

# HIV Infection in Pregnancy

The following section is entitled “**HIV Infection in Pregnancy**”. This section deals with some of the basic concepts important to the diagnosis, management and investigation of HIV infection during pregnancy. The section begins with a *learner handout* with space for the learner to make their own notes. The *learner handout* is followed by the *teaching script* for the educator. The section then concludes with several cases for discussion and a brief bibliography for this topic.

**HIV DISEASE IN PREGNANCY**

**HIV DISEASE  
IN PREGNANCY**

---

---

---

---

---

---

---

- **AIDS is a leading cause of death in U.S. women of reproductive age.**
- **Mother-to-infant transmission accounts for most HIV infections among children.**
- **HIV status does not affect reproductive choices in women.**

---

---

---

---

---

---

---

**ANTENATAL TESTING**

- **It is the law in many states that pregnant women be counseled to undergo HIV testing during their pregnancy because of the benefits of AZT therapy to the fetus.**
- **No states have instituted mandatory testing.**

---

---

---

---

---

---

---

## HIV DISEASE IN PREGNANCY

### EFFECT OF HIV ON PREGNANCY

- HIV positive women do not have different obstetrical outcomes than age matched women of similar social situation.

---

---

---

---

---

---

---

### EFFECT OF PREGNANCY ON HIV

- Little hard data support any adverse effect of pregnancy on the course of HIV disease.

---

---

---

---

---

---

---

- CD4 cell counts decline both in HIV negative and HIV positive women during pregnancy.
- Plasma HIV-1 RNA has not been well studied as measure of disease progression in pregnancy.

---

---

---

---

---

---

---

## HIV DISEASE IN PREGNANCY

### VERTICAL TRANSMISSION

- **Prospective studies show maternal-to-child transmission rates of 30%.**
- **Zidovudine if given during pregnancy, in labor, and administered postpartum to the newborn decreases maternal-to-infant transmission of HIV from 30% to 8%.**

---

---

---

---

---

---

---

---

### MANAGEMENT OF HIV IN PREGNANCY

- **Routine prenatal care**
- **Interdisciplinary approach**
- **Baseline evaluation**
  - **CD4 count (q trimester)**
  - **Plasma HIV-1 RNA (q trimester)**
  - **History of antiretroviral therapy**
  - **Firmly establish gestational age of fetus**

---

---

---

---

---

---

---

---

### ANTIVIRAL MEDICATION

- **Decisions about antiretroviral therapy are the same as in nonpregnant women, with the additional factors related to impact of choices on the fetus and infant.**
- **Careful informed consent and ongoing communication among care providers and the mother are essential.**

---

---

---

---

---

---

---

---

**HIV DISEASE IN PREGNANCY**

- **All HIV + women should be offered AZT chemoprophylaxis during pregnancy, regardless of CD4 count and stage of pregnancy.**
- **Use of newer antiretroviral agents and combination therapy in pregnancy is controversial but should be offered to patients.**

---

---

---

---

---

---

---

---

- **Discussions about antiretroviral therapy in pregnancy should include information about potential risks and benefits of *all* options.**
- **The Antiretroviral Pregnancy Registry at 1-800-722-9292 is an important resource.**

---

---

---

---

---

---

---

---

**OPPORTUNISTIC INFECTIONS**

- **Despite the normal decline in CD4 counts during pregnancy, guidelines for institution of prophylaxis on the basis of CD4 count are unchanged.**
  - **TMP/SMX remains the first line agent for prophylaxis for *Pneumocystis carinii* infections.**

---

---

---

---

---

---

---

---

**LABOR**

- **Management of labor should involve the use of universal precautions in all patients.**
- **Unnecessary instrumentation should be avoided in HIV positive women.**
- **Cesarean sections are not routinely recommended for all HIV positive women but may decrease vertical transmission in women with high viral loads.**

---

---

---

---

---

---

---

**BREAST FEEDING**

- **Breast feeding is discouraged in HIV positive women when other methods of feeding are available.**

---

---

---

---

---

---

---

**HIV and Pregnancy: Summary**

- **Vertical transmission is responsible for most HIV in children.**
- **The pregnant woman with HIV needs close, team management.**
- **Therapeutic choices need to balance maternal disease factors and the infant.**
- **AZT prophylaxis is key to prevention.**

---

---

---

---

---

---

---

# HIV DISEASE IN PREGNANCY

## *Teaching Script*

written with Jami A. Star, M.D.

