

Perspective

Prevention of Perinatal HIV Transmission: The Perinatal HIV Hotline Perspective

Among the most frequently asked questions by callers to the National Perinatal HIV Hotline are those on the use of hormonal contraception in women receiving antiretroviral therapy. Estradiol levels are reduced by ritonavir-boosted protease inhibitors (PIs), nelfinavir, and nevirapine and increased by non-ritonavir-boosted PIs (except nelfinavir), efavirenz, and etravirine. Oral contraceptives do not affect antiretroviral drug levels, and several options are available for hormonal contraception that can compensate for or avoid the effects of antiretroviral drugs on estrogen levels. Other common questions on the hotline involve interpretation and management issues that arise from indeterminate Western blot test results early and late in pregnancy and from positive rapid test results during labor. Many questions focus on appropriate selection of antiretroviral drugs in pregnancy and the need to change regimens to reduce risk of birth defects in the child. This article summarizes a presentation by Jess Fogler Waldura, MD, at the 13th Annual Clinical Conference for the Ryan White HIV/AIDS Program held in August 2010 in Washington, DC.

Hormonal Contraceptives in HIV-Infected Women

Many questions to the National Perinatal HIV Hotline (Table 1) involve the use of hormonal contraceptive drugs by HIV-infected women receiving antiretroviral therapy. Major concerns with the concomitant use of combined oral contraceptive (COC) drugs and antiretroviral drugs are the potential effects of protease inhibitors (PIs) and non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) on estrogen levels. Decreased levels of estradiol are observed with ritonavir-boosted (/r) PIs, nelfinavir, and nevirapine; increased estradiol levels are observed with non-ritonavir-boosted PIs (except nelfinavir), efavirenz, and etravirine.^{1,2} Conversely, the hormones in COCs do not substantially affect antiretroviral drug levels.

Although the effects of antiretroviral therapy on estrogen levels have led many clinicians to avoid use of COCs for their patients, a number of options

are identified in current guidelines. These include use of atazanavir/r with contraceptive drugs containing high-dose estrogen ($\geq 35 \mu\text{g}$ ethinyl estradiol), non-ritonavir-boosted atazanavir with low-dose estrogen contraceptive drugs ($\leq 30 \mu\text{g}$ ethinyl estradiol), and any COC with etravirine. Efavirenz increases estrogen levels by about 37%, but the clinical importance of such an increase is unknown; some clinicians use efavirenz with low-dose estrogen COCs.³ Drugs from other classes, including maraviroc, enfuvirtide, and raltegravir, have no effects on estrogen levels. No studies have assessed the effects of antiretroviral therapy on hormone levels with use of contraceptive patches or vaginal rings.

The effects of antiretroviral therapy on progesterone levels with hormonal contraception are variable and may be less clinically important. Depot medroxyprogesterone, which requires an injection every 3 months, is a popular option, and most studies show that antiretroviral drugs have little or no effect on progesterone levels when the progesterone is administered as an injectable.⁴ New forms of implantable progestin that consist of a single rod that releases progestin for 5 years are also increasing in popularity; however,

these have not been studied in HIV-infected women receiving antiretroviral therapy. Progesterone-containing intrauterine devices (IUDs) are safe and effective for women with HIV infection. They are very comfortable for most women, easy to insert, and effective for 5 years. Because the hormonal effect of IUDs is localized, drug interactions with antiretroviral drugs are not a concern.

HIV Testing in Pregnancy

Many questions to the Perinatal HIV Hotline concern indeterminate Western blot test results after a positive result on a screening HIV test during pregnancy. A positive Western blot test result requires that there be a full complement of positive bands representing antibody reactivity to specific HIV components. For patients in the process of seroconverting, Western blot results become positive over a period of days to weeks (Figure 1). In the United States, a positive Western blot interpretation requires detection

Table 1. Services Available Through the National HIV/AIDS Clinicians' Consultation Center^a

<p>Warmline (800) 933-3413 HIV Telephone Consultation Service. <i>Consultation on all aspects of HIV testing and clinical care</i></p>
<p>PEPline (888) 448-4911 Clinicians' Post-Exposure Prophylaxis Hotline. <i>Recommendations on managing occupational exposures to HIV and hepatitis B and C viruses</i></p>
<p>Perinatal HIV Hotline (888) 448-8765 Perinatal HIV Consultation and Referral Service. <i>Advice on testing and care of HIV-infected pregnant women and their infants</i></p>

^aMore information is available at www.ncccf.ucsf.edu.

