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Single-Dose Perinatal Nevirapine plus Standard Zidovudine to Prevent Mother-to-Child Transmission of HIV-1 in Thailand

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ABSTRACT

BACKGROUND

Although zidovudine prophylaxis decreases the rate of transmission of the human immunodeficiency virus (HIV) type 1 substantially, a large number of infants still become infected. We hypothesized that the administration, in addition to zidovudine, of a single dose of oral nevirapine to mothers during labor and to neonates would further reduce transmission of HIV.

METHODS

We conducted a randomized, double-blind trial of three treatment regimens in Thai women who were receiving zidovudine therapy during the third trimester of pregnancy. In one group, mothers and infants received a single dose of nevirapine (nevirapine–nevirapine regimen); in another, mothers and infants received nevirapine and placebo, respectively (nevirapine–placebo regimen); and in the last, mothers and infants received placebo (placebo–placebo regimen). The infants also received one week of zidovudine therapy and were formula-fed. The end point of the study was infection with HIV in the infants, established by virologic testing.

RESULTS

Between January 15, 2001, and February 28, 2003, a total of 1844 Thai women were enrolled. At the first interim analysis, the independent data monitoring committee stopped enrollment in the placebo–placebo group. Among women who delivered before the interim analysis, the as-randomized Kaplan–Meier estimates of the transmission rates were 1.1 percent (95 percent confidence interval, 0.3 to 2.2) in the nevirapine–nevirapine group and 6.3 percent (95 percent confidence interval, 3.8 to 8.9) in the placebo–placebo group ($P < 0.001$). The final per-protocol transmission rate in the nevirapine–nevirapine group, 1.9 percent (95 percent confidence interval, 0.9 to 3.0), was not significantly inferior to the rate in the nevirapine–placebo group (2.8 percent; 95 percent confidence interval, 1.5 to 4.1). Nevirapine had an effect within subgroups defined by known risk factors such as viral load and CD4 count. No serious adverse effects were associated with nevirapine therapy.

CONCLUSIONS

A single dose of nevirapine to the mother, with or without a dose of nevirapine to the infant, added to oral zidovudine prophylaxis starting at 28 weeks' gestation, is highly effective in reducing mother-to-child transmission of HIV.

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MOTHER-TO-CHILD TRANSMISSION OF the human immunodeficiency virus (HIV) remains a major health problem worldwide, even though the preventive efficacy of zidovudine was established in 1994.¹⁻³ In Thailand, where 1.3 percent of pregnant women are infected with HIV, since 1993 the Ministry of Public Health has operated programs for voluntary counseling and testing of pregnant women and has provided free infant formula to mothers infected with HIV.⁴ Since 1999, this national program has provided zidovudine therapy during the last trimester of pregnancy, at delivery, and to the newborn. Even with these interventions, however, transmission rates remain at or above 6 percent.^{5,6} When a clinical trial demonstrated the efficacy of a single dose of nevirapine (Viramune, Boehringer Ingelheim) during labor plus a single dose to the newborn,⁷ we hypothesized that, without additional toxicity, logistic complications, or significant cost, perinatal nevirapine therapy added to zidovudine therapy could further reduce mother-to-child transmission of HIV in Thailand.

METHODS

TRIAL DESIGN

We conducted a multicenter, phase 3, double-blind, randomized, placebo-controlled trial. The primary objective was to assess the safety and efficacy of a single dose of nevirapine administered to women at the onset of labor and given to infants between 48 and 72 hours after birth, added to zidovudine prophylaxis, for the prevention of mother-to-child transmission of HIV type 1. A secondary objective was to evaluate the incremental effect of the administration of perinatal nevirapine to newborns.

The ethics committees of the Thai Ministry of Public Health, Chiang Mai University, and the Harvard School of Public Health approved the protocol used in the study, including the amendments. All study sites complied with regulations of the Department of Health and Human Services for the protection of human research subjects.

PATIENTS

Eligible subjects were pregnant women participating in the national program of voluntary counseling and testing who were receiving zidovudine prophylaxis (starting at 28 weeks' gestation or as soon as possible thereafter) at any of 37 study sites in Thailand. The subjects were enrolled between

January 15, 2001, and February 28, 2003. Pre-enrollment evaluations included HIV testing; history taking and physical examination; ultrasonographic uterine imaging; measurement of hemoglobin, white-cell and differential counts; CD4 count; measurements of plasma HIV RNA, alanine aminotransferase, and creatinine; and hepatitis B surface antigen and hepatitis C virus serologic testing.

The subjects were randomly assigned to one of three study groups at enrollment if they had received zidovudine for at least 2 weeks, had provided written informed consent, agreed not to breast-feed, and had the following laboratory values within 21 days before randomization: hemoglobin level greater than 8.0 g per deciliter, absolute neutrophil count greater than 750 cells per cubic millimeter, alanine aminotransferase level less than five times the upper limit of normal (i.e., less than 35 U per liter), and creatinine level less than 1.5 mg per deciliter (132.6 μ mol per liter). Exclusion criteria included a maternal or fetal condition or a concomitant treatment that contraindicated treatment with zidovudine or nevirapine, oligohydramnios, unexplained polyhydramnios or in utero anemia, or a medical condition that required immediate use of highly active antiretroviral therapy. Open-label nevirapine was available to women who did not enroll in the study.

