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Evaluation and Management of the Infant Exposed to HIV in the United States

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Pediatricians play a crucial role in optimizing the prevention of perinatal transmission of HIV infection. Pediatricians provide antiretroviral prophylaxis to infants born to women with HIV type 1 (HIV) infection during pregnancy and to those whose mother's status was first identified during labor or delivery. Infants whose mothers have an undetermined HIV status should be tested for HIV infection within the boundaries of state laws and receive presumptive HIV therapy if the results are positive. Pediatricians promote avoidance of postnatal HIV transmission by advising mothers with HIV not to breastfeed. Pediatricians test the infant exposed to HIV for determination of HIV infection and monitor possible short- and long-term toxicity from antiretroviral exposure. Finally, pediatricians support families living with HIV by providing counseling to parents or caregivers as an important component of care.

INTRODUCTION

Each year approximately 8500 women with HIV infection give birth in the United States.¹ Through the implementation of effective, cost-saving² preventive strategies during pregnancy, the rate of perinatal transmission of HIV has remained low at <1% to 2%.¹ These preventive strategies include (1) the provision of universal opt-out HIV testing for all pregnant women and for those who have HIV infection, administration of combination antiretroviral therapy (ART) during pregnancy and labor; (2) planned cesarean delivery before the onset of labor and rupture of membranes for pregnant women with an HIV viral load of >1000 copies per mL before delivery; (3) provision of antiretroviral prophylaxis to the infant exposed to HIV for 4 to 6 weeks; and (4) complete avoidance of breastfeeding. Perinatal transmission occurs mostly when there is failure of implementation of these strategies, outlined in a separate 2008 American Academy of Pediatrics (AAP) policy statement titled "HIV Testing and Prophylaxis to Prevent Mother-to-Child Transmission in the United States."^{3,4} This clinical report offers guidance on the evaluation and

abstract

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DOI: <https://doi.org/10.1542/peds.2020-029058>

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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To cite: Chadwick EG, AAP COMMITTEE ON PEDIATRIC AIDS. Evaluation and Management of the Infant Exposed to HIV in the United States. *Pediatrics*. 2020;146(5):e2020029058

management of infants born to women with HIV infection.

In addition to standard clinical care for the newborn infant, it is important that appropriate steps are taken for early detection of HIV infection, appropriate vaccines are administered, and adequate counseling is provided to families living with HIV infection. The management of infants in whom HIV infection is diagnosed should be undertaken in consultation with a pediatric HIV specialist. This report updates previous AAP recommendations.⁵

IDENTIFICATION OF MATERNAL HIV INFECTION

Although there has been a dramatic decrease in the number of new HIV infections in infants in the United States since 1994, when antiretroviral prophylaxis was first documented to prevent perinatal transmission, transmission continues to occur, albeit rarely.¹ Documented cases of perinatal transmission declined rapidly after the adoption of the recommendation by the Centers for Disease Control and Prevention (CDC), the AAP, and the American College of Obstetricians and Gynecologists for routine HIV testing for all pregnant women in the United States. HIV testing is now part of routine prenatal care in most states unless the patient declines, which is also known as “opt-out” consent or “right of refusal.”^{6,7} A second HIV test during the third trimester, preferably before 36 weeks’ gestation, has been found to be cost-effective even in low-prevalence areas and should be considered for all pregnant women.² In particular, pregnant women at high risk for incident HIV infection (eg, those who are incarcerated, reside in communities with an HIV incidence greater than 1 per 1000 per year, inject drugs, exchange sex for money or drugs, are sex partners of individuals living with HIV, or have had a new or more than 1 sex partner

during the current pregnancy) should have HIV testing repeated in the third trimester.⁸ A plasma HIV RNA test is recommended in addition to routine antigen/antibody immunoassay testing when the possibility of acute retroviral syndrome is suspected in a pregnant woman.⁹

TESTING OF THE INFANT WHEN THE MOTHER’S HIV INFECTION STATUS IS UNKNOWN

When the HIV status of the mother is unknown, expedited HIV testing should be performed on the infant after consent procedures consistent with state and local law. Expedited HIV antigen/antibody testing allows timely identification of HIV infection in women whose HIV status is unknown late in pregnancy, during labor, or in the immediate postpartum period and is generally available on a 24-hour basis at all facilities with maternity services and/or a neonatal care unit. Positive HIV antigen/antibody test results should be urgently reported to health care providers so that presumptive HIV therapy can be initiated in the infant as soon after birth as possible and ideally within 6 to 12 hours of life. In addition, breastfeeding should be postponed, and the infant should be given formula feedings. If supplemental test results are negative, antiretroviral drugs should be stopped, and breastfeeding may be reinstated.⁸