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of at least 1 HIV envelope protein (eg, gp160, gp120, or gp41) plus the GAG protein p24 and usually the POL protein p32.

An indeterminate Western blot test result is one in which positive bands are detected but are not sufficient to meet the criteria for a positive result. The indeterminate result indicates either that the patient is in the process of seroconverting or that the prior screening HIV test result was a false positive.

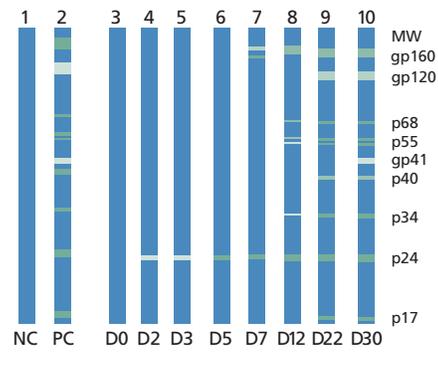


Figure 1. Western blot reactivity in a typical person during HIV-1 seroconversion. Western blot results are very specific and “evolve” over weeks to months. A positive finding requires a full complement of bands. D indicates day; MW, molecular weight; NC, negative control; PC, positive control.

Pregnancy is associated with increased false-positive results on HIV antibody tests,⁵ as it is a highly immune-stimulated state that includes alloantibody production, and some of these antibodies cross-react with the HIV tests. The incidence of false-positive results increases with higher parity (number of deliveries).⁵

For a patient who receives an indeterminate Western blot result relatively early in pregnancy, the test should be repeated approximately 4 weeks later. This timing allows for Western blot reactivity to become apparent in the majority of patients who actually have HIV infection. An option is to perform an HIV viral load test immediately, as acute seroconversion is generally accompanied by very high viral titers. However, the HIV viral load test can show false-positive results in the form of a low viral load (usually < 1000 copies/mL but can reach 10,000 copies/mL).⁶ Further,

the viral load test is not approved by the US Food and Drug Administration (FDA) for diagnosis of HIV infection.

For patients later in pregnancy, there may not be time to wait 4 weeks to repeat the Western blot test before taking steps to prevent perinatal HIV transmission. In these cases, a risk assessment should be performed to help decide how likely a positive screening test result is to be a true-positive result and whether antiretroviral therapy should be started while awaiting results of the confirmatory Western blot test. The goal of treatment at this point is to have undetectable viral load in the patient by late third trimester or, at the latest, by the time of delivery.

Other hotline questions on HIV testing in pregnancy include whether a positive rapid test result during labor should prompt antiretroviral therapy initiation in women with a negative first-trimester result and no third-trimester test. Rapid testing during labor is recommended for women without documented HIV serostatus, for women with a negative first-trimester result but ongoing risk, and for women who missed their third-trimester test. Third-trimester tests are recommended in certain states (Figure 2) and in facilities with an incidence of HIV infection in pregnancy of at least 0.1%.^{7,8} The positive predictive value (ie, the ratio of true-positive results to all positive results) of rapid testing in labor is higher in settings where the background inci-

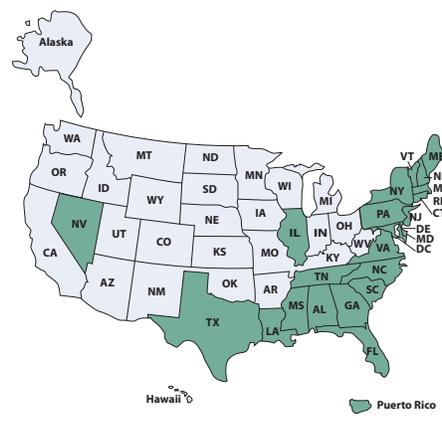


Figure 2. States (shaded) that recommend HIV testing during the third trimester of pregnancy. Adapted from National HIV/AIDS Clinicians’ Consultation Center.⁸

dence of HIV infection in pregnancy is higher. For example, considering a typical HIV rapid test sensitivity of 99.6% and a specificity of 99.9%, if the HIV infection prevalence in the population of women of childbearing age is 0.5%, the positive predictive value of the rapid test is 83%. In settings where the HIV infection prevalence is 0.1%, the positive predictive value is 50%, meaning that about half of the positive results are false positives.

