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A TRIAL OF SHORTENED ZIDOVUDINE REGIMENS TO PREVENT MOTHER-TO-CHILD TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1

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ABSTRACT

Background The optimal duration of zidovudine administration to prevent perinatal transmission of human immunodeficiency virus type 1 (HIV-1) should be determined to facilitate its use in areas where resources are limited.

Methods We conducted a randomized, double-blind equivalence trial of four regimens of zidovudine starting in the mother at 28 weeks' gestation, with 6 weeks of treatment in the infant (the long–long regimen), which is similar to protocol 076; zidovudine starting at 35 weeks' gestation, with 3 days of treatment in the infant (the short–short regimen); a long–short regimen; and a short–long regimen. The mothers received zidovudine orally during labor. The infants were fed formula and were tested for HIV DNA at 1, 45, 120, and 180 days. After the first interim analysis, the short–short regimen was stopped.

Results A total of 1437 women were enrolled. At the first interim analysis, the rates of HIV transmission were 4.1 percent for the long–long regimen and 10.5 percent for the short–short regimen (P=0.004); at this point the short–short regimen was stopped. For the entire study period, the transmission rates were 6.5 percent (95 percent confidence interval, 4.1 to 8.9 percent) for the long–long regimen, 4.7 percent (95 percent confidence interval, 2.4 to 7.0 percent) for the long–short regimen, and 8.6 percent (95 percent confidence interval, 5.6 to 11.6 percent) for the short–long regimen. The rate of in utero transmission was significantly higher with the two regimens with shorter maternal treatment (5.1 percent) than with the two with longer maternal treatment (1.6 percent).

Conclusions The short–short zidovudine regimen is inferior to the long–long regimen and leads to a higher rate of perinatal HIV transmission. The long–short, short–long, and long–long regimens had equivalent efficacy. However, the higher rate of in utero transmission with the short–long regimen suggests that longer treatment of the infant cannot substitute for longer treatment of the mother. (N Engl J Med 2000;343: 982-91.)

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A STUDY conducted by the Pediatric AIDS Clinical Trials Group (PACTG) has shown that zidovudine is effective in preventing transmission of the human immunodeficiency virus (HIV) from mother to child.[1] In this trial (protocol 076), women were given oral zidovudine between 14 and 34 weeks' gestation (median duration of treatment, 11 weeks). They also received zidovudine intravenously during labor. The newborns received zidovudine for six weeks and were fed formula. The rate of HIV transmission was reduced from 22.6 percent to 7.6 percent.[2] Subsequent studies have confirmed the efficacy of perinatal prophylaxis with zidovudine.[3,4]

To determine whether the efficacy of a shortened regimen would be equivalent to that of protocol 076, we conducted a randomized, double-blind trial comparing four zidovudine regimens of varying duration in mothers and infants. The results of the first interim analysis led to the discontinuation of the shortest regimen and modification of the study design.[5] We report the results of an intention-to-treat analysis for the period before the modification of the study design and for the overall study.

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METHODS

Trial Design

The purpose of our trial was to compare the efficacy and safety of a zidovudine regimen that resembled protocol 076 (maternal treatment starting at 28 weeks' gestation and 6 weeks of postnatal treatment in the infant) with the efficacy and safety of a shortened regimen in mothers and infants (maternal treatment starting at 35 weeks' gestation and 3 days of postnatal treatment in the infant). To determine which of the two modifications of the PACTG 076 protocol — a shorter regimen in the mother or a shorter regimen in the infant — was more important, should equivalence between protocol 076 and the shortened regimens be rejected, we added two intermediate regimens according to a two-by-two factorial design: a regimen shortened only for the mother and a regimen shortened only for the infant.

Women were randomly assigned to one of four groups. The long–long group received zidovudine from 28 weeks' gestation through delivery, with zidovudine administered in the infant from birth through week 6. The short–short group received placebo starting at 28 weeks' gestation and then received zidovudine from 35 weeks' gestation through delivery, with the infant receiving zidovudine for the first 3 days of life, followed by placebo through week 6. The long–short group received zidovudine from 28 weeks' gestation through delivery, with the infant receiving zidovudine for the first 3 days of life, followed by placebo through week 6. The short–long group received placebo starting at 28 weeks' gestation, followed by zidovudine from 35 weeks' gestation through delivery, with the infant receiving zidovudine from birth through week 6. In all groups, the women received oral zidovudine every three hours during labor.

After the first interim analysis, the short–short regimen was discontinued, and the study was redesigned to test for equivalence between the efficacy of the long–long regimen and the efficacy of the other two regimens. The randomization scheme was modified to ensure adequate statistical power.

