



Florida/Caribbean AIDS Education and Training Center

HIV CareLink

A Newsletter for HIV/AIDS Primary Care Providers

ABOUT US

The Florida/Caribbean AIDS Education and Training Center provides state-of-the-art HIV education, consultation, and resource materials to health care providers in Florida, Puerto Rico and the US Virgin Islands.

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EDITORS

Jeffrey Beal, MD, AAHIVS
239-839-4645
aetcbear@embarqmail.com

Joanne J. Orrick, PharmD, AAHIVE
813-974-6002
jorrick@usf.edu

Lois Hall, ARNP
813-974-5447
loishall@usf.edu

MANAGING EDITOR

Pamela Gatches-Fort, BA
813-974-2983
pgatches@usf.edu

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Prevention of Mother-to-Child Transmission of HIV: Review and New Perspectives

Vivian M. Tamayo-Agrait, MD

Assistant Professor Obstetrics and Gynecology, University of Puerto Rico School of Medicine, Maternal Infant Studies Center

Carmen D. Zorrilla, MD

Professor Obstetrics and Gynecology, University of Puerto Rico School of Medicine, Maternal Infant Studies Center

The marked decrease in perinatal transmission of HIV has been one of the biggest accomplishments in the U.S. and European HIV epidemics. The implementation of universal HIV screening for all pregnant women has been imperative for this success as it identifies those previously undiagnosed with HIV and offers them the needed antiretroviral therapy (ART) to prevent perinatal transmission of HIV to the infant. As reported in one of the largest natural history studies among pregnant women in the U.S. in the 1990's (The Women and Infants Transmission Study), the incidence of perinatal cases of HIV has decreased by almost 95%. The Department of Health and Human Services (DHHS) Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission has developed guidelines and recommendations for the use of ART in pregnant HIV-1-Infected women and maternal interventions to reduce perinatal HIV transmission in the U.S. for the past 25 years. Following the current treatment guidelines, 1-2% of infants may become infected with HIV from their mothers. Antepartum, intrapartum and postpartum interventions are recommended in all HIV-infected pregnant women. Yet, sentinel cases of perinatally-infected infants still occur, mostly in women who are unaware of their HIV status during their pregnancy. Intrapartum rapid testing of women who present in labor with an unknown HIV serostatus seeks to identify those cases. The purpose of this newsletter is to review the current guidelines for the management of HIV-infected pregnant women and to summarize emerging data in the field, including new treatment alternatives, which may be considered for the infants of women identified to be HIV-infected at the time of delivery.

HIV testing during pregnancy

- Universal HIV screening of all pregnant women is recommended, using an opt-out approach.
- In areas where the prevalence of HIV infection is more than 1%, re-screening in the third trimester is indicated.
- For patients who present in labor without evidence of HIV screening during gestation, rapid HIV testing is indicated. Confirmatory tests should be performed in these patients, but intrapartum treatment should not be delayed awaiting confirmation.

General considerations of perinatal transmission of HIV

- In untreated HIV-infected pregnant women, the reported risk of fetal transmission of the disease varies widely from 14.4% in a European study to 35-50% in Africa. The large variation in these rates could be due to sampling differences or risk factors in the different geographic regions.
- Most of the perinatal infections occur at the time of delivery, accounting for 66% of infected infants. Direct fetal contact with maternal blood and vaginal tract secretions are the suspected mechanisms of infection at the time of labor.
- Postpartum HIV infection through breastfeeding and antepartum or *in utero* infection account for the remaining 34% of cases.

- Current interventions to decrease the risk of fetal transmission of HIV consist of antepartum ART, intrapartum measures including intravenous zidovudine and elective cesarean section, and postpartum prophylactic treatment of the infants with zidovudine along with the use of infant formula to avoid breastfeeding. The later in gestation the interventions are initiated, the higher the risk of perinatal transmission.