Despite the potential for false-positive results with rapid testing during labor, all positive results should be treated as true positives until HIV infection can be ruled out. That is, a Western blot confirmatory test should be sent, but treatment should begin while awaiting the results, which usually take at least a few days. For women in labor, prophylaxis should be started immediately with intravenous zidovudine for the mother, which can be discontinued when the infant is delivered. The infant should be started on zidovudine and continue receiving it for 6 weeks, unless HIV testing confirms that the woman is HIV uninfected.⁷

In high-risk situations, many practitioners would add a single dose of nevirapine for both mother and infant. There is no published evidence to date that the addition of nevirapine to zidovudine reduces risk of transmission versus 6 weeks of zidovudine alone. However, an international study is in progress comparing 6 weeks of zidovudine to 6 weeks of zidovudine combined with other drugs, including nevirapine. Early analysis of this study suggests that combination antiretroviral drugs may be more effective than zidovudine alone for infants whose mothers have received no antepartum antiretroviral therapy.⁹

Although the risk of nevirapine toxicity with single-dose administration is minimal,⁷ the main risk of adding nevirapine is the emergence of NNRTI resistance. Nevirapine has a long half-life, and levels of the drug can be detected for up to 3 weeks in adults and possibly even longer in infants with poor renal function. If antiretroviral therapy is discontinued after single-dose nevirapine, the continued exposure to the nevirap-

ine component can lead to a state of functional monotherapy, which may lead to NNRTI resistance. A number of studies have shown that nevirapine resistance can be markedly reduced by treating the mother with a “tail” of zidovudine plus lamivudine for 1 week. Current US guidelines recommend use of this dual nRTI tail after discontinuing nevirapine and suggest a similar treatment of the infant with lamivudine for 1 week during the 6 weeks of zidovudine treatment.⁷

Antepartum Antiretroviral Treatment

Antiretroviral drugs currently recommended for use in pregnancy are lamivudine, zidovudine, and lopinavir/r, with nevirapine also recommended for women with CD4+ cell counts less than 250/ μ L (Table 2).⁷ These drugs have been used for many years in pregnancy and are generally well tolerated.

Among alternative options or options for use under special circumstances, tenofovir poses potential risks of bone and renal toxicities. Decreased fetal bone porosity and decreased fetal growth have been observed in monkeys given tenofovir, and long-term use has been associated with bone demineralization in children (as well as in adults).¹⁰ There has been 1 fully reported study of the safety of tenofovir in pregnancy,¹¹ and a number of other studies have been reported in scientific conference abstracts.¹²⁻¹⁵ One study indicated that use of tenofovir during pregnancy was associated with smaller birth size in infants (not intrauterine growth restriction), who then caught up to normal size within 1 year to 2 years (Richard Linde, MD; oral communication, February 2010). Thus far, there has been no evidence of statistically significant fetal bone or renal defects, but the numbers of cases studied remains small. Although there is a growing sense of comfort with use of tenofovir in pregnancy, it is prudent to reserve its use for select women, such as those who have been taking and tolerating it for a long time, or those who may be unwilling to take a twice-daily antiretroviral regimen.

The main concerns with atazanavir

Table 2. Antiretroviral Drugs in Pregnancy

	Nucleoside Analogue Reverse Transcriptase Inhibitors	Nonnucleoside Analogue Reverse Transcriptase Inhibitors	Protease Inhibitors
Recommended	Zidovudine Lamivudine	Nevirapine (if CD4+ cell count < 250/ μ L)	Lopinavir/ritonavir
Alternative	Abacavir Didanosine Emtricitabine Stavudine		Atazanavir/ritonavir Indinavir/ritonavir Nelfinavir Saquinavir/ritonavir
Special circumstances	Tenofovir	Efavirenz	

Note: Insufficient evidence for all other available antiretroviral drugs. Based on US Public Health Service Perinatal HIV Guidelines.⁷

use are the risk of hyperbilirubinemia (which theoretically can lead to infant kernicterus) and inadequate drug levels in the second and third trimesters. In the small number of cases studied thus far, use of atazanavir has been associated with a predictable rise in bilirubin level in mothers and a proportional rise in bilirubin level in infants,¹⁶ but no pathologic or dangerous elevations have been observed to date.^{17,18} No cases of exchange transfusions or kernicterus in infants have been reported. Levels of atazanavir in mothers receiving atazanavir/r may be low (sometimes undetectable) during the second and third trimesters, and there is interest in assessing the effects of increasing the atazanavir/r dose during this period.¹⁹⁻²¹ Pregnant women with prior antiretroviral therapy experience who are taking atazanavir/r along with either tenofovir or a histamine 2 (H₂) receptor antagonist should increase the oral atazanavir/r dose to 400mg/100 mg daily.^{22,23}

