

Management of HIV Infection in Pregnancy

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Most HIV-infected women are between the ages of 18 and 40 years; that is, they are in their childbearing years.¹ As a growing number of HIV-infected women live longer and feel better, pregnancy will become an increasingly important issue. More than 90% of HIV-infected children have acquired HIV from their mothers. It is important to identify HIV-positive pregnant women because effective treatments are available for decreasing perinatal transmission and maintaining the health of the mother.

The US Public Health Service encourages HIV counseling and testing for all women of childbearing age, regardless of whether they are pregnant. HIV testing should be part of preconceptual counseling.² All pregnant women should be offered HIV testing and counseling regardless of risk factors. Women should be offered the HIV enzyme-linked immunosorbent assay (ELISA) test as early in pregnancy as possible.

Studies from Europe and the United States of the impact of pregnancy on HIV disease have not indicated more rapid progression to AIDS or death in HIV-positive pregnant women.^{3,4} No benefit to maternal health from termination of pregnancy has been demonstrated.³

This article describes current epidemiologic trends in HIV infection in women in the United States and addresses the management of the HIV-infected pregnant woman, including strategies to decrease the incidence of perinatal transmission of HIV.

EPIDEMIOLOGY

The estimated number of people living with HIV/AIDS worldwide is 34.3 million, and approximately 47% of these are women.⁵ An estimated 120,000 to 160,000 women in the United States are living with HIV infection.⁶ From 1985 to 1999, the proportion of AIDS cases in the United States that were reported in women increased from 7% to 23%.⁶ For women in the United States between the ages of 25 and 45 years, HIV disease is the third leading cause of death.⁷

HIV infection in pregnant women is increasing worldwide. An estimated 2.3 million HIV-positive females

worldwide deliver each year.⁵ Approximately 10 million infants have been infected worldwide, and the majority of these children have acquired infection by vertical transmission of HIV from infected mothers.

In the United States, perinatal transmission of HIV accounts for 90% of pediatric AIDS cases and nearly all new HIV infections in children.⁸ An estimated 6,000 to 7,000 infants were born to HIV-infected women annually in the United States from 1989 through 1994.⁹ By 1995, more than 16,000 perinatally HIV-infected children had been born.^{9,10} Fortunately, perinatal transmission is on the decline in the United States, although it is increasing worldwide.¹¹

INITIAL VISIT

The initial prenatal evaluation of the HIV-infected woman should include a thorough history and physical examination (**Table 1**). Baseline examinations should include funduscopic, neurologic, and pelvic examinations. The initial visit should also include counseling about perinatal transmission of HIV and the importance of compliance with antiretroviral regimens. If appropriate, the patient should be referred to drug treatment or detoxification programs. Perinatal screening should also include testing for infections such as tuberculosis, syphilis, and bacterial vaginosis, which may increase the risk of vertical transmission. Baseline antibody titers of *Toxoplasma gondii* and cytomegalovirus (CMV) should be obtained. Liver function testing and screening for hepatitis B and C virus infection should be performed. HIV viral load and CD4+ lymphocyte count should be measured at baseline and repeated each trimester to follow the response to therapy or to detect indications for therapy. During pregnancy, CD4+ T-cell percentage (CD4%) may be a more

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reliable indicator than absolute counts because of hemodynamic fluctuations.

HIV-infected pregnant women should receive polyvalent pneumococcal vaccine, conjugated *Haemophilus influenzae* type b vaccine, and combination influenza A and B vaccine (during the influenza season).

PROPHYLAXIS OF OPPORTUNISTIC INFECTIONS DURING PREGNANCY

Prophylaxis of opportunistic infections during pregnancy should be based on criteria similar to those for nonpregnant HIV-infected women.^{12,13} Indications for prophylaxis of opportunistic infections and the drugs frequently used are summarized in **Table 2**. Primary prophylaxis for *Pneumocystis carinii* pneumonia (PCP) should be given to women with absolute CD4+ lymphocyte counts below 200/mm³ (or CD4% < 14), unexplained fever for 2 weeks or more, or a history of oropharyngeal candidiasis. Secondary prophylaxis should be given to women with a history of prior PCP infection. The drug of choice for PCP prophylaxis is trimethoprim/sulfamethoxazole (TMP/SMX), 1 double-strength tablet (TMP: 160 mg; SMX: 800 mg) once daily. Alternative therapies for PCP prophylaxis are aerosolized pentamidine, oral dapsone, and oral atovaquone.