STRATEGIES FOR PREVENTION OF PERINATAL HIV TRANSMISSION

Maternal Treatment During Pregnancy

Most women with HIV infection in the United States have access to free prenatal care, which allows for the initiation of effective ART in women in whom HIV is newly diagnosed or continuation of treatment in those who are currently receiving ART.¹⁰ The determination of the appropriate mode of delivery and the decision not

to breastfeed is also made during the prenatal period. The current US Department of Health and Human Services (HHS) Panel on Treatment of Pregnant Women With HIV Infection and Prevention of Perinatal Transmission (Perinatal Guidelines Panel) recommends the use of a combination of at least 3 antiretroviral drugs during pregnancy and labor for all pregnant women with HIV infection regardless of the plasma HIV RNA viral load or CD4⁺ T-lymphocyte count.¹¹

Interventions During Labor and at Delivery

Pregnant women with HIV infection generally continue the routine dosing schedule of their ART regimen during labor if possible. Intravenous zidovudine (ZDV), also known as azidothymidine (AZT), is added for pregnant women with HIV RNA >1000 copies per mL close to delivery and may be considered for RNA levels between 50 and 999 copies per mL, but it is no longer recommended for pregnant women with documented HIV RNA levels <50 copies per mL near delivery.¹² Planned cesarean delivery before labor and the rupture of membranes at 38 weeks’ gestation is recommended for all pregnant women with HIV RNA levels of ≥1000 copies per mL near the time of delivery regardless of maternal HIV treatment.¹³ Cesarean delivery solely for the prevention of transmission is not recommended for pregnant women with HIV RNA levels <1000 copies per mL because of the low risk of perinatal transmission of HIV in this group and the increased risk of complications with a major surgical procedure.¹³

Women who present in labor with unknown HIV status should receive expedited HIV testing with a combined HIV antigen/antibody test. If the screening result is positive, supplemental testing with an HIV-1/HIV-2 antibody differentiation

immunoassay and HIV RNA testing should be performed urgently, and intravenous ZDV should be initiated pending the result of the supplemental test.¹² Prompt initiation of intravenous ZDV, followed by infant antiretroviral prophylaxis, may decrease the risk of perinatal transmission of HIV in these settings.¹⁴ Cesarean delivery before rupture of membranes, if feasible, may also be considered, but there is insufficient evidence to determine if cesarean delivery during labor reduces perinatal transmission.¹³ If the supplemental results are negative, maternal and infant antiretroviral prophylaxis should be stopped.

Antiretroviral Management for the Infant Exposed to HIV

Postnatal antiretroviral drugs should be provided to all infants exposed to HIV to reduce the risk of perinatal HIV transmission. Antiretroviral prophylaxis is defined as the administration of 1 or more antiretroviral drug(s) to a newborn infant without confirmed HIV infection to reduce the risk of HIV acquisition, whereas presumptive HIV therapy consists of the administration of a 3-drug combination antiretroviral regimen to newborn infants at highest risk of HIV acquisition. Presumptive HIV therapy is intended to be preliminary treatment of a newborn infant who is later confirmed to have HIV infection but also serves as prophylaxis against perinatal transmission. Prophylaxis has historically been achieved by giving a 6-week neonatal ZDV chemoprophylaxis regimen. However, term infants born to women who received ART during pregnancy with documented viral suppression can be given a 4-week course.¹⁵ In higher-risk cases, experts on the Perinatal Guidelines Panel recommend combining a 6-week infant ZDV prophylaxis regimen with 2 additional antiretroviral drugs including lamivudine (also known as "3TC") and either nevirapine (NVP)

or raltegravir (RAL) to construct a presumptive HIV therapy regimen (see tables in ref 15).¹⁵ This 3-drug combination antiretroviral drug regimen is recommended for infants born to mothers who (1) received prenatal antiretroviral drugs but had suboptimal viral suppression at delivery, (2) received only intrapartum antiretroviral drugs, (3) received no antepartum or intrapartum antiretroviral drugs, or (4) have known drug-resistant virus. Decisions about using a combination antiretroviral regimen over ZDV monotherapy can be made after balancing the benefits of enhanced prevention of perinatal transmission of HIV infection over possible toxicity from multiple drugs. The most information about the use of antiretroviral combinations in neonates is available for older regimens such as ZDV in combination with either single-dose nevirapine¹⁶⁻¹⁹ or 3 doses of nevirapine in the first week of life²⁰ or the dual combination of ZDV and lamivudine.²¹⁻²⁴

When making decisions to use combination antiretroviral drugs, consultation with a pediatrician experienced in the care of children with HIV infection or the National Clinician Consultation Center (<https://nccc.ucsf.edu/clinician-consultation/perinatal-hiv-aids/>) is beneficial. Monitoring for hematologic toxicity is necessary for any combination of ZDV and lamivudine compared to ZDV alone. Long-lasting resistance is possible if the infant is already infected when prophylaxis is given; this was most evident when nevirapine was used as a single agent for prophylaxis.²⁵ The HHS Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission¹⁵ and Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV²⁶ each publish an extensive discussion of considerations for infant

antiretroviral prophylaxis regimens for different clinical scenarios and provide specific neonatal antiretroviral dosing recommendations.