### **Epidemiology of AIDS in Women**

AIDS is one of the leading causes of death in women of reproductive age in the United States. Since 1981, when the first case of HIV infection in a woman was reported, the incidence of HIV infection among women has been increasing. Seroprevalence rates vary geographically, with the highest rates detected in urban centers. In addition, racial and ethnic minorities, such as Latinas and African Americans, comprise the majority of infected individuals in the United States. Worldwide, the prevalence of disease in sub-Saharan Africa and Southeast Asia has taken on epidemic proportions. The tragedy is compounded when one considers that mother to infant transmission accounts for almost all cases of HIV infection among children.

Intravenous drug use was initially responsible for the majority of HIV infection in women, but recently the pattern of transmission has changed. Since 1993, heterosexual contact has been the primary means by which women are infected with HIV, suggesting that all pregnant women are at risk by virtue of their exposure to unprotected vaginal intercourse. Additional risk factors include: blood products received between 1977-1985, history of a sexually transmitted disease (or sexual contact with someone with that history), origin from a country with a high rate of HIV infection (i.e. Africa, Southeast Asia, Caribbean), or involvement with multiple sexual partners.

### **Antenatal Testing**

It is the law in most states that all pregnant women be counseled regarding the option of HIV testing at the beginning of their pregnancy. Screening only those women with reported risk factors will detect, at most, 60% of infected women. The use of zidovudine (AZT), discussed later in this article, has been shown to significantly limit the risk of vertical transmission.

Therefore, the law also requires that women be counseled as to the benefits of this therapy should they test positive for HIV. However, because of the issues related to privacy and discrimination, and the impossibility of forcing patients to take unwanted AZT, no states have instituted mandatory HIV testing of all pregnant women. Requirements to notify the partner of an infected individual vary by state as well.

HIV status does not appear to affect reproductive choices in women. HIV positive women appear to become pregnant and choose to keep their pregnancies at a similar frequency as do HIV negative women. Studies have shown that the majority of HIV positive women will not elect to terminate a pregnancy, and many have chosen to reproduce more than once after the diagnosis of HIV infection has been made.

### **Effect of Pregnancy on Clinical Course of HIV infection and AIDS**

One of the questions considered early on in the HIV epidemic was whether pregnancy had any adverse effects on the course of HIV disease. While several clinical manifestations of the infection are specific to women, the overall course of HIV infection in men and women who receive similar care is comparable. However, because pregnancy is often considered a state of relative immunosuppression, there was initial concern that this condition would accelerate disease progression. It is now known that pregnancy can be associated with a drop in CD4 counts in both HIV positive and negative women, with a nadir reached approximately two months prior to delivery. Some, but not all, of the decline is due to plasma volume expansion, making the combination of CD% and CD4 count a more accurate composite reflection of changing immune status related to HIV in the pregnant woman.

Only one study has evaluated the longitudinal course of HIV-1 RNA levels in pregnancy. This cohort of 198 women did show higher plasma HIV-1 RNA levels at 6 months postpartum than during antepartum in many women, regardless of AZT use during or after pregnancy. No clear difference from expected course was identified, however. Thus, although studies are limited regarding long-term survival after pregnancy, there appears to be no acceleration of disease either during or after pregnancy in HIV positive women. Likewise, the incidence of

Obstetric Medicine Curriculum Teaching Script

opportunistic infections has not been found to increase during pregnancy. Overall, CD4 counts and plasma levels of HIV-1 RNA continue to be the primary means of disease assessment during pregnancy.