Prophylaxis for *Mycobacterium avium* complex (MAC) infection should be offered for patients with CD4+ lymphocyte counts lower than 50/mm³. Azithromycin 1200 mg once weekly is the first choice for MAC prophylaxis during pregnancy. Clarithromycin should be avoided in pregnancy because of teratogenicity in animals.

For women with a history of previous toxoplasmic encephalitis or with antibodies to *T. gondii*, administration of TMP/SMX may be used for prophylaxis. However, sulfur-containing drugs should be discontinued for a few weeks during the peripartum period. Women with positive tuberculin skin tests without prior treatment, or who have had contact with active tuberculosis but with no evidence of active disease themselves, may receive isoniazid prophylaxis during pregnancy.

Primary prophylaxis for mucosal candidiasis and other fungal infections should be avoided during pregnancy. Primary prophylaxis for CMV disease is not recommended during pregnancy because of the potential toxicity of the drugs. Live virus vaccines (eg, rubella, measles, mumps, varicella) are contraindicated during pregnancy regardless of HIV status.

ANTIRETROVIRAL THERAPY FOR PREGNANT WOMEN

HIV-positive pregnant women should receive the same antiretroviral regimen management as nonpregnant women.¹⁴ Antiretroviral therapy should not be

Table 1. Components of the Evaluation of the HIV-Positive Pregnant Woman

History
Physical examination
Tuberculin skin testing
Laboratory testing
Complete blood count, including differential
Serum creatinine level
Urinalysis and urine culture
Liver function testing
Rapid plasma reagin (for syphilis)
Hepatitis B surface antigen testing
Hepatitis C virus second-generation ELISA
IgG antibody to <i>Toxoplasma gondii</i>
CD4+ and CD8+ lymphocyte counts and percentages
Plasma HIV RNA quantitative PCR
Sexually transmitted diseases screening (vaginal wet mount, testing for <i>Neisseria gonorrhoeae</i> and <i>Chlamydia trachomatis</i>)

ELISA = enzyme-linked immunosorbent assay; PCR = polymerase chain reaction.

withheld unless clear fetal or maternal contraindications to standard therapy exist. Therapy should aim for optimal clinical benefits to the mother while reducing the risk of perinatal transmission of the virus to the fetus or newborn.

The choice of therapy should be individualized based on the woman's clinical, virologic, and immunologic status, as well as the gestational age of the fetus (**Table 3**). Women with stable CD4+ cell counts and undetectable viral loads who are already on an antiretroviral regimen prior to pregnancy should continue the same therapy, even during the first trimester. Women with rising viral loads should have genotypic resistance testing performed in order to determine optimal therapeutic regimens. For women diagnosed with HIV infection during the first trimester and who are not on antiretroviral therapy, treatment should be delayed until the second trimester. Genotypic resistance testing should also be performed in this group.

Because it has been shown to reduce the risk of perinatal transmission, zidovudine (ZDV) should be included as part of the antenatal therapeutic regimen whenever possible. However, if a woman does not receive ZDV as a part of her antenatal antiretroviral regimen, the newborn component of the regimen should still be given (*see Table 6*).

Table 2. Prophylaxis for Opportunistic Infections

Opportunistic Infection	Indication(s) for Prophylaxis	Drugs
<i>Pneumocystis carinii</i> pneumonia (PCP)	CD4+ lymphocyte counts < 200/mm ³ (or 14% of lymphocytes) Unexplained fever (> 100°F) for > 12 wk History of oropharyngeal candidiasis Previous PCP infection	TMP/SMX 160 mg/800 mg by mouth daily (1st choice) OR Aerosolized pentamidine 300 mg monthly OR Dapsone 100 mg by mouth daily OR Atovaquone 1500 mg by mouth daily
<i>Mycobacterium avium</i> complex infection	CD4+ cell count < 50/mm ³	Azithromycin 1200 mg by mouth weekly OR Rifabutin 300 mg by mouth daily
Toxoplasmosis	Presence of antibodies of <i>Toxoplasma gondii</i> Previous toxoplasmic encephalitis	TMP/SMX 160 mg/800 mg by mouth daily
Tuberculosis	Positive PPD test without prior treatment Contact with active tuberculosis, but no evidence of active disease	Isoniazid 300 mg by mouth daily for 9 months <i>plus</i> Pyridoxine 50 mg by mouth daily OR Isoniazid 900 mg by mouth plus Pyridoxine 100 mg by mouth twice weekly for 9 months
Herpes simplex virus (HSV)	Recurrent HSV	Acyclovir 400 mg by mouth twice daily

PPD = purified protein derivative (tuberculin); TMP/SMX = trimethoprim/sulfamethoxazole.

