Perspective

HIV Infection in Women: Perinatal Issues and Cervical Cancer Surveillance

Issues of HIV infection in women include perinatal care to prevent mother-child transmission and screening for cervical dysplasia. Antiretroviral therapy has been very successful in reducing perinatal transmission rates. Ongoing issues in this setting include absence of relevant pharmacokinetics data for new drugs and formulations, implementation of new resistance testing guidelines, and recent apparently conflicting findings on the potential role of protease inhibitor treatment in preterm delivery. Recent findings also include a similar low transmission rate with vaginal delivery and emergency cesarean delivery versus elective cesarean delivery in women on antiretroviral therapy with HIV viral load of less than 1000 copies/mL, and a low rate of postpartum morbidity in women undergoing elective cesarean delivery. Recent changes in recommendations for cervical cancer screening in the general population should not be applied to HIV-infected women. However, the recent finding that HIV-infected women with CD4+ cell counts greater than 500/µL do not have a greater rate of squamous intraepithelial lesions than women without HIV infection suggests that the former can be followed less frequently if they have normal Pap tests. This article summarizes a presentation on HIV infection in women made by Carmen D. Zorrilla, MD, at the 9th Annual Ryan White CARE Act Clinical Update in Washington, DC, in August 2006. The original presentation is available as a Webcast at www.iasusa.org.

Perinatal Issues

Preconception Care

Among the issues involved in pregnancy and childbirth for HIV-infected women are preconception care and counseling. Preconception care "aims to promote the health of women of reproductive age before conception and thereby improve pregnancy-related outcomes. Improving preconception health can result in improved reproductive health outcomes, with potential for reducing social costs as well" (*MMRW Mortal Morbid Wkly Rep*, 2006). It is important for all women and crucial for women living with HIV who have postponed but now want to achieve pregnancy, particularly HIV-infected women who are receiving antiretroviral therapy. Since about half of pregnancies in the general population are unplanned, preconception counseling and care should also be extended to women of reproductive age even if they are not actively seeking a pregnancy (Henshaw, *Fam Plann Perspect*, 1998).

Health care visits for women of reproductive age are opportunities to provide preconception care. A question such as: *Are you planning a pregnancy?* or, *Could you become pregnant?* might be a springboard to a discussion and may facilitate planning of the diverse reproductive options available (contraception, pregnancy preparation, infertility evaluation and so forth). Antiretroviral treatment options may differ if future pregnancy is a possibility. For new patients in HIV care, suspicion for and detection of early pregnancy is essential to appropriate management, including avoidance of potentially teratogenic drug treatments and the initiation of preventive strategies such as folic acid supplementation.

Perinatal Care

Transmission of HIV can occur in utero, during birth, and during breastfeeding. Although rates of transplacental transmission appear to be low, HIV has been found in fetal brain and liver tissues after spontaneous abortion, indicating that the virus can infect internal organs during development. Most transmission occurs during labor and delivery. Because most transmissions occur during birth, the reduction of perinatal HIV transmission has been very successful.

HIV-seropositive women can be identified during prenatal care and antiretrovirals can be given to reduce the risk of transmission. Breastfeeding increases the risk of transmission by 16%, with risk increasing with duration of breastfeeding. Interventions such as scheduled cesarean deliveries and infant formula are important in the reduction of perinatal HIV transmission.

Drug Therapy

The use of antiretroviral therapy during pregnancy followed by postexposure treatment for the newborn has been highly successful in preventing perinatal transmission of HIV in the United States. The number of cases of perinatally acquired infection in 2004 decreased by approximately 95% from the peak reported incidence in 1992, largely because of antiretroviral drug therapy during pregnancy. Data on pharmacokinetics during pregnancy are needed for new drugs and new formulations. New resistance testing recommendations need to be implemented. Also, whether use of protease inhibitors (PIs) in pregnancy is associated with increased risk of preterm delivery needs to be determined.

Obtaining information on antiretroviral pharmacokinetics in pregnancy is of particular importance in the case of PIs, since blood levels of most PIs are reduced in pregnancy. Currently there are no data in pregnancy for the newer agents fosamprenavir, tipranavir, atazanavir, and darunavir. Lopinavir/ritonavir capsules (133/50 mg) have been replaced with the higher-dose tablet

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formulation (200/100 mg), for which there are also no data in pregnancy.

