

PREVENTION OF PERINATAL TRANSMISSION

ANTIRETROVIRAL REGIMENS FOR HIV-INFECTED PREGNANT WOMEN

95. Will aggressive therapy of the pregnant woman resolve the issue of vertical transmission?

Dr Schooley: The mechanism(s) by which HIV-1 transmission is prevented by zidovudine monotherapy has not yet been delineated. Although the likelihood of transmission decreases as the maternal plasma HIV RNA level declines, no level has yet been identified below which transmission does not occur. It has not been demonstrated that the effect of zidovudine on decreasing plasma HIV-1 RNA levels is responsible for prevention of transmission. Thus, although it is possible that it will be demonstrated that lowering viral load in the mother does play a role in prevention of vertical transmission, it is also possible that the most important issue will be intensification of the regimen delivered to the baby.

Dr Thompson: In studies to date, transmission has occurred even with very low levels of HIV RNA in some patients. It is not certain therefore that more complete viral suppression will result in the absence of vertical transmission. Maternal and obstetric factors may contribute, and the importance of treating the neonate should be stressed. From clinical trials of nonpregnant patients we know that suppression of plasma viral RNA does not fully account for the treatment effect. However, if potent combinations are capable of more completely turning off viral reproduction, additional benefit will likely be seen.

96. What studies are being conducted in pregnant women, both to enhance their health and to prevent perinatal transmission by using combination therapy and decreasing viral load, especially at delivery?

Dr Schooley: Second-generation studies using combinations of antiretroviral drugs are in the pilot phase. Studies are also under way that seek to identify whether antiretroviral treatment of the mother or the child, or both, are important in preventing transmission. Finally, there is increasing interest in "eradication" studies in infected infants based on pilot data generated with triple-drug regimens.

Dr Thompson: Safety studies are under way using stavudine monotherapy, combination lamivudine/zidovudine,

and combination nevirapine/zidovudine. A large combination study of zidovudine/lamivudine has been initiated and many have chosen to use this combination because of reasonable safety experience to date. The most interesting data on combination therapy come from a trial using nevirapine in combination with zidovudine just prior to delivery, but even these data are insufficient to uniformly recommend this regimen for all pregnant women. The Panel will be watching these data closely as they mature. As of this publication, no studies have been initiated using protease inhibitors in pregnancy and there are only rare cases of pregnant patients being treated in the expanded access programs for indinavir, ritonavir, and saquinavir. In all cases, clinical trials of protease inhibitors have excluded pregnant women or mandated discontinuation of the drugs if pregnancy occurred. There is particular concern about indinavir in this setting because of the known complication of hyperbilirubinemia with this drug. Animal toxicology studies found an increased incidence of ventricular septal defect (VSD) in animals treated with delavirdine and to date only a few pregnant women have been treated with the drug. In one pregnancy that ended in premature birth, the neonate had a VSD that closed within four weeks and was felt to be typical of prematurity rather than an effect of delavirdine treatment. Numerous studies are being planned using protease inhibitors or NNRTIs in third-trimester pregnancy and in neonates. Development of a formulation appropriate for neonates is a challenge in the case of some of these drugs.

97. Why is the committee being so timid regarding vertical transmission and combination therapy given the good preliminary data?

Dr Schooley: The Panel has sought to make recommendations that represent a reasonable balance between data that have emerged from clinical trials and inferences that can be made from the rapidly developing understanding of HIV-1 pathogenesis. In rapidly moving fields such as this, one should expect that recommendations will evolve as data emerge and that there will be a number of opinions about specific issues that are in transition. In the case of perinatal transmission, we are hampered by the fact that only a single clinical trial, which was planned at the beginning of the decade and which used only a single drug that we now know to be a relatively weak antiretroviral drug, has been completed. It is likely, nonetheless, that several members of the Panel might be on the more aggressive end of the spectrum (as it appears the questioner might be).

Dr Thompson: As mentioned above, there are actually scant preliminary data regarding the use of combinations

in pregnancy. There have been no completed studies of combination therapy with enough patients to demonstrate effectiveness. Because of the unique safety issues associated with treatment during pregnancy, it is important to have a substantial safety database from clinical trials before recommending use of a particular combination for all women. Broad guidelines with public health implications must be somewhat more conservative than one might wish, particularly when not even scant safety data exist. The unique feature of the IAS-USA *Guidelines* is that they are dynamic and will be updated regularly to accommodate rapidly emerging new data.

98. The life and well-being of the mother is the single most important factor for the health and well-being of the child. What data do you have to recommend that treating a pregnant mother for her own infection is secondary to that of the child?

Dr Schooley: The Panel does not believe that treating the mother should be secondary to that of the child. Although data have not been unequivocally established that antiretroviral therapy in the mother improves fetal well-being, in other settings the health of the mother and that of the child are closely related.