The administration of ZDV (possibly with other antiretroviral agents) to the infant should be initiated as soon as possible after birth and certainly within 6 to 12 hours after delivery.²⁷ If the infant's HIV exposure is first recognized between 12 and 48 hours after delivery, presumptive HIV therapy should be initiated in that time period.¹⁵ Data from animal studies indicate that the longer the delay in institution of prophylaxis, the less likely that infection will be prevented. In most animal studies, antiretroviral prophylaxis initiated 24 to 36 hours after exposure is not as effective for preventing infection.²⁸⁻³⁰

The full course of drug supply needed for the entire 4 to 6 weeks should be supplied to the infant before discharge from the hospital irrespective of availability of out-of-pocket payment or insurance coverage because pediatric antiretroviral formulations are not widely available in commercial pharmacies.¹⁵

Avoidance of Postnatal HIV Infection

Postnatal transmission of HIV through ingestion of human milk from a mother with HIV infection is well documented, and prolonged breastfeeding from untreated mothers has resulted in rates as high as 9% to 15%.³¹ However, studies in low-resource countries have revealed that maternal and/or infant antiretroviral drug administration during lactation reduces the risk of HIV transmission to the infant via human milk.^{32,33} Because the risk of infant mortality from infectious diseases and malnutrition is low in the United States and effective alternative sources of feeding are readily available, women with HIV infection, including those receiving ART, should be counseled not to

breastfeed their infants or donate their milk.³⁴ Although maternal ART has been shown to reduce the concentration of cell-free HIV in human milk, it does not affect the amount of cell-associated virus in human milk.³⁵ In addition, discordance between the viral load in plasma and human milk has been observed. There is also differential penetration of antiretroviral drugs into human milk, with some antiretroviral drugs having concentrations in human milk that are higher than in maternal plasma, and others have lower or undetectable human milk concentrations.³⁶ These factors raise concerns about infant drug toxicity and the potential for selection of drug-resistant virus within human milk. Therefore, in the United States, where safe alternatives to breastfeeding are available, all women with HIV infection should avoid breastfeeding.³⁷

Cultural differences require that counseling the mother about the avoidance of breastfeeding should be conducted in a sensitive manner. For some women, not being able to breastfeed may be the hardest component of their effort to protect their newborn infant from acquiring HIV infection.³⁷ Other mothers, particularly those who have emigrated from parts of the world where breastfeeding is nearly universal, may feel that formula feeding their infant discloses their own HIV infection to family or friends. As a result, recommendations to prevent perinatal transmission may not always be followed. Open, nonjudgmental communication about feeding practices facilitates appropriate follow-up and testing of all infants, including those whose mothers choose to breastfeed after appropriate counseling.³⁴ Education covering appropriate formula feeding and the cost of formula can be provided to women. Referrals, including enrollment in the Special

Supplemental Nutrition Program for Women, Infants, and Children, are helpful in many cases. Evaluation of infant feeding practices with suggestions for safer feeding options and advice against pre-mastication (the practice of prechewing solid food before feeding it to another), which is a potential risk factor for HIV transmission, are indicated.³⁸

Framework for the Total Elimination of Perinatal Transmission of HIV

Several strategies have been documented that could potentially lead to the elimination of perinatal transmission of HIV. Early detection of HIV infection in the mother and evaluation and management of infants exposed to HIV remain the key to preventing perinatal transmission. This involves coordination of clinical care and social services, long-term follow-up of infants exposed to HIV, and ongoing HIV surveillance.³⁹ In many cases, early detection is not achieved because of social issues such as lack of access to mental, preventive, and general health care or substance use.^{40,41} Interventions targeted to at-risk populations can minimize missed opportunities for the prevention of perinatal transmission of HIV. To be most effective, these efforts should be sustained and involve integrated clinical management and social services.³⁹

CARE OF THE INFANT EXPOSED TO HIV

Testing to Determine the Infant's HIV Infection Status

Identification of the infant born to a mother with HIV infection and early determination of the presence or absence of HIV infection in the infant are critical to allow early initiation of prophylaxis or presumptive HIV therapy and provision of needed care. Appropriate HIV diagnostic testing for infants and children younger than 18 months differs from that for older children, adolescents, and adults.

Passively transferred maternal HIV antibodies may be detectable in an exposed but uninfected infant's bloodstream until approximately 18 months of age. Therefore, routine serological testing of infants exposed to HIV and children before the age of 18 months is generally only informative if the test result is negative.

Polymerase chain reaction (PCR) assays that directly detect HIV DNA or RNA (generically referred to as HIV nucleic acid amplification tests [NAATs]) represent the gold standard for diagnostic testing of infants and young children younger than 18 months. With such testing, the diagnosis or the presumptive exclusion of HIV infection can be established within the first several weeks of life among nonbreastfed infants. Although neonatal antiretroviral drugs may decrease the concentration of HIV RNA in infant plasma in the first 6 weeks of life,⁴² HIV DNA PCR results generally remain positive in most individuals taking ART who have undetectable plasma HIV RNA. The sensitivity of both DNA and RNA PCR testing is high,^{43,44} so either can be used for the diagnosis of HIV infection in infancy.⁴⁵ False-positive results with low-level viral copy numbers have been described when using HIV RNA assays,^{42,46,47} reinforcing the importance of repeating any positive assay result to confirm the diagnosis of HIV infection in infancy. False-negative results occur rarely, and retesting could be considered (perhaps by using a different test) if clinical findings suggest the presence of HIV infection.

