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THIS ACTIVITY HAS EXPIRED.

CME CREDIT IS NO LONGER AVAILABLE

The following content is provided for informational purposes only.
LEARNING OBJECTIVES
Upon completion of this activity, participants should be able to:

1. Describe the circumstances in which the 1-drug or 2-drug therapy is used to treat HIV exposed infants.
2. Recognize clinical scenarios where pediatric infectious disease specialist consultation is recommended.
3. Describe the consideration of the pediatric infectious disease specialist when prescribing a prophylactic regimen for infants at high risk for HIV infection.

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PERINATAL HIV PREVENTION: GUIDELINES FOR Labor, Delivery and Infant Prophylaxis

Release Date: December 1, 2014 • Expiration Date: November 30, 2016 • Course Code: 17HH01

SPONSOR
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This activity is supported by an educational grant from the New Jersey Department of Health (NJDOH)—Division of HIV, STD and TB Services, through an MOA titled “Education and Training for Physicians and other Healthcare Professionals in the Diagnosis and Treatment of HIV/AIDS.”

STATEMENT OF NEED
With the advent of antiretroviral drugs, women have the option of child bearing regardless of their HIV status. Although HIV-infected women, children born to these women do not have to be born infected as long as the mother knows her infection status, receives the adequate care and treatment during pregnancy, labor and delivery and once the infant is born. A breakthrough for pediatric HIV/AIDS came in 1994 with the successful clinical trial that showed if pregnant women adhered to antiretroviral use during pregnancy, infants could expect a 70% decrease in becoming infected with the virus. Since then, children born to women who are HIV-infected have been on the decline. Statewide data shows the overall total number of cases of pediatric infected children is 1,380 while the number of perinatally exposed is 4,752 reported in 2013. In 2009 there were 5 cases of infants born with HIV. Although the absolute number is low, New Jersey strives to bring this number to 0, suggesting that there is still work to do, most importantly, “Every diagnosis of an infant who is infected with HIV represents a missed opportunity for prevention” (Burr, 2012).

This year the guidelines around treatment for HIV exposed infants were updated. An excerpt from the guidelines states that the “the potential benefit of combining zidovudine infant prophylaxis with additional antiretroviral (ARV) drugs must be weighed against the potential risks to infants of multiple drug exposure. There is a spectrum of transmission risk that depends on a number of maternal and infant factors, including maternal viral load, mode of delivery, and gestational age at delivery.” This activity will seek to educate those to the new information in treatment recommendations using an evidence-based approach to continue to lessen the number of infants that are exposed to HIV and the medical and practical steps in treating potential HIV exposure.

TARGET AUDIENCE
This activity is designed for physicians, nurses, health educators, and other health care professionals in New Jersey who are involved in the care of women and newborns.

METHOD OF PARTICIPATION
Participants should read the learning objectives, review the activity in its entirety, and then complete the self-assessment test, which consists of a series of multiple-choice questions. Upon completing this activity as designed and achieving a passing score of 70% or more on the self-assessment test, participants will receive a letter of credit and the test answer key (4) weeks after receipt of the self-assessment test, registration, and evaluation materials. This activity may also be completed online at http://ccoe.rbhs.rutgers.edu/catalogue/.

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Field Test: This activity was field tested for time required for participation by Debra Chew, MD, Noa’s Shimoni, MD, MPH, Howard A. Grossman, MD, Anna M. Haywood, RN, MSN, Juanita Howell, RN, MSN, and Laura Bogert, RN, BSN.

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PERINATAL HIV PREVENTION: GUIDELINES FOR
Labor, Delivery and
Infant Prophylaxis

Jason Zucker, MD, Internal Medicine Chief Resident, Rutgers-New Jersey Medical School, University Hospital
David Cennimo, MD, FACP, FAAP, AAHIVS, Assistant Professor, Department of Medicine and Pediatrics, Division of Infectious Disease, Rutgers-New Jersey Medical School

Upon completion of this activity, participants should be able to:

- Describe the circumstances in which the 1-drug or 2-drug therapy is used to treat HIV exposed infants.
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To receive continuing education (CE) credit, complete the exam, registration, and evaluation forms on-line at http://ccoe.rbhs.rutgers.edu/catalog/ or that follow this article.
HIV has become a chronic disease with the number of women living with HIV infection continuing to increase while the number of HIV-infected infants born each year in the United States declines. This is due in no small part to increases in screening and prevention during pregnancy as well as post-exposure prophylaxis for newborns. On March 28, 2014, the Health and Human Services Panel on the Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission released updated guidelines titled “Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States”. With the implementation of universal HIV screening during pregnancy, combination antiretroviral therapy (cART) during pregnancy and throughout labor, cesarean delivery (when indicated), antiretroviral (ARV) prophylaxis for infants and the avoidance of breastfeeding, the estimated risk of perinatal transmission is now less than 2%. The most recent data from the Centers for Disease Control and Prevention estimated that 162 patients were perinatally infected with HIV in 2010.2