Table 3. Guidelines for Antiretroviral Treatment of HIV-Positive Pregnant Women

No prior therapy

CD4+ cell count > 350/mm³ or HIV RNA load* < 55,000 copies/mL: begin zidovudine after the first trimester.

CD4+ cell count < 350/mm³ or HIV RNA load* > 55,000 copies/mL: begin HAART after doing genotypic resistance testing.

Consider delaying therapy until after the first trimester.

On HAART

Continue the same therapy if the woman is able to tolerate it and if CD4+ cell counts are stable and virus is undetectable.

If the decision is made to stop antiretroviral therapy, all drugs should be stopped simultaneously and then restarted during the second trimester.

If pregnancy is diagnosed after the first trimester, continue same treatment.

Presentation in labor without prior antiretroviral therapy

Administer intrapartum intravenous zidovudine, along with zidovudine syrup to the newborn for 6 weeks.

Consider single-dose nevirapine for the mother (200 mg orally).

Consider elective cesarean section.

HAART = highly active antiretroviral treatment.

*Measured by polymerase chain reaction.

Recommendations from 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 Morb Mortal Wkly Rep 1998;47(RR-2): 1–30; and Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services and the Henry J. Kaiser Family Foundation. February 5, 2001 update. Living document available at <http://www.hivatis.org/trtgdlns.html>. Accessed June 6, 2001.

Table 4. Factors that Increase Risk of Vertical Transmission of HIV

Advanced stage of HIV infection
Low relative or absolute CD4+ cell counts
Increased levels of maternal HIV RNA*
Artificial rupture of membranes
Prolonged interval between rupture of membranes and delivery
Placement of internal monitoring devices during labor
Ascending bacterial infection of the placental-fetal unit during the peripartum period
Vitamin A deficiency

*Measured by polymerase chain reaction.

ZDV monotherapy may be an option for management of HIV-positive pregnant women whose health status is such that antiretroviral therapy would not normally be indicated (ie, CD4+ cell counts > 350/mm³ or HIV RNA load measured by polymerase chain reaction [PCR] < 55,000 copies/mL).¹⁵ The impact of ZDV monotherapy on maternal health, viral load, and the potential for the development of resistant viral mutations remains a concern. Among women receiving ZDV in the Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076, only 1 developed genotypic resistance on therapy, and she did not transmit HIV to her infant.¹⁴ Although more data are needed, short-term ZDV monotherapy of HIV-positive pregnant women does not seem to have a negative impact on development of resistance or maternal health.¹⁶

VERTICAL TRANSMISSION OF HIV INFECTION

Modes of Transmission

Perinatal transmission of HIV infection encompasses 3 possible means of viral spread from mother to child: intrauterine, intrapartum, and postpartum. Intrauterine infection is defined by the ability to culture virus or detect HIV DNA from the infant's peripheral blood lymphocytes within 48 hours of delivery. Intrapartum infection occurs during passage of the fetus through the birth canal. Postpartum infection has been documented to occur through exposure to breast milk. The rate of mother-to-child transmission of HIV ranges from 5% to 25% in the United States.

Risk Factors for Vertical Transmission

Increased vertical transmission of HIV is associated with several factors, including advanced stage of HIV infection and low relative or absolute CD4+ cell counts (Table 4). Findings of the Women and Infants Trans-

Table 5. Factors that Decrease Risk of Vertical Transmission of HIV

Undetectable maternal HIV RNA*
Zidovudine administration (to mother and/or infant)
Nevirapine administration (to mother and/or infant)
Cesarean section
Treatment of sexually transmitted diseases
Highly active antiretroviral therapy (HAART)

*Measured by polymerase chain reaction.

mission Study revealed that the risk of transmission increased for women whose membranes ruptured more than 4 hours before delivery, women who used illicit drugs during pregnancy, and those who had low antenatal CD4+ cell counts.¹⁷