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

Patients

Women presenting at any of 27 Thai study sites before 26 weeks' gestation received counseling about HIV infection, and those who provided consent underwent HIV testing. Pre-enrollment studies included confirmation of the results of the HIV test, history taking and physical examination, ultrasonographic imaging, measurement of hemoglobin, white-cell and differential counts, a CD4 count, and measurements of serum alanine aminotransferase and creatinine.

Women were enrolled at 28 weeks' gestation if they provided written informed consent and agreed not to breast-feed and if the following criteria were met within 21 days before randomization: hemoglobin level, higher than 8.0 g per deciliter; absolute neutrophil count, more than 750 per cubic millimeter; serum alanine aminotransferase level, less than five times the upper limit of normal; and creatinine level, less than 1.5 mg per deciliter (132.6 μmol per liter). The exclusion criteria were a maternal or fetal condition or concomitant treatment contraindicating treatment with zidovudine, oligohydramnios, unexplained hydramnios, and in utero anemia. Women with a CD4 count of less than 200 per cubic millimeter were offered trimethoprim–sulfamethoxazole prophylaxis. Women who did not meet the inclusion criteria were offered open-label zidovudine.[6]

Treatment and Evaluation

During pregnancy, the women received one 300-mg tablet of zidovudine twice daily. One 300-mg zidovudine tablet was taken at the onset of labor and every three hours thereafter until delivery. If oral medication was not tolerated, zidovudine was administered intravenously.[1] The women were monitored at 32, 35, 38, and 40 weeks' gestation, every week thereafter until delivery, and 6 weeks and 18 months after delivery.

The infants received 2 mg of zidovudine per kilogram of body weight orally every six hours. If an infant could not tolerate oral fluids, zidovudine was administered intravenously.[1] Twins were assigned the same study regimen. Evaluation of the infants at birth included physical examination and measurement of hemoglobin, neutrophil count, serum creatinine, alanine aminotransferase, and serum bilirubin. Treatment was started as soon as the infant could tolerate fluids, except when zidovudine was contraindicated or the infant had a clinical condition that was expected to be fatal. Trimethoprim–sulfamethoxazole was given to the infants from the age of six weeks until their HIV status could be confirmed.

The infants were evaluated 2, 4, and 6 weeks after birth; at 4 and 6 months; and then every 3 months until they were 18 months old. Peripheral blood obtained at birth, 6 weeks, and 4 and 6 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 (Prototype Amplicor HIV-1 DNA, version 1.5, Roche Molecular Systems, Alameda, Calif.).[7] HIV-infected, symptomatic infants were given antiretroviral therapy supplied by the Thai Ministry of Public Health.

Compliance with treatment was assessed by counting pills and weighing oral-suspension bottles. Serious adverse events were reported to the Thai Ministry of Public Health and to Glaxo Wellcome.[8]

Randomization and Blinding

The study drugs, packaged by Glaxo Wellcome, were identified by random numbers with the use of permuted blocks of six in a ratio of 2:1:1:2 for the long–long, short–long, long–short, and short–short groups, respectively. After the first interim analysis, new supplies were provided in blocks of five, with a new randomization scheme in a ratio of 1:2:2 for the long–long, long–short, and short–long groups, respectively.

Primary End Point

Infants were considered to be infected with HIV if the results of the PCR test were positive for blood samples 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. Infants were considered to have been infected in utero if the first positive test result was obtained within seven days after birth.[9] Twins were considered a single entity for the purpose of the primary end point; discordant twins were counted as one infected infant.

Statistical Analysis

Because the reference treatment in this study was a regimen of established efficacy, we tested for equivalent efficacy of the experimental treatments, choosing a threshold for equivalence that would balance public health concerns with clinical benefits. Using a cost-effectiveness approach, we determined that an absolute increase of 6 percent in the rate of transmission of HIV infection would be the limit beyond which the clinical risk associated with the experimental treatment would not be balanced by its economic and logistical advantages.

With this criterion for equivalence, we calculated that a sample of 1398 mother–infant pairs would be required to provide more than 90 percent statistical power with a 5 percent one-sided type I error and an 11 percent overall transmission rate. Equivalence would be established if the upper limit of the one-sided 95 percent confidence interval for the arithmetic difference in the percentage rates of HIV transmission was less than 6.[10,11]

Interim safety analyses were planned when 40 and 70 percent of the total number of women had been enrolled. An increased rate of HIV transmission associated with the shorter regimens, as

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compared with the long–long regimen, would be considered significant if any of the nominal P values for the differences were less than 0.007 in the first interim analysis and less than 0.012 in the second (with the use of one-sided tests with Bonferroni's adjustment for multiple comparisons).[12]

