

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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Case 32-2005: A 34-Year-Old HIV-Positive Woman Who Desired to Become Pregnant

Laura E. Riley, M.D., and Sigal Yawetz, M.D.

PRESENTATION OF CASE

A 34-year-old woman who was infected with the human immunodeficiency virus (HIV) was evaluated in the infectious-disease and obstetrics outpatient divisions because of a desire to become pregnant.

HIV infection had been diagnosed nine years earlier while the patient was undergoing treatment for cervical dysplasia at another hospital. She believed that she had been infected through heterosexual contact with a previous boyfriend. Two years later, she transferred her care to this hospital. She was asymptomatic and was taking no medications. Laboratory-test results on evaluation are shown in Table 1. She had no other medical problems. She lived with her boyfriend and her eight-year-old daughter, who were HIV-negative; she reported using condoms regularly, but she had had two unplanned pregnancies in the previous four months, which were electively terminated. She did not use illicit drugs or alcohol and smoked cigarettes occasionally. Her mother had died of cervical cancer at 46 years of age.

The patient had been seen every three months in the infectious-disease outpatient division for the past seven years. Her CD4 T-cell counts remained stable and her viral loads had been low (Table 1) without antiretroviral medications, and she had no opportunistic infections. Six years before the current evaluation, colposcopy was performed because of two Papanicolaou (Pap) smears that showed atypical squamous cells of undetermined clinical significance; a biopsy of the cervix showed cervical intraepithelial neoplasia grade 1, with changes consistent with infection with the human papillomavirus (HPV). Large-loop excision of the cervical transformation zone showed chronic cervicitis with squamous metaplasia and focal reactive cytologic atypia, but no evidence of dysplasia. Papanicolaou (Pap) smears were performed semiannually thereafter.

Two years before the current evaluation, the patient and her boyfriend were married, and at that time she stopped smoking. Her husband was HIV-negative. One year later, a Pap smear showed mild dysplasia (low-grade squamous intraepithelial lesion), with cellular changes consistent with HPV infection. One month later, an unplanned pregnancy ended in a spontaneous first-trimester abortion. Colposcopy nine months and again six months before the current evaluation showed chronic cervicitis, and repeated Pap smears showed a low-grade squamous intraepithelial lesion with cellular changes consistent with HPV infection. A pelvic examination revealed a retroverted uterus, no vaginal discharge, and no adnexal enlargement.

From the Obstetrics and Gynecology Service, Massachusetts General Hospital (L.E.R.); the Division of Infectious Diseases, Brigham and Women's Hospital (S.Y.); and the Departments of Obstetrics, Gynecology, and Reproductive Biology (L.E.R.) and Medicine (S.Y.), Harvard Medical School — all in Boston.

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Table 1. Laboratory-Test Results.

Variable	7 Years Earlier	4 Years Earlier	3 Years Earlier	1 Year Earlier	3 Months Earlier	On Evaluation
CD3+CD4+ lymphocytes (per mm ³)	786	719	645	522	499	454
HIV RNA (copies/ml)	300	1020	3310	9010	6750	6810
Cytomegalovirus antibody	Positive					
Toxoplasma antibody	Negative			Negative		
Rapid plasma reagin	Nonreactive			Nonreactive		Nonreactive
Hepatitis B surface antigen				Negative		Negative
Hepatitis C antibody				Negative		
HIV-resistance genotype						
Reverse transcriptase				None		
Protease				L63P*		

* L63P denotes the type of protease present.

Three months before the current evaluation, the patient and her husband decided they wished to have a child. She was referred to specialists in infectious diseases and obstetrics. She felt well and had had no recent fevers, chills, cough, shortness of breath, abdominal pain, vaginal discharge, night sweats, weight loss, or other symptoms. The couple used condoms at all times. She appeared well. The vital signs and physical examination were normal.

Options for initiation and management of pregnancy were discussed.

DISCUSSION OF MANAGEMENT

Dr. Nancy Lee Harris (Pathology): Two related but distinct problems arise in a patient infected with HIV who wishes to become pregnant: management of pregnancy in an HIV-positive woman and management of HIV infection in a pregnant woman. An obstetrician and a specialist in infectious diseases will discuss how these issues were addressed in the management of this case.