Detection of Non-Subtype B HIV and HIV-2

For infants born to women known or suspected to have infection with non-B subtypes of HIV, use of HIV RNA assays may be preferable to the use of HIV DNA assays for diagnostic testing. Women who acquire HIV infection in

North America are most commonly infected with HIV subtype B.⁴⁸ Women who acquire HIV outside of North America are often infected with other HIV subtypes. Subtypes C and D predominate in southern and eastern Africa, subtype C predominates on the Indian subcontinent, and subtype E predominates in much of Southeast Asia.⁴⁸ HIV DNA PCR assays may be less sensitive in the detection of non-B subtype HIV, and false-negative HIV DNA PCR assay results have been reported in infants infected with non-B subtype HIV.^{49,50} Some of the currently available HIV RNA assays have improved sensitivity for detection of non-B subtype HIV infection, although even these assays may not detect all non-B subtypes, such as the uncommon group O HIV strain. When testing infants suspected of infection with non-B subtype HIV, consultation with a pediatrician experienced in the care of infants and children with HIV infection is recommended.

HIV-2 is a retrovirus similar to HIV and is found most commonly in western Africa. It is less virulent, with a slower rate of progression of clinical disease and lower rates of perinatal transmission.⁵¹ However, NAATs for HIV will not identify HIV-2, so if infection with HIV-2 is suspected, consultation with the CDC via the state department of health may be sought to help arrange specific HIV-2 testing.

Timing of Diagnostic Testing in Infants With Known Perinatal Exposure to HIV

For infants with known perinatal exposure, it is recommended that diagnostic testing with HIV DNA or RNA assays be performed at 14 to 21 days of age, and if results are negative, they should be repeated at 1 to 2 months of age and again at 4 to 6 months of age (Table 1).⁵² For infants at a higher risk of perinatal HIV transmission who receive multiple antiretroviral drugs,

additional virological diagnostic testing at birth as well as 2 to 4 weeks after cessation of antiretroviral prophylaxis should be considered.¹²

An HIV NAAT should be performed at birth or in the first few days of life for infants at highest risk of infection, including those whose mothers received no antiretroviral drugs during pregnancy, when maternal prophylaxis was started late in pregnancy or during labor, or if the mother had primary HIV infection during pregnancy. In the absence of maternal ART, as many as 30% to 40% of infants with HIV infection can be identified by 48 hours of age.^{53,54} Infants with a positive NAAT result at or before 48 hours of age are considered to have in utero infection with HIV, whereas infants who have a negative NAAT result during the

first week of life and a subsequent positive test result are considered to have intrapartum infection.⁵⁵ Cord blood specimens are not used for HIV RNA or DNA testing because they are associated with an unacceptably high rate of false-positive test results.

When a mother's HIV status is unknown at delivery or after birth, expedited HIV testing (preferably a combined test for HIV antigen and antibody) for mother and/or infant should be performed. In the event of a positive initial test result, presumptive HIV therapy is initiated in the infant as soon as possible pending the result of a supplemental test.¹⁵ Treatment should be stopped if results of supplemental testing with HIV antibody and a NAAT are negative.

TABLE 1 Evaluation and Treatment of the Infant Exposed to HIV-1 (Birth to 18 Months of Age), in Addition to Routine Pediatric Care and Immunizations

Action ^a	Infant Age						
	Birth	14 d	4 wk	6 wk	8 wk	4 mo	12–18 mo
Antiretroviral prophylaxis or presumptive HIV therapy ^b	X	X	X	X	—	—	—
Recommend against breastfeeding and premaritication	X	X	X	X	X	X	X
Hemoglobin or complete blood cell count	X	—	X ^c	—	X ^c	—	—
HIV-1 DNA or RNA PCR assay ^d	^e	X ^f	X	—	^g	X	—
Initiate PCP prophylaxis ^h	—	—	—	X	—	—	—
Antibody to HIV-1 ⁱ	—	—	—	—	—	—	X

X, indication to conduct the specified action; —, not applicable.

^a See the text for detailed discussion of each action. If during this period, HIV infection is diagnosed in the infant, laboratory monitoring and immunizations should follow guidelines for treatment of pediatric HIV infection.⁵²

^b Antiretroviral prophylaxis or presumptive HIV therapy, depending on the infant's risk of acquiring HIV (see text) is initiated as soon as possible after birth but certainly within 6–12 hours. ZDV prophylaxis is continued for 4–6 weeks, at which time it is stopped.

^c Checked at 4 weeks by some experts and rechecked at 8 weeks if the week 4 hemoglobin level was significantly low.

^d All infants exposed to HIV-1 should undergo virological testing for HIV-1 with HIV-1 DNA or RNA PCR assays at 14 to 21 days of age and, if results are negative, they should be repeated at 1 to 2 and 4 to 6 months of age to identify or exclude HIV-1 infection as early as possible. Any positive test result at any age is promptly repeated to confirm the diagnosis of HIV-1 infection.