Until delivery, the women in the study had an obstetrical examination every two weeks; every other week, blood was drawn for hematologic, virologic, and biochemical testing. Adherence to zidovudine therapy was assessed at each visit by counting pills. After delivery, the women were seen at 10 days, 6 weeks, and 4 months for a physical examination and for hematologic and virologic monitoring. They were referred to an internist for further follow-up.

Infants were examined at birth, and follow-up visits were scheduled at 10 days (for measurement of hematocrit and alanine aminotransferase levels), 6 weeks (for hematologic tests), and 4, 6, 9, and 12 months. At each visit, a supply of powdered formula was provided to the mother; the child's health history since the previous visit was recorded, including the measurement of weight, recumbent length, and head circumference; and a clinical examination of the infant was performed. To determine the presence or absence of HIV infection, peripheral blood obtained at birth, six weeks, and four and six months was spotted onto filter papers, dried, and stored at -20°C to await shipping to the New England Newborn Screening Program for testing with a polymerase-chain-reaction (PCR) DNA assay for

HIV (Amplicor HIV-1 DNA, version 1.5, Roche Molecular Systems).⁵ Serious adverse events were reported to the ministry of public health and Boehringer Ingelheim.

All the women received 300 mg of zidovudine twice daily starting at 28 weeks' gestation or as soon as possible thereafter; the dosing regimen was changed to 300 mg every three hours from the onset of labor until delivery. Infants received 2 mg of zidovudine per kilogram of body weight in an oral suspension every six hours for one week after birth. In accordance with national guidelines, if the mother had received zidovudine for a period of less than four weeks, the infant was treated for four to six weeks.⁸

Prophylaxis against opportunistic infections was provided as necessary, including the administration of oral trimethoprim-sulfamethoxazole to immunocompromised women⁹ and to infants from six weeks of age until it was established that they were not infected.¹⁰ After delivery, immunocompromised women and HIV-infected, immunocompromised infants were offered antiretroviral treatment that was provided by the Ministry of Public Health.⁸

TREATMENT

Women were randomly assigned to one of three treatment groups. In the nevirapine-nevirapine group, women received one dose of oral nevirapine (200 mg) at the onset of labor and neonates received nevirapine oral suspension (6-mg fixed dose, 0.6 ml) between 48 and 72 hours after birth. In the placebo-placebo group, women received placebo at the onset of labor and neonates received placebo between 48 and 72 hours after birth. In the nevirapine-placebo group, women received one dose of oral nevirapine (200 mg) at the onset of labor and neonates received placebo between 48 and 72 hours after birth.

In instances of prolonged and false labor, additional doses were provided to women every 48 hours until delivery. Infants born less than one hour after the mother had ingested nevirapine or placebo while in labor, according to the random assignment of treatment, were to be given the assigned treatment within six hours after birth.

RANDOMIZATION AND BLINDING

On enrollment, women were provided with the study drug, either nevirapine or matched placebo, to be taken at home at the onset of labor. The study drugs were identified by random numbers with the

use of permuted blocks of six in a ratio of 1:1:1. Twins were assigned to receive the same study drug. Additional doses were accessible in a blinded fashion at any hospital participating in the study with the use of a shared code. The study drugs were provided by Boehringer Ingelheim and were repackaged at the pharmacy of Children's Hospital, Boston, in individual blisters or oral syringes (Exacta-Med dispenser, Baxa).

PRIMARY END POINT

Infants were considered to be infected with HIV if the results of the PCR test were positive in blood obtained on two separate occasions, and infants were considered to be uninfected if the test results were negative on two occasions after one month of age.¹¹ Infants who did not meet this definition were evaluated and classified as infected (six infants) or uninfected (three infants) by a clinician and a virologist before unblinding. In twins, infection in one or both was counted as one transmission.

STATISTICAL ANALYSIS

The study was designed primarily to test the superiority of the nevirapine-nevirapine regimen over the placebo-placebo regimen. We calculated that 484 mother-infant pairs were needed in each treatment group for a 0.05 one-sided type I error with 0.8 power, assuming a transmission rate of 8 percent in the placebo-placebo group and 4 percent in the nevirapine-nevirapine group. The nevirapine-placebo group was added in order to estimate, as a secondary objective, the proportion of overall transmission that was prevented by treating infants with nevirapine. Assuming that 5 percent of the cases could not be evaluated, the initial target sample size was 1530.