Two separate analyses were conducted: a comparison of the short–short and long–long groups, including all mother–infant pairs enrolled before December 4, 1998 (without unblinding), and the final analysis of the equivalence of the long–long regimen with the long–short and short–long regimens, with stratification according to the study period (before or after the randomization scheme was modified). Some of the 87 women enrolled in the short–short group on or after December 4, 1998, had not delivered when the results of the first interim analysis became available, in March 1999. The treatment assignments for these women were unblinded to ensure that their infants received the long regimen. To avoid any bias, none of these 87 women were included in the efficacy analyses. The date by which all infants had completed drug treatment, May 31, 2000, was chosen as the cutoff date for the analysis of adverse events. Characteristics of the mother, the infant, and the delivery were compared among the treatment groups with the use of the chi-square and Kruskal–Wallis tests, with the data stratified according to the enrollment period when appropriate. Because clinical trials of short zidovudine regimens have generally started treatment at 36 weeks' gestation,[13] subgroup analyses were performed for women who delivered before 36 weeks' gestation and for those who delivered at or after 36 weeks' gestation.

The Kaplan–Meier method and Greenwood's formula were used to estimate transmission rates and their standard errors. The comparison of efficacy between treatment groups was based on the 95 percent one-sided confidence interval for the difference in the percentage of infected infants at six months. P values were determined from Z statistics, which were calculated from the differences between Kaplan–Meier estimates at six months and their standard errors. Because of the change in the randomization scheme, we used stratification and weighting to avoid any bias due to temporal trends. A common set of weights was calculated on the basis of the fraction of subjects in each randomization period. For each treatment group, estimates of HIV transmission rates according to the randomization period were averaged with use of these weights to obtain an overall estimate. The time to the first positive HIV test was considered the time to the end point. Data from infants with unconfirmed negative tests were censored at the time of the last confirmed negative test.

All analyses were performed according to the intention-to-treat principle. Except for the results of the efficacy analysis, all reported P values are two-sided, without adjustment for multiple testing.

RESULTS

From June 24, 1997, to December 3, 1999, 1437 women were randomly assigned to a treatment group (1114 assigned to the long–long, long–short, or short–long group; 236 assigned to the short–short group before December 4, 1998; and 87 assigned to the short–short group on or after December 4, 1998, and excluded from the analyses of efficacy). Data on treatment assignments, loss to follow-up, and the outcomes of pregnancy are summarized in Figure 1. A total of 1411 women (98.2 percent) were followed through delivery. Data on end points were available for 99.5 percent of the 1409 live-born infants.

Characteristics of the Women and Infants

The base-line characteristics of the women included in the efficacy analysis were similar among the treatment groups (Table 1). Eleven percent of the women were under 20 years of age, and 17 percent were over 30; 58.1 percent were primiparous. The median length of gestation at enrollment was 27.9 weeks; the length of gestation was more than 29 weeks in 4.5 percent of the women. The body-mass index (the weight in kilograms divided by the square of the height in meters) was less than 20 in 6.0 percent of the women. At enrollment, 90.3 percent of the women had no symptoms of HIV infection or AIDS. None of the women had received antiretroviral drugs.

The groups did not differ significantly with regard to treatment characteristics (Table 1). A total of 97.7 percent of the women attended all scheduled antenatal visits, and 93.0 percent took more than 80 percent of the prescribed dose of the study drug. The median duration of labor was 8.2 hours. The median time from the onset of labor to the first dose of zidovudine taken during labor was 0.5 hour. Three percent of the women received an intravenous loading dose of zidovudine during labor.

The characteristics of delivery were similar among the groups (Table 1). The median length of gestation was 39.1 weeks; 4.9 percent of the women delivered before 36 weeks' gestation. The median interval between rupture of the membranes and delivery was 0.7 hour. Fifty-six percent of cesarean sections were performed on an emergency basis, and 44 percent were elective; 3 percent were performed before the onset of labor. Prevention of perinatal HIV infection was not reported as an indication for cesarean section.

The characteristics of the infants were also similar among the treatment groups (Table 1). The median gestational age at birth (Ballard fetal-maturation score) was 40 weeks; 4.3 percent of the infants had a score of less than 37 weeks. The time from birth to the administration of the first dose of zidovudine in the infant was similar in all the groups (median, 1.4 hours); 0.8 percent of the newborns received intravenous zidovudine. There was one report of breast-feeding by the mother.

Women enrolled later in the study had lower CD4 counts than those enrolled earlier (P=0.003, data not shown). None of the other characteristics of the mothers, infants, or deliveries differed significantly according to the time of enrollment.