Other maternal risk factors for perinatal transmission are the presence of sexually transmitted diseases and increased maternal HIV RNA load as measured by quantitative PCR. Mofensen et al¹⁸ found that in women who took ZDV during pregnancy, increased mean levels of HIV RNA were associated with increased vertical transmission rates. Obstetric risk factors include artificial rupture of the membranes and invasive procedures such as amniocentesis or placement of internal monitoring devices (eg, fetal scalp electrodes) during labor.¹⁹ Ascending bacterial infection of the placental-fetal unit during the peripartum period may also facilitate vertical transmission of HIV.²⁰ Nutritional factors such as vitamin A deficiency may also promote disease transmission.²¹

Measures to Prevent Vertical Transmission

An undetectable maternal viral load lessens, but does not completely eliminate, the risk of perinatal HIV transmission (Table 5). The PACTG Protocol 076 demonstrated that a ZDV regimen given to HIV-infected women during pregnancy and labor and to the neonate for the first 6 weeks of life could reduce perinatal transmission from 26% to 8.3%.^{18,22,23} Recommended ZDV regimens for preventing vertical transmission are shown in Table 6.

For the HIV-positive pregnant woman who presents during active labor and has had no prior antiretroviral therapy, an alternative regimen is nevirapine 200 mg given orally to the mother and 2 mg/kg body weight to the infant within 72 hours of birth.²⁴ A single dose of nevirapine 200 mg orally at the onset of labor, with an additional dose given to the baby, lowered the risk of HIV transmission during the first 14 to 16 weeks of life

Table 6. Recommended Zidovudine (ZDV) Regimen to Reduce Perinatal Transmission of HIV

Time of ZDV Administration	Regimen
Antepartum	ZDV 100 mg orally 5 times daily, or 200 mg orally 3 times daily, initiated after 13 weeks' gestation.
Intrapartum	Loading dose of 2 mg/kg body weight intravenously over 1 hour followed by 1 mg/kg per hour intravenously until delivery.
Postpartum (newborn dose)	ZDV syrup 2 mg/kg orally every 6 hours (total 8 mg/kg per day) for 6 weeks, beginning 8–12 hours after birth.

Recommendations from 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 Morb Mortal Wkly Rep* 1998;47 (RR-2):1–30; and 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.

by nearly 50% in a breast-feeding population, compared with a regimen of ZDV given orally during labor and to the infant for 1 week.²⁴

Obstetric management to decrease perinatal HIV transmission should concentrate on minimizing direct and prolonged exposure of the fetus to the maternal lower genital tract. In most cases, cesarean section should be reserved for the usual obstetric reasons. However, a cesarean section may be indicated in the following settings: (1) women who present in labor and have not taken antiretroviral therapy during pregnancy, and (2) women with persistently rising viral loads.²⁵

ANTIRETROVIRAL DRUG TOXICITIES

Common adverse effects of several antiretroviral drugs, as well as concerns specific to pregnancy, are shown in **Table 7**. All cases of antiretroviral use during pregnancy should be reported to the Antiretroviral Pregnancy Registry (800-258-4263).

Nucleoside Analogue Reverse Transcriptase Inhibitors

Nucleoside analogue reverse transcriptase inhibitors (NRTIs) have been shown to induce mitochondrial dysfunction, leading to toxicity and resulting neuropathy, myopathy, cardiomyopathy, hepatic steatosis, and lactic acidosis. There have been reports of severe lactic acidosis, including some fatalities, in HIV-infected pregnant women who received NRTIs, including lami-

vudine, didanosine, and stavudine.^{26,27} In all cases, the women affected were receiving treatment with these agents at the time of conception and treatment continued throughout pregnancy. All presented with symptomatic disease late in gestation.

Symptomatic lactic acidosis and steatosis have similarities to the acute fatty liver of pregnancy and the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) that may occur during the third trimester of pregnancy. Physicians caring for HIV-infected pregnant women receiving NRTIs must therefore be alert for diagnosis of the syndrome of lactic acidosis, as pregnancy itself may mimic some of the early symptoms and may also be associated with other disorders of liver metabolism. Pregnant women on NRTIs should have liver enzymes and electrolytes assessed frequently during the last trimester of pregnancy (eg, monthly).

All NRTIs except didanosine have been shown in animal studies to carry potential fetal risk and are classified as Food and Drug Administration pregnancy category C.