PREPREGNANCY CONSULTATION

Dr. Laura E. Riley: Prepregnancy consultation with both obstetrical and infectious-disease specialists was provided to this patient, as it should be to all HIV-positive patients. This provides an opportunity to discuss maternal factors that influence mother-to-child transmission of HIV, the rates of transmission with optimal therapies, drugs that are potentially toxic to the mother and the fetus, the importance of adherence to antiretroviral therapy,

and neonatal HIV testing and treatment. Although most HIV-infected women are reassured to learn that pregnancy does not appear to accelerate the progression of HIV disease, the majority of them are concerned about the effect of HIV and its treatment on their babies.

Maternal Risk Factors for Mother-to-Child HIV Transmission

In addition to the mother's HIV viral load and her CD4 T-cell count, other maternal factors that may increase the risk of mother-to-child transmission of HIV include coexisting sexually transmitted infections, drug use, and several labor-related factors. The patient under discussion did not smoke or use alcohol or illicit drugs. Prepregnancy or early-pregnancy screening for and treatment of syphilis, gonorrhea, and chlamydia are encouraged, since these infections may be transmitted to the fetus and be associated with poor fetal outcomes that range from birth defects to neonatal pneumonia. Although screening for antibodies to toxoplasma and cytomegalovirus is not recommended for the general obstetrical population, these studies had been obtained as part of this patient's routine HIV care. There have been case reports of congenital toxoplasmosis in babies born to HIV-infected women despite preexisting antibodies.¹ There is also a theoretical concern that preexisting cytomegalovirus antibodies are not as protective in HIV-positive women as they are in HIV-negative women. Both of these concerns underscore the need for a detailed second-trimester fetal survey. In addition

to testing for hepatitis B surface antigen, which is performed in all pregnant women at the beginning of pregnancy, testing for antibodies to hepatitis C virus (HCV) is performed in women at high risk. This patient with HIV would be at greater risk for transmitting HCV to her baby if she were HCV-positive than a woman who was HCV-positive and HIV-negative.^{2,3} Testing revealed no evidence of infection with either HCV or the hepatitis B virus.

This patient has a history of infection with HPV and cervical dysplasia. Studies have shown that HIV-infected women, particularly those with advanced disease, have an increased risk of cervical dysplasia.^{4,5} As this patient's history shows, dysplasia with recurrent disease may occur despite surgical excision. Therefore, even while pregnant, HIV-positive women continue regular evaluations — with Pap smears, colposcopy, and biopsies, if indicated.

Mother-to-fetus transmission of HPV is manifested as juvenile laryngeal papillomatosis. Two studies have found low rates of HPV DNA or clinical papillomatosis among offspring born to mothers with the HPV infection.^{6,7} However, the effects of maternal immunosuppression on mother-to-child transmission of HPV are not known. To reduce both the potential for transmission of HIV and the possible risk of transmission of HPV to her infant, treatment of the HIV infection in this patient needs to be considered.

Treating Maternal HIV Infection

Dr. Sigal Yawetz: Does this woman with established asymptomatic HIV infection, who has had no treatment to date for the condition and now hopes to become pregnant, need treatment for her HIV infection? The updated Department of Health and Human Services guidelines for the use of antiretroviral agents in adults suggest initiating antiretroviral therapy when the patient's CD4 T-cell count falls below 200 to 350 cells per cubic millimeter and the level of HIV RNA is greater than 100,000 copies per milliliter of plasma.⁸ These guidelines, based on data from several observational cohorts, reflect the greater risk of progression to the acquired immunodeficiency syndrome (AIDS) in persons with lower CD4 T-cell counts and higher plasma levels of HIV RNA.^{9,10} On the basis of these guidelines, we can advise this patient that she does not need antiretroviral therapy for her own health; however, we should offer her antiretroviral therapy to prevent transmission of HIV to her fetus.¹¹

Goals of Antiretroviral Therapy

Maximizing viral suppression by the time of delivery is the primary goal of treating this patient. Several studies conducted before the era of highly active antiretroviral therapy (HAART) showed a strong correlation between maternal levels of HIV RNA at the time of delivery and the risk of HIV transmission.^{12,13} More recent studies, summarized in Table 2, confirm these early findings in the HAART era.