Analysis of Efficacy

The rates of HIV transmission among the women assigned to the long–long group and those assigned to the short–short group before December 4, 1998, confirmed the results of the interim analysis: 4.1 percent in the long–long group (95 percent confidence interval, 1.4 to 6.7 percent) and 10.5 percent in the short–short group (95 percent confidence interval, 6.4 to 14.4 percent; P=0.004). Among the women who delivered before 36 weeks' gestation, the transmission rates were 13.3 percent (95 percent confi-

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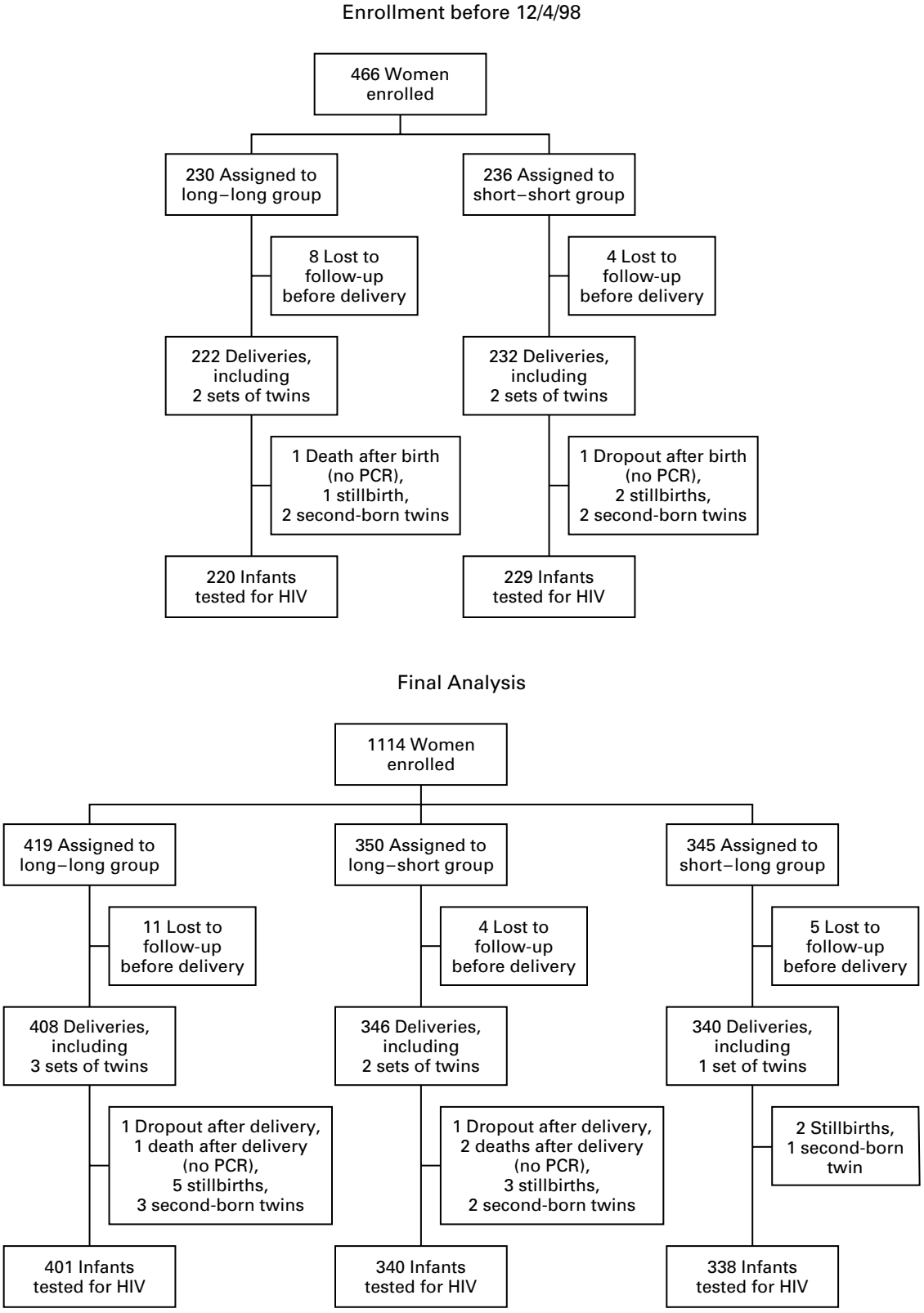

Figure 1. Treatment Assignment, Loss to Follow-up, and Outcome of Pregnancy.

Eighty-seven women assigned to the short–short group on or after December 4, 1998, were not included in any of the analyses of efficacy.

