Care of the HIV-infected pregnant woman in the developed world

Erica Hardy^{1,2} and Susan Cu-Uvin^{2,3}

Abstract

The reduction of human immunodeficiency virus (HIV) transmission from mother to child is one of the success stories of modern medicine and public health. In the developed world, with universal HIV counseling and testing, antiretroviral prophylaxis, scheduled Cesarean delivery if indicated, and avoidance of breastfeeding, HIV transmission from mother to infant can be <2%. Despite this, transmissions continue to occur, often due to lack of knowledge of HIV status. Missed opportunities for prevention and prevention challenges include late prenatal care, lack of HIV testing in pregnancy, lack of preconception counseling, unintended pregnancy, and substance abuse. We review preconception counseling including options for serodiscordant couples, and antepartum, peripartum and postpartum care of the HIV-infected woman in the developed world, and advocate for a comprehensive, collaborative, multidisciplinary approach.

Keywords

Infectious diseases, immunology, high-risk pregnancy, maternal fetal medicine

Introduction

The reduction of human immunodeficiency virus (HIV) transmission from mother to child is one of the success stories of modern medicine and public health. In the developed world, with universal HIV counseling and testing, antiretroviral prophylaxis, scheduled Cesarean delivery if indicated, and avoidance of breastfeeding, which is the current standard of care in the developed world, HIV transmission from mother to infant has been reduced from 25%, with no intervention, to <2%.^{1–6} Less than 200 infants per year are born with HIV.^{7–9} Despite this, transmissions continue to occur, often due to lack of knowledge of HIV status. In the US, there are 120,000–160,000 HIV-infected women and 6000–7000 of them give birth annually. It is estimated that 1 in 4 do not know they are HIV infected.¹⁰ Missed opportunities for prevention and prevention challenges include late prenatal care, lack of HIV testing in pregnancy, lack of preconception counseling, unintended pregnancy, substance abuse, and high-risk sexual behavior (such as multiple sexual partners, no barrier protection, or exchange of money for sex).

Preconception counseling

More than half of US pregnancies are unintended, therefore, it is important that preconception counseling be incorporated into routine medical care in all populations, especially women of childbearing age. Among other things, this preconception care should include HIV and sexually transmitted infection (STI) testing, as well as education about contraception in order to avoid unintended pregnancy.^{11,12} Preconception counseling is equally important in HIV-infected women, and should be included in routine HIV medical care, including discussion about reproductive options, contraception, safe sex to avoid unintended pregnancy and STIs, risk factors for perinatal transmission, the effects of antiretroviral medications on hormonal contraception, medication effects on a fetus should pregnancy occur, and vaccination as appropriate. In the US, the Centers for Disease Control and Prevention, the American College of Obstetricians and Gynecologists, and other national organizations have formal recommendations for preconception care.¹³

Reproductive options for serodiscordant couples

Expert consultation is recommended for couples where one partner is HIV infected as the care may differ depending on the individual case.

Two areas of rapidly developing research warrant mention in this review. One recent landmark study, HIV Prevention Trials Network 052, was a randomized clinical trial that evaluated HIV transmission rate in serodiscordant heterosexual couples.¹⁴ The authors demonstrated that initiation of early antiretroviral therapy in the HIV-infected partner lead to a decreased risk of transmission to the uninfected partner (27 infections in the delayed antiretroviral therapy group versus 1 infection in the early antiretroviral therapy group). Based on this data, antiretroviral therapy is recommended in the HIV-infected partner prior to conception in a serodiscordant couple, especially in those with CD4 counts less than 550, and is recommended and would likely be beneficial in those with higher CD4 counts, although this benefit is less well defined. While antiretroviral therapy does decrease the risk of HIV transmission, it does not eliminate it, and there are reports of transmission across all viral loads.³ This may be partially due to the fact that there may be discordance between serum and genital tract viral loads.^{15–18}

For discordant couples in which the female is the infected partner, the artificial insemination is the safest option, with consistent condom use for all sexual activity.¹³ For discordant couples in which the male is the infected partner, then sperm preparation (“sperm washing”) with subsequent artificial insemination can be considered.^{19,20}

