Efficacy and Safety of an Extended Nevirapine Regimen in Infant Children of Breastfeeding Mothers With HIV-1 Infection for Prevention of Postnatal HIV-1 Transmission (HPTN 046): A Randomized, Double-Blind, Placebo-Controlled Trial


**PURPOSE OF THE STUDY.** Nevirapine prophylaxis until age 6 weeks reduces transmission of HIV-1 via breast milk. This study evaluated the incremental safety and efficacy of infant nevirapine prophylaxis from ages 6 weeks to 6 months.

**STUDY POPULATION.** Breastfeeding infants born to mothers with HIV-1 in South Africa, Tanzania, Uganda, or Zimbabwe were recruited within 7 days of birth.

**METHODS.** In this randomized, double-blind, placebo-controlled trial, all infants received once-daily nevirapine from birth to age 6 weeks. Infants without HIV-1 at 6 weeks were randomly allocated to receive once-daily nevirapine prophylaxis or placebo until age 6 months or breastfeeding cessation, whichever occurred first. Randomization was stratified by recruitment site and maternal antiretroviral treatment status. Kaplan–Meier analyses were used to compare HIV-1 infection at age 6 months and adverse events.

**RESULTS.** Overall, 1527 infants received nevirapine (n = 762) or placebo (n = 765). From 6 weeks to 6 months, HIV-1 developed in 1.1% (95% confidence interval [CI]: 0.35–1.8%) of infants on nevirapine and 2.4% (95% CI: 1.3%–3.6%) of infants on placebo (54% reduction, P = .049). Infants of mothers not on antiretroviral therapy were less likely to develop HIV-1 on nevirapine (1.3%) than placebo (3.4%, P = .027), even among mothers with higher CD4 counts (0.7% vs 2.8%, P = .014). The effects of nevirapine prophylaxis were no longer significant by ages 9 to 12 months, and >95% of infants were no longer breastfed by age 9 months. Mortality at age 6 months (nevirapine, 1.2%; placebo, 1.1%; P = .81) and adverse events did not differ between treatment groups.

**CONCLUSIONS.** Once-daily nevirapine prophylaxis reduces mother-to-child HIV-1 transmission via breast milk up to age 6 months, especially if the mother is not taking antiretroviral therapy.

REVIEWER COMMENTS. Although extended nevirapine prophylaxis reduced mother-to-child HIV-1 transmission in the first 6 months, risk of transmission returned once prophylaxis was stopped and overall infant mortality did not change. Further studies should evaluate the relative safety and efficacy of extending nevirapine prophylaxis beyond age 6 months and the relative benefits of breastfeeding until age 24 months for prevention of infant mortality due to respiratory and diarrheal illnesses versus the continued risk of HIV-1 transmission.

Age and CD4 Count at Initiation of Antiretroviral Therapy in HIV-Infected Children: Effects on Long-Term T-Cell Reconstitution


**PURPOSE OF THE STUDY.** US guidelines for initiating antiretroviral therapy (ART) for children with HIV infection suggest treatment in all patients younger than 12 months of age and for children older than 12 months of age depending upon immunologic (CD4 count) and virologic (plasma viral load) measures. The guidelines, therefore, assume that it is safe to delay therapy in some older children. However, poorer reconstitution of CD4 count has been demonstrated in pediatric patients who start ART at an older age and/or at lower CD4 counts. The purpose of this study is to describe the effects of age and pre-ART CD4 count on CD4 reconstitution with specific reference to the naïve T-cell population.

**STUDY POPULATION.** One hundred thirty perinatally HIV-infected, treatment-naïve, European children 3 months to 16 years of age were prospectively observed for a median of 5.7 years.

**METHODS.** Subjects were randomly assigned to various treatment interventions. CD4 counts (z score modeled) and viral loads were recorded. Changes in naïve (CD4+, CD45RA+) and memory (CD4+, CD45RO+) sub-populations of T-cells were measured in a substudy of 26 patients.

**RESULTS.** One hundred twenty-seven patients started ART. Older patients had lower age-adjusted CD4 counts at the time of ART therapy initiation and long-term. At all ages, lower CD4 counts before therapy were associated with impaired CD4 recovery. Naïve CD4 counts increased comparably with overall CD4 counts. In a prediction model, a higher pretherapy CD4 score corresponded to a higher long-term T-cell score, and younger children had higher scores pretherapy and long-term.

