Perspective

HIV Infection in Women: Selected Issues in Pregnancy

At the International AIDS Society–USA course in Denver in May 2002, Judith S. Currier, MD, discussed issues in the management of HIV-infected women, focusing primarily on those related to pregnancy. She used 2 case presentations to illustrate questions concerning sex differences in viral load and CD4+ cell counts, appropriate antiretroviral therapy for pregnant women, prevention of mother-to-child transmission, and adverse events in pregnancy.

Case 1: Viral Load in HIV-Infected Women and Antiretroviral Treatment in Pregnancy

Case Presentation

A 36-year-old woman recently tested seropositive for HIV infection and is interested in beginning antiretroviral therapy. She believes that she was infected 3 years previously. Her current CD4+ cell count is 270/µL and her plasma HIV-1 RNA level is 9000 copies/mL; 6 months ago, her levels were 320/µL and 5000 copies/mL, respectively. The patient lives with her boyfriend and works as a physical therapist. She has no history of injection drug use, does not smoke tobacco, and only occasionally consumes alcohol. She has no significant past medical history; her current physical exam and laboratory evaluation, including PAP smear, are unremarkable; and she has no signs or symptoms of HIV infection. The patient is receiving no medication other than oral contraceptives (ethinyl estradiol/norethindrone). Should antiretroviral therapy be initiated in this patient? If so, with what type of regimen—for example, nevirapine plus 2 nucleoside reverse transcriptase inhibitors (nRTIs), 3 nRTIs, a protease inhibitor (PI)-based regimen, or efavirenz plus 2 nRTIs?

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Discussion

For some clinicians, this patient's CD4+ cell count alone would provide sufficient rationale for beginning treatment. The relatively low viral load might be a point in favor of delaying treatment in an asymptomatic patient. In this regard, however, it is important to consider that several studies have shown that viral load in women is lower than that in men in early disease (Figure 1), both among patients infected through injection drug use and among those infected through sex. Data from these studies consistently suggest a 0.3- to 0.5-$\log_{10}$ difference in viral load by sex. These data also indicate that CD4+ cell counts are somewhat elevated in women, similar to findings in HIV-uninfected populations. Although some studies have shown no difference in viral load between men and women, these have tended to be studies in small numbers of patients or in patients with advanced HIV infection. Thus, if the decision about whether to initiate therapy involves consideration of viral load, it is reasonable to interpret viral load in this patient as being equivalent to a somewhat higher viral load in a male patient.

With regard to a potential initial regimen, one primary consideration is the patient's current use of oral contraceptives. Avoidance of drugs that would interact with the oral contraceptive via the cytochrome P450 system is recommended if oral contraceptive use is to be maintained. Also, women taking amprenavir should be instructed not to use estrogen-based hormonal contraceptives containing ethinyl estradiol/norethindrone, because these drugs have been found to decrease the concentration of amprenavir. Thus, the triple-nRTI regimen and the efavirenz/double-nRTI regimen are likely candi-

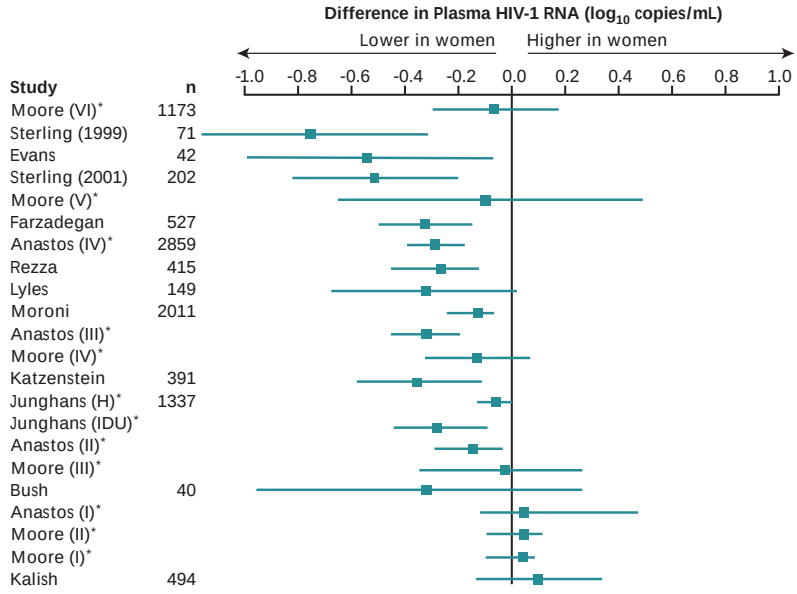

Figure **1.** Estimated differences in mean $\log_{10}$ plasma HIV-1 RNA levels between men and women. Studies are listed in ascending order of median CD4+ cell count, and multiple strata are indicated in parentheses for studies by Moore (I-VI) and Anastos (I-IV). Two groups of subjects are shown for Junghans: heterosexual transmission (H) and injection drug use (IDU). Adapted with permission from Gandhi et al, *Clin Infect Dis,* 2002. *Number represents total in study and not total in strata.

dates for use in this patient. If efavirenz is chosen, a second form of birth control is recommended given the teratogenic potential of this agent and the lack of sufficient data on the impact of efavirenz on contraceptive efficacy.

