MANAGEMENT OF WOMEN WITH HIV INFECTION*

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ABSTRACT

The impact of HIV infection among women has increased steadily in recent years, especially among racial and ethnic minority women. Women with HIV infection face many challenges, including—but not limited to—poverty, homelessness, substance abuse, comorbid mental health disorders, racism, the legacy of childhood sexual abuse, and barriers to HIV care. The management of HIV infection in women includes not only attention to the medical issues associated with HIV infection, but also the many survival needs these women experience, such as housing, food, and safety. The evaluation of a woman with HIV infection must include a thorough history (including screening for depression, substance use, and intimate partner violence) and physical examination. Baseline viral and immunologic markers should be assessed, and substance abuse and psychiatric services should be made available if screening tests indicate a need. Fertility and pregnancy planning should be openly discussed. The management of HIV infection in pregnancy requires the healthcare provider to balance the benefit of antiviral therapy to prevent mother-to-child transmission against the potential risk of fetal harm and the development of antiretroviral resistance in the mother. The goals of therapy in HIV-infected pregnant women are: (1) control of HIV replication; (2) protection of mother and fetus; and (3) prevention of maternal-to-infant HIV transmission. Guidelines for the use of highly active antiretroviral therapy in pregnancy have been developed and are updated regularly. These guidelines are posted on the Department of Health and Human Services Web site (http://aidsinfo.nih.gov). Drug toxicity and potential complications of treatment require careful monitoring of mother and fetus.


Since the first reported cases of AIDS, the rate of HIV infection among women has increased consistently, especially among women of color. From 1999 to 2003, the annual number of estimated AIDS cases increased 15% among women as compared to 1% among men. In 2003, 50% of the HIV cases reported in the group aged 13 to 19 years were female. For women younger than 50 years, HIV is one of the 10 leading causes of death. Despite several barriers and challenges to treatment and care, successful strategies do exist for the management of HIV infection in women.

HIV INFECTION AMONG WOMEN

HIV infection disproportionately affects women of color, particularly black and Hispanic women. Between 2000 and 2003, non-Hispanic blacks accounted for more than 50% of the HIV/AIDS diagnoses reported by 32 states, with a rate of AIDS diagnoses for black women approximately 25 times the
rate among non-Hispanic white women and 4 times the rate among Hispanic women. In many urban areas in the United States, the rates of HIV infection among women of color rival those found in resource-poor settings internationally.

The most common route of HIV transmission among women is heterosexual contact. There are data to suggest that women may be more susceptible to sexual transmission of HIV infection. Although the data on the effect of hormonal contraceptives and increased susceptibility are conflicting, oral contraceptives often produce cervical ectopy, yielding a friable area that has been suggested as a mechanism for increased risk of HIV infection. Concomitant sexually transmitted infections are known to increase the risk of HIV acquisition, especially in the presence of genital ulcerations. High-risk sexual behavior, an immature genital tract associated with adolescence, or cervical ectopy may increase HIV susceptibility. Increased risk of HIV infection also is seen during pregnancy from the immediate peripartum period through the early postpartum period. These factors, in addition to gender roles and power differences in dyadic or other relationships, combine to exert a significant multifactorial effect on HIV risk in women.

CHALLENGES TO HIV CARE FOR WOMEN

Women with HIV infection face many challenges, including poverty, homelessness, and substance abuse. Comorbid mental health issues often exist, in addition to stigma and the fear it brings, including ignorance and social isolation. Women with HIV infection are more likely to have a history of childhood sexual abuse, or prior or ongoing domestic violence. For many women with HIV infection, access to healthcare is only the beginning of several challenges to overcome in managing and controlling their HIV infection. As most HIV-infected women belong to racial and ethnic minority groups, there is often mistrust of the healthcare system, usually arising from their prior experience seeking treatment in the system. Superimposed upon misinformation and stigma, it is not surprising that many of these women do not present for care until the underlying HIV infection is advanced. Many of these women also have experienced domestic violence or intimate partner violence. This experience in conjunction with a history of childhood sexual abuse leaves these women vulnerable, depressed, and more socially isolated. Many of these women continue in abusive relationships that may be overlooked by the healthcare provider.

MANAGING HIV IN WOMEN

The management of HIV in women includes an assessment of their basic survival needs, in addition to medical, physical, and psychological needs. Survival needs, including housing, food, and safety, must be assessed. Women will engage in “survival sex”—sex for money, sex for food, sex for shelter—placing themselves and others at risk. Medical needs must be assessed, hence a detailed medical history, physical and laboratory examinations, in addition to a risk-behavior assessment, and a review of safer sexual practices is essential. A sexual history is important to determine potential for additional risk of disease transmission to or from the patient. Screening for depression, substance use, and alcohol use should be performed, as depression is one of the strongest predictors of nonadherence in women who discontinue highly active antiretroviral therapy (HAART). HIV-infected women are at an increased risk of depression as a result of many factors, including drug abuse, a history of intimate partner violence, and childhood sexual and psychological abuse.