Ideally all couples who desire assisted reproduction would have access to this resource; however, if not, then other potential conception options warrant careful discussion with the patient about risks and benefits. Utilizing antiretroviral therapy in an HIV uninfected patient in order to decrease the risk of transmission from an HIV-infected partner (who ideally should be on antiretroviral therapy with a maximally suppressed viral load), otherwise known as pre-exposure prophylaxis or “PrEP,” is one potential option. Results from clinical trials of PrEP usage have been mixed, but promising.^{21–24} Studies are ongoing to evaluate the effect of periconception PrEP on HIV transmission and pregnancy rates with this method but further study is needed.²⁵ The Centers for Disease Control and Prevention has

¹Infectious Disease and Obstetric Medicine, Women & Infants Hospital, Providence, RI, USA

²The Alpert Medical School of Brown University, Providence, RI, USA

³Infectious Disease, The Miriam Hospital, Providence, RI, USA

Corresponding author:

Erica Hardy, Women & Infants Hospital, 101 Dudley St, Providence, RI 02905, USA.

Email: ehardy@wihri.org

published interim guidelines on the use of PrEP in heterosexual couples.²⁶ Consultation with an expert is recommended if periconception PrEP is considered.

Antepartum care

The care of the HIV-infected pregnant woman should be multidisciplinary, with HIV providers, obstetricians, pediatricians, and social service providers working collaboratively. The initial evaluation of the pregnant woman with HIV is outlined in Table 1. Combination antiretroviral therapy (at least three drugs) is the standard of care for all pregnant women in the developed world and is recommended for all women, regardless of CD4 count or HIV viral load.²⁷ Combination antiretroviral therapy and a longer duration of antepartum antiretroviral therapy is more effective at reducing perinatal transmission than single drug therapy or shorter course therapy.¹³ Patients with CD4 counts <500 cells/mm³ should be started on antiretroviral therapy both for their own health and to prevent perinatal HIV transmission, as soon as possible during pregnancy. Pregnant patients with CD4 counts >500 cells/mm³, will also need antiretroviral therapy to prevent perinatal transmission of HIV. If any patient is already on antiretroviral medication for their HIV prior to pregnancy, in general she should continue her medication regimen throughout pregnancy, provided the regimen is effectively suppressing the viral load. The risk of discontinuing medication and the potential for an increase in replicating virus may be greater than the risk of any potential teratogenic effects of the antiretroviral medication early in pregnancy. Recently, the United States Health and Human Services Panel on Prevention of Perinatal HIV Transmission updated their treatment guidelines to recommend continuing efavirenz in women who are on an efavirenz-containing regimen and present for antenatal care in the first trimester, as long as the regimen is effectively suppressing the viral load.¹³ This medication has been associated with a small increased risk of neural tube defects in animal studies which has not been replicated in limited human reports.¹³

If a woman has not been on antiretroviral medication, she will need to start combination therapy to prevent perinatal transmission. Pregnant women with CD4 counts >500 cells/mm³ who have not already been on therapy, or have been on therapy in a prior pregnancy and discontinued postpartum, can consider delaying the start of antiretroviral therapy until 12 weeks gestation. However, there is growing evidence that lack of early and sustained viral control was associated with perinatal HIV transmission.³ The timing of the start of antiretroviral therapy in patients with CD4 counts >500 cells/mm³ who have not been on medication requires consideration of the patient's history, viral load, and unknown fetal effects of exposure to antiretrovirals early in the first trimester (when the fetus is most susceptible to potential teratogenic effects of medications). Antiretroviral medications are also recommended in women who have undetectable viral loads even in the absence of antiretroviral medication, because there is no absolute viral load threshold below which transmission has not been reported.^{28–30}

Pregnant women with a viral load above the threshold for resistance testing (HIV RNA >500 – 1000 copies/mL) should undergo HIV resistance testing prior to the start of antiretroviral therapy. However, beginning antiretroviral medications should not be delayed while awaiting genotype results if the woman is in the second trimester of pregnancy or later. If antiretrovirals are started prior to the genotype results, then a protease inhibitor is preferred over a non-nucleoside reverse transcriptase inhibitor in addition to the nucleoside reverse transcriptase inhibitor backbone because more mutations are required to produce resistance to the protease inhibitors.

The choice of which antiretrovirals should be individualized based on a woman's disease state, prior treatment, and resistance history, after discussion about known benefits and potential risks to the mother and fetus. Potential antiretroviral options are outlined in Table 2. Because one of the mechanisms of prevention of perinatal HIV transmission is likely pre-exposure prophylaxis for the infant in

Table 1. The initial evaluation of the HIV-infected pregnant woman.