In order to minimize the risk of perinatal HIV transmission, optimal treatment starts prior to conception. Initiation of cART in females of childbearing age should consider not only resistance and side effect profiles but also minimize the risk of potential teratogenicity. Of note recommendations specifically state that efavirenz based regimens should be avoided in patients at risk for pregnancy. After pregnancy is confirmed, cART should be reassessed to ensure that the medications are indicated for use during pregnancy. Because the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy and pregnancy is rarely recognized before 4 to 6 weeks of pregnancy, and unnecessary changes in ARV drugs during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission, efavirenz can be continued in pregnant women receiving an efavirenz-based regimen who present for antenatal care in the first trimester, provided the regimen produces virologic suppression.1 For pregnant females not on cART, the guidelines recommend initiating a maximally suppressive ARV regimen as early as possible regardless of viral load or CD4 count. In general, the same regimen should be used as part of the cART strategy.

Recommendations regarding HIV screening and treatment of pregnant women and prophylaxis for perinatal transmission have been developed and are regularly updated by The Department of Health and Human Services Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (the Panel), a working group of the Office of AIDS Research Advisory Council (OARAC). The Guidelines can be viewed and downloaded at: http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0

Free clinical consultation and referral to local or regional pediatric HIV specialists is available to providers caring for HIV-infected pregnant women and their infants from the Clinicians Consultation Center.

For additional information or to submit a case you may contact the AETC Program’s National Clinician Consultation Center (CCC) (888)-448-8765 or online at http://ccc.ucsf.edu/clinicianconsultation/perinatal-hiv-aids Monday - Friday, 11 a.m. - 6 p.m. EST

Virologic control is a central component to reducing transmission and earlier initiation of cART is more effective in reducing in utero transmission.3 The Women and Infants Transmission Study clearly demonstrated that the transmission risk is based on HIV RNA levels as the risk of transmission was <2% for patients with HIV RNA <30,000 copies/mL and 4.8% in those with HIV RNA levels >30,000 copies/mL.4 However these benefits must be assessed against the potential effects of first-trimester drug exposure. Notably the PHTP-1 study in Thailand demonstrated that most in utero transmission occurred between 28 and 36 weeks.5 Earlier initiation of cART should allow enough time to suppress the maternal viral load before in utero transmission can occur.

Mothers who have an undetectable viral load consistently in late pregnancy and around the time of delivery (34 to 36 weeks gestation) and no concerns regarding medication adherence have a low risk of transmission. These individuals do not require intrapartum zidovudine (ZDV) and a delivery birth plan with either C-section or vaginal delivery is typical. (See Table 1: Summary of Panel Recommendations Related to Mode of Delivery) For low risk neonates, 6 weeks of oral ZDV prophylaxis, started as close to the time of birth as possible, is generally recommended. A 4 week regimen may be considered in a full term neonate when the mother’s HIV was fully suppressed and there were no concerns related to maternal cART adherence. For low risk infants combining ARV does not reduce the risk of transmission and any potential benefits are outweighed by known toxicities.
Scheduled cesarean delivery at 38 weeks’ gestation to minimize perinatal transmission of HIV is recommended for women with HIV RNA levels >1000 copies/mL or unknown HIV levels near the time of delivery, irrespective of administration of antepartum antiretroviral drugs (AII). Data are insufficient to evaluate the potential benefit of cesarean delivery used solely for prevention of perinatal transmission in women receiving combination antiretroviral therapy with HIV RNA levels ≤1000 copies/mL and given the low rate of transmission in these patients, it is unclear whether scheduled cesarean delivery would confer additional benefit in reducing transmission (BIII). In women with HIV RNA levels ≤1000 copies/mL, cesarean delivery performed for standard obstetrical indications should be scheduled at 39 weeks’ gestation.

It is not clear whether cesarean delivery after rupture of membranes or onset of labor provides benefit in preventing perinatal transmission. Management of women originally scheduled for cesarean delivery who present with ruptured membranes or in labor must be individualized at the time of presentation based on duration of rupture and/or labor, plasma HIV RNA level, and current antiretroviral regimen (BII).

Women should be informed of the risks associated with cesarean delivery. If the indication for cesarean delivery is prevention of perinatal transmission of HIV, the risks to a woman should be balanced with potential benefits expected for the neonate (AII).