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TABLE 1. CHARACTERISTICS OF MOTHERS AND INFANTS IN THE STUDY, ACCORDING TO THE TREATMENT REGIMEN.*

CHARACTERISTIC	ENROLLMENT BEFORE 12/4/98		FINAL ANALYSIS		
	LONG–LONG (N=221)	SHORT–SHORT (N=230)	LONG–LONG (N=403)	LONG–SHORT (N=343)	SHORT–LONG (N=338)
Mothers					
Median age (yr)	24.5	24.9	24.7	24.9	24.8
Median body-mass index†	23.6	23.1	23.6	23.6	23.6
Median hemoglobin (g/dl)	10.7	10.5	10.7	10.8	10.8
Median neutrophil count (per mm³)	6032	5840	6068	6079	5982
CD4 count					
Median (per mm³)	380	360	370	350	360
≤200/mm³ (%)	14	20	17	20	19
Syphilis (%)	3.7	1.8	3.8	3.0	1.8
Other sexually transmitted diseases (%)	4.7	8.6	4.0	6.0	3.6
Median duration of study regimen (wk)	11.3	11.1	11.1	11.1	11.3
Median duration of zidovudine treatment (wk)	11.3	4.1	11.1	11.1	4.4
Delivery					
Median length of gestation (wk)‡	39.0	39.0	39.1	39.1	39.3
Delivery before 36 wk of gestation (%)‡	6.9	5.8	5.5	5.0	2.7
Median duration of labor (hr)	8.2	8.4	8.3	7.9	8.3
Mode of delivery (%)					
Vaginal	83	83	82	81	83
Cesarean	17	17	18	19	17
Interval since rupture of membranes, >4 hr (%)	22.0	19.9	20.9	25.7	22.3
Median maternal hemoglobin (g/dl)	11.4	11.4	11.3	11.3	11.6
Infants					
Birth weight					
Median (g)	2910	2915	2920	2940	3000
<2500 g (%)	12.2	10.0	12.4	11.1	7.4
Median hemoglobin (g/dl)					
At birth	14.2	14.9	14.3	14.4	15.1
At 6 wk	9.2	9.6	9.2	9.7	9.4

*The total number shown for each group is the number of mother–infant pairs. Only women with live-born infants were included in the analyses. All the patients enrolled in the long–long group before December 4, 1998, were included in the final analysis.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡Data on gestational age are based on the obstetrician's estimate at base line.

dence interval, 0 to 28.9 percent) and 43.8 percent (95 percent confidence interval, 0 to 68.4 percent) in the long–long and short–short groups, respectively. Among the women who delivered at or after 36 weeks' gestation, the respective rates were 3.4 percent (95 percent confidence interval, 0.9 to 5.9 percent) and 9.1 percent (95 percent confidence interval, 5.2 to 12.9 percent).

Table 2 shows the estimated transmission rates for the three treatment groups, with and without stratification according to the period of randomization. In the unstratified analysis, the Kaplan–Meier estimates were 6.5 percent (95 percent confidence interval, 4.1 to 8.9 percent), 4.7 percent (95 percent confidence interval, 2.4 to 7.0 percent), and 8.6 percent (95 percent confidence interval, 5.6 to 11.6 percent) in the long–long, long–short, and short–long groups, respectively. In the stratified analysis, the rates were the same or similar: 7.8 percent (95 percent confidence interval, 4.6 to 10.9 percent), 4.8 percent (95 percent confidence interval, 2.5 to 7.2 percent), and 8.6 percent (95 percent confidence interval, 5.5 to 11.7 percent). According to our definition of equivalence, the efficacy of the short–long regimen and that of the long–short regimen were statistically equivalent to the efficacy of the long–long regimen.

An unstratified analysis showed that at six months, the rates of HIV transmission or death were 7.6 percent (95 percent confidence interval, 4.9 to 10.2 percent), 5.6 percent (95 percent confidence interval, 3.1 to 8.0 percent), and 8.9 percent (95 percent confidence interval, 5.8 to 11.9 percent) in the long–long, long–short, and short–long groups, respectively (Table 2). In the analysis stratified according to the randomization period, the respective rates were 9.1 percent (95 percent confidence interval, 5.6 to 12.6 percent), 5.8 percent (95 percent confidence interval,

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TABLE 2. KAPLAN–MEIER ESTIMATES OF THE RATE OF HIV TRANSMISSION AND OF THE RATE OF TRANSMISSION OR DEATH AT SIX MONTHS.*

ANALYSIS	ENROLLMENT BEFORE 12/4/98				FINAL ANALYSIS						
	LONG–LONG	SHORT–SHORT	DIFFERENCE FROM LONG–LONG	P VALUE†	LONG–LONG	LONG–SHORT	DIFFERENCE FROM LONG–LONG	P VALUE†	SHORT–LONG	DIFFERENCE FROM LONG–LONG	P VALUE†
HIV transmission											
No. of infants who could be evaluated	220	229			401	340			338		
No. of transmissions	9	24			26	16			29		
Rate, without stratification (%)	4.1 (1.4 to 6.7)	10.5 (6.4 to 14.4)	6.4 (−100.0 to 10.4)	0.004	6.5 (4.1 to 8.9)	4.7 (2.4 to 7.0)	−1.8 (−100.0 to 1.0)	0.86	8.6 (5.6 to 11.6)	2.1 (−100.0 to 5.3)	0.15
Rate, with stratification and weighting (%)‡	—	—			7.8 (4.6 to 10.9)	4.8 (2.5 to 7.2)	−3.0 (−100.0 to 0.3)	0.93	8.6 (5.5 to 11.7)	0.8 (−100.0 to 4.5)	0.36
HIV transmission or death											
No. of infants at risk	221	230			403	343			338		
No. of transmissions or deaths	10	25			30	19			31		
Rate, without stratification (%)	4.5 (1.8 to 7.3)	10.9 (6.8 to 14.8)			7.6 (4.9 to 10.2)	5.6 (3.1 to 8.0)			8.9 (5.8 to 11.9)		
Rate, with stratification and weighting (%)‡	—	—			9.1 (5.6 to 12.6)	5.8 (3.2 to 8.4)			9.2 (6.0 to 12.4)		