Dr Thompson: The Panel's recommendation to use zidovudine alone in pregnancy is not based on the premise that the mother's treatment is less important than the child's. Yet we cannot ignore that significant birth defects can occur when drugs are given during pregnancy and it would be irresponsible to recommend the use of drugs for which there are no safety data. Because pregnancy is a time-limited condition, it is expected that more aggressive treatment, for example, with nucleoside/protease inhibitor combinations, may be appropriate for many patients following delivery. There is no evidence to suggest that deferring treatment with protease inhibitors during pregnancy is detrimental to the patient's long-term course. At present, the optimal time for initiating treatment with protease inhibitors is uncertain.

99. What changes in therapy should be made for an HIV-infected woman who is considering becoming pregnant?

Dr Thompson: There are no specific recommendations for women who are contemplating pregnancy, although it should be recognized that there are no data at all to guide us on giving protease inhibitors in any stage of pregnancy, particularly the first trimester. Nevirapine has only been given in the last trimester, and most safety studies involve only the last trimester. A concern that cannot be fully addressed at this time is whether protease inhibitors

should be stopped in women who become pregnant. Although there are no safety data to support continuing therapy, the risk of developing viral resistance must be considered. In the absence of safety data, a conservative approach may be to delay the initiation of protease inhibitors in a woman who is actively trying to conceive. The safety database on these drugs will be expanding rapidly within the next year.

100. For most women who present for prenatal care, the time of their seroconversion is unknown. Should we provide combination therapy with two drugs only if she is zidovudine-naïve, or should we be more aggressive if her CD4+ cell count is less than 350/μL? What is the alternative to zidovudine?

Dr Schooley: Opinions in this area are changing rapidly. Although the zidovudine monotherapy recommendation for previously untreated women is well-founded in the ACTG 076 data, more aggressive regimens are being introduced outside the clinical trials setting. Several nucleoside combinations could be considered, and caution must be exercised regarding these drugs and with drugs that have a significant effect on bilirubin excretion (such as indinavir) in the perinatal period.

Dr Thompson: Many would consider zidovudine/lamivudine during pregnancy in the setting of more advanced disease and in a patient who is zidovudine-experienced. This is the nucleoside combination with the largest body of safety data. A short course of nevirapine prior to delivery may also be considered in light of recent clinical trial data.

101. In mothers with CD4+ counts >500 cells/μL, do you continue antiretroviral therapy postpartum? What are the risks of HIV-resistant strains developing after therapy is stopped?

Dr Thompson: In most cases I would not discontinue antiretroviral therapy in the mother following pregnancy, but would intensify it since zidovudine monotherapy is no longer appropriate long-term therapy. Until we are able to achieve viral eradication, therapy for HIV should be considered a lifelong endeavor. Although we do not currently have data to confirm that treatment at higher CD4+ cell counts confers long-term benefit, my treatment approach is rather aggressive based on the theory that early disease is the optimal time to initiate potent treatments to achieve the most complete viral suppression. There is little doubt that therapy should be continued with more than one drug for a woman who is symptomatic despite a high CD4+ count. Likewise, if viral load either before or following pregnancy was detectable, I would continue and optimize treatment.

The issue is less clear for a woman with a high CD4+ count, an undetectable viral load, and no symptoms. If viral load before and after pregnancy was undetectable some might consider discontinuing. However, if treatment is discontinued, I would monitor viral load 2 to 4 weeks after discontinuation and restart treatment with a more aggressive regimen if HIV RNA is measurable.

Dr Richman: The treatment for adults with >500 CD4+ cells/ μ L depends on the deliberations of patient and physician, as discussed in the *Guidelines*. The plasma HIV RNA level should help in this decision. Resistance should only develop in the presence of the selective pressure of drug therapy, not after discontinuation.

WHEN SHOULD TREATMENT FOR THE NEONATE BEGIN

102. Up to what age should a neonate be treated for 6 weeks with zidovudine? For example, the mother is found to be HIV-infected when the baby is 1 week of age, should you still treat the baby?

Dr Schooley: There are no data that specifically address this point. If it is true, as some suspect, that the major impact of perinatal antiretroviral chemotherapy is to essentially preemptively treat primary infection, a week's delay might greatly decrease the likelihood of prevention of transmission. Nonetheless, in that data are not available, it would be an error to impose a specific cutoff of hours or days past delivery after which one would not treat a child in this setting. At the very least, if infection is not prevented, emerging data in adults that suggest a benefit of treating primary infection, by extension, raise the possibility that the child might benefit even if transmission is not prevented.

Dr Thompson: Treatment of the neonate is important even if it is not begun prenatally or immediately following birth. The child should be treated regardless of whether the mother was treated and regardless of the interval elapsed since birth. However, it is reasonable to suspect that zidovudine alone will be less effective in preventing primary infection the longer treatment is delayed. If treatment cannot be initiated early, more aggressive therapy such as combination zidovudine/lamivudine could be considered.

REGIMENS FOR NEONATES

103. Which protease inhibitor would you recommend for the treatment of HIV-infected

neonates? Would you assess the mutation pattern in mothers before treating the infant?

