cohort with in utero exposure to ZDV with 3TC or to ZDV alone.[62] Two of these infants developed severe neurologic disease and died (both exposed to ZDV with 3TC); 3 had mild-to-moderate symptoms (including a transient cardiomyopathy); and 3 had no symptoms but transient laboratory abnormalities including high lactate concentration.[62] Another evaluation of mitochondrial toxicity was conducted in 4392 uninfected or HIV-indeterminate children (2644 with perinatal antiretroviral exposure) followed within the French Pediatric Cohort or identified within a France National Register developed for reporting possible mitochondrial dysfunction in

TABLE 3. Regimens for PCP Prophylaxis in Infants

Drug	Dose	Route	Schedule
Trimethoprim-sulfamethoxazole	Trimethoprim 150 mg/m^2 per day, with sulfamethoxazole 750 mg/m^2 per day	PO	Twice daily for 3 days per wk (consecutive days, eg, Monday, Tuesday and Wednesday) or alternate days (every Monday, Wednesday, and Friday) Alternatives: once daily for 3 days per wk or twice daily for 7 days per wk
Dapsone	2 mg/kg	PO	Once daily
	4 mg/kg	PO	Once weekly
Pentamidine	4 mg/kg	IV	Every 2–4 weeks
Atovaquone			
Infants 1–3 mo of age	30 mg/kg	PO	Once daily
Infants 4–24 mo of age	45 mg/kg	PO	Once daily

IV indicates intravenous; PO, oral.

HIV-exposed children. Evidence of mitochondrial dysfunction was identified in 12 children (including the previous 8 reported cases), all of whom had perinatal antiretroviral exposure, an 18-month incidence of 0.26%.[63] Similar findings have not been reported from other cohorts.[10,64] The French Perinatal Cohort Study Group has also reported a potential increase in the rate of early febrile seizures in uninfected infants with antiretroviral exposure (cumulative risk of first febrile seizure by 18 months of age of 1.1% in antiretroviral-exposed infants, compared with 0.4% in unexposed infants).[65] The strength of the association of these clinical and laboratory findings with in utero antiretroviral exposure is controversial.[59,64] However, if causal, significant disease or death seem to be extremely rare, and the potential morbidity or mortality needs to be compared with the proven benefit of ZDV in decreasing the risk of mother-to-child transmission of a fatal infection by nearly 70%. These data emphasize the importance of long-term follow-up for any child with exposure to antiretroviral drugs regardless of infection status.[13]

Although the use of ZDV monotherapy does not seem to be teratogenic, in utero exposure to multiple antiretroviral drugs is increasingly frequent, and little is known of the teratogenic risk of such exposures.[13,56,66,67] For example, efavirenz, a nonnucleoside reverse-transcriptase inhibitor, is teratogenic in monkeys, causing significant central nervous system malformations in infant cynomolgus monkeys.[56] There has been a case report of myelomeningocele in a human infant born to a woman who was receiving efavirenz at conception and during the first trimester.[67,68] Exposure of fetal monkeys to tenofovir was not associated with gross structural abnormalities, but lower circulating concentrations of growth factors, a 13% decrease in birth weight, and a transient decrease in bone porosity were observed.[56] Hydroxyurea is another antiretroviral agent for which teratogenicity has been observed in several animal species, but information in human pregnancies is limited.[69–71] Other medications given to the mother for complications associated with HIV-1 infection also can be teratogenic. For example, fluconazole has been associated with congenital craniofacial, skeletal, and cardiac anomalies in infants, but the strength of this association remains controversial.[72–74]

Until there are more data on the safety of in utero antiretroviral exposure, infants should be monitored by examination at birth for congenital anomalies[13,56] and assessed at 6 months of age and at annual visits for long-term adverse effects of drug exposure. The assessment at follow-up includes evaluation for symptoms and signs suggestive of mitochondrial toxicity.[75,76] Symptoms and signs of mitochondrial toxicity are varied and generally nonspecific, but serious signs and symptoms would include neurologic manifestations including encephalopathy, afebrile seizures or developmental delay, cardiac symptoms attributable to cardiomyopathy, and gastrointestinal symptoms attributable to hepatitis. The physical examination should include a developmental assessment. If abnormalities suggestive of mitochondrial toxicity are observed, then consultation should be obtained with a specialist knowledgeable in this field. There will be regional variation in the specialists knowledgeable in this topic; they may be neurologists, specialists in metabolic disorders, or HIV-1–infection specialists.