Clinical Course, Continued

How would selection of treatment differ if the patient stated that she was planning to become pregnant or if it were found that she was already pregnant? For example, should the initial regimen be zidovudine/lamivudine, or zidovudine/lamivudine combined with nevirapine, a PI, or efavirenz? Would it be prudent to delay therapy until the end of the first trimester of pregnancy?

Discussion

Among these treatment options, the dual nRTI combination of zidovudine/lamivudine alone should be avoided because it produces suboptimal viral suppression and is thus likely to result in drug resistance. As noted above, efavirenz should be avoided in women who are planning pregnancy or who are pregnant because of its potential teratogenic effects. In a patient who is planning pregnancy, initiation of treatment might be recommended to provide viral suppression and to evaluate response to the regimen selected. In a woman who is already pregnant, delay of treatment after the first trimester is a reasonable option, as is initiation of treatment with a safe and effective regimen.

Goals of treatment during pregnancy are to achieve optimal viral suppression in the mother, prevent transmission to the child, and maximize the safety of both. Some reassurance regarding safety of antiretroviral treatment for the developing fetus has been provided by data from the Antiretroviral Pregnancy Registry (Garcia et al, 41st ICAAC, 2001). The prevalence rates of birth defects were 2.4% (20/819; 95% confidence interval [CI], 1.5-3.8) among infants with exposure to any antiretroviral drug during the first trimester, 2.2% (26/1207; 95% CI, 1.4-3.2) among infants with exposure during the second/third trimesters, and 2.3% (46/2026; 95% CI, 1.7-3.0) among all exposed infants. These figures compare well with the overall prevalence rates of birth defects of 3.1/100 and 2.2/100 for the first day of life reported by the Centers for Disease Control and Prevention (CDC) in HIV-unaffected pregnancies.

The mode of delivery has been an issue in prevention of transmission. A meta-analysis and a randomized trial have demonstrated the efficacy of elective cesarean delivery in preventing vertical transmission of HIV from mothers receiving zidovudine alone or no antiretroviral treatment. However, whether there is additional benefit from this mode of delivery in mothers receiving potent antiretroviral therapy remains undefined. The Pediatric AIDS Clinical Trials Group study 367 assessed outcomes of 2087 pregnancies in HIV-infected women at 67 centers between 1998 and 2000 (Shapiro et al, 9th CROI, 2001). Transmission rates were 4.3% in 1998, 4.1% in 1999, and 1.6% in 2000. The use of combination antiretroviral therapy increased from 74% in 1998 to 78% in 1999 and 86% in 2000. Elective cesarean delivery was used in 12%, 29%, and 29% of deliveries during these 3 years. Overall, transmission rates were lower with more intensive antiretroviral therapy and did not vary by mode of delivery.

PACTG study 367 found that mother-to-child transmission rates did not vary by mode of delivery

Case 2: Pregnancy and Adverse Effects of Treatment

Case Presentation

Dr Currier next presented the case of a 35-year-old HIV-infected woman at 38 weeks of gestation who presented to the emergency department with nausea, vomiting, and abdominal pain for 48 hours. She had a nontoxic appearance, with blood pressure of 120/70 mm Hg, heart rate of 90 bpm, no fever or diarrhea, and no vaginal discharge. She reported mild right upper quadrant pain. Laboratory evaluation showed normal complete blood count, platelet count, and coagulation. Alanine aminotransferase (ALT) was 138 U/L, aspartate aminotransferase (AST) was 200 U/L, and amylase and lipase levels were normal. Electrolytes were sodium, 132 mEq/L; potassium, 4.5 mEq/L; chloride, 96 mmol/L; and bicarbonate, 18 mEq/L. The urinalysis was unremarkable. The transaminitis and metabolic acidosis suggested the potential for lactic acidosis. Further work-up showed that the patient had normal to mild fatty changes to the liver on ultrasound testing, negative hepatitis serology, pH of 7.43 mm Hg, P_{CO_2} of 24 mm Hg, P_{O_2} of 108 mm Hg, and negative toxicology screen; her venous lactate level, however, was 13.8 mmol/L.