For mothers on cART with sub-optimal viral suppression (viral loads >1000 copies/mL) the newborn is at an increased risk of HIV infection. Mothers should receive intrapartum ZDV at least 3 hours prior to delivery, regardless of their previous cART or resistance pattern. Data suggest that wild-type virus is preferentially transmitted allowing ZDV to be an appropriate choice for prophylaxis in spite of the mother’s resistance pattern. Furthermore ZDV crosses the placenta readily and penetrates the central nervous system helping to eliminate a potential HIV reservoir. In addition to intrapartum ZDV, cesarean section is highly desirable with the ideal scenario being a planned cesarean at 38 weeks prior to the rupture of membranes. In cases of appropriate intrapartum ARV and planned cesarean the risk of transmission is low and the decision as to whether to utilize one or two drug ARV prophylaxis should be made in conjunction with a pediatric HIV specialist. Maternal HIV viral load should be checked around 34 to 36 weeks gestation to provide the information necessary to formulate these plans. The benefit of cesarian delivery after spontaneous rupture of membranes is unclear at this time and management of such cases should be dictated by the individual circumstances and discussed with a HIV specialist.

For infants born to mothers not receiving cART and/or who may have only received intrapartum intravenous ZDV, infant prophylaxis with two drugs is an important component to decreasing the newborn’s risk of acquiring HIV. Again a cesarean section should be performed if possible; in addition to intrapartum ZDV at least 3 hours prior to delivery. All infants whose mothers were not on cART should receive oral ZDV for 6 weeks with oral nevirapine at birth and 48 hours after the first dose and 96 hours after the second dose. Newborn HIV prophylaxis should be initiated as soon as possible and ideally within the first 12 hours to increase its potential efficacy. The Pediatric AIDS Clinical Trials Group 1043 study demonstrated that patients receiving two or three drug prophylaxis had approximately half the rate of transmission when compared to those receiving standard ZDV. However while the transmission rate was statistically similar between the two and three drug groups the patients receiving three drugs had significantly increased side effects. In all cases, decisions about utilizing combination ARV in infants should be made in consultation with a pediatric HIV specialist. (See Table 2: Recommended Neonatal Dosing for Prevention of Perinatal Transmission of HIV)
### Table 2: Recommended Neonatal Dosing for Prevention of Perinatal Transmission of HIV

<table>
<thead>
<tr>
<th>Zidovudine (ZDV)</th>
<th>Dosing</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥35 weeks’ gestation at birth: 4 mg/kg/dose PO twice daily, started as</td>
<td>Birth through 4-6 weeks</td>
</tr>
<tr>
<td></td>
<td>soon after birth as possible and preferably within 6–12 hours of delivery (or, if unable to tolerate oral agents, 3 mg/kg/dose IV, beginning within 6–12 hours of delivery, then every 12 hours)</td>
<td></td>
</tr>
<tr>
<td>ZDV</td>
<td>≥30 to &lt;35 weeks’ gestation at birth: 2 mg/kg/dose PO (or 1.5 mg/kg/dose IV), started as soon after birth as possible, preferably within 6–12 hours of delivery, then every 12 hours, advanced to 3 mg/kg/dose PO (or 2.3 mg/kg/dose IV) every 12 hours at age 15 days</td>
<td></td>
</tr>
<tr>
<td>ZDV</td>
<td>&lt;30 weeks’ gestation at birth: 2 mg/kg body weight/dose PO (or 1.5 mg/kg/dose IV) started as soon after birth as possible, preferably within 6–12 hours of delivery, then every 12 hours, advanced to 3 mg/kg/dose PO (or 2.3 mg/kg/dose IV) every 12 hours after age 4 weeks</td>
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</tr>
</tbody>
</table>

**Additional Antiretroviral Prophylaxis Agents for HIV-Exposed Infants of Women who Received No Antepartum Antiretroviral Prophylaxis (initiated as soon after delivery as possible)**

- Birth weight 1.5–2 kg: 8 mg/dose PO
- Birth weight >2 kg: 12 mg/dose PO

3 doses in the first week of life
- 1st dose within 48 hrs of birth (birth–48 hrs)
- 2nd dose 48 hrs after 1st
- 3rd dose 96 hrs after 2nd

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**Key to Abbreviations:** IV = intravenously; NVP = nevirapine; PO = orally; ZDV = zidovudine


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Infants born to mothers with an unknown HIV status present a unique problem. Rapid HIV screening should be available within 60 minutes. If rapid screening returns positive, infant ARV prophylaxis with two drugs should be initiated immediately and does not require waiting for supplemental testing. If supplemental testing later returns negative, prophylaxis can be discontinued. For patients who may have had a negative HIV screen at the start of pregnancy, high suspicion for acute HIV is required. Recent data have demonstrated a >1% risk of acute HIV infection in pregnancy. The same study showed an 8-fold increase in the risk of perinatal transmission during acute HIV infection as opposed to chronic infection. Repeat HIV testing in the third trimester is recommended for any women at high risk. For patients diagnosed with acute HIV during pregnancy starting an cART regimen prior to resistance testing is recommended in order to reduce the viral load as rapidly as possible prior to delivery.