### **Effect of HIV Infection and AIDS on Pregnancy**

In the United States, HIV positive women do not have measurably different obstetrical outcomes than age-matched women of a similar socioeconomic status. Despite initial findings to the contrary, repeated studies show no increase in preterm delivery, premature rupture of membranes, intrauterine growth restriction, fetal infection or miscarriage in HIV infected women. There is an increase in the presence of sexually transmitted diseases, however. The absence of adverse effects on pregnancy may be related to the fact that most HIV positive pregnant women studied in this country have not progressed to AIDS. By contrast, in Kenya, for example, where women may be at a more advanced state of disease, and where different viral serotypes may be prevalent, there have been findings of decreased birth weight, prematurity and increased risk of postpartum endometritis in pregnancies complicated by HIV.

### **Treatment of the HIV Infected Woman During Pregnancy**

Management of pregnancy in HIV positive women includes “routine” prenatal care, as well as careful observation for any evidence of disease progression. This is best accomplished with a multi-disciplinary approach, involving obstetricians, internists and ancillary service providers such as nutritionists and social workers. Symptoms such as dyspnea, fatigue and sweats are quite common in normal pregnancy, but should be considered more carefully in pregnant patients with HIV. A thorough physical exam at each visit is advised, with adjunctive laboratory testing as indicated. Additional issues during pregnancy might include: serologic testing for hepatitis C (in addition to routine testing for hepatitis B), testing for “TORCH” infections (toxoplasmosis, cytomegalovirus, rubella and herpes) which may have both maternal and fetal implications, baseline liver function tests, aggressive follow-up of any abnormalities on the Pap smear (cervical cancer has recently become a disease-defining diagnosis), evaluation and workup for anemia and thrombocytopenia and PPD testing for tuberculosis with more definitive skin testing if anergic.

The optimal antiretroviral treatment regimen of the pregnant HIV positive woman has not yet been determined. All pregnant HIV positive women should be offered treatment with AZT, to the dramatic reduction in vertical transmission noted with this drug. While transmission rates were generally found to be approximately 30% worldwide in the absence of treatment, the AIDS Clinical Trials Group Protocol 076 documented a significant decrease in the transmission rate to 8% in conjunction with AZT therapy. This randomized, placebo-controlled trial was conducted in pregnant women with CD4 counts greater than 200/cubic millimeter and absence of prior exposure to anti-retroviral therapy. Women were treated antepartum (100 mg zidovudine five times a day) and during labor, and infants were treated for six weeks postnatally. Side effects were minimal in both mothers and infants. The findings were so dramatic as to mandate premature termination of the trial, with subsequent recommendations to treat all HIV positive pregnant women with AZT. However, the trial did not provide information about the minimal dose or duration of zidovudine prophylaxis nor its optimal timing with respect to efficacy. For women who do not or can not receive AZT exactly as administered in the 076 protocol, the CDC has outlined consensus recommendations on alternatives to optimize prevention of vertical transmission.

### **Multi-drug Therapy in Pregnancy**

Several clinical uncertainties with ethical dimensions have come to light by newer treatment options for HIV that expand the effective; alternatives for improving long term morbidity and mortality for the mother. To begin with, there are uncertainties regarding optimal dosing in pregnancy. Also, in patients who are not pregnant, AZT monotherapy is avoided due to an increased risk of development of viral resistance. While it has never been shown to be the case, it is reasonable to be concerned that zidovudine monotherapy, even limited to the duration of pregnancy, may encourage the development of resistant viral strains and compromise later treatment and/or survival. Most standard treatment protocols use a combination of drugs, including nucleoside reverse transcriptase inhibitors (such as didanosine and lamivudine, in addition to zidovudine), protease inhibitors (such as indinavir, saquinavir and ritonavir) and non-nucleoside reverse transcriptase inhibitors (such as nevirapine and efavirenz). While small pharmacokinetic studies have been conducted and documented placental transfer of several other agents, only zidovudine has been studied extensively in pregnancy. Interestingly, the presence of

AZT-resistant strains in the mother has not been shown to limit the effectiveness of the drug as chemoprophylaxis for vertical transmission.