Medical management of women with HIV includes a complete medical history and physical examination, in addition to vaginal and rectal examinations. Screening for sexually transmitted diseases and vaginal and anal Pap smears should be performed because of the high rate of human papillomavirus infection. Healthcare providers must remember that HIV-positive heterosexual women also may engage in anal intercourse, and hence, are at risk for rectal dysplasia and carcinoma.

Breast self-examination should be taught. Healthcare providers also should inspect for signs of trauma, in addition to tracks from injection drug use. These findings could aid in opening communication with a patient who may be uncomfortable discussing her home situation, especially if domestic violence or illicit drug use is involved. It is also important to obtain baseline hematologic and metabolic laboratory values, including viral and immunologic markers, such as antibody markers of prior infection, such as the hepatitides and toxoplasmosis. Sources of support for the patient also should be identified and may include...
a woman's support group, case managers, treatment educators, and treatment advocates; as such, a support network can serve as part of a multidisciplinary management team. Fertility and pregnancy planning also should be discussed at the outset, especially if use of antiviral regimens is planned. Patients also should be provided with access to psychiatric and substance abuse services, as depression treatment clearly increases the likelihood of HAART adherence. If indicated, antiviral therapy should be initiated after a discussion about several important treatment-related issues, including treatment adherence, potential side effects, the link between resistance and nonadherence, and the desired treatment outcome. If treatment is initiated, medication adherence, and monitoring for treatment fatigue and adherence will become important.

**Management of HIV Infection in Pregnancy**

There are several goals of HIV management in pregnancy, including reduction in HIV morbidity and mortality for the mother and the infant. Additional goals include decreasing the risk of perinatal transmission, maximizing durable suppression of viral load, restoring or preserving immune function, and improving the patient's quality of life. The healthcare provider must carefully balance the desires of the patient and the best interest of the fetus. Patient issues, such as underlying substance abuse, alcohol use, depression, intimate partner violence, and healthcare access and utilization, may present particular challenges.

Certain antivirals are not recommended for use during pregnancy, including zalcitabine, tenofovir, and delavirdine. There also is positive evidence of fetal harm with the use of efavirenz, which has recently received a Class D Pregnancy category rating from the Food and Drug Administration. Amprenavir oral solution also is not recommended as it contains propylene glycol, which may not be adequately metabolized in pregnancy, and stavudine/didanosine combinations because of their synergistic toxicities, including lactic acidosis, pancreatitis, and hepatic steatosis. Use of hydroxyurea and nevirapine in combination also should be avoided, and hydroxyurea should be avoided completely in pregnancy. There are several drugs, including fosampravir, atazanavir, tipranavir, and enfuvirtide, which are considered to have insufficient data for recommended use with major concerns about pharmacokinetics in pregnancy. “The Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1–Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States” guidelines can be found on the Department of Health and Human Services AIDS Info Web site [http://aidsinfo.nih.gov](http://aidsinfo.nih.gov).

Several studies have assessed the safety of HAART in pregnancy. In 1998, Lorenzi et al followed 37 HIV-infected pregnant women on double reverse transcriptase inhibitor therapy with or without protease inhibitors (PI). Of the 30 births that occurred, there was 1 case (3%) of mother-to-child HIV transmission. Ten cases of premature (33%) were reported, of which 5 of the neonates were delivered at or under 35 weeks of gestation (17%). Two cases of glucose intolerance (7%) during pregnancy occurred. In a study of HIV-positive pregnant women in the United States who delivered their infants between 1990 and 1998, adverse pregnancy outcomes were compared in 1143 women receiving no antiretroviral therapy (ART) with 2123 women receiving ART (1590 received monotherapy, 396 combination therapy without PIs, and 137 combination therapy with PIs). There was no difference in the rate of premature delivery, low birth weight, low Apgar scores, or stillbirths between groups. However, 7 of the infants born to women who received combination therapy with PIs (5%) had very low birth weight infants (<1500 g), as compared to 9 of the infants born to women who received monotherapy or combination therapy without PIs (2%). Although this result was not clinically significant, this study suggests that further investigation is warranted.