After initiating prophylactic ARV, HIV testing and confirmation with an HIV DNA PCR should be done at 14 days and one month of life. Negative HIV DNA PCRs at age 14 days or older AND one month or older are considered evidence that the infant is presumptively negative. Many experts also check HIV DNA PCR at birth to evaluate for in utero transmission especially in the setting of suboptimal maternal ARV response. The DNA PCR is the test of choice for the newborn exposed to maternal HIV. Maternal antibodies can be present for as long as 18 months and therefore HIV antibody testing may yield false positive results. Additionally ARV prophylaxis may reduce the HIV viral load levels below the lower limit of detection of the RNA PCR resulting in
false negative results. Patients unable to be declared presumptively negative at 4 to 6 weeks of life should be started on trimethoprim-sulfamethoxazole until definitively negative. A non-breast fed infant is considered definitely negative when the DNA PCR is negative at 1 and 4 months of life. Many check HIV antibody at 18 months of life to demonstrate seroreversion. Rare instances have shown persistence of maternal antibody after 18 months but this finding should provoke concern for and evaluation of the possibility of perinatal HIV infection. After the initiation of chemoprophylaxis, infants should be monitored closely due to the risk of hematologic suppression. A check of hemoglobin and neutrophil counts is recommended at birth and may be considered 4 weeks after the initiation of prophylaxis for infants receiving ZDV. Families should be educated about the risks of HIV transmission from breast feeding or premasticated food and these practices should be discouraged.

A positive conversion occurs when the patient has two separate samples test positive for HIV DNA PCR. In newborns receiving post-exposure prophylaxis, if they are found to be HIV-infected, prophylaxis should be discontinued and treatment for HIV initiated with standard cART in accordance with the Pediatric Antiretroviral Guidelines and in consultation with a pediatric HIV provider.

Optimized ARV treatment is effective when used correctly, as a full term infant with a maternal viral load less than 50 copies/mL has a transmission risk of less than 0.5% however optimized treatment requires intensive cooperation between obstetrics, pediatrics, and both adult and pediatric HIV providers for maximal benefit.  

References:


Evidence-Based Treatment of HIV Exposed Infants: 1-Drug, 2-Drugs, or cART?

Interest in the use of combination antiretroviral (cART) prophylaxis for high-risk infants was heightened after initial reports of a “functional cure” of an infant in 2013. The “Mississippi baby” was born in 2010 to a mother diagnosed with HIV infection during labor. The infant received zidovudine, lamivudine, and nevirapine at the age of 30 hours; nevirapine was replaced by ritonavir-boosted lopinavir for treatment of HIV infection at seven days of life. Treatment continued through the age of 18 months when it was self-discontinued by the mother. In October 2013, the doctors caring for the infant reported that at 30 months (twelve months after ARVs stopped) HIV levels in the child were found to be below detectable levels.1 Interest in the case was intense among the scientific community and the case was widely reported as a “cure” in the media. On July 10, 2014, however, it was reported that the child had detectable levels of HIV and whether the worldwide study of multi-drug infant ARV prophylaxis planned by the National Institutes of Health will be conducted remains uncertain.2

While viral remission was achieved for 27 months without treatment in the child in this case, viral rebound after the prolonged period of remission supports the hypothesis that left untreated, HIV infections are re-seeded from viral DNA carried in dormant cells. Researchers must now work to better understand what enabled the child to remain without HIV treatment for over two years while maintaining an undetectable viral load and without evident impact on immunological markers of infection.

The use of combination antiretroviral (cARV) prophylaxis is for HIV-exposed infants considered at high risk for HIV infection appears to be increasing in the United States and in Europe.3,4 However, continued on next page
the available evidence does not support the routine use of cARV prophylaxis for infants considered at high risk of HIV infection and there are safety issues related to such use that must be carefully considered. There have been no studies in infants less than two weeks of age to determine the appropriate dosing or safety of nevirapine administered at therapeutic doses. Ritonavir-boosted lopinavir is not recommended for neonates younger than age 14 days because of the potential for significant toxicity.\(^5\)

Decisions about use of cARV prophylaxis in infants should be made in consultation with a pediatric HIV specialist. Whenever possible, such decisions should be discussed and reviewed before delivery. Potential risk and benefits related to the use of cARV prophylaxis should also be discussed with the mother. Free clinical consultation and referral to local or regional pediatric HIV specialists is available to providers caring for HIV-infected pregnant women and their infants from the Clinicians Consultation Center (888)-448-8765 or online at http://nccc.ucsf.edu/clinicianconsultation/perinatal-hiv-aids/.

References