Interim safety analyses were planned when 40 percent and 70 percent of the total number of women had been enrolled. An increased rate of transmission associated with any of the three treatment regimens would be considered significant if any nominal P value was less than 0.0004 at the first interim analysis (with the use of O'Brien-Fleming boundaries as modified by Lan and DeMets and the use of one-sided tests with Bonferroni adjustments for multiple comparisons).¹²⁻¹⁴

After the first interim analysis, on May 2, 2002, the independent data and safety monitoring committee recommended stopping enrollment in the placebo-placebo group. The trial design was modified, and the target sample size was increased to

695 per treatment group to ensure 0.8 power to test for noninferiority of the nevirapine–placebo regimen as compared with the nevirapine–nevirapine regimen. Noninferiority would be declared if the upper limit of the 95 percent one-sided confidence interval of the observed difference was lower than 2.5 percent.

Two separate efficacy analyses were performed. The first efficacy analysis included all three treatment groups and all mothers who delivered before the first interim analysis. The second tested the noninferiority of the nevirapine–placebo regimen as compared with the nevirapine–nevirapine regimen. In addition to an as-randomized analysis, a per-protocol analysis was performed, primarily to test for noninferiority, in which the populations compared were defined according to actual intake of the assigned study drug, major deviations from the protocol, and adherence to zidovudine prophylaxis.¹⁵ Infants were analyzed according to the actual intake of the maternal or infant study drug. For the per-protocol analysis, criteria for exclusion were the intake of placebo by the mother and nevirapine by the infant, an infant's receipt of nevirapine more than 72 hours after birth or more than 6 hours after birth if the mother delivered less than 1 hour after receiving nevirapine, undocumented timing of intake by the mother or infant of the study drug, intake by the mother of the study drug more than 96 hours before delivery, less than 50 percent adherence to zidovudine prophylaxis or adherence that was not documented, breast-feeding, and maternal initiation of highly active antiretroviral therapy during pregnancy.

Characteristics of the mother, the delivery, and the infant were compared among the treatment groups with the use of the chi-square and Kruskal–Wallis tests. The Kaplan–Meier method and Greenwood's formula were used to estimate transmission rates and their standard errors. The time to the first positive HIV test was considered the time to the end point. Data on infants with negative HIV test results were censored at the time of their last HIV test. The method developed by Balasubramanian and Lagakos, which does not require a predefined operational definition of HIV infection, was used for confirmation; the results are not presented, because they were not different from the transmission rates estimated with the Kaplan–Meier method and Greenwood's formula.¹⁶

The differential effect of nevirapine was tested by a comparison within subgroups, defined according

to known risk factors for transmission, of the difference in transmission rates between the placebo–placebo group and the nevirapine–nevirapine group (before the first interim analysis) and between the nevirapine–placebo group and the nevirapine–nevirapine group (at the final analysis). In case of rejection of homogeneity of the effect of nevirapine across subgroups with the use of a chi-square test,¹² the differential effect was also examined within each subgroup. Except for noninferiority testing, all reported P values are two-sided, without adjustment for multiple testing. Adverse events in mothers and infants were analyzed from enrollment until six months after the birth of the infant.

