EFFECTIVE COMBINATION THERAPY INCLUDING PROTEASE INHIBITORS ON MORTALITY AMONG CHILDREN AND ADOLESCENTS INFECTED WITH HIV-1


Purpose of the Study. Combination antiretroviral therapy (highly active antiretroviral therapy [HAART]) has been shown to be effective in the management of adults with human immunodeficiency virus (HIV) disease. However, only limited data regarding the benefits to children and adolescents are available. The objective of this study was to assess the effect of HAART on the mortality of children with HIV infections.

Methods. A cohort of 1028 HIV-infected children and adolescents from birth through 20 years of age were followed in Pediatric AIDS Clinical Trials Group Protocol 219. Subjects were enrolled before 1996 and were followed prospectively through 1999. Proportional-hazards regression models were used to estimate the effect of combination antiretroviral therapy on mortality in this cohort.

Results. In 1996 only 7% of subjects were receiving combination therapy, but by 1999 73% were receiving such therapy which included protease inhibitors. Mortality declined dramatically from 5.3% in 1996 to 2.1% in 1997, 0.9% in 1998, and 0.7% in 1999 (P for trend < .001). Reductions in mortality were noted in all subgroups defined by age, sex, CD4+ lymphocytes at initiation of therapy, educational level of the parent or guardian, and race or ethnic background.

Conclusion. Combination antiretroviral therapy has markedly reduced the mortality among children and adolescents infected with HIV.

Reviewer’s Comments. This carefully conducted prospective study of children treated with “HAART” reveals the dramatic, albeit relatively short-term, improvements in mortality in children and adolescents with HIV. The findings clearly justify the use of such combinations in infected children. However, although combination antiretroviral therapy delays mortality, it is unlikely in its current form to have this effect indefinitely. Many patients have been treated with multiple combinations over years and are now highly resistant to many or most of the drugs available to them. Further, as long-term adverse effects of combination therapy become apparent, the benefits to individual patients will likely be compromised. The need for simpler, safer, and more potent agents is apparent. Further, the harnassing of the host immune response to control HIV replication indefinitely must be achieved if normal life expectancy and quality-of-life are to be expected for our HIV-infected children.

T-Help er Cell Responses to HIV Envelope Peptides in Cord Blood: Protection Against Intrapartum and Breastfeeding Transmission


Purpose of the Study. Perinatal transmission of human immunodeficiency virus (HIV) from mother to infant occurs in approximately 25% of untreated pregnancies. HIV-specific cell-mediated immune responses have been observed in exposed yet uninfected individuals and it has been suggested that such responses may protect, in part, newborns from HIV infection.

Methods. Cord blood from HIV-infected women in South Africa was tested for in vitro reactivity to HIV-specific envelope peptides using a bioassay for IL2 production. Infants were followed with repeat HIV nucleic acid testing for up to 18 months of age to establish the acquisition of HIV infection.

Results. T-cell responses to envelope peptides were detected in 33 out of 86 (38%) of cord blood samples from infants of HIV-positive women and in none of 9 control samples. Of the 33 responders, 3 were shown to be infected on the day of birth, 2 were lost to follow-up, and none of the others were found to be infected with HIV on subsequent visits. In comparison, 6 of 53 unresponsive infants were infected at the time of delivery, and 8 of 47 of the others were found to have acquired HIV peripartum or postpartum through breastfeeding.

Conclusion. The presence of HIV-specific T-cell responses in cord blood is associated with a significant degree of protection against perinatal infection with HIV.

Reviewer’s Comments. HIV transmission appears to occur in 3 time frames: intrauterine, intrapartum, and postpartum. The presence HIV-specific T-cell responses in cord blood appears to be highly associated with protection against perinatal transmission of HIV both intrapartum and through breastfeeding. The mechanisms of this apparent protection are unclear but suggest that host immune responses can be programmed to protect against the development of infection to this currently incurable virus infection.

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LAMIVUDINE-ZIDOVUDINE COMBINATION FOR PREVENTION OF MATERNAL-INFANT TRANSMISSION OF HIV-1


Purpose of the Study. Zidovudine (AZT) has been shown to reduce maternal-infant transmission of human immunodeficiency virus (HIV) by two thirds. Combination antiretroviral therapy may improve this transmission rate. The objectives of this study were to assess the safety of the combination of lamivudine (3TC)-AZT therapy for the prevention of maternal-infant HIV transmission.

Methods. An open label, nonrandomized trial was conducted at 48 clinical sites in France. Four-hundred forty-five HIV-infected pregnant women were enrolled in the study. The study cohort received 3TC in addition to standard AZT prophylaxis. The 3TC was initiated in women at 32 weeks’ gestation and given through delivery at 150 mg twice daily. Children born to these women received 3TC in addition to their AZT twice daily for 6 weeks after birth. Retrospective controls included 889 pregnant women who had received standard AZT monotherapy.

Results. The transmission rate in the study group was 1.6%. In a multi-variable analysis, this transmission rate was fivefold lower than in the control groups. The 3TC resistance mutation was detected 6 weeks after delivery in 52 of 132 women. The most frequent serious adverse events in the children included neutropenia and anemia, requiring blood transfusions in 9 children and premature treatment discontinuation in 19. Two uninfected infants died at 1 year of age from neurologic complications suggestive of mitochondrial dysfunction.
Conclusions. AZT-3TC appears to be effective in reducing maternal-infant HIV transmission. However, serious adverse events and the emergence of resistance to 3TC occurred.

Reviewer’s Comments. The safety and toxicity data presented by this study emphasize the need for close monitoring of women and children treated with combination antiretroviral therapy. Particular attention must be paid to the potential for hematologic and hepatologic toxicity in the infants born to women treated with combination therapy. The occurrence of mitochondrial dysfunction-related neurological complications, although not confirmed in retrospective US studies, emphasize the need for long-term follow up of children treated with perinatal antiretroviral combination therapy. Finally, the use of a 2-drug regimen in any individual must be considered less than optimal therapy. The rapid emergence of 3TC resistance in 40% of the women studied is of great concern. In the United States, the current practice is to treat pregnant women with highly active antiretroviral combinations that minimize her viral levels in the blood. This will substantially reduce the degree of maternal-infant transmission of HIV, but ongoing monitoring for toxicity to the fetus/infant is critical.

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Lamivudine-Zidovudine Combination for Prevention of Maternal-Infant Transmission of HIV-1

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