When counseling this patient, it is important to emphasize to her that although transmission rates will become substantially lower as her plasma levels of HIV RNA decrease, transmission of HIV may occur even with levels of the virus below the limit of detection. For any given viral load, even those below 1000 copies per milliliter, the rate of transmission is lower among women undergoing therapy than women receiving no antiviral therapy,¹⁶ and the use of combination therapy further reduces the likelihood of transmission (Tables 2 and 3).^{14,15}

Choosing Antiretroviral Agents

The choice of a drug regimen for this patient should be made on the basis of clinical experience with individual agents in pregnancy, their known and suspected toxic effects on mother and fetus, pharmacokinetic data in pregnancy, long-term efficacy, and

Table 2. Mother-to-Child Transmission of HIV, According to Antenatal Viral Load.*

Maternal RNA (copies/ml)	Transmission Rate (%)†
Data from WITS	
>30,000	23.4
10,000–29,999	14.7
3500–9999	9.3
400–3499	5.3
<400	1.0
Data from PACTG 367	
Unknown	17.1
>10,000	5.6
1000–10,000	2.0
<1000	0.7

* Maternal RNA was determined by the Amplicor HIV-1 Monitor Test (Roche Diagnostics). WITS denotes Women and Infants Transmission Study (data from Cooper et al.¹⁴). PACTG 367 denotes Pediatric AIDS Clinical Trials Group Protocol 367 (data from Shapiro et al.¹⁵).
 † P for trend=0.001.

Table 3. Mother-to-Child Transmission of HIV, According to Antenatal Antiretroviral Therapy Regimen.*

Maternal Antiretroviral Therapy	Transmission Rate (%)
Data from WITS	
None	20.0
Zidovudine monotherapy	10.4
Dual-drug therapy	3.8
HAART	1.2
Data from PACTG 367	
None	18.5
Single agent	5.1
2 NRTIs	1.4
≥3 Agents	1.3
NRTIs only	3.4
+NNRTI (no PI)	1.5
+PI	1.1

* WITS denotes Women and Infants Transmission Study (data from Cooper et al.¹⁴). Dual-drug therapy denotes mostly therapy with dual nucleoside reverse-transcriptase inhibitors (NRTI) but may include nonnucleoside reverse-transcriptase inhibitors (NNRTI) or protease inhibitors (PI). HAART denotes highly active antiretroviral therapy, defined as three or more drugs including at least one NNRTI or PI. PACTG 367 denotes Pediatric AIDS Clinical Trials Group Protocol 367 (data from Shapiro et al.¹⁵).

the patient's concerns (Table 4). A test for drug resistance should be performed before treatment begins, as it was in this patient. Although she had never been treated with antiretroviral agents, there was a small chance that she had acquired a drug-resistant virus, which could lead to a suboptimal virologic response to empirical therapy during her pregnancy.

Zidovudine, a nucleoside reverse-transcriptase inhibitor used in the Pediatric AIDS Clinical Trials Group Protocol 076 study, was the first antiretroviral agent shown to reduce perinatal transmission by approximately two thirds, when the mother received antepartum and intrapartum therapy and the newborn received it post partum for six weeks.²⁰ This regimen remains a chief component of HIV therapy in pregnancy in the United States and should be used in patients, such as this woman, who show no signs of resistance or intolerance. However, as shown in Figure 1, combination therapy has been increasingly used for the prevention of mother-to-child transmission of HIV in the United States, because it has been shown to be more effective. Zidovudine, therefore, should not be used alone, but in combination with another drug.¹⁴ This pa-

tient should be informed that although many antiretroviral agents are considered safe in pregnancy, the long-term effects on exposed infants are not known.

Data on antiretroviral toxicity and teratogenicity in pregnancy are available through the Antiretroviral Pregnancy Registry (www.apregistry.com) and are also summarized in the treatment guidelines¹¹ (Table 4). In particular, a recent advisory from the Food and Drug Administration (FDA) recommended against initiating nevirapine in women whose CD4 T-cell counts are greater than 250 cells per cubic millimeter because of a higher observed risk of serious hepatotoxic effects than seen in patients with lower CD4 T-cell counts. With limited options for nonnucleoside reverse-transcriptase inhibitors, the use of protease inhibitors for prevention of mother-to-child transmission of HIV is increasing.