Antepartum management of HIV-infected pregnant women

- ART is the recommended treatment during pregnancy.
- Unless indicated earlier for maternal health reasons, ART should not be started during the first trimester.
- The DHHS guidelines recommend ART be started at 12-14 weeks of gestation in naïve patients. A recent review from the Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS) French Perinatal Cohort reported lower transmission rates (0.5% [95%CI 0.2 to 0.8]) in HIV pregnant women who began ART before conception and continued without treatment interruption throughout the pregnancy as compared to those who started ART during the pregnancy. The rate of HIV transmission to the infant was 0.6% if ART was started during the first trimester, 1.2% if ART was started during the second trimester, and rose to 2.6% if ART was started after the third

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- trimester (28 weeks). This report also looked at the patient's HIV viral load (<400 vs <50 copies/mL) near delivery to compare the HIV transmission rate to the infant. The patients with a viral load <50 copies/mL in the 3rd trimester had a transmission rate of 0.8% while the rate increased in those with a viral load of <400 copies/mL to 1.8%.
- Baseline genotype, CD4 count and HIV RNA quantification (viral load) should be obtained prior to initiation of therapy.
 - ART regimens during pregnancy should include a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTIs).
 - The preferred NRTI combination is zidovudine and lamivudine. Zidovudine should be included in the antiretroviral (ARV) regimen of every pregnant woman unless resistance is documented or if contraindicated due to adverse effects or medical conditions.
 - The preferred PI during pregnancy is twice daily lopinavir/ritonavir. Some experts would increase the dosage to three tablets (200/50 mg adult tablet strength) twice daily in the third trimester secondary to extrapolated pharmacokinetic data. Atazanavir, indinavir, and saquinavir (all boosted with ritonavir) and nelfinavir are alternate PIs that can be used with proven efficacy during pregnancy. Recent (2/4/11) label changes to atazanavir now include a recommended dosing of atazanavir 400 mg with ritonavir 100 mg for experienced pregnant women in their second or third trimester when atazanavir is given with either an h₂-receptor antagonist or tenofovir. Close postpartum monitoring for adverse events is also recommended secondary to the possibility of higher levels of atazanavir during the first two months after delivery.
 - In cases that require use of an NNRTI, nevirapine is the only recommended agent for use during pregnancy. Due to risk of life-threatening hepatotoxicity, nevirapine should not be used in women with CD4 > 250 cells/mm³. Women who become pregnant while on nevirapine regimens and are tolerating the regimen well, may continue therapy without regard to CD4 count. Due to teratogenic potential, efavirenz should not be used in the 1st trimester of pregnancy and should only be used after the 1st trimester if it is determined to be the best choice for an individual patient. With other available treatment options, most clinicians would not consider efavirenz use during pregnancy. Adequate contraception must be assured if efavirenz is used in women with child-bearing potential.
 - For patients already on ART at the beginning of their pregnancy, all the components of regimen should be carefully evaluated, as well as potential risks and benefits. When other alternatives are feasible, drugs with teratogenic potential (e.g. efavirenz) should be changed to drugs with proven safety and efficacy during pregnancy.

- Discontinuation of ART during pregnancy should be avoided given the risk of rebound viremia and the potential for vertical transmission of HIV to the infant.

Intrapartum management of HIV-infected women

- For women using antepartum ART, oral therapy should be continued on schedule as much as possible prior to and during labor and delivery.
- Elective cesarean section at 38-39 weeks of gestational age should be offered to all women with a viral load >1000 copies/mL near the time of delivery, with counseling on the potential benefits and complications. Discussions about the risks and benefits of the different delivery routes should be started early in pregnancy, and the patient's autonomy must be respected at all times.
- All pregnant, HIV-infected women should be treated with intravenous zidovudine at the onset of labor until delivery of infant. The dose of intravenous zidovudine is as follows:
 - Loading dose: 2mg/kg over one hour
 - Maintenance dose: 1mg/kg/h (for at least two additional hours)
- Women with unknown HIV status at the time of labor/delivery should be screened using HIV rapid testing. Treatment should be initiated immediately if a reactive HIV result is obtained. Although not widely available, a combined HIV antigen/antibody assay (ARCHITECT HIV Ag/Ab Combo) is now U.S. Food and Drug Administration (FDA) approved for diagnosing acute or primary HIV. This assay may be used as an aid in the diagnosis of HIV-1/HIV-2 infection/s in pregnant women.
- Studies are underway to determine whether adding additional drugs to the intravenous zidovudine regimen will enhance the efficacy in special circumstances, including women diagnosed intrapartum, women with high viral loads at the time of labor and women with known zidovudine resistance.
- The most studied intervention is the addition of single-dose nevirapine to the maternal/newborn regimen. The theoretical advantages of nevirapine include: short-term safety, excellent transplacental passage, and greater antiviral activity than zidovudine. However, addition of single-dose nevirapine when a woman has received antepartum drugs is generally not recommended secondary to the risk of development of resistance and the lack of data to suggest added efficacy. Single-dose nevirapine may be used in special circumstances (e.g. patient with high HIV viral load who is delivering vaginally). If single-dose nevirapine is used, the use of maternal postpartum zidovudine/lamivudine for at least 7 days is suggested by the DHHS guidelines to prevent nevirapine resistance.