^e HIV-1 DNA or RNA PCR assay testing in the first few days of life allows identification of in utero infection and should be considered if maternal antiretroviral agents were not administered during pregnancy or in other high-risk situations. A negative test result at this age requires repeat testing to exclude HIV-1 infection.

^f A negative test result at this age requires repeat testing to exclude HIV-1 infection. Presumptive uninfected indicates a negative NAAT result at ≥ 14 days and ≥ 4 weeks (1 month) of age; definitive uninfected indicates a negative NAAT result at ≥ 1 and ≥ 4 months of age (see text for complete details).

^g For higher-risk infants, additional virological diagnostic testing should be considered 2 to 4 weeks after cessation of antiretroviral prophylaxis (ie, at 8–10 weeks of life).

^h Infants with indeterminate HIV-1 infection status should receive prophylaxis starting at 4–6 weeks of age until they are deemed to be presumptively or definitively uninfected with HIV-1. Prophylaxis is not recommended for infants who meet criteria for presumptive or definitive lack of HIV-1 infection; therefore, a NAAT at 2 and 4–6 weeks of age allows for avoidance of PCP prophylaxis if both results are negative.

ⁱ Many experts confirm the absence of HIV-1 infection with a negative HIV-1 antibody assay result at 12–18 months of age.

If an HIV NAAT for the newborn infant was not performed shortly after birth, or if such test results were negative, diagnostic testing with an HIV NAAT is performed at 14 to 21 days of age because the diagnostic sensitivity of virological assays increases rapidly by 2 weeks of age.⁵³ This change in assay sensitivity reflects the biology of perinatal transmission, such that when HIV is acquired at the time of delivery, it may take up to 2 weeks for a NAAT to be able to detect the virus.⁵⁵ Therefore, negative results of HIV DNA PCR or RNA tests performed before 14 days of age are less helpful in excluding HIV infection acquired at the time of birth than are results of tests performed at or after 14 days of age.

Management if an HIV Virological Test Result Is Positive

If any of the HIV NAAT results are positive, an immediate repeat HIV NAAT is recommended to confirm the diagnosis of HIV infection. A diagnosis of HIV infection can be made on the basis of 2 separate blood samples, each of which is positive for HIV DNA or RNA. If infection is confirmed, a pediatric HIV specialist should be consulted for advice regarding ART and care. HIV disease can progress rapidly in infants with HIV infection, and neither CD4⁺ T-lymphocyte count nor HIV RNA copy number is a reliable predictor of the risk of disease progression in infants.⁵³

Interpretation of Negative HIV Test Results

On the basis of analysis of HIV DNA or RNA assay results from multiple studies, the CDC has revised the case definition for exclusion of HIV infection in infants for surveillance purposes.⁵⁶ The definitions supplied here are based on the CDC surveillance definitions and are appropriate for the management of children born to women with HIV infection. These definitions of exclusion of HIV infection are only for

use in infants who do not meet the criteria for HIV infection noted above.⁵²

In nonbreastfeeding infants younger than 18 months with no positive HIV NAAT results, presumptive exclusion of HIV infection is based on the following:

- two negative HIV RNA or DNA NAAT results, from separate specimens, both of which were obtained at ≥ 2 weeks of age and 1 of which was obtained at ≥ 4 weeks of age; or
- one negative HIV RNA or DNA NAAT result from a specimen obtained at ≥ 8 weeks of age; or
- one negative HIV antibody test result obtained at ≥ 6 months of age.

Definitive exclusion of HIV infection in a nonbreastfed infant is based on the following:

- two or more negative HIV RNA or DNA NAAT results, with 1 negative result at age ≥ 1 month and 1 negative result at age ≥ 4 months; or
- two negative HIV antibody test results from separate specimens obtained at age ≥ 6 months.

In the unusual case of an infant with a positive HIV NAAT result followed by a negative NAAT result, an expert in the care of children with HIV infection can be consulted for further testing recommendations.

Many experts confirm the absence of HIV infection with a negative HIV antibody assay result at 12 to 18 months of age (see next section). For both presumptive and definitive exclusion of infection, the child should have no other laboratory (eg, no positive NAAT results) or clinical (eg, no AIDS-defining conditions) evidence of HIV infection. For infants who have been breastfed, a similar testing algorithm can be followed, with additional testing every 3 months during breastfeeding followed by monitoring at 4 to 6

weeks, 3 months, and 6 months after breastfeeding cessation.⁵²

Role of HIV Antibody Testing in Infants Exposed to HIV

In infants exposed to HIV who are not infected with HIV, maternal HIV antibodies transferred in utero may persist through 18 months of age. Loss of HIV antibody in an infant with previously negative HIV NAAT results (seroreversion) definitively confirms that the infant is not infected with HIV. Many infants exposed to HIV serorevert to HIV antibody negativity by 12 months of age.⁵⁷ Many experts confirm the absence of HIV infection with a negative HIV antibody assay result at 12 to 18 months of age. If an infant exposed to HIV who is not known to be infected is tested at 12 months of age and is still antibody-positive, then testing should be repeated at 18 to 24 months of age. Performing the first antibody test at 18 months of age to confirm seroreversion may avoid the cost and pain of performing 2 tests. Positive HIV antibodies at 24 months of age or older may indicate HIV infection and should be confirmed with an HIV virological test.²⁶ A confirmed NAAT result at or beyond 24 months of age in an infant with infection previously excluded as outlined above suggests that the infant was infected after infancy, such as through breastfeeding, pre-mastication of solid food by a caregiver with HIV infection,³⁴ or sexual abuse.