The main concern with efavirenz is the potential for serious central nervous system defects. Efavirenz is rated as FDA category D in pregnancy. Monkeys exposed to efavirenz have exhibited anencephaly, anophthalmia, and cleft palate,²⁴ and there have been 7 reports of central nervous system defects in infants with first-trimester exposure.²⁵ However, the overall incidence of birth defects reported in the antiretroviral

pregnancy registry (involving 600–700 cases of efavirenz exposure), is 2.8%, equivalent to the rate in the general population. The birth defects appear to be largely a risk during first-trimester exposure, before the neural tube has closed. Currently, there is increasing use of efavirenz in the second and third trimesters of pregnancy, including fixed-dose efavirenz/emtricitabine/tenofovir and fixed-dose emtricitabine/tenofovir.

Among newer antiretroviral drugs, darunavir and raltegravir are categorized as FDA pregnancy category C, and maraviroc and etravirine as category B. There is accumulating anecdotal experience with these drugs in pregnant women with highly resistant virus, likely reflecting the sentiment that theoretical risks of toxicity are not as great as the potential for transmission of HIV. Thus far, there are no reports of adverse outcomes in exposed infants.

Intrapartum Care

No major changes have been made recently in recommendations for intrapartum care. It is still recommended that the mother receive intravenous zidovudine and that instrumentation and artificial rupture of membranes be avoided. Caesarean section should be scheduled at 38 weeks gestation if the maternal plasma HIV RNA level is greater than 1000 copies/mL.⁷

Pneumocystis jiroveci **Pneumonia Prophylaxis for HIV-Exposed Infants**

A major change was made in 2008 to the US Public Health Service infant HIV testing recommendations with introduction of the “presumptive” ruling out of HIV infection. Thus, prophylaxis for *Pneumocystis jiroveci* pneumonia in the infant can be avoided if HIV infection is presumptively ruled out on the basis of negative HIV test results at 14 days and 1 month. In practice, this means that most HIV-exposed infants can avoid months of trimethoprim-sulfamethoxazole prophylactic treatment.

Summary

The National Perinatal HIV Hotline is a source to clinicians for free, around-the-clock advice about the management of HIV-infected pregnant women and their exposed infants. Experience with callers to the hotline shows that common questions include the use of hormonal contraception in conjunction with antiretroviral therapy, the interpretation of indeterminate HIV tests in pregnant women, and the optimal choice of antiretroviral drugs in pregnancy. Staff answering the calls provide expert guidance on these and related issues, helping practitioners incorporate the latest information into their clinical decision making.

Lecture presented by Dr Waldura in August 2010. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Waldura in February 2011.

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References

1. US Department of Health and Human Services and Health Resources and Services Administration. A Guide to the Clinical Care of Women with HIV/AIDS, 2005 edition. <http://hab.hrsa.gov/publications/womencare05/index.htm>. Accessed March 4, 2011.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 10, 2011; 1-166. [http://www.aidsinfo.nih.gov/ContentFiles/](http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf)