Elements of the history and exam (disease status)	Laboratory data
Antiretroviral medication history	CD4 count
History of opportunistic infections	HIV viral load
Evidence of any sexually transmitted infections or opportunistic infections	HIV genotype (resistance testing)
Evaluation of immunization status	Baseline complete blood count, renal function, liver function

the antepartum period, at least one agent that crosses the placenta (such as the nucleoside reverse transcriptase inhibitors lamivudine, zidovudine, tenofovir, emtricitabine, or abacavir) should be chosen for the maternal regimen. In general, nevirapine should not be initiated in women with CD4 counts >250 cells/mm³ because of the risk of hepatotoxicity, although the data is mixed.^{31,32} Viral load should be monitored every 2–4 weeks until viral suppression and then every 3 months or at least once per trimester during pregnancy. More frequent viral load monitoring should be considered in patients with suboptimal adherence to antiretrovirals. A viral load should be checked close to delivery so that mode of delivery can be planned.

Intrapartum care

Women who are on an effective antiretroviral regimen during pregnancy should continue it surrounding labor and delivery as much as possible. Intravenous zidovudine (AZT) is indicated if the viral load close to delivery is >1000 copies/mL. If indicated, intravenous zidovudine is started at the onset of labor and continued until clamping of the cord.¹³ A Caesarean section has been shown to decrease the rate of HIV transmission if the viral load is >1000 copies/mL close to delivery.¹³ With a viral load below 10000 copies/mL the benefit is less clear. Expert guidelines in some developed countries would recommend consideration of a Caesarean section with a viral load between 50 and 1000 copies/mL, taking into consideration the actual viral load, as well as the trajectory, the length of time on antiretroviral therapy, adherence issues, obstetric factors and maternal preference.³³ If intravenous AZT is indicated and the woman is undergoing a Caesarean section, then AZT should be started 3 to 4 h prior to surgery. If a Caesarean section is indicated for obstetric reasons in a woman with a viral load >1000 copies/mL, then it is reasonable to schedule it at 38 weeks to decrease the chance of spontaneous rupture of membranes, after which the benefit of Caesarean section on decrease in perinatal HIV transmission is not clear. Similarly, if a Caesarean section is scheduled to reduce the risk of perinatal transmission in a woman with a viral load >1000 copies/mL, then it should be scheduled at 38 weeks for the same reason. If a woman has an undetectable or low (<1000 copies/mL) viral load near delivery and a Caesarean section is scheduled for obstetric reasons, then it can be scheduled at 39 weeks to decrease the risk of neonatal morbidity.

If a woman presents in labor without a known HIV status, then she should be tested for HIV infection urgently to guide immediate management. Where available, rapid point of care tests may be used in this setting. If the results are positive, then intravenous AZT should be initiated while awaiting results of the confirmatory test. It is important to note that a rapid HIV test cannot be used to diagnose HIV infection and a confirmatory test is needed. If the confirmatory test is positive then intravenous AZT should continue throughout labor and delivery, and a Caesarean section should be offered in consultation with a maternal fetal medicine provider or obstetrician with expertise in care of HIV in pregnancy. If the confirmatory test is positive, then the infant should receive antiretroviral prophylaxis for 6 weeks.

Table 2. Antiretroviral medications in pregnancy.^a Preferred regimens would contain a preferred NRTI backbone + either a preferred PI or a preferred NNRTI. An alternative regimen would include a preferred NRTI backbone + an alternative PI, an alternative NNRTI, or an integrase inhibitor.