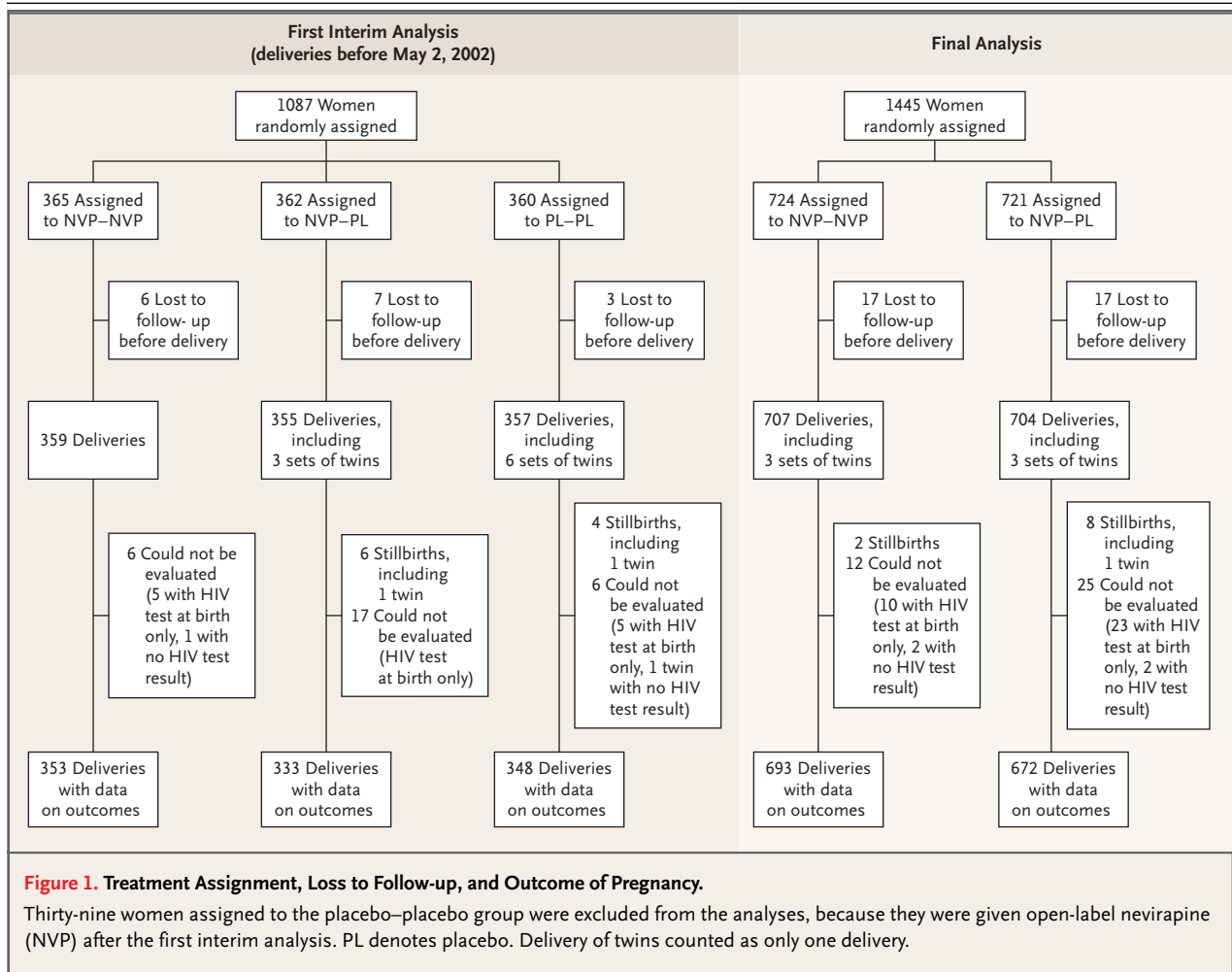
RESULTS

ENROLLMENT

Of 3061 pregnant women who underwent testing for HIV at the study sites and whose results were positive, 1844 were randomly assigned to study treatment and 1807 were followed through to delivery. Of those not enrolled, 316 women declined enrollment, 395 moved to another town or were lost to follow-up, 50 enrolled in a perinatal nevirapine pharmacokinetics substudy, 104 delivered before pre-enrollment evaluations, 129 terminated their pregnancy, 5 had a spontaneous abortion, 3 started highly active antiretroviral therapy, 2 died before inclusion, and 213 did not meet the inclusion criteria, including 184 who delivered after less than two weeks of zidovudine prophylaxis and were offered open-label nevirapine. Thirty-nine women randomly assigned to the placebo–placebo group were excluded from the analysis because they were provided with open-label nevirapine after the first interim analysis. There were 12 twin pregnancies and 14 fetal deaths (including 1 twin). Enrollment, loss to follow-up, pregnancy outcomes, and available end points for each treatment group in the study are summarized in Figure 1. End points were available for 97.6 percent of the 1766 live-born infants included in the analysis.

CHARACTERISTICS OF THE WOMEN, DELIVERIES, AND INFANTS

Baseline characteristics of the women, the deliveries, and the newborns were similar across treatment groups (Table 1). Zidovudine prophylaxis was initiated at a median of 28.7 weeks' gestation. The median duration of zidovudine prophylaxis was 9.7 weeks. The median CD4 count among the women



was 372 cells per cubic millimeter, and the median viral load was $4.0 \log_{10}$ copies per milliliter. Fifty-six women had received antiretroviral therapy during a previous pregnancy.

Thirteen percent of the women delivered at or before 37 weeks' gestation. The median interval between the onset of labor and administration of a dose of the assigned treatment was 2.1 hours, and the median interval between receipt of the dose of the assigned treatment and delivery was 6.5 hours. Seventy women received two doses of the assigned treatment because of false or prolonged labor. Twenty percent of the deliveries were by cesarean section, of which 28 percent were performed before the onset of labor.

Nine percent of the infants weighed less than 2500 g (5.5 lb) at birth. The median interval between birth and administration of the first dose of the assigned treatment was 48.4 hours. Eight percent of

infants received zidovudine for at least one month, because their mothers had received less than four weeks of zidovudine prophylaxis. There was one report of breast-feeding by the mother.

ANALYSIS OF EFFICACY

First Interim Analysis

In women who delivered by May 2, 2002, the as-randomized transmission rate among those in the nevirapine–nevirapine group was 1.1 percent (95 percent confidence interval, 0.3 to 2.2), which was significantly lower than the rate of 6.3 percent (95 percent confidence interval, 3.8 to 8.9) in the placebo–placebo group ($P < 0.001$). This finding confirmed the results of the first interim analysis, at which time the data and safety monitoring board recommended stopping the placebo–placebo regimen. In the nevirapine–placebo group, the rate was 2.1 percent (95 percent confidence interval, 0.6 to

Table 1. Characteristics of Mothers, Deliveries, and Infants in the Study, According to the Treatment Assignment.*