Exposure to lopinavir/ritonavir during late pregnancy was lower than in the postpartum period and than in nonpregnant historic controls at the Pediatric AIDS Clinical Trials Group (PACTG) 1026 study (Stek et al, *AIDS*, 2006). The following statements are available at the US Department of Health and Human Services website (aidsinfo.nih.gov): "Increasing the dose of lopinavir/ritonavir in the third trimester to 4 capsules twice a day achieved adequate exposure during the third trimester but resulted in higher levels by 2 weeks postpartum (Stek et al, CROI, 2006). Another study of 16 HIV-infected primarily antiretroviral naive pregnant women who were receiving standard dosage of lopinavir/ritonavir throughout pregnancy found that 94% had trough levels above 1000 ng/mL (the minimum trough level required to inhibit wild-type HIV), and most (88%) had virologic suppression." (Lyons et al, CROI, 2006).

The saquinavir hard-gel capsule (1200 mg) has replaced the soft-gel capsule (800 mg) in regimens with lower-dose (100 mg) ritonavir. Although the drug in the soft-gel capsule formulation had good pharmacokinetics in pregnancy, there are few data thus far on the drug in the hard-gel formulation.

"In a pharmacokinetic study of 4 pregnant women receiving saquinavir hard-gel capsule 1000 mg/ritonavir 100 mg-based regimen twice daily, trough concentrations ranged from 656 ng/mL to 2169 ng/mL and peak concentrations from 845 ng/mL to 4002 ng/mL. The minimum trough concentration for wild-type virus is 100 ng/mL." (Hanlon et al, CROI, 2006). In a separate population pharmacokinetic study of 15 pregnant women receiving saquinavir hard-gel capsule 1000 mg/ritonavir 100 mg-based regimen twice daily, the projected median trough level was 1041 ng/mL (range, 96 ng/mL-2238 ng/mL). One woman had a trough level of less than 100 ng/mL but achieved adequate levels at an increased dose of 1200 mg saquinavir hard-gel capsule/100 mg ritonavir (Khan et al, IAC, 2004). Finally, in a study of 2 women who received saquinavir hard-gel capsule 1200 mg/ritonavir 100 mg given once daily, trough levels were 285 ng/mL and 684 ng/mL and the area-under-the concentration curve (AUC_{0-24}) were 28,010 ng•hour/mL and 16,790 ng•hour/mL, above the target AUC of 10,000 ng•hour/mL (Lopez-Cortes et al, *HIV Clin Trials*, 2003). Thus, the available data suggest that 1000 mg saquinavir hard-gel capsule/100 mg ritonavir given twice daily should achieve adequate trough levels in HIV-infected pregnant women, but data are too limited to recommend once-daily dosing. Saquinavir hard-gel capsule should always be given with low-dose ritonavir boosting (Hanlon et al, CROI, 2006).

The US Department of Health and Human Services released recommendations for antiretroviral resistance testing in pregnant women in mid-2006. Drug resistance testing is recommended for: (1) all pregnant women not currently receiving antiretrovirals before starting treatment or prophylaxis and (2) all pregnant women receiving antenatal antiretroviral therapy who have virologic failure with persistently detectable HIV RNA or who have suboptimal viral suppression after initiation of antiretroviral therapy.

Lack of availability of resistance testing might present issues in settings with limited resources. Particular attention to the quick turnaround of results is necessary due to the short time interval for antiretroviral treatment during pregnancy. Health care providers for pregnant women living with HIV need to ensure that testing results are available in a short turnaround time in order to start optimal therapy or implement treatment change if necessary.

The experience with PI-containing regimens during pregnancy has been diverse and sometimes conflicting. Some data indicate that PI-containing regimens are associated with preterm delivery, resulting in a trend among European practitioners to avoid PIs during pregnancy. In a recent report, outcome of pregnancy was evaluated in a cohort of 999 women followed up at the University of Miami from 1990 to 2002 according to whether they had received antiretroviral monotherapy (n = 492), a combination without a PI (n = 373), a combination with a PI (n = 134), or no therapy (n = 338; Cotter et al, *J Infect Dis*, 2006). Treatment with a PI-containing combination was associated with an increased risk of preterm delivery (odds ratio [OR], 1.8; 95% confidence interval [CI], 1.1-3.0) compared with any other combination. No differences were observed in risk for low birth weight or stillbirth. A confounding factor in this analysis was that PI treatment during pregnancy was given to those women who had already been receiving PI treatment, who had low CD4+ cell count or high viral load, or who had exhibited poor clinical response to prior treatment.