The patient had been diagnosed with HIV infection 3 years earlier, 2 months after a severe (possible seroconversion-associated) viral illness. Her initial CD4+ cell count was 320/µL and her plasma HIV-1 RNA level was 750,000 copies/mL. She was started on a regimen of fixed-dose lamivudine/zidovudine plus ritonavir/saquinavir, and developed zidovudine-related nausea that did not improve over time. At 6 and 9 months after starting treatment, plasma HIV-1 RNA level was less than 50 copies/mL, and CD4+ cell count had increased to 627/µL at 9 months. Her treatment was changed to didanosine/stavudine/nevirapine and she remained on this regimen throughout the pregnancy because she tolerated it well and her plasma HIV-1 RNA level remained less than 50 copies/mL. No problems occurred during the pregnancy until the time of her presentation.

After hydration, the patient had a lactate level of 15 mmol/L. Should the patient stop antiretroviral therapy and have a cesarean delivery with or without zidovudine coverage during delivery? Should therapy be stopped and delivery held off? Or should the patient be given riboflavin and L-carnitine and undergo delivery while continuing antiretroviral treatment?

Discussion

Lactic acidosis is a rare but potentially fatal complication associated with nRTI treatment. Symptoms include nausea and vomiting, abdominal pain, weight loss, malaise, and dyspnea or tachypnea. Laboratory findings include increased anion gap and increased lactic acid and lactate/pyruvate levels. Hepatic steatosis, consistent with the finding of the mild fatty change to the liver observed in this patient, can occur during pregnancy in association with lactic acidosis, and the condition may be indistinguishable from steatosis associated with nRTI use. Acute fatty liver of pregnancy develops in approximately 1 in 7000 to 13,000 pregnancies. It occurs during the third trimester and is accompanied by symptoms of abdominal pain, nausea, vomiting, and rapid onset of hepatic failure with coagulopathy and encephalopathy. Histology shows a predominantly microvesicular steatosis with mitochondrial disruption on electron microscopy and no necrosis. Management is focused on early diagnosis and prompt delivery. There are limited data on risk of recurrence, although recurrence has been observed with subsequent pregnancy.

In this case, antiretroviral therapy was stopped and the baby was delivered by cesarean section under zidovudine coverage, with the mother also receiving riboflavin and L-carnitine. The baby was in good condition. The mother, however, developed coma and hepatic and renal failure requiring intubation and intensive care unit support for 10 days. Lactate levels improved very slowly to 9.5 mmol/L at 7 days and 5.0 mmol/L at 14 days postpartum. Liver and muscle biopsies showed no mitochondrial abnormalities and a predominantly microvesicular hepatic steatosis, although macrovesicular changes were also detected. It could not be determined whether the patient had fatty liver of pregnancy or hepatic steatosis associated with nRTI use.

Shortly after this patient was seen, details of the deaths of 3 women receiving didanosine and stavudine during pregnancy were released in a "Dear Health Care Provider" letter issued by the manufacturer (Food and Drug Administration, 2001). All 3 women had received didanosine/stavudine throughout their pregnancy. One woman also had received the investigational agent atazanavir, and one, whose fetus expired in utero, also had received nelfinavir. The third woman, whose death was reported in postmarketing surveillance and whose infant expired during cesarean delivery, also had received nevirapine. These deaths resulted in the addition of a warning to the prescribing information that didanosine/stavudine should be used with caution during pregnancy and only if potential benefits outweigh risks.

More recently, at the 9th Conference on Retroviruses and Opportunistic Infections (Marcus et al, 2002), information was reported on 6 additional women who had received didanosine/stavudine for more than 12 weeks in the manufacturer's studies since 1997. Among the 6 women, there were 3 uncomplicated term deliveries, 1 late therapeutic abortion, and 2 pregnancies that were ongoing in women who had switched regimens after the initial report of deaths. An earlier study found that short-term use of the combination in the third trimester in a mother-to-child transmission prevention study resulted in no complications among 77 women treated. Thus, length of exposure may be an important determinant of risk of complications with this combination.

Clinical Course, Continued

The patient gradually improved. Off antiretroviral therapy, her plasma HIV-1 RNA level was less than 200 copies/mL and CD4+ cell count was 326/µL at day 14. Three weeks later, plasma HIV-1 RNA level increased to 151,000 copies/mL and the patient complained of night sweats and mild swollen glands. At this time, the patient's ALT was 22 U/L, AST was 38 U/L, and lactate level was 0.5 mmol/L. Should the patient be restarted on antiretroviral treatment using a nonnucleoside reverse transcriptase inhibitor (NNRTI) and PI, a regimen of abacavir/lamivudine/NNRTI, or some other regimen, or should she continue to be observed off treatment?