My choice for treatment for the woman under discussion today would be a combination of zidovudine and lamivudine, with which we have the most experience in pregnancy, with a ritonavir-boosted protease inhibitor, such as ritonavir with lopinavir. An adjustment of the dose of ritonavir with lopinavir toward the end of pregnancy may be required.²¹ The combination of nucleoside reverse-transcriptase inhibitors and nelfinavir (rather than ritonavir with lopinavir) or triple-nucleoside therapy with zidovudine, lamivudine, and abacavir could be considered as well.

Starting Antiretroviral Treatment

I would prefer to initiate antiretroviral therapy before conception to allow time to optimize therapy and manage side effects. However, since the risk associated with exposing the fetus to antiretroviral agents during the period of organogenesis (the first 13 weeks of gestation) is unknown, many women and providers may choose to defer the initiation of treatment until the second trimester of pregnancy. If this patient elects to defer therapy, any nausea and vomiting caused by pregnancy should be well controlled before the initiation of treatment. All antiretroviral agents should be temporarily discontinued if hyperemesis develops.

Monitoring for Efficacy and Toxic Effects

This patient started treatment with zidovudine, lamivudine, and nevirapine before conception and before the recent FDA advisory against the use of nevirapine. Once therapy had been initiated, the pa-

Table 4. Drugs Used to Prevent Mother-to-Child Transmission of HIV.*

Drug Category	Drug Names	Selected Adverse Effects in Pregnancy	Recommended Monitoring
Nucleoside or nucleotide reverse-transcriptase inhibitors	Zidovudine	Anemia†; mitochondrial toxic effects (lactic acidosis, pancreatitis, hepatosteatorrhea) in mother and possibly fetus; neuropathy; hypersensitivity	Complete blood counts and hemoglobin levels; monitoring for mitochondrial toxic effects (measurement of electrolytes and liver enzymes)
	Lamivudine		
	Stavudine		
	Didanosine		
	Abacavir		
	Tenofovir	Possible effect on fetal bone metabolism	
Nonnucleoside reverse-transcriptase inhibitors	Efavirenz	Neural malformations	Avoid in pregnancy
	Nevirapine	Hepatotoxic effects (especially with CD4 T cells >250/mm ³), rash	Aminotransferase levels (every two weeks initially, then monthly)
Protease inhibitors	Amprenavir	Hyperglycemia, gestational diabetes, possible increase in preterm births, hepatitis	Glucose levels (standard one-hour glucose loading test early in pregnancy and repeated in third trimester)
	Atazanavir		
	Indinavir		
	Lopinavir		
	Nelfinavir		
	Ritonavir		
	Saquinavir		

* Data are from Lorenzi et al.,¹⁷ the European Collaborative Study and the Swiss Mother and Child HIV Cohort Study,¹⁸ and Tuomala et al.¹⁹

† Anemia is a side effect caused only by zidovudine, whereas the other effects listed are associated with the drug class. A complete list of side effects may be found in the guidelines published by the Department of Health and Human Services.⁸

tient was evaluated for adverse effects and the HIV viral load and CD4 T-cell counts were periodically measured. Although the Public Health Service Task Force guidelines¹¹ suggest that the same standards should be used as when monitoring patients who are not pregnant, I prefer checking laboratory values (Table 2) and HIV viral loads every four to six weeks (more frequently if nevirapine is used), especially in the second half of pregnancy.

Dr. Riley: After the antiretroviral therapy was initiated, the HIV viral load rapidly became undetectable. The husband was evaluated for HIV by enzyme-linked immunosorbent assay, which was negative. The risk of transmission of HIV to the husband during each act of unprotected intercourse was low, but it was not eliminated even though his wife's viral load was undetectable. Therefore, artificial insemination was recommended, and the patient became pregnant by this method within two months.