Dr Thompson: At present, no protease inhibitor can truly be recommended since there are no safety data on any of them. However, there would be safety concerns about using indinavir because of the known hyperbilirubinemia with this compound. Genotypic analysis is not routinely available to most clinicians and the clinical implications of the results are not yet understood. It is premature to routinely use genotypic analysis to guide therapy. However, in a woman who is likely to carry zidovudine-resistant virus, treatment with combination zidovudine/lamivudine or a nevirapine-containing regimen may be considered.

Dr Richman: Until safety and pharmacokinetic studies with protease inhibitors are completed in neonates, the use of these drugs cannot be recommended.

104. Is therapy recommended for all children born to HIV-infected mothers? Instead, should the viral load of neonates be measured, and, if the infant is infected, should the infant be treated? There is no point in offering treatment to a child who is not infected, as there is a 20% to 30% probability of infection in untreated mothers and a 2% to 8% probability of infection in treated mothers.

Dr Thompson: Therapy is recommended for all children born to HIV-infected mothers. Since viral load cannot be assessed instantaneously at birth, it appears safer to treat the child first. There is no evidence from ACTG 076 that treatment in the neonatal period is harmful to the child, and early therapy has the best chance of preventing transmission. It should be noted that neonates were also treated in ACTG 076 and that neonatal treatment may have contributed to the lowering of the transmission rate to 8% seen in that study.

BREAST-FEEDING ISSUES

105. Does the Panel's recommendation that HIV-infected mothers not breast-feed conflict with the World Health Organization's recommendation for women in developing countries?

Dr Thompson: The Panel's recommendation is to avoid breast-feeding "where local conditions permit." This recommendation seeks to recognize the very complicated issues surrounding breast-feeding and the use of bottled nutrition in developing countries. The Panel supports the World Health Organization (WHO) recommendation for

breast-feeding in general, but not in the case of HIV infection if there are other viable options for neonatal nutrition.

106. Can breast milk be treated with drugs to eradicate the virus in the milk itself, thus making it safe for the baby?

Dr Thompson: There are no data regarding treatment of milk to eradicate virus.

107. When both mother and baby are taking zidovudine and breast-feeding continues, should we worry about toxic zidovudine levels in the neonate?

Dr Thompson: As noted, breast-feeding should be avoided, when possible. Although zidovudine can be detected in the breast-milk in women who were taking the drug, the risk for additional toxicity in the neonate appears to be low.

OTHER ISSUES

108. Since zidovudine has been shown to reduce the rate of vertical transmission, is it unethical to include a placebo arm in the UNAIDS clinical trial that will be conducted in Africa?

Dr Richman: Ethical decisions are often relative. The circumstances in the United States and western Europe are such that it would be inappropriate to conduct a placebo controlled study. In many African countries the introduction of chemotherapeutic prophylaxis for maternal-fetal transmission can be supported only if modifications of the relatively complex and expensive ACTG 076 are sufficiently effective. Consequently, the UNAIDS study of zidovudine/lamivudine includes a number of potentially simplified, shorter regimens and a placebo control to assess efficacy and cost-benefit in a different socioeconomic setting. An expert advisory panel consisting primarily of representatives from developing countries concurred that, in this situation, a placebo control was not only acceptable, but necessary.

Dr Thompson: It should be noted that the standard of care in the communities involved in this study is still "no treatment" because of the complexity and expense of the ACTG 076 regimen.

109. Do you recommend abortion for all HIV-positive pregnant women?

Dr Richman: No.

Dr Thompson: No.

110. Since an 8% transmission risk is still very high, the mother is unlikely to be able to raise the child to adulthood, and the long-term risk of antiretroviral exposure is uncertain, even if the baby is not known to be infected, should infected women be strongly encouraged to have an abortion?

Dr Richman: Decisions about abortion are the ultimate responsibility of the mother. In the ideal situation, this decision involves deliberation with the guidance of the health care provider and family members taking into consideration all the important and relevant issues including personal, medical, economic, and religious ones, among others. The risk of infection to the newborn and the existence of a chronic medical condition in the mother, of course, should be included in the complex decision-making process.

Dr Thompson: While abortion is a viable option for many women with HIV, it should not be presumed that it is the preferred option, and the provider's biases should not be visited upon the patient. Abortion should be discussed in the context of information about the risk of transmission, the importance of antiretroviral treatment during pregnancy, the patient's support system, and the patient's overall wishes for children and means to support them.

111. In view of the dramatic decrease possible in vertical transmission to neonates given zidovudine, should prenatal testing of pregnant women be mandatory?

Dr Richman: Ideally, all pregnant women should be tested for medical conditions that could impact the newborn, including the presence of hepatitis B virus (HBV) and HIV infection. The potential negative consequences of mandatory testing probably make organized educational efforts and voluntary consent to prenatal testing a more effective policy.

Dr Thompson: Voluntary testing is extremely well received (98% or better in some studies). Mandatory testing cannot do much better and may result in avoidance of prenatal care and lack of trust in the health care provider at a time when the establishment of trust is critical for the health of the pregnancy.