*Numbers in parentheses are 95 percent confidence intervals. Differences in rates are arithmetic differences in the point estimates between the shortened regimens and the long–long regimen. All the patients enrolled in the long–long group before December 4, 1998, were included in the final analysis. The efficacy of a shortened regimen was considered to be equivalent to that of the long–long regimen if the upper limit of the 95 percent confidence interval for the arithmetic difference in the percentage rates of transmission was less than 6.

†P values were calculated by one-sided testing for the difference in rates between the shortened regimen and the long–long regimen.

‡The data were stratified according to the time of enrollment (before or after the randomization scheme was changed). Before the randomization scheme was changed, 312, 156, and 151 women were enrolled in the long–long, long–short, and short–long groups, respectively, and the respective transmission rates were 5.2 percent (95 percent confidence interval, 2.7 to 7.6 percent), 5.2 percent (95 percent confidence interval, 1.6 to 8.6 percent), and 8.6 percent (95 percent confidence interval, 4.0 to 13.0 percent). After the change in the randomization scheme, 89, 184, and 187 women were enrolled in the long–long, long–short, and short–long groups, respectively, and the respective transmission rates were 11.3 percent (95 percent confidence interval, 4.4 to 17.6 percent), 4.4 percent (95 percent confidence interval, 1.4 to 7.3 percent), and 8.6 percent (95 percent confidence interval, 4.5 to 12.5 percent). For the final analysis, the weights used were the fraction of the total number of women in each enrollment period (0.574 before the change in the randomization scheme and 0.426 after the change).

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3.2 to 8.4 percent), and 9.2 percent (95 percent confidence interval, 6.0 to 12.4 percent).

In a stratified analysis of pooled data for the two groups in which the women received the long regimen of zidovudine (the long–long and long–short groups) and for the two groups in which the women received the short regimen (the short–short and short–long groups), the respective rates of transmission in utero were 1.6 percent (95 percent confidence interval, 0.7 to 2.6 percent) for the long maternal regimen and 5.1 percent (95 percent confidence interval, 3.2 to 7.0 percent) for the short maternal regimen ($P<0.001$). The rates were identical in the unstratified analysis.

Safety

None of the women discontinued the study treatment because of intolerance or toxicity. Differences in the hemoglobin level between the women who received the long zidovudine regimen and those who received the short regimen were as expected (Table 1). The rate of serious adverse events was similar in the two groups of women (Table 3). All cases of severe anemia and neutropenia resolved spontaneously after completion of the treatment regimen.

As expected, the hemoglobin level at birth was significantly lower in the infants of mothers who received the long regimen of zidovudine than in the infants of mothers who received the short regimen, and the postnatal fall in the hemoglobin level was slightly greater in the infants treated for six weeks than in those treated for three days. The rate of serious adverse events was similar in all four groups of infants. The Kaplan–Meier estimate of the mortality rate at 12 months for all four groups combined was 16.2 deaths per 1000 infants. When HIV-infected infants were excluded, the rate was 8.0 deaths per 1000.

DISCUSSION

The reference treatment in this study (the long–long regimen) was a simplified version of PACTG protocol 076 (300 mg of zidovudine twice a day instead of 100 mg five times a day, with oral rather than intravenous administration during labor). Our regimen provided an average of 11 weeks of maternal treatment before delivery plus 6 weeks of treatment in the infant after birth — a duration of treatment that was virtually identical to that in the PACTG trial. The regimen we used is simpler and less costly ($174) than the 076 regimen ($800).[13] The rate of HIV transmission from mother to child in the long–long group in our study (6.5 percent) is similar to that in the PACTG study of protocol 076 and in all subsequent studies of this regimen, confirming the appropriateness of using protocol 076 as the reference regimen.[14]

All the regimens were well tolerated in our study, and compliance was excellent. This was true even for the initial doses of zidovudine administered during labor, which the women took at home. The study was performed at 27 hospitals, including many rural and several large provincial hospitals, all of which were able to comply with all the study procedures.[6] Formula feeding did not appear to affect the safety of the infants. The mortality rate was low among the infants (16.2 deaths per 1000 overall, and 8.0 per 1000 after the exclusion of HIV-infected infants).