The specific effect of PIs was examined in 233 pregnancies by Morris et al. Of the 231 live infants delivered, there were 4 sets of twins and 1 set of triplets. Perinatal transmission of HIV occurred in 2 (0.9%) of 221 infants and the prematurity rate was 22%. Twelve women (5.2%) had premature rupture of membranes and 10 (4.3%) had preterm labor. Cesarean section was elected in 56% of the deliveries, as compared to 34% of women who delivered vaginally with 10% having unscheduled cesareans. Infant and fetal adverse events included 41 with anemia, 10 with cardiac abnormalities, 7 with pulmonary problems, and 5 with hyperbilirubinemia. Six pregnancies ended in fetal deaths, in which 3 of the women (50%) were actively abusing alcohol, heroin and/or cocaine, 2 other
SCENARIO #1
HIV-1–infected pregnant women who have not received prior ART
• Pregnant women with HIV-1 infection must receive standard clinical, immunologic, and virologic evaluation. Recommendations for initiation and choice of ART should be based on the same parameters used for persons who are not pregnant, although the known and unknown risks and benefits of such therapy during pregnancy must be considered and discussed.
• The 3-part ZDV chemoprophylaxis regimen, initiated after the first trimester, is recommended for all pregnant women with HIV-1 infection, regardless of antenatal HIV RNA copy number, to reduce the risk for perinatal transmission.
• The combination of ZDV chemoprophylaxis with additional antiretroviral drugs for treatment of HIV-1 infection is recommended for infected women whose clinical, immunologic, or virologic status requires treatment or who have HIV-1 RNA over 1000 copies/mL regardless of clinical or immunologic status, and can be considered for women with HIV-1 RNA <1000 copies/mL.
• Women who are in the first trimester of pregnancy may consider delaying initiation of therapy until after 10–12 weeks’ gestation.

SCENARIO #2
HIV-1–infected women receiving ART during the current pregnancy
• HIV-1–infected women receiving ART in whom pregnancy is identified after the first trimester should continue therapy. ZDV should be a component of the antenatal ART regimen after the first trimester whenever possible, although this may not always be feasible.
• For women receiving ART in whom pregnancy is recognized during the first trimester, the woman should be counseled regarding the benefits and potential risks of antiretroviral administration during this period, and continuation of therapy should be considered. If therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid the development of drug resistance.
• Regardless of the antepartum antiretroviral regimen, ZDV administration is recommended during the intrapartum period and for the newborn.

SCENARIO #3
HIV-1–infected women in labor who have had no prior therapy
• Several effective regimens are available.* These include:
  – Intrapartum intravenous ZDV followed by 6 weeks of ZDV for the newborn;
  – Oral ZDV and lamivudine during labor, followed by 1 week of oral ZDV and lamivudine for the newborn;
  – A single dose of nevirapine at the onset of labor followed by a single dose of nevirapine for the newborn aged 48 hours; and
  – The single-dose maternal/infant nevirapine regimen combined with intrapartum intravenous ZDV and 6-week ZDV for the newborn.
• If single-dose nevirapine is given to the mother, alone or in combination with ZDV, consideration should be given to adding maternal ZDV and lamivudine starting as soon as possible (intrapartum or immediately postpartum) and continuing for 3–7 days, which may reduce development of nevirapine resistance.
• In the immediate postpartum period, the woman should have appropriate assessments (eg, CD4+ count and HIV-1 RNA copy number) to determine whether ART is recommended for her own health.

SCENARIO #4
Infants born to mothers who have received no ART during pregnancy or intrapartum
• The 6-week neonatal ZDV component of the ZDV chemoprophylactic regimen should be discussed with the mother and offered for the newborn.
• ZDV should be initiated as soon as possible after delivery, preferably within 6–12 hours of birth.
• Some clinicians may choose to use ZDV in combination with other antiretroviral drugs, particularly if the mother is known or suspected to have ZDV-resistant virus. However, the efficacy of this approach for prevention of transmission has not been proven in clinical trials, and appropriate dosing regimens for neonates are incompletely defined for many drugs.
• In the immediate postpartum period, the woman should undergo appropriate assessments (eg, CD4+ count and HIV-1 RNA copy number) to determine if ART is required for her own health. The infant should undergo early diagnostic testing so that if HIV infected, treatment can be initiated as soon as possible.

Note: Discussion of treatment options and recommendations should be noncoercive, and the final decision regarding the use of antiretroviral drugs is the responsibility of the woman. A decision to not accept treatment with ZDV or other drugs should not result in punitive action or denial of care. Use of ZDV should not be denied to a woman who wishes to minimize exposure of the fetus to other antiretroviral drugs and who therefore chooses to receive only ZDV during pregnancy to reduce the risk for perinatal transmission.