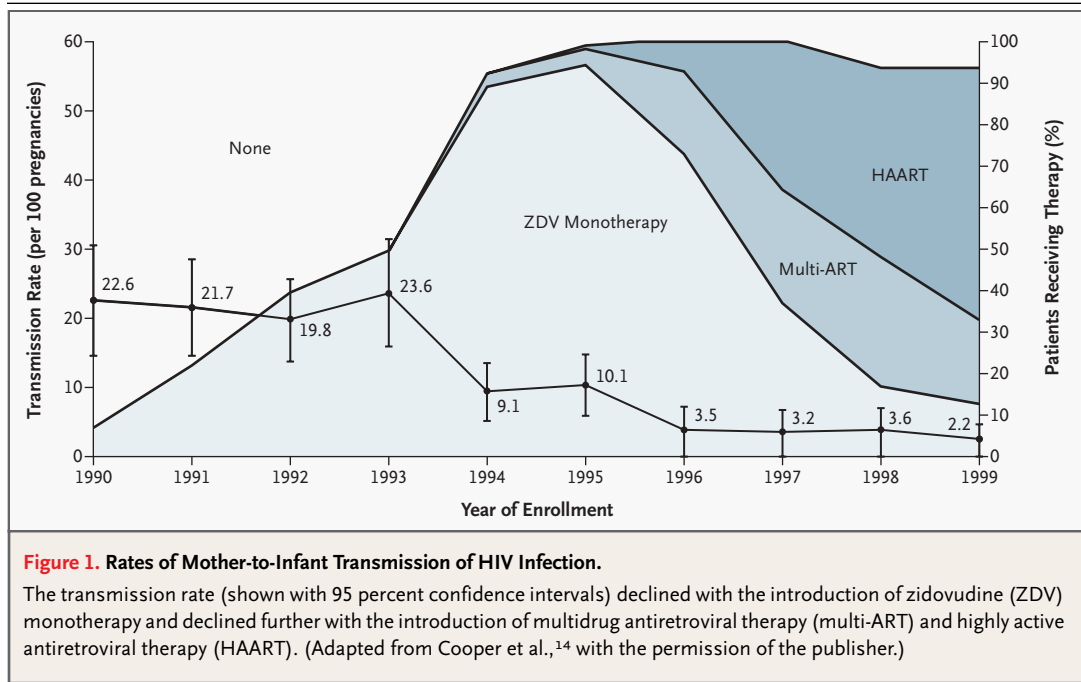
LABOR AND DELIVERY

The patient remained well throughout her pregnancy, with normal laboratory-test results. A detailed fetal ultrasonographic survey obtained in the second trimester was normal. At 35 weeks' gestation, her viral load was less than 50 copies per mil-

liliter of plasma and her CD4 T-cell count was 482 cells per cubic millimeter. A routine rectovaginal culture for group B streptococcus was positive and necessitated antibiotic prophylaxis for vaginal delivery.

Cesarean or Vaginal Delivery

As delivery approached, the issue of whether to recommend cesarean or vaginal delivery had to be addressed. In both a meta-analysis²² and a prospective trial²³ involving women receiving zidovudine monotherapy, elective cesarean delivery reduced the rate of vertical transmission of HIV by as much as five times, as compared with the rate among women who had vaginal delivery. Elective cesarean delivery is most protective in women with viral loads of 1000 copies per milliliter of plasma or more and who are receiving zidovudine monotherapy. The American College of Obstetricians and Gynecologists recommends offering the option of cesarean delivery to women with viral loads more than 1000 copies per milliliter of plasma, with cesarean section performed at 38 weeks' gestation, without amniocentesis to document lung maturity. In addition to viral load, we considered the surgical complications of cesarean delivery, such as fever, en-



dometritis, and wound infection, which are more common in HIV-infected women, whether the cesarean delivery is elective or nonelective.²⁴ Since she had an undetectable viral load, this patient was an appropriate candidate for vaginal delivery.

On routine pelvic examination at 38.5 weeks' gestation, a tender, ulcerated lesion, 1 cm in diameter, was noted on the left labium. A culture was obtained. Acquisition of primary genital herpes or nonprimary first-episode herpes in the late third trimester is the greatest risk factor for vertical transmission leading to devastating neonatal herpes infection. This patient probably had recurrent herpes simplex infection, because on further questioning, she recalled having a similar lesion 10 years earlier. She began taking acyclovir that day, in an effort to speed resolution of the lesion. Several studies have shown that acyclovir administered from 36 weeks of gestation through delivery decreases the incidence of outbreaks of the herpes simplex virus, viral shedding at delivery, and the need for cesarean delivery.²⁵ Thus, if this patient had reported a history of genital herpes earlier, I would have suggested acyclovir treatment beginning at 36 weeks' gestation.