Characteristic	First Interim Analysis			Final Analysis	
	NVP–NVP Group	NVP–PL Group	PL–PL Group	NVP–NVP Group	NVP–PL Group
Mothers					
No. of women randomly assigned	365	362	360	724	721
Age (yr)					
Median	26	26	26	26	26
Interquartile range	22–30	23–30	23–30	23–30	23–30
Length of gestation at entry (wk)					
Median	31	31	31	31	31
Interquartile range	30–33	30–34	30–34	30–33	30–33
Length of gestation at start of zidovudine therapy (wk)					
Median	29	29	29	29	29
Interquartile range	28–31	28–31	28–31	28–30	28–31
Hemoglobin level (g/dl)					
Median	11.1	10.9	11.0	11.0	10.9
Interquartile range	10.3–11.7	10.2–11.6	10.2–11.8	10.2–11.6	10.2–11.6
Viral load at baseline (log ₁₀ copies per ml) †					
Median	4.2	4.0	4.2	4.1	3.9
Interquartile range	3.5–4.7	3.3–4.6	3.4–4.7	3.4–4.7	3.3–4.5
CD4 count					
Median (cells per mm ³)	371	373	372	363	381
Interquartile range	232–522	256–543	241–526	238–510	249–546
≤200 cells per mm ³ (%)	20.0	17.2	19.2	18.2	17.0
Hepatitis B surface antigenemia (%)	6.3	5.0	5.8	5.8	5.3
Hepatitis C antibodies (%)	3.6	5.8	6.1	3.3	4.3
Alanine aminotransferase >200 IU/liter (%)	1.1	0.5	0.5	1.4	1.1
Deliveries					
Total no. of deliveries ‡	359	355	357	707	704
Length of gestation at delivery (wk)					
Median	39	39	39	39	39
Interquartile range	38–40	38–40	38–40	38–40	38–40
Duration of zidovudine therapy (wk)					
Median	9.7	9.4	9.4	9.9	9.9
Interquartile range	7.1–11.1	7.1–11.0	7.1–10.9	7.7–11.1	7.9–11.1
Adherence to zidovudine therapy <90 percent (%)	7.3	5.1	4.0	5.5	4.6
Delivery ≤37 weeks' gestation (%)	12.7	13.0	11.5	12.3	11.9
Time from onset of labor to study-drug intake (hr)					
Median	2.1	2.3	2.3	2.1	2.1
Interquartile range	0.6–4.3	0.8–4.1	0.8–4.1	0.7–4.2	0.6–4.0
Time from study-drug intake to delivery (hr)					
Median	6.4	7.5	6.7	6.1	6.8
Interquartile range	3.1–12.0	3.5–15.0	2.8–11.0	2.7–11.6	3.1–13.0
Cesarean delivery (%)	20.3	22.8	21.3	19.2	22.5
Live-born infants					
Total no. of live-born infants	359	352	359	708	699
Birth weight					
Median (kg)	3.0	3.0	3.0	3.0	3.0
Interquartile range	2.8–3.3	2.7–3.3	2.7–3.3	2.7–3.3	2.7–3.3
<2.5 kg (%)	7.0	9.5	11.0	7.9	9.3
Time from birth to study-drug intake (hr)					
Median	48.5	48.4	48.4	48.4	48.4
Interquartile range	48.0–51.2	48.0–50.4	48.0–51.7	48.0–50.8	48.0–50.4

* The first interim analysis included all deliveries before May 2, 2002. NVP–NVP denotes nevirapine–nevirapine, NVP–PL nevirapine–placebo, and PL–PL placebo–placebo.

† Data on viral load at baseline were available for 356 women in the NVP–NVP group, 353 in the NVP–PL group, and 354 in the PL–PL group at the first interim analysis and for 703 women in the NVP–NVP group and 702 in the NVP–PL group in the final analysis.

‡ Delivery of twins counted as one delivery.

Table 2. Kaplan–Meier Estimates of the Rate of Transmission of HIV at Six Months, According to Assigned and Actual Treatment.*

Variable	First Interim Analysis			Final Analysis	
	NVP–NVP Group	NVP–PL Group	PL–PL Group	NVP–NVP Group	NVP–PL Group
As-randomized analysis					
No. of mother–infant pairs at risk	359	350	354	705	697
No. of deliveries that could be evaluated	353	333	348	693	672
No. of HIV transmissions at birth	1	2	11	7	11
No. of deliveries with missing data at birth	0	0	2	1	1
Rate of HIV positivity at birth (%)†	0.3±0.3	0.6±0.4	3.1±0.9	1.0±0.4	1.6±0.5
No. of transmissions overall	4	7	22	14	19
Overall rate of transmission (%)‡	1.1±0.6	2.1±0.8	6.3±1.3	2.0±0.5	2.8±0.6
Per-protocol analysis					
No. of mother–infant pairs at risk	321	312	316	636	628
No. of deliveries that could be evaluated	318	300	310	627	611
No. of transmissions overall	4	6	20	12	17
Overall rate of transmission (%)§	1.3±0.6	2.0±0.8	6.5±1.4	1.9±0.6	2.8±0.7

* The first interim analysis included all deliveries before May 2, 2002. Positivity at birth denotes a positive test result within three days after birth. NVP–NVP denotes nevirapine–nevirapine, NVP–PL nevirapine–placebo, and PL–PL placebo–placebo. Plus–minus values are means ±SE.