Prevention of *Pneumocystis jirovecii* Pneumonia

The most common severe opportunistic infection in infants and children with HIV infection is *Pneumocystis jirovecii* pneumonia (PCP). PCP incidence in untreated infants with HIV is highest during the first year of life, with cases peaking at 3 to 6 months of age.^{58,59} Chemoprophylaxis is highly effective in the prevention of PCP and should be administered to infants in whom HIV infection is diagnosed from 4 to

6 weeks of age until their first birthday. Thereafter, the need for prophylaxis is based on age-specific CD4⁺ T-lymphocyte counts and/or percentages.⁶⁰ Trimethoprim-sulfamethoxazole is the most common drug used for prophylaxis because of its high efficacy, relative safety, low cost, and broad antimicrobial spectrum⁶⁰ (for further discussion, see ref 60).

PCP prophylaxis is not recommended for infants with presumptive lack of HIV infection (see previous section) but should be initiated for infants with indeterminate HIV infection status starting at 4 to 6 weeks of age.⁶⁰ Thus, for infants with negative HIV NAAT results at 2 and 4 to 6 weeks of age (presumptively not infected with HIV), PCP prophylaxis can be avoided completely. For an infant exposed to HIV with indeterminate HIV infection status who initiated prophylaxis at 4 to 6 weeks of age and subsequently meets criteria for presumptive or definitive lack of HIV infection, PCP prophylaxis can be stopped.

Prevention of Tuberculosis

Increased risk of tuberculosis (TB) among adults living with HIV infection is well documented. Because infants and children with TB infection and disease are usually infected by an adult with whom they live and have daily contact, TB infection status information should be obtained about the mother and all other household contacts of infants born to mothers with HIV. Bacille Calmette-Guerin immunization is not recommended for infants born to women with HIV infection in the United States and should not be administered to infants and children with known HIV infection because of its potential to cause disseminated disease.⁶¹

If an infant is exposed to anyone with active TB, the infant should be evaluated for TB disease and managed according to published guidelines.⁶¹ If the infant's mother or

any other person in the family receives a diagnosis of acid-fast bacillus smear-positive TB, the infant should be separated from that person until the TB infection has been treated with anti-TB medications and a physician has determined that the person is no longer contagious. In the event that a pregnant woman has documented TB that can be spread by the hematogenous route, the infant should be evaluated for congenital TB by a pediatric infectious disease expert.

Immunizations

Each year, the CDC publishes immunization schedules for children and adolescents 0 to 18 years of age⁶² as well as for children with HIV infection.⁶³ All routine infant immunizations should be given to infants exposed to HIV. If HIV infection is confirmed in an infant exposed to HIV, then guidelines for the child with HIV infection should be followed.^{62,63}

Monitoring for Toxicity From In Utero and Neonatal Antiretroviral Drug Exposure

Monitoring for and Management of Short-term Toxicity During Infant Antiretroviral Prophylaxis

Because exposure to maternal antiretroviral drugs taken during pregnancy can cause small but apparent variations of hemoglobin and neutrophil counts, a baseline complete blood cell and differential count has been recommended for the newborn infant.⁶⁴ The risk of anemia and neutropenia is greater in infants whose mothers received ART during pregnancy, but mild anemia was also observed commonly in infants whose mothers received ZDV monotherapy compared with infants whose mothers received no antiretroviral drugs during pregnancy.⁶⁵

Nonetheless, the advantages of maternal ART for prevention of perinatal transmission are far greater than hematologic toxicity in the newborn infant.^{66,67}

The 6-week ZDV regimen in infants can cause anemia, which largely remains clinically insignificant and generally resolves after termination of ZDV prophylaxis. If anemia persists even after stopping the ZDV regimen, alternative etiologies are likely responsible. Anemia can be severe in infants taking ZDV who were born prematurely or with other medical problems. Also, administration of ZDV in combination with other antiretroviral drugs can cause hematologic toxicity.⁶⁸ The timing of monitoring of hematologic toxicity from ZDV prophylaxis depends on many factors such as baseline hematologic values, gestational age at birth, clinical condition of the child, receipt of concomitant medications, and maternal antepartum therapy. Hemoglobin and neutrophil counts should be measured in infants who have taken ZDV- and/or lamivudine-containing antiretroviral regimens for 4 or more weeks.