Much uncertainty surrounds optimal management of the mother in order to provide the best longterm balance of safety and effectiveness for the infant being exposed in utero. Animal studies, primarily in rats and rabbits, suggest limited teratogenicity. Most of these drugs have been labeled as FDA category B or C. Category B suggests the absence of risk for humans based on animal and/or human studies. As an example, many drugs administered during pregnancy, including most antibiotics, are in this category. By contrast, category C implies that human and/or animal studies have either shown risk or data are unavailable. Among those classified as Category C, the most concerning risk profile is with efavirenz, which at plasma levels in monkeys treated throughout gestation comparable to those used clinically resulted in severe malformations. Nonetheless, the use of drugs in this category is warranted when potential benefit appears to outweigh risk.

The traditional model of therapeutic conservatism in the clinical management of pregnant women, and awaiting extensive human “testing” before utilization of otherwise standard of care medications, may not be applicable in the face of the significant morbidity and mortality risks in both mothers and infants infected with HIV. Certainly, the safety of zidovudine was not firmly established when its use in pregnancy was initiated. Nor are its longterm risks to the fetus yet known. The importance of avoiding drug resistance and its potential risks to the mother may justify the use of antiretroviral agents other AZT. Given the lack of definitive data in all of these areas, pregnant patients with HIV must be counseled about the potential risks and benefits of the treatment options available and therapeutic decisions made based on informed consent.

Regardless of the antiviral regimen decided upon, all pregnant women treated with any antiretroviral should be enrolled, preferably at the time of exposure, in the collaborative Antiretroviral Pregnancy Registry. Its toll-free telephone number appears in the current package inserts/PDR for all approved antiretroviral agents.

## **Opportunistic Infection Prophylaxis**

Treatment of HIV infected women with respect to prophylaxis and treatment for opportunistic infection is largely the same as for the nonpregnant individual. Trimethoprim/sulfamethoxazole remains the first line agent for prophylaxis of *Pneumocystis carinii* infections. While this medication is associated theoretically with a risk of neonatal encephalopathy due to displacement of bilirubin from albumin, there have been no reported cases as a result of in utero exposure and therefore the drug should be considered safe for use in pregnancy for this indication. Pentamidine is an acceptable alternative in the presence of other contraindications such as maternal allergy.

## **Other Prevention Measures to Reduce Vertical Transmission**

Despite the use of various therapies, it is clear that in utero transmission does occur and has been documented as early as 8 weeks gestation in abortuses. This suggests that vertical transmission is unlikely to be completely eliminated. Maternal risk factors for increased transmission include viral load (evidenced by high plasma viral RNA or decreased CD4 counts), degree of maternal P24 antigenemia, presence of symptomatic infection, and concurrent sexually transmitted disease. Other risk factors are maternal smoking and unprotected sexual intercourse during pregnancy. Virus levels in the maternal genital tract, which may not be completely correlated with plasma viral levels, are increasingly believed to be associated with risk of vertical transmission. This concept is supported by additional factors shown to influence transmission if it has not already occurred. For example, rupture of membranes for greater than four hours prior to delivery may increase the risk of perinatal infection. For the same reason invasive procedures, such as fetal heart rate monitoring with a scalp electrode, fetal blood sampling through a scalp incision, and operative vaginal delivery with forceps or vacuum are relatively contraindicated due to a theoretical risk of transmission through a broken skin barrier.

Mode of delivery (vaginal birth versus cesarean section) has not been shown clearly to affect transmission, however. The European Collaborative Study in 1991 documented a slightly decreased risk of transmission with cesarean section which was not statistically significant. This question is currently under further study. Based on this data, cesarean section is performed at present for usual obstetric indications, because the efficacy of abdominal delivery in preventing transmission has not been confirmed but remains a risk to the mother. In addition, the effect of

delivery route on risk of transmission has not been studied in the setting of aggressive anti-retroviral treatment, including AZT.