**CONCLUSIONS.** The immune system of HIV-infected children, in contrast to that of adults, appears to be capable of efficient CD4 recovery through naïve T-cell population and expansion. This potential progressively decreases with duration of infection.

REVIEWER COMMENTS. Current guidelines for starting children on ARV have been encumbered by the need to consider
short- and long-term adverse effects of anti-HIV medications, and the difficulty of maintaining adherence to complex regimens containing unpalatable formulations of limited potency. As these obstructions are overcome, it is prudent to reconsider early initiation of ART with lifelong maintenance. Of interest, this reviewer’s experience finds that children started on ART at younger than 1 year of age and adherent to their regimen are among the only patients who normalize their CD4:CD8 ratio. The relevance of this finding is yet to be clarified but suggests more effective immune reconstitution in children treated early in their course.

**Prevalence of Congenital Anomalies in Infants With In Utero Exposure to Antiretrovirals**


**PURPOSE OF THE STUDY.** The use of effective, fully suppressive antiretroviral (ARV) therapy during pregnancy dramatically lowers mother-to-child transmission of HIV. Currently, nucleoside reverse transcriptase inhibitors form the foundation of ARV combination therapy for pregnant women; however, these drugs have potential negative consequences for the developing fetus. This study examined the prevalence of congenital anomalies in infants who were exposed in utero to ARV drugs.

**STUDY POPULATION.** International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) protocol P1025 is a prospective, observational study of infants born to HIV-infected mothers. The current study population included 1112 singleton infants enrolled in P1025 for whom the congenital anomalies case-report form had been completed.

**METHODS.** Affected infants were identified through computerized screening of the case-report form. These cases were then reviewed and classified by a panel of clinicians who were not aware of the mother’s ARV exposure during pregnancy.

**RESULTS.** Eighty congenital anomalies were identified in 1112 infants, resulting in a congenital anomaly rate of 5.49 per 100 births and included: cardiovascular (33), musculoskeletal (15), renal (9), genitourinary (6), craniofacial (4), and central nervous system (2) events. The only specific ARV drug association was with efavirenz, a known teratogen.

**CONCLUSIONS.** ARV use during pregnancy has been associated with increased risks for prematurity and mitochondrial toxicity. A number of studies (reviewed in the current report) have documented that the congenital anomaly prevalence rate in infants born to HIV-infected mothers is significantly higher than for the general US population (~3 per 100 live births). Cardiovascular anomalies were most frequent, and except for efavirenz, no significant association between in utero exposure and congenital anomalies was identified.

**REVIEWER COMMENTS.** As with all medical interventions, the use of ARV therapy for prevention of mother-to-child transmission of HIV is not risk free. The increase in congenital anomalies seen in this and other cohorts of children exposed to ARV drugs in utero is significant. Although the severity and long-term impact of these findings on the overall outcome and quality of life of affected infants were not described, it is unlikely that these would justify alteration in the approach to prevention of perinatal HIV disease.

**Performance of HIV-1 DNA or HIV-1 RNA Tests for Early Diagnosis of Perinatal HIV-1 Infection During Anti-retroviral Prophylaxis**


**PURPOSE OF THE STUDY.** The identification of HIV-derived nucleic acid in the blood of perinatally exposed infants is the most sensitive and specific method for the early detection of HIV infection in this population. HIV DNA is measured in peripheral blood mononuclear cells and HIV RNA in the plasma. This study compares the performance of HIV DNA polymerase chain reaction (PCR) and HIV RNA PCR for the diagnosis of HIV infection in exposed infants.

**STUDY POPULATION.** A total of 1567 children, representing a subgroup born to HIV-infected women, were enrolled in a prospective, multicenter, French perinatal cohort.

**METHODS.** Plasma HIV RNA and peripheral blood mononuclear cell HIV DNA were measured by using standard assays generally obtained at birth and then at 1, 3, and 6 months of age in the absence of breastfeeding.

**RESULTS.** A total of 1502 infants were considered uninfected at 6 months of age, and 65 were considered infected. The following table demonstrates the ability of the 2 assays to identify infection in these 65 patients.

<table>
<thead>
<tr>
<th>Age</th>
<th>Positive DNA PCR, %</th>
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<td>55</td>
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<td>89</td>
<td>91</td>
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<td>3 mo</td>
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Joseph A. Church

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