The decision of whether to discontinue antiretroviral prophylaxis early because of identification of hematologic abnormalities is made on the basis of factors such as severity of the laboratory abnormality, associated clinical symptoms, duration of infant prophylaxis already received, the magnitude of the risk of HIV infection in the infant (as assessed by maternal receipt of ART, maternal viral load near delivery, and mode of delivery), and availability of alternative interventions (eg, red blood cell transfusion) in consultation with a pediatric HIV specialist.

Routine measurement of serum lactate concentration in asymptomatic neonates to screen for possible mitochondrial toxicity related to ZDV prophylaxis is not recommended because the clinical relevance of increased lactate concentrations in the absence of symptoms is unknown, transient elevations return to normal, and there is poor predictive value for later appearance of symptomatic

toxicity.^{69,70} However, if severe clinical symptoms, particularly neurologic symptoms, develop in the infant, a serum lactate concentration should be obtained. If the serum lactate concentration is significantly elevated in an infant with compatible clinical symptoms, a pediatric HIV expert can help determine if antiretroviral prophylaxis should be terminated. In general, prophylaxis should continue unless there is a compelling reason to stop.

Long-term Toxicity

Research has not revealed significant risk of neoplasia or organ-system toxicities from in utero exposure to ZDV or other antiretroviral drugs.⁷¹ The issue of mitochondrial dysfunction from the use of ART has been unsubstantiated⁶⁹ but remains under investigation. However, in children exposed to HIV with severe clinical symptoms, neurologic or cardiac in particular, mitochondrial dysfunction is part of the differential diagnosis in HIV infection.^{70,72-77}

Information regarding in utero and/or neonatal antiretroviral exposure is an important part of a permanent record, particularly in uninfected children. Uninfected children perinatally exposed to HIV have been found to have a higher rate of childhood infections in the first year of life than unexposed children and benefit from regular medical care.^{78,79} Yearly follow-up into adulthood to monitor for long-term toxicity such as cancer or neurodevelopmental or metabolic disorders is appropriate.⁷¹

Testing Family Members

HIV screening should be recommended and offered to all immediate family members with unknown HIV infection status; this should be performed with the mother's consent to include the infant's father and/or mother's sexual partners. All siblings of the infant exposed to HIV, regardless of age of

the siblings, should be tested because it is possible, albeit unusual, for perinatally infected children to remain asymptomatic into adolescence.^{80,81}

Counseling and Support

An HIV diagnosis can have a significant impact on an individual and his or her family. When counseling the mother of an infant exposed to HIV, exploring whether HIV infection was recently diagnosed in the mother during or after pregnancy and whether she needs a referral for her own care may contribute to care of the whole family. Additionally, some families may require support related to an HIV-associated illness or death in other family members.

Increased need for social and psychological support services may result from factors including economic hardship, substance use, depression, social isolation, lack of health care, unemployment, difficulty in finding housing, or domestic violence. In addition, fear of loss of existing supports and services, such as loss of support from a partner or loss of employment, insurance, or health care coverage are important considerations.⁸²⁻⁸⁴ Particularly vulnerable are pregnant adolescents with HIV infection.⁸⁵

Additional factors may be present for women who have emigrated from other countries, in particular factors related to culture and concerns about immigration status. This population may have been subject to or know of stigmatization and discrimination against people with HIV infection. In addition, distrust or misunderstanding of the US medical system may complicate care and follow-up of the infant.

An outline of plans for medical care for the infant will help new parents, foster parents, or other caregivers optimally care for their infant exposed to HIV. Important topics

include adherence to medications to prevent perinatal transmission of HIV and prompt assessment of illness in the infant exposed to HIV as well as the schedule of follow-up visits for assessment and laboratory assays (both for diagnosis of HIV infection and to check for any adverse effects of antiretroviral exposure). Breastfeeding is not recommended even if mothers are receiving ART for their own HIV disease.³⁷

Counseling should include education about the risks of HIV transmission, including the lack of transmission risk in family activities such as eating, bathing, or sleeping together. Planning regarding future reproductive plans for the family, likely in collaboration with the family's adult HIV and gynecologic and obstetric providers, can minimize the risk of HIV acquisition for sexual partners and perinatal transmission in future pregnancies.

Confidentiality should be maintained at all times. In some cases, one or more family members may not be aware of the HIV infection status of the mother, which warrants extra caution in the labor and delivery unit and when discussing the postpartum management of the infant or in the pediatric office when discussing care of the child.

HIV Exposure and Infection Status Reporting

Name-based HIV reporting to state health departments is required in all states and territories for surveillance purposes.⁸⁶ In addition, many states require reporting pregnancy in women living with HIV and the infection status of their infants. To facilitate the required reporting, even when reporting is delegated to another party, the pediatrician should collect the maternal antiretroviral treatment history, maternal demographics, labor and delivery record, and newborn records at the time of birth.