Delivery of twin pregnancy offers some possible insight with respect to peri-partum transmission. Considerable discordance in seropositivity has been found between the first and second born twin, with the risk of infection in the first-born markedly elevated. This was shown to be true regardless of the mode of delivery, but the disparity was greater in those born vaginally, with almost a three-fold difference. This finding suggests increased risk based on exposure to an infected birth canal, such that studies are now underway in Malawi regarding antiseptic lavage of the vagina prior to delivery.

### **Post-Partum Management**

The postpartum period is an opportunity ripe for multiple preventive health interventions. Following delivery, HIV positive mothers must be observed carefully for any signs or symptoms of infection, as there may be an increased risk of postpartum endometritis. Infant bonding should be encouraged, although contact with maternal body fluids should be avoided. In the US, breast-feeding is contraindicated in HIV positive women. Virus is present in breast milk and the risk of transmission from breast-feeding alone is approximately 7 to 22%. Women with a history of high-risk behaviors may also be counseled against breast-feeding in the event that they may not have developed seropositivity to a recent infection. In developing countries, where acceptable alternatives to breast milk may not be available due to poor sanitation, high rates of infectious disease and economic limitations, bottle feeding may be associated with a higher infant mortality.

HIV positive women must be advised as to their increased risk of cervical dysplasia or cancer and should be encouraged to see their care providers at least twice yearly for Pap smears. Patients also should be counseled extensively regarding options for contraception. Arrangements for medical follow-up must be ensured prior to discharge. Finally, many patients with this diagnosis are at risk for depression and social isolation and may have few resources for support. Patients should be made aware of services in the community which are available to them during this period of significant adjustment.

In summary, HIV is an important cause of morbidity and mortality in women of child-bearing age. Pregnancy does not appear to have any adverse effects on the course of HIV disease, nor does the disease predispose to poor obstetrical outcomes. AZT use in pregnancy dramatically decreases maternal-fetal transmission of HIV. It is the opinion of the authors, as well as recommended by a large, comprehensive Public Health Service Task Force, that women be given the option of multi-drug therapy during pregnancy, in addition to AZT, in the hope of decreasing maternal morbidity and perhaps further decreasing vertical transmission.

## HIV DISEASE IN PREGNANCY

### *Case Discussion*

#### Case #1

MK is a 35 year old woman who has been followed by you for primary care for three years. She comes in for an annual physical, this year accompanied by LK, her husband of 10 years. She reports feeling tired and not herself for six months with a 13 pound weight loss but no other specific symptoms. She denies recent upper respiratory or other illnesses, but the couple eventually tell you that they have recently learned that he is HIV positive with a CD4 cell count of 980. He learned of his diagnosis when he underwent routine screening as part of his military reserve requirements.

LK and his physician have concluded that he most likely contracted the virus while stationed in Germany five years ago where he had encounters with prostitutes. The couple has been monogamous with each other since his return. They are now concerned that MK may be HIV positive and that she may be pregnant. Their first child, a six year old girl, was born prior to LK's tour in Germany. LK tested HIV negative at the start of that tour.

You confirm a 15 pound weight loss in MK since last year. The exam is otherwise normal. Her urine HCG done in your office comes back positive and you conclude from her menstrual history that she is 9 weeks pregnant. You draw her HIV screen and schedule her for a routine appointment in one week to review the results. Three days later the test result returns to your desk. MK has a positive HIV ELISA and Western Blot.

***How will you counsel MK about the risk of transmission of HIV to her unborn child?***

***At what point during a pregnancy is vertical transmission felt to usually occur?***

MK and LK listen intently as you explain the risks of transmission of HIV to their baby. They have read a great deal about HIV and have many questions.

***Should MK take ZDV? If so, when should she begin? Are there other drugs that she could take to try to prevent transmission of HIV to the baby?***

You send MK's blood for CD4 count. the couple leaves, wishing to consider all you have told them. They return a week later for more discussion. Her CD4 cell count is 730. This time their concerns focus on what risks MK will be exposing herself to if she remains pregnant. They tell you they are considering whether or not to electively terminate the pregnancy.