The analysis of women enrolled before December 4, 1998, confirmed that the short–short regimen was less efficacious than the long–long regimen (transmission rate, 10.5 percent vs. 4.1 percent). The short–short regimen in our study was similar to the regimen used in a study in Bangkok, Thailand, with treatment started at 36 weeks' gestation, although in that study, the infants received no treatment.[13] The rate of transmission in the Bangkok study was 9.6 percent, but only women who delivered after 36 weeks were included. In our study, the rate of transmission was 9.1 percent for the women who delivered at or after 36 weeks, whereas it was 43.8 percent for those who delivered earlier. If a policy of treating women with the short zidovudine regimen were adopted, the actual transmission rate would probably be higher than 9.1 percent, since women delivering before 36 weeks' gestation would not receive the drug.

After discontinuing the short–short regimen, we modified the study design to determine whether the efficacy of the long–short regimen and the efficacy of the short–long regimen were equivalent to that of the long–long regimen. The primary analysis showed that the transmission rates in the long–short and short–long groups were statistically equivalent to the rate in the long–long group. A closer examination of the data provided further important insights. The primary analysis and all secondary analyses confirmed that the efficacy of the long–short regimen was equivalent to that of the long–long regimen. Thus, if women receive zidovudine starting at 28 weeks' gestation, treatment of infants for more than 3 days after birth appears to be unnecessary.

The rate of transmission in the short–long group was almost midway between the rate in the short–short group and the rates in the long–long and long–short groups. Indeed, unlike the strict equivalence of rates in the long–short and long–long groups, the equivalence of rates in the short–long and long–long groups was marginal; the upper limit of the 95 percent confidence interval for the difference between the rates in the two groups was 5.3 percent (close to the boundary of 6.0 percent). This finding suggests an interaction between treatments in the mothers and the infants. A long regimen in the infant, which appears unnecessary when the mother starts zidovudine treatment early in pregnancy, may be beneficial if the mother starts to take zidovudine late in pregnancy. This finding is consistent with observational data in-

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TABLE 3. SERIOUS ADVERSE EVENTS.*

EVENT	LONG MATERNAL REGIMEN (N=769)	SHORT MATERNAL REGIMEN (N=668)	TOTAL (N=1437)
	no. of women (%)		
Women			
Death†	3	8	11
Stillbirth	8	4	12
Severe anemia	7	4	11
Neutropenia	0	1	1
Infection or other HIV-related event	20	17	37
Event related to pregnancy or delivery	24	17	41
Other	6	13	19
≥1 Event	48 (6)	45 (7)	93 (6)

	LONG–LONG (N=403)	LONG–SHORT (N=343)	SHORT–LONG (N=338)	SHORT–SHORT (N=315)	TOTAL (N=1399)
	no. of infants (%)				
Infants					
Death‡	5	7	5	4	21
Severe anemia (requiring hospitalization and transfusion)	4	0	1	4	9
Congenital abnormalities§	7	7	6	1	21
Neutropenia or leukopenia¶	7	3	5	2	17
Infection or other HIV-related event	43	43	40	33	159
Neonatal or obstetrical event	22	12	9	14	57
Other	6	4	5	5	20
≥1 Event	71 (18)	63 (18)	55 (16)	52 (17)	241 (17)

*Serious adverse events, defined according to the Good Clinical Practice guidelines,[8] were reported immediately to the Thai Ministry of Public Health and the Department of International Product Safety and Pharmacovigilance at Glaxo Wellcome. Events were reported during pregnancy and for the first six months post partum for the mothers and during the first six months of life for the infants. In the case of twins, only the first twin was included in the analysis.

†All 11 maternal deaths occurred after delivery. Five women died from pneumonia, two from sepsis, one from cryptococcal meningitis, and one from an AIDS-defining event; two deaths were suicides.

‡Seven infants died from recurrent infections, four from severe prematurity, three from neonatal events, two from AIDS, one from anemia and pneumonia at 10 weeks, one from tuberculosis, one from congenital diaphragmatic hernia and patent ductus arteriosus, one from an accidental injury, and one from neonatal asphyxia due to a cleft palate.

§There were 24 congenital abnormalities in 21 infants; 5 infants had a ventricular septal defect, 4 had polydactyly, 3 had a cleft lip or cleft palate or both, 3 had congenital heart disease, 2 had Down's syndrome, 2 had monorchidism, 1 had a diaphragmatic hernia, 1 had omphalocele, 1 had hydrocephalus, 1 had microcephaly, and 1 had a microcornea.