Two days later, the patient reported rupture of the membranes and was instructed to come to the hospital. The ulcerated labial lesion remained, and the culture confirmed the presence of herpes simplex virus type 2. Cesarean delivery for women with

active herpes simplex virus infection at the time of birth reduced the risk of mother-to-child transmission of the herpes simplex virus in one study to 1.2 percent, as compared with a risk of 7.7 percent associated with vaginal delivery.²⁶ At this point, then, it was clear that the mode of delivery would be cesarean, but the optimal timing was a problem. The rupture of membranes could already have exposed the baby to the herpes simplex virus, negating the protective effects of cesarean delivery; prolonging the interval between the rupture of membranes and delivery might increase the risk of exposing the baby to the herpes simplex virus. However, the patient had group B streptococcus infection, which would necessitate penicillin prophylaxis before vaginal delivery; the most significant reduction in neonatal infection occurs with more than four hours of prophylaxis.²⁷ Finally, the Public Health Service Task Force guidelines recommend beginning intravenous zidovudine at least three hours before cesarean delivery. In this patient, whose viral load was undetectable and who had been taking oral zidovudine until delivery, that recommendation seemed less crucial than the concern about transmitting the herpes simplex virus. Therefore, cesarean delivery was performed shortly after the patient's arrival at the hospital, after the administration of broad-spectrum antibiotics for surgical prophylaxis, and without intravenous zidovudine.

Management of Antiretroviral Therapy during and after Delivery

Dr. Yawetz: For delivery in most patients, zidovudine should be administered intravenously during labor and until the umbilical cord is clamped. All other antiretroviral drugs are continued orally. Since this patient began antiretroviral therapy at a CD4 T-cell count that was greater than 350 cells per cubic millimeter, the therapy may be discontinued post partum. However, she was taking nevirapine, and resistance to nonnucleoside reverse-transcriptase inhibitors may develop rapidly when a nevirapine-containing regimen is stopped, because of the drug's long half-life and the low genetic barrier to resistance. Therefore, we thought it might be prudent to have her continue with zidovudine and lamivudine for seven days after stopping nevirapine, although the value of such strategy is still under investigation.

TREATMENT AND MONITORING OF THE INFANT

Most infants born to mothers who are HIV-positive are treated with a six-week course of oral zidovudine initiated as soon as possible after birth. A combination regimen or alternative therapy is used if zidovudine resistance in the mother is known or suspected or if the risk of transmission is high. Serial testing for HIV and evaluations for symptoms of HIV infection and toxic effects of drugs should be scheduled.

Dr. Riley: The female infant weighed 3036 g, and the Apgar scores were 9 at one minute and 9 at five minutes. Although the baby appeared well, her blood culture was positive for group B streptococcus; her cerebrospinal fluid was negative. The baby

was treated with 10 days of intravenous ampicillin. The baby's HIV viral load was less than 50 copies per milliliter of plasma. HIV-positive mothers are advised to bottle-feed when possible because HIV is found in breast milk and may be transmitted to the neonate²⁸; therefore, when the baby was discharged home, she was bottle-fed and would be taking zidovudine syrup for six weeks. The mother discontinued nevirapine therapy three weeks after delivery and zidovudine and lamivudine therapy one week later.

At the patient's two-week postnatal visit, she and her baby appeared well. The patient was reminded to use condoms and encouraged to use a second contraceptive method in view of her history of multiple pregnancies despite reported condom use. Her options included oral contraceptives, injectable medroxyprogesterone acetate, an intrauterine device, or tubal ligation. The estradiol levels in oral contraceptives may be decreased by antiretroviral agents such as nevirapine, rendering the oral contraceptives less effective. One study found that the overall rate of infections up to four months after the insertion of an intrauterine device was the same among HIV-negative women as among HIV-positive women.²⁹ Therefore, in the case of this woman, who is monogamous, an intrauterine device is a reasonable option. At six months, the infant's viral load remains undetectable. The mother continues to use only condoms for contraception.

DIAGNOSIS

HIV infection, asymptomatic.

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