Nonnucleoside Reverse Transcriptase Inhibitors

Severe, life-threatening (sometimes fatal) hepatotoxicity has been reported in HIV-infected patients receiving nevirapine in combination with other drugs for treatment of HIV^{28,29} and also in persons receiving nevirapine for postexposure HIV prophylaxis.³⁰ Hypersensitivity skin reactions, including Stevens-Johnson syndrome, have been reported in HIV patients receiving nevirapine for treatment. Neither of these complications have been reported in women or infants receiving the 2-dose nevirapine regimen for prevention of perinatal transmission of HIV.

Efavirenz should be avoided during pregnancy because it has been shown to cause teratogenicity in animal studies.

Ribonucleotide Reductase Inhibitors (Hydroxyurea)

Hydroxyurea has been studied for treatment of HIV in combination with NRTIs. Its role in HIV therapy is not well defined. Hydroxyurea should be avoided during pregnancy because it has been shown to cause teratogenicity in animal studies.

Protease Inhibitors

New-onset diabetes, exacerbation of preexisting diabetes, diabetic ketoacidosis, and hyperglycemia have been reported in HIV patients receiving protease inhibitors. Pregnancy itself is a risk factor for hyperglycemia. However, it is unknown whether protease inhibitors increase the risk of pregnancy-associated hyperglycemia. Glucose levels should be closely monitored

Table 7. Antiretroviral Drugs: Adverse Effects and Concerns Specific to Pregnancy

Drug		FDA	Common Adverse Effects/ Major Toxicities	Concerns Specific to Pregnancy
Generic Name	Brand Name	Pregnancy Category		
Nucleoside analogue reverse transcriptase inhibitors (NRTIs)				
Zidovudine (ZDV, AZT)	Retrovir	C	Nausea, headache, fatigue, myopathy Bone marrow suppression	None identified
Lamivudine (3TC)	Epivir	C	Generally well tolerated Pancreatitis increased in children	None identified
Didanosine (ddl)	Videx	B	Peripheral neuropathy in 15% Pancreatitis	Pregnancy may complicate diagnosis of pancreatitis
Zalcitabine (ddC)	Hivid	C	Peripheral neuropathy in 17%–31%	None identified
Stavudine (d4T)	Zerit	C	Peripheral neuropathy in 24% of patients with CD4+ cell counts < 50/mm ³	None identified
Abacavir	Ziagen	C	3% hypersensitivity reaction: fever, malaise, rash Gastrointestinal upset	None identified
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)				
Delavirdine	Rescriptor	C	Transient rash Multiple drug interactions	None identified
Nevirapine	Viramune	C	Transient rash Hepatitis	None identified
Efavirenz	Sustiva	C	Initial dizziness, insomnia Transient rash Multiple drug interactions	Teratogenic
Ribonucleotide reductase inhibitors				
Hydroxyurea	Hydrea	C	Aphthous ulcers, hair loss Peripheral neuropathy Bone marrow suppression	Teratogenic
Protease inhibitors (PIs)				
Amprenavir	Agenerase	C	Rash (20%) Stevens-Johnson syndrome in 1% Diarrhea, nausea	Inadequate data
Indinavir	Crixivan	C	Kidney stones in 6%–8% Occasional nausea and gastrointestinal upset Hyperbilirubinemia	Hyperbilirubinemia and kernicterus in newborn
Nelfinavir	Viracept	B	Diarrhea, occasional nausea	None identified
Ritonavir	Norvir	B	Nausea, diarrhea Numb lips ≥ 5 weeks Occasional hepatitis	None identified
Saquinavir	Fortovase	B	Diarrhea, nausea	None identified
Lopinavir/ritonavir	Kaletra	C	Pancreatitis, hepatitis Diarrhea	None identified

in HIV-infected pregnant women receiving protease inhibitors.

Indinavir use late in pregnancy increases the risk of hyperbilirubinemia and nephrolithiasis in the mother.

CONCLUSION

HIV infection is increasing among women in the United States, and women now account for 20% of AIDS cases reported to the Centers for Disease Control and Prevention. The US Public Health Service recommends that all pregnant women in the United States be encouraged to undergo HIV testing. All HIV-infected women of childbearing age should receive preconception counseling, and all pregnant women should be tested for HIV regardless of risk factors. HIV-positive pregnant women need to be identified and therapy instituted promptly to prevent vertical transmission. Antiretroviral regimens should be based on gestational age of the fetus at the time that HIV is diagnosed, maternal CD4+ cell count, and HIV viral load, as well as on maternal wishes, and should be developed in consultation with HIV specialists. Therapy should achieve optimal clinical benefit to the mother and prevent vertical transmission. **HP**

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