¶All episodes of neutropenia and leukopenia resolved spontaneously without complications.

dicating that six weeks of treatment in the infant was beneficial when the mother received little or no treatment.[4] Since the short–short regimen was terminated early, our study did not have sufficient power to test the difference in efficacy between the long and short regimens in the infants of women who received the short regimen.

The transmission rate in the short–short group was between the rate in the long–long group and the rates in placebo groups in earlier trials. It also was similar to the rates reported with other shortened regimens of zidovudine, with or without lamivudine, in women in Thailand and Africa.[15]

The benefit of giving pregnant women longer treatment was unequivocally established by our finding that the rate of in utero transmission was lower in the combined groups in which the women received the long regimen (1.6 percent) than in the combined groups in which the women received the short regimen (5.1 percent). The extent of suppression of in utero transmission depends on the duration of antiretroviral treatment during the later part of pregnancy. We suggest that to improve prevention programs that currently use a short course of zidovudine, the best option would be to implement the long–short regimen. The seven additional weeks of maternal treatment will prevent an important fraction of in utero transmissions and at a minimal extra cost, given that most women will have already received counseling and undergone HIV testing. If maternal treatment

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can be started only at or after 35 weeks of gestation, treatment of the infant for 6 weeks should be considered.

In industrialized countries, planned cesarean section and combination therapies available to women have reduced the overall rate of HIV transmission to less than 2 percent.[15] Widespread implementation of these approaches is not yet feasible in countries with limited resources. Since transmission during delivery accounts for most cases of HIV infection among the infants of women treated prenatally with a long regimen of zidovudine, similarly low transmission rates may be achieved at low cost by administering a potent antiretroviral drug, such as a single dose of nevirapine, at the onset of labor.[16]

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APPENDIX

The following centers and investigators participated in the trial (the number of women enrolled at each hospital is given in parentheses): Rayong (161): S.L. Weerawatgoompa, V. Karnchanamayul, C. Tantiyaworawongse, S. Ariyadej; Chiang Rai Provincial (140): R. Hansudewechakul, J. Achalapong, R. Srismith, P. Wattanaporn (deceased); Prapokklao (117): S. Phongpanich, P. Yuthavisuthi, C. Ngampiyasakul, S. Sooksengchai; Phayao Provincial (100): S. Bhakeecheep, J. Hemvuttiphan, L. Thambhitak, V. Lattiwongsakorn; Banglamung (87): J. Ithisukanan, S. Siritathandon, K. Boonrod, S. Piyaman; Chonburi (72): P. Pinchan, N. Chotivanich, S. Hongsiriwan, P. Kittikoon; Bhumibhol Adulyadej (66): S. Prommat, S. Nimkarn, S. Charnivises, V. Suraseranivong, P. Layangool, B. Gulakirt; Chiang Kham (57): C. Putiyanun, S. Limsuwan, S. Charkrit; Mae Sai (55): H. Sirichai, P. Jindaapilukkul, S. Kunkongkapan; Hat Yai (47): S. Lamlertkittikul, B. Warachit, K. Veerapradist; Chachoengsao (43): A. Kanjanasing, R. Keawsonthi, C. Jirawison; Klaeng (42): S. Hotrawarikarn, S. Techapalokul, A. Palasudhi; Bamrasnaradura (42): P. Tunthanathip, S. Sirikawin, A. Chaovavanich; Mae Chan (41): S. Tantanarat, S. Piyaworawong; Phan (40): P. Lersruangpanya, S. Jeungphichanwanit, T. Jhangjit; Health Promotion Center Region I (38): I. Tangtitawong, S. Sirinontakan, V. Japikanond, B. Ngamsiriudom; Somdej Prapinklao (38): S. Suphanich, S. Maitrisathit, N. Tawornpanit, N. Kalawantavanich; Nopparat Rajathanee (35): T. Chanpoo, S. Ruangsirinusorn, N. Thamanavat, P. Hotrarapavanond; Phranangklao (33): S. Mokkamakkul, S. Wanwaisart, S. Hongyok; Banchang (32): S. Tragarngool, S. Chutimanukul, G. Kunawudhi; Somdej Pranangchao Sirikit (31): W. Pornkijprasarn, T. Hinjiranandana, S.N. Nakorn; Nakornping (30): V. Gomutbutra, P. Leelanitkul, K. Kunsuikmengrai, S. Kanjanavanit, S. Kahintapongs; Lamphun (28): K. Pagdi, W. Matanasaravoot, R. Somsamai, W. Chavengchaiyong; Buddhachinaraj (24): P. Thanomrat, W. Wannapira, W. Artong, C. Chaipat; Chiang Khong Royal Crown Prince (15): C. Taiyaitiang, S. Parinya; Phayamengrai (12): P. Tantiwattanakul, T. Onchomjum (deceased); McCormick (11): C. Tangchaitrong, S. Suwansarakul, C. Phimphilai.

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