ART = antiretroviral therapy; ZDV = zidovudine.
*See Table 5 from the original source.
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women (33%) were living with symptomatic AIDS, and 3 of the women (50%) had received stavudine and didanosine during their pregnancy.

The effect of the type of HAART regimen on pregnancy outcome was examined in 3740 maternal-child pairs enrolled in the European Collaborative Study between 1986 and 2003. The study included 1973 infants exposed to ART in utero, of which 602 were exposed to HAART. The study population was predominantly white (72%), 21% were black (mainly from sub-Saharan Africa), and the median CD4 cell count at delivery based on 55% of the women was 420 cells per mm³. Congenital abnormalities were reported in 55 (1.5%) of the 3740 children, 31 of who were exposed to ART in utero and 14 who were exposed during the first trimester. Abnormalities included ear malformations, cleft palate, ventricular septal defect, atrial septal defect, polydactyly, Down’s syndrome, polycystic kidney, and hydronephrosis. Esophageal atresia was reported in at least 2 children. The study found no evidence of an increase in the prevalence of congenital abnormalities beyond those found in the general population as a result of ART in this population.

Guidelines regarding the use of ART in the HIV-positive pregnant woman have been published and can be found on the Department of Health and Human Services AIDS Information Web site (http://aidsinfo.nih.gov). Four distinct treatment scenarios for the management of HIV infection in pregnancy to reduce the risk of perinatal HIV transmission are provided in the Table. A woman diagnosed with HIV before pregnancy with a HIV RNA less than 1000 copies per mL may remain on the same ART unless toxicity or teratogenicity are concerns. If the woman is not on ART and has a CD4 cell count greater than 350 cells per mm³, zidovudine and 2 nucleoside reverse transcriptase inhibitors should be considered. HAART, including zidovudine, should be initiated in women with an HIV RNA over 100 000 copies per mL combined with CD4 cell counts less than 350 cells per mm³, and a cesarean section should be considered at term if HIV RNA is greater than 1000 copies per mL. A woman receiving no prior healthcare and presenting in labor should receive a short-course regimen of zidovudine and nevirapine and an infant regimen with referral into care. The Table provides a more detailed approach for several distinct clinical scenarios.

Women receiving treatment must be monitored for drug toxicities and complications, such as lactic acido-
mother-to-child transmission in the context of appropriate care for the mother. And that has been consistently ignored in much of the debate about how to manage HIV in pregnancy. I think it is also part of the perception that women of color have about the shortcomings of the healthcare system. They are often viewed as a “vector” of transmission and not as a person to be treated in her own right. One difficult issue is the use of efavirenz. It’s a cornerstone of the standard of care for modern HIV treatment. How do we put efavirenz into the context of avoidance of pregnancy for people who do not wish to become pregnant? People are starting to be labeled as bad doctors for prescribing efavirenz to women of childbearing age. We need to be able to teach people how to avoid pregnancy if they are using efavirenz as an effective antiretroviral drug.

**Dr Cargill:** Taking a look at women across the life span, with pregnancy as one part of life, has a couple of benefits. You can engage women and retain them in care for substance use and depression, which are heavily represented in this population and make management more difficult. Secondly, if I can be open with a woman about the nature of her relationship and safe sex practices, and whether children are something she is considering, we can talk about how we can approach it. Having the conversation around fertility planning as opposed to having the patient show up pregnant, allows you to talk about the methods that are going to be used, because some agents interfere with contraception, but also, how can we plan for this pregnancy so that we can have resources in place. That doesn’t address that some women are raped by a domestic partner or spouse. The efavirenz issue is also difficult. What I do now is to take an approach that it is not either/or, but a graded response. If I have someone who I have gotten to know and who has been fairly vigilant about her clinic visits, and it is an individual that I feel that I can talk with, I talk with her openly about the risk of efavirenz. I explain to her in patient-friendly language, and I write down the main points. It is time consuming. I go over it with her, and I have her sign the chart. In someone who has out-of-control substance use, I would not consider using this agent.

**Dr Benson:** One of the issues that I think we all struggle with as healthcare providers who take care of women is that we don’t have good information about antiretroviral drugs and the drugs we use for prevention of conception. Telling women to have their partners use condoms is not an effective strategy for management of prevention of conception in HIV-infected women. One of the other issues is that this is also a challenging population to research. Thus we have no data to formulate evidence-based recommendations. We know very little about how to adjust doses to make them effective. Some of the activities we have described about engaging people in clinical care also work very well in engaging people in the research setting. Multidisciplinary teams can work together to engage people in the healthcare system and to attract them into a research setting.