† In the interim as-randomized analysis, the difference in the rate of HIV-positivity at birth between the PL–PL group and the two groups that received nevirapine was 2.7 percentage points (95 percent confidence interval, 0.8 to 4.6; $P < 0.001$).

‡ In the interim as-randomized analysis, the difference in the overall rate of transmission between the NVP–NVP group and the PL–PL group was 5.2 percentage points (95 percent confidence interval, 2.4 to 8.0; $P < 0.001$), and the difference between the NVP–PL group and the PL–PL group was 4.2 percentage points (95 percent confidence interval, 1.2 to 7.2; $P = 0.006$). In the final as-randomized analysis, the difference between the NVP–PL group and the NVP–NVP group was 0.8 percentage point (95 percent confidence interval, –0.9 to 2.4). The upper limit of the one-sided 95 percent confidence interval for rejection of inferiority was 2.2 ($P = 0.021$).

§ In the first interim per-protocol analysis, the difference between the NVP–NVP group and the PL–PL group was 5.2 percentage points (95 percent confidence interval, 2.2 to 8.2; $P = 0.007$), and the difference between the NVP–PL group and the PL–PL group was 4.5 percentage points (95 percent confidence interval, 1.3 to 7.6; $P = 0.006$). In the final per-protocol analysis, the difference between the NVP–PL group and the NVP–NVP group was 0.9 percentage point (95 percent confidence interval, –0.8 to 2.6). The upper limit of the one-sided 95 percent confidence interval for rejection of inferiority was 2.3 ($P = 0.029$).

3.7). Per-protocol transmission rates were very similar (Table 2).

Final Analysis

The final per-protocol transmission rate among those in the nevirapine–nevirapine group (1.9 percent; 95 percent confidence interval, 0.9 to 3.0) was not statistically inferior to the rate in the nevirapine–placebo group (2.8 percent; 95 percent confidence interval, 1.5 to 4.1). The upper limit of the one-sided confidence interval of the difference between these observed rates was 2.2, which was below the predefined 2.5 percent inferiority threshold. The rates in the as-randomized analysis were similar — 2.0 percent (95 percent confidence interval, 1.0 to 3.1) in the nevirapine–nevirapine group and 2.8 percent (95 percent confidence interval, 1.6 to 4.1) in the nevirapine–placebo group.

Other Analyses of Transmission

Among infants, the rate of testing positive for HIV within three days after birth in the placebo–placebo group (3.1 percent) was significantly higher than the rate among mothers in the study groups assigned to receive nevirapine before the interim analysis (0.4 percent) ($P < 0.001$) (Table 2). In the final analysis, the overall rate of testing positive within three days after birth was 1.3 percent (95 percent confidence interval, 0.7 to 1.9). An analysis of the rate of death or HIV infection in infants before six months of age did not modify the conclusions of the efficacy analysis (Table 3).

EFFECT OF NEVIRAPINE ACCORDING TO KNOWN RISK FACTORS FOR TRANSMISSION

Nevirapine had an effect according to the known risk factors for transmission, including viral load

Table 3. Estimates of the Rate of Transmission of HIV or Death at Six Months, According to Treatment Assignment.*

Variable	Interim Analysis			Final Analysis	
	NVP–NVP Group	NVP–PL Group	PL–PL Group	NVP–NVP Group	NVP–PL Group
No. of infants at risk	359	350	354	705	697
No. of transmissions overall	4	7	22	14	19
Infants who died by 6 months (no.)					
HIV-positive	0	0	2	1	2
HIV-negative	0	0	1	0	0
Indeterminate HIV status with severe congenital malformations	0	2	0	0	6
Other indeterminate HIV status	1	1	2	1	2
Total no. of deaths at six months†	1	3	5	2	10
No. of transmissions or deaths overall	5	10	25	15	27
Rate (%)‡	1.4±0.6	3.0±0.9	7.2±1.4	2.2±0.6	4.0±0.8
No. of transmissions or deaths excluding infants with congenital malformations and HIV-negative infants	5	8	24	15	21
Rate (%)‡	1.4±0.6	2.5±0.8	6.9±1.4	2.2±0.6	3.1±0.7

* The interim analysis included all deliveries before May 2, 2002. NVP–NVP denotes nevirapine–nevirapine, NVP–PL nevirapine–placebo, and PL–PL placebo–placebo. Plus–minus values are means ±SE.