***Is there any chance that being pregnant could make MK's HIV progress more rapidly?***

***How will pregnancy affect her CD4 cell counts?***

***Will HIV make MK's pregnancy more complicated or increase her risk of a bad outcome?***

***Should you measure her plasma HIV-1 RNA?***

***How would you counsel MK and LK regarding whether or not to continue this pregnancy?***

The couple decides to continue the pregnancy. MK starts ZDV in her 15th week of pregnancy and tolerates it well. Her CD4 cell counts fluctuate but remain relatively stable. Her HIV-1 RNA levels remain low. The nurse midwife who is to deliver the baby calls you with some questions.

***Are there any special OI prophylaxis needs in pregnant women who are HIV positive?***

***How should the patient's HIV status affect the mode of delivery used (i.e., vaginal delivery versus cesarean section)?***

MK delivers a 7 lb. 13 oz. boy at term without complications. You see her while she is in the hospital and find her tearful while feeding the baby from a bottle. She explains that she has been told by the pediatricians that breast feeding may transmit the HIV to the baby.

***What are the risks of HIV transmission via breast milk?***

***Is her baby likely to be continued on ZDV after birth?***

***What medications should MK be sent home on?***

## HIV DISEASE IN PREGNANCY

### *References*

Carpenter CJ, Fischl MA, Hammer SM, et al: Antiviral therapy for HIV infection in 1997. *JAMA* 1997; 277:1962-69.

**\*CDC. Public health service task force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing perinatal HIV-1 transmission in the United States. *MMWR* 1998; 47: 1-30.**

**\*Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med* 1994; 331: 1173-80.**

Cooper ER, Nugent RP, Diaz C, et al. After AIDS Clinical Trial 076: the changing pattern of zidovudine use during pregnancy, and the subsequent reduction in vertical transmission of human immunodeficiency virus in a cohort of infected women and their infants. *J Infect Dis* 1996; 174: 1207-11.

**\*Cu-Uvin S, Flanigan TP, Rich JD, et al: Human immunodeficiency virus infection and acquired immunodeficiency syndrome among North American women. *Am J Med* 1996; 101:316-22.**

**\*Johnstone FD: HIV and pregnancy. Review. *British Journal of Obstetrics and Gynaecology* 1996; 103: 1184-90.**

Landesman SH, Kalish LA, Burns DN, et al: Obstetrical factors and the transmission of human immunodeficiency virus type I from mother to child. *New Engl. J Med* 1996; 334:1617-23.

Luzuriaga K, Bryson Y, Krogstad, et al: Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type I infection. *New Engl. J Med* 1998; 336: 1343-9.

Minkoff H: The case for rapid HIV testing during labor. (Commentary) *JAMA* June 3, 1998; 279(21):1743-44.

Minkoff H: Human immunodeficiency virus infections in pregnancy. In: Lee RV, Garner PR, Barron WM, Coustan DR, eds. Current Obstetric Medicine, 1996, 4:1-18.

Minkoff H, Augenbraun M: Antiretroviral therapy for pregnant women. *Am J Ostet Gynecol* 1997; 176: 478-89.

Nakchbandi IA, Longenecker C, Ricksecker A, Latta RA, Heaton C, Smith DG: A decision analysis of mandatory compared with voluntary HIV testing in pregnancy women. *Ann Intern Med* 1998;128:760-67.

Peckham C, Gibb D: Mother-to-child transmission of the human immunodeficiency virus. *New Engl. J Med* 1995; 333:298-302.

Saade GR: Human immunodeficiency virus (HIV)-related pulmonary complications in pregnancy. *Seminars in Perinatology* 1997; 21(4):336-50.

Sperling RS, Shapiro DE, Coombs RW: Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. *New Engl. J Med* 1996; 335: 1621-9.

Tuomala RE, Kalish LA, Zorilla C: Changes in Total, CD4+, and CD8+ Lymphocytes during pregnancy and 1 year postpartum in human immunodeficiency virus-infected women. *Obstet Gynecol* 1997; 89: 967-74.

Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med* 1998; 339: 1409-1414.