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Postpartum management of HIV-infected women and their infants

- In developed countries where infant formula is readily available, breastfeeding is strictly contraindicated in HIV-infected women.
- Infants of HIV-infected women should be treated with oral zidovudine for 6 weeks.
 - Ideally, the first dose should be administered within 6 to 12 hours of birth.
 - The dose of zidovudine for a term infant is 2mg/kg every 6 hours.
 - Dosage modification is indicated in infants born prior to 35 weeks of gestation.
- If the mother does not have a rapid HIV antibody test and her HIV status is unknown, rapid HIV antibody testing of the mother and/or infant should be done as soon as possible after birth. If the mother's HIV antibody test is positive, maternal HIV infection is presumed until a confirmatory test clarifies her status. If the infant's rapid HIV antibody test is positive, prophylactic therapy with zidovudine should be started and a confirmatory test (Western Blot) ordered. As the confirmatory test only indicates maternal HIV infection, but not necessarily infant HIV infection, if the infant's confirmatory test is positive, HIV DNA PCR should be ordered. Some providers would immediately order HIV DNA PCR for any infant with a positive rapid HIV antibody test. If the infant's HIV DNA PCR test is positive, unfortunately, the infant is HIV-infected. Prophylaxis should be stopped and the newborn referred to a pediatric HIV specialist.
- Some circumstances may warrant the use of additional ARVs for infants exposed to HIV. These may include:
 - Infants of mothers not completely suppressed at the time of delivery
 - Infants of mothers who only received intrapartum prophylaxis
 - Infants of mothers who did not receive antepartum nor intrapartum prophylaxis
 - Infants of mothers with known ARV resistant virus

Emerging Data

- Several limited studies have addressed the efficacy, risks and benefits of using alternative ARVs to prevent perinatal transmission of HIV, with single-dose nevirapine being one of the most studied concomitant ARVs.
- Many of these studies have reported a high rate of development of resistance (specifically the K103N) after use of single-dose nevirapine. The use of a "tail" (short course of alternate ARVs classes) substantially reduces the risk of development of resistance. Currently, there is no consensus regarding the composition and duration of the "tail" regimen. One reasonable approach is the use of zidovudine/lamivudine for 7 days postpartum in the mother. Some experts would also add lamivudine to the infant's zidovudine prophylaxis regimen for 7 days.

- A recent large, multi-center study (NICHD HPTN 040/ PACTG 1043) funded by the National Institutes of Health (NIH) evaluated the safety and efficacy of adding ARV agents to the standard zidovudine regimen to infants whose mothers did not receive ARVs in the current pregnancy (except zidovudine in labor). This study was carried out in 19 sites, including the U.S. and international countries. A total of 1,684 infants were randomized to the following treatment arms:
 - Zidovudine only x 6 weeks
 - Zidovudine x 6 weeks plus three doses of nevirapine
 - Zidovudine x 6 weeks plus lamivudine and nelfinavir x 2 weeks
- The only statistically significant difference in terms of safety was a higher rate of neutropenia among infants receiving zidovudine, lamivudine, and nelfinavir. There was no significant difference in the rates of anemia, transaminitis or thrombocytopenia between the groups. The proportion of HIV- infected infants per group was as follows:
 - Zidovudine only: 4.9%
 - Zidovudine plus nevirapine: 2.2%
 - Zidovudine plus lamivudine plus nelfinavir: 2.5%
 - The differences between ZDV alone and the two or three drug regimens was statistically significant (p=0.045).

When ART during pregnancy is not possible, adding one or two drugs to the current infant prophylaxis regimen provides another important method to reduce the chance for mother-to-child HIV transmission. The investigators concluded that the two and three drug regimens were superior to the standard treatment with zidovudine.



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CONCLUSIONS

- Near universal HIV testing during pregnancy, as well as antepartum, intrapartum and postpartum treatment measures have significantly reduced the incidence of vertically-transmitted HIV to 1-2%. Yet, there are still sentinel cases in developed countries and a high proportion of infants infected in resource-limited areas. Since the majority of cases of perinatal transmission of HIV occur at the time of delivery, intrapartum and postpartum interventions still have some benefit in the reduction of vertical transmission of the virus. Adding additional ARV agents to the standard zidovudine regimen in selected circumstances may be beneficial to further reduce the incidence of perinatal HIV infection.

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