Drug name and class	Pregnancy specific information
NRTI – Preferred	Recommended for use as part of combination regimen – usually 2 NRTIs (zidovudine/lamivudine, tenofovir/emtricitabine, or abacavir/lamivudine) in combination with one PI or one NNRTI
• Zidovudine	Extensive experience in pregnancy. Zidovudine in combination with lamivudine is the recommended dual-backbone for pregnant women.
• Lamivudine	Extensive experience in pregnancy. Lamivudine in combination with zidovudine is the recommended dual-backbone for pregnant women.
• Abacavir	Must document negative HLA-B*5701 testing prior to initiation and educate woman about potentially serious fatal hypersensitivity reaction.
• Emtricitabine	Alternative NRTI for dual-NRTI backbone.
• Tenofovir	Renal function should be monitored. Clinical studies in children show bone demineralization with chronic use. Clinical significance is unknown.
NNRTI – Preferred	
• Efavirenz	See text for details. Significant malformations in nonhuman primates. Five case reports of neural tube defects. Malformations limited to exposure prior to 5–6 weeks gestation. May be continued in women on efavirenz-containing regimen who present early in pregnancy with viral suppression.
NNRTI – Alternative	For use in combination with 2 NRTIs
• Nevirapine	Increased risk of liver toxicity when initiated in women with CD4 counts less than 250 cells/mm ³ .
NNRTI – Insufficient evidence to recommend use	
• Etravirine	Limited experience in human pregnancy. No evidence of teratogenicity in rats and rabbits.
• Rilpivirine	No published experience in human pregnancy.
PI – Preferred^b	For use in combination with two NRTIs
• Atazanavir	Some recommend increase dose in 2nd and 3rd trimester. Theoretical concern for increase in physiologic fetal hyperbilirubinemia has not been observed in clinical trials. Must boost with ritonavir.
• Lopinavir + ritonavir	Some experts recommend increase dose in 2nd and 3rd trimester. Once daily dosing not recommended in pregnancy.
• Ritonavir	Must use in combination with another PI.
PI – Alternative	
• Darunavir	Limited safety and PK data in pregnancy. Must boost with ritonavir.
Integrase inhibitor – Alternative	
• Raltegravir	Limited data on use in pregnancy. May be used with a preferred NRTI backbone if drug interactions with a protease inhibitor regimen is a concern.

^a Adapted from recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission (Table 6).¹³

^b To minimize the risk of resistance, a PI regimen is recommended in those women who may discontinue antiretroviral therapy in the postpartum period.

If the confirmatory test is negative, then intravenous AZT can be discontinued as can the infant prophylaxis. The evidence for the administration of a single dose of nevirapine to a woman with an unknown or suboptimally controlled viral load who presents at delivery has been evaluated, and this practice is recommended in some developed countries (UK) and not recommended in others (USA).^{13,33} However, the infant may benefit from the addition of other antiretroviral medications in addition to oral AZT for post exposure prophylaxis.³⁴ In an infant born to a mother who only received intrapartum antiretrovirals or no antiretrovirals prior to delivery, the US guidelines recommend a two drug regimen for the infant, to consist of six weeks of zidovudine plus 3 doses of nevirapine in the first week of life.¹³ Invasive fetal monitoring such as scalp electrode or assisted delivery with forceps or vacuum should be avoided if possible as this may break the skin barrier and increase the risk of transmission of HIV to the infant, although this risk will depend on the maternal HIV viral load.

Postpartum care

The continuation of maternal antiretroviral therapy after delivery will largely be based on the indications for the nonpregnant adult. In

general antiretroviral medication is recommended for all HIV-infected adults regardless of CD4 count or viral load, although the strength of that recommendation varies based on CD4 count or other details such as HIV negative partner, need for hepatitis B treatment, renal disease, and history of opportunistic infection as well as other characteristics.³⁵ Because there is significant risk of HIV transmission to the infant, breastfeeding is contraindicated in the developed world where there are safe and acceptable alternatives. Avoidance of breastfeeding should be discussed with the patient over the course of her antepartum visits and again postpartum. The infant will usually receive 6 weeks of oral antiretroviral medication (usually AZT as a single agent). However, a 4 week regimen of zidovudine can be considered in the infant of a mother who has consistently maintained viral suppression on a standard combination antiretroviral regimen and in whom there are no concerns about adherence. The importance of adherence to the infant's medications should be stressed as well as the need for regular HIV testing of the infant over the course of the first year of life.

Adherence to antiretroviral medication in the postpartum period can be poor and support should be provided if possible, as poor adherence can have lifelong implications for drug resistance, future options for antiretroviral therapy, and opportunistic infections.^{36,37} Comprehensive family planning including choices for effective

contraception should be discussed in the antepartum as well as the postpartum period. There may be some pharmacologic interactions between antiretroviral medication and hormonal contraception so these should be taken into consideration when choosing a contraceptive method or methods.^{38–41}

Summary

With routine HIV testing in reproductive age women as recommended by the CDC and recently by the United States Preventive Services Task Force, as well as HIV testing early in pregnancy, antiretroviral therapy during pregnancy, planned mode of delivery based on disease status, and antiretroviral medication to the infant postnatally, a significant burden of HIV disease in future generations can be prevented.^{11,12} The care of a pregnant woman with HIV, and her infant, requires a comprehensive, collaborative, multidisciplinary approach.

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EH performed a literature search, reviewed the literature, and wrote the manuscript. EH and SC edited the manuscript and approved the final draft.

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