† Nineteen deaths have been recorded, including two of children born to mothers for whom blinding was discontinued after the interim analysis. The causes of death were as follows: in the NVP–NVP group, meconium aspiration and diarrhea with dehydration; in the NVP–PL group, esophageal atresia, Down's syndrome with cardiac malformation, multiple malformations (microcephaly, cleft palate, and patent ductus arteriosus), congenital heart malformation, birth asphyxia with suspected congenital anomaly (in two infants), severe prematurity, diarrhea with dehydration (in three infants); in the PL–PL group, pneumonia, twin–twin transfusion syndrome, meningitis, diarrhea with dehydration (in two infants). In the cases of the two children whose mothers were randomly assigned to the PL–PL group, blinding was discontinued; one infant who was HIV-positive died of pneumonia, and the other of neonatal bacterial infection.

‡ Rates of transmission or death were calculated as follows: rate of death + (1 – rate of death) × rate of transmission among surviving infants. The rate of death and the rate of transmission were estimated separately by Kaplan–Meier methods.

and CD4 count at baseline, gestational age at the initiation of zidovudine treatment, gestational duration, and the duration of zidovudine prophylaxis, although the effect often varied across subgroups (Table 4).^{2,5,17–21} In addition, the nevirapine–nevirapine regimen was somewhat superior to the nevirapine–placebo regimen in most subgroups.

MATERNAL SAFETY

No severe rashes were observed. At 10 days, mild rashes were reported in 3.8 percent of mothers. Alanine aminotransferase levels were 36 to 42 IU per liter in 8.5 percent of mothers and 43 to 69 IU per liter in 0.9 percent (none of the mothers had levels above 70 IU per liter); there was no significant difference among the treatment groups. Rates of serious adverse events were similar across the groups (216 reports) and were related to pregnancy (59 percent), infection or HIV (26 percent), possibly zidovudine prophylaxis (anemia in 7 percent), possi-

bly nevirapine (e.g., allergic reaction during therapy in one woman), and other conditions (7 percent).

INFANT SAFETY

In infants, the rates of rash were 15.9 percent and 7.5 percent at 10 and 45 days of life, respectively, with no significant difference among treatment groups. Likewise, increases in alanine aminotransferase levels (36 to 69 IU per liter in 4.8 percent of infants and 260 IU per liter in one infant; none had levels above 350 IU per liter) and the presence of hyperbilirubinemia were not associated with exposure to nevirapine. The rates of serious adverse events were similar across treatment groups (598 reports) and were related to neonatal or obstetrical conditions (11 percent), to congenital abnormalities (6 percent), to any infection, including HIV (72 percent), possibly to zidovudine (anemia in 2 percent), and to other causes (9 percent). Prolonged neonatal icterus (1 percent) was classified as possi-

Table 4. Effect of Nevirapine among Infants with Known Risk Factors for Transmission of HIV.*

Risk Factor	First Interim Analysis (As-Randomized)				Final Analysis (Per-Protocol)				
	NVP–NVP Group	PL–PL Group	Difference between PL–PL and NVP–NVP Groups		NVP–NVP Group	NVP–PL Group	Difference between NVP–PL and NVP–NVP Groups		
	no. HIV-positive/ no. at risk	no. HIV-positive/ no. at risk	percentage points	P value†	P value‡	no. HIV-positive/ no. at risk	percentage points	P value†	P value§
Viral load (copies/ml)				0.020				0.874	0.033
<25,000	0/207	4/199	2.0±1.1		0.028	1/387	7/434	1.4±0.7	
≥25,000	4/143	18/146	9.5±3.1		<0.001	11/238	10/177	1.0±2.2	
Gestational age at start of zidovudine therapy (wk)				0.059					0.032
<30	3/225	10/227	3.1±1.6		0.025	9/446	6/412	–0.6±0.9	<0.001
≥30	1/128	12/121	9.2±2.8		<0.001	3/181	11/199	3.9±1.9	0.770
CD4 count (cells/mm ³)				0.013					0.289
≤200	1/71	11/67	15.1±4.8		<0.001	4/119	7/99	3.7±3.1	
>200	3/282	11/281	2.9±1.3		0.015	8/508	10/511	0.4±0.8	
Duration of gestation (wk)				0.165	<0.001				0.679
≤37	0/50	5/43	11.6 (5.1)			2/85	1/68	–0.9±2.2	
>37	4/303	17/305	4.3 (1.5)			10/542	16/543	1.1±0.9	
Duration of zidovudine treatment (wk)				0.025					0.693
≤8.5	1/130	13/135	8.9 (2.7)		<0.001	4/191	8/194	2.0±1.8	
8.6–10.5	0/97	6/100	6.0 (2.5)		0.008	2/190	3/190	0.5±1.2	
>10.5	3/126	3/111	0.3 (2.0)		0.448	6/246	6/227	0.2±1.5	

* The interim analysis included all deliveries before May 2, 2002. NVP–NVP denotes nevirapine–nevirapine, NVP–PL nevirapine–placebo, and PL–PL placebo–placebo. Plus–minus values are ±SE.

† The P value corresponds to the test of homogeneity of the effect of nevirapine across risk-factor categories. P<0.05 indicates that the effect of nevirapine varies significantly among risk-factor subgroups, that a common estimate of the difference in the rate of transmission in all subgroups should not be used, and that the effect of nevirapine should be tested within each subgroup. P≥0.05 indicates that the effect of nevirapine does not vary significantly among risk-factor subgroups and that a common estimate should be used to test the effect of nevirapine globally.