Testing Family Members

The infant's father and all siblings should be offered testing for HIV-1 infection. Testing should be strongly recommended. The age of the sibling should not be a deterrent to testing, because it is possible that perinatally infected children may remain asymptomatic for many years, even into adolescence.

Counseling and Support

When counseling the mother of an HIV-1–exposed infant, the pediatrician should take into account that the diagnosis may be recent for the mother, whose infection may have been identified during or after pregnancy. The diagnosis has profound implications for the mother and the family. If the mother is not already receiving care, she should be referred for HIV-1 care for herself. Some families may require additional support because of HIV-1 illness or death in other family members. Other social factors that may lead to an increased need for social services are poverty, substance abuse, depression, lack of health care, unemployment, difficulty finding housing, domestic violence, and fear of loss of existing supports and services, such as loss of support from partner or loss of employment, insurance, or health care coverage. Pregnant adolescents are a particularly vulnerable group, especially early adolescents (10–14 years of age). For women and their families from other countries, there are frequently additional factors related to their culture and concerns about their immigration status.

When counseling new parents or caregivers of an HIV-1–exposed infant, the pediatrician should provide an outline of plans for medical care (Table 2). Important topics to cover are medications to prevent perinatal acquisition of HIV-1 infection and opportunistic infections such as PCP, as well as the schedule of follow-up visits for assessment and laboratory assays (both for the diagnosis of HIV-1 and to check for any adverse effects associated with exposure to antiretroviral drugs). Mothers should be advised not to breastfeed.[28] Parents and caregivers should be advised of the importance of prompt assessment if the infant becomes ill. For the infant in foster care, caregivers should have sufficient information about the infant's health, including HIV-1 infection status, to ensure appropriate health care. The necessity of maintaining confidentiality should be emphasized.[77] HIV-1 infection is not a reason for exclusion from child care.[78] Pediatricians should discuss the need for planning for future care if the mother were to become ill with her HIV-1 infection.[79]

SUMMARY

1. Whenever possible, maternal HIV-1 infection should be identified before or during pregnancy, because this allows for earlier initiation of care

for the mother and for more effective interventions to prevent perinatal transmission.
2. If the maternal HIV-1 infection status is unknown at the time of the infant's birth, then HIV-1 testing of the mother or the infant is recommended with maternal consent and with results available within 24 hours of birth. The expedited EIA and rapid HIV-1 test are screening tests that may be used in this setting.
3. If the test result for HIV-1 is positive, prophylactic antiretroviral therapy should be started promptly in the infant and confirmatory HIV-1 testing should be performed.
4. HIV-1–infected mothers should not breastfeed their infants and should be educated about safe alternatives.[28]
5. Maternal health information should be reviewed to determine if the HIV-1–exposed infant may have been exposed to maternal coinfections including TB, syphilis, toxoplasmosis, hepatitis B or C, cytomegalovirus, and herpes simplex virus. Diagnostic testing and treatment of the infant are based on maternal findings.
6. Pediatricians should provide counseling to parents and caregivers of HIV-1–exposed infants about HIV-1 infection, including anticipatory guidance on the course of illness, infection-control measures, care of the infant, diagnostic tests, and potential drug toxicity.
7. All HIV-1–exposed infants should undergo virologic testing for HIV-1 at birth, at 4 to 7 weeks of age, and again at 8 to 16 weeks of age to reasonably exclude HIV-1 infection as early as possible. If any test result is positive, the test should be repeated immediately for confirmation. If all test results are negative, the infant should have serologic testing repeated at 12 months of age or older to document disappearance of the HIV-1 antibody, which definitively excludes HIV-1 infection.
8. All infants exposed to antiretroviral agents in utero or as infants should be monitored for short- and long-term drug toxicity.
9. Prophylaxis for PCP should be started at 4 to 6 weeks of age in HIV-1–exposed infants in whom infection has not been excluded. PCP prophylaxis may be discontinued when HIV-1 infection has been reasonably excluded.
10. Immunizations and TB screening should be provided for HIV-1–exposed infants in accordance with national guidelines. In the United States, immunization guidelines are established by the AAP, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention, and the American Academy of Family Physicians; in Canada, guidelines are established by the National Advisory Committee for Immunizations.
11. HIV-1 testing should be offered and recommended to family members.
12. The practitioner providing care for the HIV-1–exposed or HIV-1–infected infant should consult with a pediatric HIV-1 specialist and, if the HIV-1–infected mother is an adolescent, also consult with a practitioner familiar with the care of adolescents.

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