- AdultandAdolescentGL.pdf. Accessed January 21, 2011.
3. Perinatal HIV Guidelines Working Group. Public Health Service Task Force recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. April 29, 2009. pp 1-90. <http://aidsinfo.nih.gov/ContentFiles/PerinatalGL001317.pdf>. Accessed March 16, 2011.
4. Cocohoba J. Hormonal contraception for HIV positive women. *BETA*. 2010;22:36-40.
5. Celum CL, Coombs RW, Jones M, et al. Risk factors for repeatedly reactive HIV-1 EIA and indeterminate Western blots. A population-based case-control study. *Arch Intern Med*. 1994;154:1129-1137.
6. Daar ES, Little S, Pitt J, et al. Diagnosis of primary HIV-1 infection. Los Angeles County Primary HIV Infection Recruitment Network. *Ann Intern Med*. 2001;134:25-29.
7. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. 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. May 24, 2010. pp 1-117. <http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf>. Accessed July 20, 2010.
8. National HIV/AIDS Clinicians' Consultation Center. State HIV Testing Laws. http://www.nccc.ucsf.edu/consultation_library/state_hiv_testing_laws/. Accessed January 24, 2011.
9. Nielsen-Saines K, Watts H, Veloso VG, et al. Phase III randomized trial of the safety and efficacy of 3 neonatal ARV regimens for prevention of intrapartum HIV-1 transmission: NICHD HPTN 040/PACTG 1043. [Abstract 124LB.] 18th Conference on Retroviruses and Opportunistic Infections (CROI). February 27-March 2, 2011; Boston, MA.
10. Tarantal AF, Castillo A, Ekert JE, Bischofberger N, Martin RB. Fetal and maternal outcome after administration of tenofovir to gravid rhesus monkeys (*Macaca mulatta*). *J AIDS*. 2002;29:207-220.
11. Nurutdinova D, Onen NF, Hayes E, Mondy K, Overton ET. Adverse effects of tenofovir use in HIV-infected pregnant women and their infants. *Ann Pharmacother*. 2008;42:1581-1585.
12. Vigano A, Zuccotti GV, Stucchi S, et al. Exposure during gestation to HAART, including tenofovir, does not impair bone status and metabolism in HIV- children born to HIV+ mothers. [Abstract 926.] 17th Conference on Retroviruses and Opportunistic Infections (CROI). February 16-19, 2010; San Francisco, CA.
13. Linde R, Königs C, Rusicke E, Haberl A, Reitter A, Kreuz W. Tenofovir therapy during pregnancy does not affect renal function in HIV-exposed children. [Abstract 925.] 17th Conference on Retroviruses and Opportunistic Infections (CROI). February 16-19, 2010; San Francisco, CA.
14. Chidziva E, Zwalango E, Russell E, et al. Outcomes in infants born to HIV-infected mothers receiving long-term ART in the

- DART trial, 2004 to 2009. [Abstract 924.] 17th Conference on Retroviruses and Opportunistic Infections (CROI). February 16-19, 2010; San Francisco, CA.
15. Haberl A, Linde R, Reitter A, et al. Safety and efficacy of tenofovir in pregnant women. [Abstract 627a.] 15th Conference on Retroviruses and Opportunistic Infections (CROI). February 3-6, 2008; Boston, MA.
16. Ferreira C, Floch-Tudal C, Meier F, et al. Atazanavir in pregnancy: influence on neonatal hyperbilirubinemia. [Abstract 625.] 15th Conference on Retroviruses and Opportunistic Infections (CROI). February 3-6, 2008; Boston, MA.
17. Ripamonti D, Cattaneo D, Airoldi M, et al. Atazanavir-based HAART in pregnancy. [Abstract 742.] 14th Conference on Retroviruses and Opportunistic Infections (CROI). February 25-28, 2007; Los Angeles, CA.
18. Natha M, Hay P, Taylor G, et al. Atazanavir use in pregnancy: a report of 33 cases. [Abstract 750.] 14th Conference on Retroviruses and Opportunistic Infections (CROI). February 25-28, 2007; Los Angeles, CA.
19. Mirochnick M, Stek A, Capparelli E, et al. Atazanavir pharmacokinetics with and without tenofovir during pregnancy. [Abstract 941.] 16th Conference on Retroviruses and Opportunistic Infections (CROI). 2009; Montreal, Canada.
20. Ripamonti D, Cattaneo D, D'Avolio A, et al. Steady state pharmacokinetic of ritonavir-boosted atazanavir in 31 pregnant women before and after delivery. [Abstract 907.] 17th Conference on Retroviruses and Opportunistic Infections (CROI). February 16-19, 2010; San Francisco, CA.
21. Eley T, Vandeloise E, Child M, et al. Steady state pharmacokinetics and safety of atazanavir after treatment with ATV 300 mg once daily/ritonavir 100 mg once daily+ZDV/3TC during the third trimester in HIV+ women. [Abstract 624.] 15th Conference on Retroviruses and Opportunistic Infections (CROI). February 3-6, 2008; Boston, MA.
22. Atazanavir [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2011.
23. US Food and Drug Administration. Reyataz (atazanavir) label revised, adding dosing recommendations for pregnancy and postpartum period. February 4, 2011. <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm242383.htm>. Accessed March 11, 2011.
24. Nightingale SL. From the Food and Drug Administration. *JAMA*. 1998;280:1472.
25. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral pregnancy registry international interim report for 1 January 1989 to 31 July 2009. <http://www.apregistry.com>. Accessed February 26, 2010.