‡ The P value corresponds to the two-sided test for difference between the PL–PL and NVP–NVP groups, either per stratum (P<0.05 for the test of homogeneity) or globally through a common estimate of the difference (P≥0.05 for the test of homogeneity).

§ The P value corresponds to the one-sided test of the noninferiority of NVP–PL relative to NVP–NVP, either per subgroup (if P<0.05 for the test of homogeneity), or globally through a common estimate of the difference (P≥0.05 for the test of homogeneity).

bly related to nevirapine even in the placebo–placebo group, since classification was performed by persons blinded to treatment assignment. Nineteen infants died within six months after birth (Table 3).

DISCUSSION

This study demonstrates the high efficacy of adding a single dose of nevirapine in the mother, with or without a dose in the infant, to oral zidovudine prophylaxis for the reduction of perinatal transmission of HIV. The observed reduction by 80 percent that led to the early interruption of enrollment in the placebo–placebo group was much higher than we had hypothesized when we designed the study. The transmission rate observed in the placebo–placebo group was consistent with rates observed in

other studies in which zidovudine prophylaxis was initiated at the beginning of the last trimester of pregnancy,^{1,19–21} in particular in our previous trial, which was performed in a similar population.⁵

Although the efficacy of a single maternal dose of nevirapine was declared statistically noninferior to that of a maternal dose plus an infant dose with the use of our predetermined criteria (2.5 percent as the upper limit of the one-sided 95 percent confidence interval for the difference between the observed rates of transmission), in fact, two doses appeared consistently better than one throughout our analysis (Table 4). Moreover, because the nevirapine–placebo group had a somewhat lower median viral load at baseline than the nevirapine–nevirapine group, the difference in transmission rates might be an underestimate. On the basis of these findings

and for additional logistic reasons, the ministry of public health in Thailand has recommended administration of nevirapine to both mother and infant, with a slight modification, that of giving nevirapine to the mother on arrival at the hospital and to the infant as soon as possible after birth.²²

The percentage of infants with a positive HIV test within three days after birth was significantly lower in the nevirapine–nevirapine and the nevirapine–placebo groups than in the placebo–placebo group. This surprising finding suggests either that infants become HIV-positive earlier after infection than previously suspected or that perinatal nevirapine may delay the detection of HIV positivity or even abort infection completely when transmission occurs in the last few weeks of pregnancy.

Newborns in this study were formula-fed. This recommendation, made by the Ministry of Public Health in 1993, is strongly adhered to and has been shown to have no negative effect either on the health of the infant or on the promotion of breast-feeding among HIV-negative women.^{5,23,24}

In the South African Intrapartum Nevirapine Trial, the rate of intrapartum transmission of HIV was three times as high when the mother had received nevirapine less than two hours before delivery as when the mother had received it earlier.²⁵ Our study did not confirm this finding. However, since the administration of nevirapine to infants appears to be safe whatever the delay between birth and receipt of the drug^{7,25} and given that in clinical practice women may take their nevirapine dose later during labor and stay in the hospital for a shorter period, it may be preferable to administer the dose of nevirapine to the infant shortly after birth, with the first dose of zidovudine.

In the Pediatric AIDS Clinical Trials Group study known as PACTG 316, which evaluated the efficacy of perinatal nevirapine therapy added to standard antiretroviral therapy, no benefit of nevirapine was shown.²⁶ The effect of nevirapine was not observed even in the subgroup of women who received only zidovudine in addition to nevirapine. This subgroup, however, may have been selected to receive zidovudine monotherapy because of the subjects' low viral load. In addition, 43 percent of the women in the group delivered by planned cesarean section. We also found that in the subgroup of women whose viral load at entry was less than 25,000, the transmission rate was very low in the placebo–placebo group (2 percent) and only marginally lower in the nevirapine groups. Although a subgroup analysis

has the potential for bias, the effect of perinatal nevirapine was observed in most of the subgroups, a finding that suggests that there is no population for whom nevirapine prophylaxis would not be beneficial.

The discovery of drug-resistance mutations in a substantial proportion of the recipients of perinatal nevirapine²⁷⁻³⁴ has raised questions of a possible risk to mothers who subsequently receive nonnucleoside reverse-transcriptase inhibitors as therapy for their own disease. The resistance consequences among the participants of our study are described by Jourdain et al. elsewhere in this issue of the *Journal*.³⁵ The maternal risk is juxtaposed with the clear benefit to the babies. The relative value of this or other interventions in any particular setting will depend on considerations of cost, medical logistics, and drug access, as well as on data from future studies of outcomes in women receiving both perinatal prophylaxis and antiretroviral therapy.³⁶ Nevirapine at delivery added to third-trimester zidovudine results in very low transmission rates with minimal medical and financial burdens — rates that are very similar to those achieved with more complex, expensive, and potentially toxic multidrug maternal regimens.³⁷⁻⁴³

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