**Dr Bartlett:** One of the reasons that statements about the effects on contraception are so vague is that we don’t know what the changes that we see with these drugs mean. We know what the PIs do to the statins, for example, because we have a measurable endpoint, which is drug levels that correlate with toxicity. With the contraceptives, we may know that it produces an increase or decrease in estradiol, but nobody knows what that means in terms of contraceptive effectiveness.

**Dr Cargill:** Part of the way we address recruitment of racial and ethnic minorities in clinical trials has to do with fixing structural barriers. If we do a trial Monday to Friday, 8 AM to 5 PM, we are not going to recruit these women, because for many people who are racial and ethnic minorities, there are more single heads of households in the African-American community that are headed by women now than any other time in our history, except slavery. If it’s a choice between her job and feeding her children or coming in to do this trial, the woman will choose to feed her kids. Another part of the fix has to do with people’s perceptions of the healthcare system, and therefore, their entrusting themselves to research. There is an extensive oral history in certain ethnic populations, such as with the Tuskegee experiments among African Americans. And finally, part of the fix is going to be that it has to be a long-term investment. Some degree of racial concordance between medical staff and patients is helpful, and we have so few racial and ethnic minority investigators. Even if you just use the same basic language for all patients to tell them about trials so that they even know about it, rather than assuming that they won’t understand or be interested, would be helpful.

**Dr Rich:** For women, the system of healthcare providers conspires to make it maximally complicated. If we think about how we set up the clinical trial networks or how services are delivered, a woman in some centers may be seeing interns for her HIV,
an obstetrician-gynecologist for her pregnancy issues, and then a pediatrician. They all may be in separate places, with separate bureaucracies, cultures, and staffs.

**Dr Cargill:** One of the other reasons to push for multidisciplinary care and support is to engage the woman early on and get her support. I have seen women who have lost their children, gotten them back, but then because their HIV has progressed or they have presented for care so late, they have not had the kind of response we would like. They are fearful they are going to lose their children again because they are now getting “healthier” and therefore should be able to return to the workplace. But they are so ill, because they are dependent on erythropoietin for their hematocrit, or they have chronic herpes simplex virus and other infections. We have actually had more than 1 patient discontinue her medications, and part of her reason was because she was afraid that when she reached a certain point and she could not return to work and take care of her children, her children would be taken away again, and she would not put herself at that risk. Without having some sort of advocate, or some way to work through the system with them, it is hard to provide the support and services.

**Dr Bartlett:** There is one issue that comes up only once in a great while, but when it comes up, it is very important. And that is the discordant couple that wants a child. If it is the woman that’s infected, it’s easy and simple, and cheap. But I often treat male patients with hemophilia, and although sperm washing is often advocated, there are no good data to support it, and we don’t really know if it works or not. You also have to go to a city where you can find someone who provides the service, and you have to live there for a while while the procedure is completed.

**Dr Mayer:** Nobody has done a randomized control trial. It’s the same protocol used for male factor infertility, so they have been doing it for decades. The semen is spun in a centrifuge, the spermatozoa go into the tip of a nipple tube, and the white cells layer at the top and can be easily removed. There are a couple of large cohorts from Europe of more than 1000 people with no seroconversions. The principal reason it is not done more widely is because of concerns about legal liability.

**Dr Bartlett:** What about transmission of HIV with standard intercourse by people with undetectable viral load?

**Dr Benson:** This is obviously a very difficult study to do because of the risk of seroconversion in a discordant couple. Dr Mayer has demonstrated that you have people occasionally who have peripheral plasma viral load below levels of detection but have very high semen viral loads.

**Dr Mayer:** Though it is uncommon. It would be hard to do a clinical trial. We need a patient registry, and nobody is taking the initiative to set one up.

**Dr Benson:** I don’t think you can do a randomized clinical trial, but it may be possible to do a study among a group of investigators who are committed to investigating this issue. An example is transplantation. Nobody is going to do a randomized trial of transplant versus no transplant in an HIV-infected hepatitis C virus-coinfected individual. But they can systematically collect information on those individuals who do get transplants. I think you could do the same thing with this issue, if you could organize a group of centers who really are concentrating on HIV-infected women, collecting systematically the data on women who want to become pregnant, collecting data on what has happened in the context of the partner, and what methods were used. I think it’s time to try to address this question. All of us have had women or men who are infected but who can now expect longer life spans and who want to have children.

**Dr Bartlett:** I think one thing that we have to face is the reality that resources are going to go down and that cuts may be fairly deep. Most of us worked in clinics that are funded by Ryan White; funding is not keeping up with the growing number of people who require care. The amount of support for transportation, homelessness, food, for example, are probably going to decrease to support the direct cost of HIV.

### REFERENCES