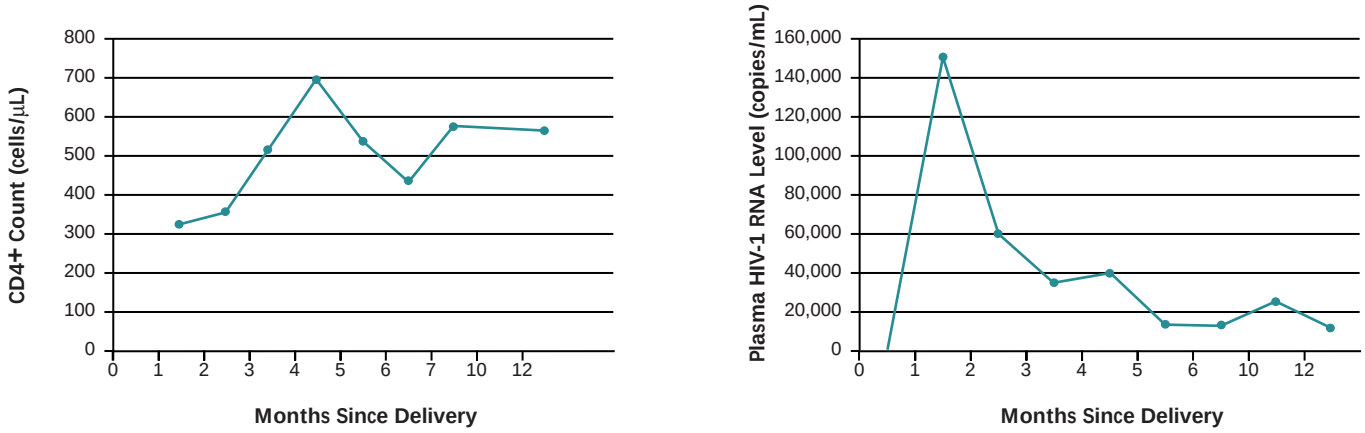

Figure **2.** CD4+ cell count (left) and plasma HIV-1 RNA level (right) by months after delivery and cessation of antiretroviral therapy for patient in Case 2.

Discussion

In this case, the best course would appear to be observing the patient off treatment, both because of the need for recovery from the near fatal episode of lactic acidosis and because of the potential for resolution of what seemed to be recurrence of antiretroviral syndrome after cessation of therapy. After 6 months of observation off therapy, the patient's CD4+ cell count had increased to 576/µL and plasma HIV-1 RNA level had decreased to 14,374 copies/mL (Figure 2). With continued follow-up for more than 1 year, the patient's CD4+ cell count leveled off at approximately 550/µL and plasma HIV-1 RNA level remained below 20,000 copies/mL. The patient remains off antiretroviral therapy with close follow-up and the baby is doing very well.

There are limited data on rechallenge of patients with nRTIs after episodes of symptomatic lactic acidosis. In one report by Lonergan and colleagues (8th CROI, 2001) involving 17 patients, 9 who had been receiving stavudine/lamivudine at presentation were rechallenged with either abacavir/lamivudine (n=7) or zidovudine/lamivudine (n=2), 4 who had been receiving stavudine/didanosine were given either abacavir/zidovudine/lamivudine (n=2) or abacavir/didanosine (n=1), 3 who had been receiving stavudine/didanosine/lamivudine were given abacavir/zidovudine/lamivudine (n=2) or abacavir/didanosine/lamivudine (n=1), and 1 who had been receiving stavudine 80 mg/abacavir was given stavudine 40 mg/abacavir. Patients had received their former nRTI regimens for a median of 12 months (range, 3.5-24 months) and received their rechallenge regimens for a median of 10 months (range, 6-17 months). During the rechallenge period, compared with the former nRTI-treatment period, the number of patients with gastrointestinal symptoms decreased from 16 to 0, median lactate level decreased from 4.4 mmol/L (range, 3.3-19 mmol/L) to 1.5 mmol/L (range, 1.0-1.9 mmol/L), and median ALT level decreased from 135 U/L (range, 26-288 U/L) to 22 U/L (range, 10-159 U/L). The number of patients with plasma HIV-1 RNA level less than 400 copies/mL was 12 on the former regimen and 14 during rechallenge.

In cases such as the one discussed here, risk of complications during future pregnancy remains unknown. A prudent course if the patient desires to become pregnant again is first to ensure that an antiretroviral regimen can be tolerated and provide maximal suppression for a defined period (eg, 6 months). If this goal is achieved, pregnancy can be considered with very close follow-up if the patient is aware that recurrent fatty liver is possible and that its risk cannot be quantified.

Conclusion

Important factors in managing antiretroviral therapy in women include consideration of the patient's childbearing goals or plans before initiation of treatment, use of therapy that maximizes benefit to the mother during pregnancy while reducing risk to the fetus, and heightened awareness of the potential for lactic acidosis. Although routine monitoring of lactate levels is not recommended in asymptomatic patients, levels should be monitored in patients with unexplained weight loss, nausea, or abdominal pain, and possibly during pregnancy.

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Suggested Reading

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