SUMMARY (SEE TABLE 1)

1. Whenever possible, maternal HIV infection should be identified before or during pregnancy, which allows earlier initiation of care for the woman and for more effective interventions to prevent perinatal transmission. The AAP recommends documented, routine HIV testing for all pregnant women in the United States after notifying the patient that testing will be performed, unless the patient declines HIV testing (opt-out consent or right of refusal). All HIV testing, including during the third trimester, should be performed in a manner consistent with state and local laws.
2. If the mother's HIV serostatus is unknown at the time of labor or birth, the newborn infant's health care provider should perform expedited HIV antibody testing on the mother or the newborn infant or antigen/antibody testing on the mother, with appropriate consent consistent with state and local laws. The results should be reported to health care providers quickly enough to allow effective antiretroviral prophylaxis to be administered to the infant as soon as possible after birth and certainly within 6 to 12 hours after birth.
3. Intravenous ZDV for the mother and presumptive HIV therapy for the newborn infant should be administered promptly on the basis of a positive rapid antibody or antigen/antibody test result without waiting for the results of supplemental HIV testing, and breastfeeding should not be initiated. If the rapid test result is positive, supplemental testing should be performed, and if supplemental test results are negative (indicating that the infant was not truly exposed to HIV), then antiretroviral drugs should be stopped and breastfeeding can be initiated.
4. Avoidance of breastfeeding has been and continues to be a standard, strong recommendation for women living with HIV in the United States because maternal ART dramatically reduces but does not eliminate breast milk transmission, and safe infant feeding alternatives are readily available in the United States.
5. Pediatricians should provide counseling to parents and caregivers of infants exposed to HIV about HIV infection, including routine care of the infant, diagnostic tests, and potential drug toxicities.
6. All infants exposed to HIV should undergo virological testing with HIV DNA, RNA, or total nucleic acid assays at 14 to 21 days of age. If results are negative, these tests should be repeated at 1 to 2 and 4 to 6 months of age to identify or exclude HIV infection as early as possible. If any test result is positive, the test should be repeated immediately for confirmation.
7. Initial testing in the first few days of life allows identification of in utero infection and should be considered if maternal antiretroviral drugs were not administered during pregnancy or in other high-risk situations (see text). If an HIV NAAT for the newborn infant was not performed shortly after birth, or if such test results were negative, diagnostic testing with an HIV NAAT is performed at 14 to 21 days of age because the diagnostic sensitivity of virological assays increases rapidly by 2 weeks of age.
8. For nonbreastfeeding infants and children younger than 18 months with no positive HIV virological test results, presumptive exclusion of HIV infection is based on 2 negative HIV RNA or DNA NAAT results from separate specimens, both of which were obtained at ≥ 2 weeks of age and 1 of which was obtained at ≥ 4 weeks of age, 1 negative HIV RNA or DNA NAAT result obtained at ≥ 8 weeks of age, or 1 negative HIV antibody test result obtained at ≥ 6 months of age.
9. Definitive exclusion of HIV infection in a nonbreastfed infant is based on 2 or more negative HIV RNA or DNA test results, with 1 negative result at age ≥ 1 month and 1 negative result at age ≥ 4 months, or 2 negative HIV antibody test results from separate specimens obtained at age ≥ 6 months.
10. Many experts confirm the absence of HIV infection with a negative HIV antibody assay result at 12 to 24 months of age. These laboratory tests can only be used to exclude HIV infection if there is no other laboratory or clinical evidence of HIV infection (ie, no subsequent positive results from NAATs if tests were performed and no AIDS-defining condition for which there is no other underlying condition of immunosuppression) and the child is not receiving antiretroviral drugs.
11. PCP prophylaxis is not recommended for infants who are presumptively or definitively not infected with HIV (see recommendations 9 and 10). Infants with indeterminate HIV infection status after 6 weeks of age should receive prophylaxis until they are determined presumptively or definitively not to be infected with HIV.
12. All infants exposed to antiretroviral agents in utero or

as newborn infants should be monitored for short- and long-term drug toxicity.

13. Immunizations and TB screening should be provided for infants exposed to HIV in accordance with published guidelines. A BCG vaccine should not be administered to infants in whom HIV infection is diagnosed.
14. HIV testing should be offered and recommended to immediate family members of infants exposed to HIV.
15. The practitioner providing care for an infant with HIV infection should consult with a pediatric HIV specialist. An alternative service for advice on prevention of perinatal HIV transmission or HIV management is the National Clinician Consultation Center (<https://nccc.ucsf.edu/clinician-consultation/perinatal-hiv-aids/>). If the infant's mother is an adolescent, consultation with a practitioner familiar with the care of adolescents is advised.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
ART: antiretroviral therapy
CDC: Centers for Disease Control and Prevention
HHS: US Department of Health and Human Services
NAAT: nucleic acid amplification test
PCP: *Pneumocystis jirovecii* pneumonia
PCR: polymerase chain reaction
TB: tuberculosis
ZDV: zidovudine

FINANCIAL DISCLOSURE: Dr Chadwick disclosed a financial relationship in which her spouse owns stock in pharmaceutical companies that manufacture drugs used to treat HIV/AIDS; and Dr Ezeanolue has indicated he has no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: Dr Chadwick disclosed a financial relationship in which her spouse owns stock in pharmaceutical companies that manufacture drugs used to treat HIV/AIDS; and Dr Ezeanolue has indicated he has no potential conflicts of interest to disclose.

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