These findings appear to be consistent with increased risk of preterm delivery in women receiving PI treatment in a European cohort reported in 2000. In this report, preterm delivery occurred in 16% of women using no antiretroviral therapy (n = 2819), 17% using monotherapy (n = 555), 22% using a non-PI combination (n = 188), and 29% using a combination including a PI (n = 101; European Collaborative Study and Swiss Mother and Child HIV Cohort Study, *AIDS*, 2000). On the contrary, a PACTG analysis indicated that preterm delivery occurred in 27% of women receiving no antiretroviral therapy (n = 66), compared with 18% for those receiving monotherapy (n = 256), 11% for those receiving a non-PI combination (n = 533), and 15% using a combination including a PI (n = 617).

In Dr Zorrilla's setting the women at highest risk for preterm delivery are the women not receiving therapy because these women often are not receiving prenatal care and might exhibit other risk behaviors that place them at risk for preterm delivery. An examination of outcomes of PI use in 233 pregnancies showed an HIV transmission rate of 0.9%, prematurity rate (<37 weeks) of 22% (20% excluding multiple [twin and triplet] pregnancies), and an extreme prematurity rate (<32 weeks) of 2.5%. As expected, premature delivery was more common in multiple gestations (9.2-fold increased risk) and with injection drug use as the HIV risk fac-

tor (3.9-fold increased risk; Morris et al, *J Acquir Immune Defic Syndr*, 2005). No particular PI was associated with increased risk of preterm delivery; a recent report from Spain indicates increased risk of preeclampsia and fetal death when women receive antiretroviral therapy (Suy et al, *AIDS*, 2006).

This analysis showed rates of preeclampsia and fetal death of 2% and 2%, respectively, in women who mostly received no antiretroviral therapy between 1985 and 2003 (n = 472), 6% and 4%, respectively, among those mostly on antiretroviral therapy between 1998 and 2003 (n = 122), and 3% and 1%, respectively, among non-HIV-infected controls (n = 8768) between 2001 and 2003. These findings have not been corroborated in the United States, and it is possible that rates of preeclampsia are lower in US settings because of the frequent use of elective cesarean delivery that is performed before term is reached. Although the etiology of preeclampsia is still unknown, it has been associated with nutritional, immunologic, and obstetric variables and additional studies are needed to confirm the findings of the Spanish study.

Cesarean Delivery

Cesarean delivery has also played a role in reducing HIV transmission rates. However, the benefit of such delivery may be reduced or absent in settings in which viral load is suppressed by antiretroviral therapy to low levels in the mother. A PACTG study abstracting charts of 3081 deliveries showed no difference in transmission rates according to elective cesarean delivery versus vaginal delivery or emergency cesarean delivery among women receiving antiretroviral therapy who had HIV RNA levels below 1000 copies/mL (Table 1). Nevertheless, elective cesarean delivery should be considered as an option in all HIV-infected women. Women may have additional benefits with elective surgery, including to whom to disclose and potential cultural preferences. Antiretrovirals need to be taken correctly during labor as missing doses during a prolonged labor might lead to viral replication.

Table **1**. Rates of HIV Transmission in 3081 Deliveries in Pediatric AIDS Clinic Trials Group 367 Chart Abstraction Study

HIV-1 RNA Level	Transmission Rate	
	Elective cesarean delivery	Vaginal delivery or emergency cesarean delivery
>1000 Copies/mL		
Single drug	1.8%	7.4%
Antiretroviral therapy	2.3%	1.8%
<1000 Copies/mL		
Single drug	1.8%	4.3%
Antiretroviral therapy	0.8%	0.5%

Adapted from Shapiro et al, CROI, 2004.

There are currently no published data regarding these issues.

Active genital tract herpes simplex virus (HSV-1 or -2) infection is an indication for cesarean delivery among women in the general population. Recurrent genital manifestations of herpes infection are an indication for antiretroviral treatment during pregnancy. The strong association between self-report or clinical manifestation of genital HSV infection and HIV transmission was recently pointed out again by a retrospective analysis of 402 pregnancies in New York City between 1994 and 1999. In the context of an overall HIV transmission rate of 11.4%, the transmission rate for women with HSV infection was 28.6% (OR, 4.8; 95% CI, 1.3-17.0; $P = .02$; Chen et al, *Obstet Gynecol*, 2005). A limitation of this analysis was the lack of HSV cultures or HSV DNA testing to confirm the clinical or self-report diagnoses. Although cesarean delivery may expose women to morbidity not associated with vaginal delivery, a recent study indicates that the risk is not so great as has been previously thought.

In the National Institute of Child Health and Development International Site Development Initiative Perinatal Study in Latin American and Caribbean countries, overall risk for postpartum morbidity was low in both vaginal and cesarean deliveries, with elective cesarean delivery being associated with a statistically nonsignificant 16% increase in risk compared with vaginal delivery (Duarte et al, *Am J Obstet Gynecol*, 2006). In this prospective cohort study, unadjusted ORs (95% CIs) for morbidity were 1.16 (0.5-2.7) for elective cesarean delivery before labor or rupture of membrane (n = 260) and 2.96 (1.3-6.7) for cesarean delivery with labor or rupture of membrane (n = 139) compared with vaginal delivery (n = 299).

Cervical Cancer Screening

In addition to annual examinations, the American College of Obstetricians and Gynecologists still recommends annual screening with conventional Pap or thin prep tests for cervical cancer for women under 30 years of age. For those 30 years or older, screening options consist of annual cytology, less frequent screening (every 2-3 years) in those with 3 consecutive normal test results, and combined human papillomavirus (HPV) DNA testing and cervical cytology. These guidelines, however, are for women in the general population. Until more data are available, they cannot be extended to women with HIV infection, since it is known that HIV-infected women are prone to cervical squamous intraepithelial lesions (SIL).

In examining the cumulative incidence of SIL according to baseline HPV DNA, HIV serostatus, and CD4+ cell count, the Women's Interagency HIV Study showed that the incidence of SIL in HIV-infected women with CD4+ cell counts below 500/μL was greater than

that in women without HIV infection on multivariate analysis, with the rate in HIV-infected women with higher CD4+ cell counts being comparable to that in HIV-seronegative women.

For now, the existing recommendations regarding surveillance of lower genital tract neoplasia in HIV-infected women should generally be followed. These include inspection of the external anogenital area as part of an annual physical exam and taking of samples of all suspicious external lesions for biopsy. Two Pap tests taken 6 months apart should be obtained within the first year of HIV diagnosis. If the results of both are negative, tests can be repeated annually in those women with CD4+ cell counts greater than 500/µL.

In those with lower counts and in those with abnormal findings Pap tests should be done every 6 months and combined with HPV testing. Colposcopy should be performed in all cases in which Pap tests reveal atypical squamous cells of undetermined significance (ASCUS) or worse. Cervical intraepithelial neoplasia (CIN) should be treated, with excisional techniques (loop electrosurgical excision procedure) being favored over cryosurgery. Localized vulvar and anal intraepithelial neoplasia should be treated conservatively — for example, with carbon dioxide laser vaporization, fulguration, or trichloroacetic acid. It should be noted that trichloroacetic acid is nonteratogenic and can thus be safely used during pregnancy or in women who might become pregnant.

All extensive external anogenital and intra-anal lesions should be monitored biannually. Antiretroviral therapy significantly enhances regression of CIN. There is a high rate of recurrence of CIN after surgery in HIV-infected women.

Other Issues

Two additional recent studies regarding HIV infection in women need mentioning. One is a study showing that teen daughters of parents with HIV infection have higher pregnancy rates than do adolescents in the general population (May et al, *Am J Health Behav*, 2006).

In this study, 181 adolescent daughters (mean age, 15 years) of people with HIV infection received either family-based counseling (intervention group) or routine family case management services (observation group) and were followed up for up to 7 years. Pregnancy rates were 38% in the family-based counseling group and 67% in the observation group, compared with a teen pregnancy rate of 10% in the city in which the study was conducted.

A second study shows that cigarette smoking worsens HIV status in HIV-infected women (Feldman et al, *Am J Public Health*, 2006). In this Women's Interagency HIV Study report involving 924 women who initiated antiretroviral therapy between 1995 and 2003, smokers had significantly greater risks (hazard ratio; 95% CI) for poorer virologic response (0.79; 0.67-0.93), poorer immunologic response (0.85; 0.73-0.99), virologic rebound (1.39; 1.06-1.69), more frequent immunologic failure (1.52; 1.18-1.96), death (1.53; 1.08-2.19), and developing AIDS (1.36; 1.07-1.72). Smokers did not have a significantly increased risk of death due to AIDS. If cigarette smoking is a significant factor for progression of disease and mortality, its impact can be modified with smoking cessation interventions.

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Suggested Reading

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