Administration of Zidovudine During Late Pregnancy and Delivery to Prevent Perinatal HIV Transmission — Thailand, 1996–1998

Worldwide, approximately 500,000 infants are perinatally infected with human immunodeficiency virus (HIV) each year, most of whom are born in developing countries (*1*). In 1994, a clinical trial in the United States and France demonstrated that zidovudine (ZDV) administered orally five times a day to HIV-infected pregnant women starting at 14–34 weeks' gestation, intravenously during labor, and orally to their newborns for 6 weeks reduced the risk for perinatal HIV transmission by two thirds (*2*). In 1994, this regimen was recommended as standard care in the United States (*3*); however, because of its complexity and cost, this regimen has not been implemented in most developing countries, and no other intervention had been efficacious in reducing perinatal HIV transmission. In 1996, the Ministry of Public Health of Thailand and Mahidol University, in collaboration with CDC, initiated a randomized, placebo-controlled trial of a simpler and less expensive regimen of ZDV to prevent perinatal HIV transmission. This report describes preliminary trial results, which indicate that a short-term antenatal regimen of ZDV reduced the risk for perinatal HIV transmission by approximately half.

HIV-infected pregnant women gave written informed consent for participation and were randomly selected at each of two study hospitals in Bangkok to receive either ZDV or a placebo. The ZDV regimen consisted of 300 mg orally twice a day from 36 weeks' gestation until onset of labor and 300 mg every 3 hours from onset of labor until delivery. All women were provided infant formula and counseled not to breastfeed, consistent with national guidelines for HIV-infected women in Thailand. The planned sample size was 392 women, selected to provide 80% power to detect a 50% lower transmission rate in the ZDV group compared with a transmission rate of 24% in the placebo group. The study endpoint was the HIV-infection status of the infant at age 6 months, determined by results of polymerase chain reaction (PCR) testing for HIV DNA performed on blood specimens obtained at birth, 2 months, and 6 months.

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The proportion of children found to be infected by age 6 months in each treatment group was estimated by using the Kaplan-Meier method. The null hypothesis of no treatment effect was tested by using a normally distributed Z statistic computed from these estimates. As a result of two interim evaluations of treatment efficacy for data and safety monitoring in July 1997 and January 1998, the critical value of the Z statistic for rejecting the null hypothesis of no treatment effect at the end of the study was 2.05. The trial protocol was approved by human subjects committees in Thailand and at CDC, and the conduct of the trials was monitored by a data and safety monitoring board at the U.S. National Institutes of Health, which included a senior health official from Thailand.

From May 23, 1996, through December 31, 1997, a total of 397 women were enrolled; four women were lost to follow-up before delivery, and 393 women delivered 395 live-born infants (Table 1). At enrollment, the median age was 24 years, and the median CD4+ cell count was 424 cells/μL. Fourteen percent of women had cesarean deliveries. The median duration of antenatal treatment was 25 days, and the median number of doses during labor was three. Of these enrollees, 99% took at least 90% of the prescribed doses of ZDV during the antepartum period, and 99% took at least one dose during labor; 96% of study visits were kept. Baseline and delivery characteristics, protocol adherence, and adverse event rates were similar in the two trial groups. No women breastfed their infants.

As of February 13, 1998, PCR data were available for 391 children (Table 1). Of these, 52 children have tested PCR positive (17 in the ZDV group and 35 in the placebo group), all by their 2-month visit. Of the remaining 339 children, 310 tested PCR negative at age ≥2 months, and 29 children tested PCR negative at birth but have not yet been evaluated further. The estimated HIV transmission risk for the ZDV and placebo groups were 9.2% (95% confidence interval [CI]=5.0%–13.5%) and 18.6% (95% CI=13.0%–24.0%), respectively, representing a 51% (95% CI=15%–71%) decrease in

TABLE 1. Study outcome of perinatal zidovudine (ZDV) trial, by treatment group — Bangkok, Thailand, 1998

Category	Treatment group	
	ZDV (n=198)	Placebo (n=199)
Median CD4+ count (cells/μL) at enrollment	428	410
No. women lost to follow-up before delivery	3	1
No. women who delivered infants	195	198
No. live-born children*	196	199
No. children with at least one polymerase chain reaction (PCR) result†	193	198
No. children with positive PCR	17	35
Risk for perinatal transmission *(95% confidence interval)*§	9.2% *(5.0%–13.5%)*	18.6% *(13.0%–24.0%)*
No. children died	3	4

*Includes one set of twins in each treatment group.
†Excludes one child from each set of twins. In addition, one child died without a PCR result, and one child's first result is pending.
§Estimated using the Kaplan-Meier method.

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transmission risk. On the basis of these data, the Z statistic for testing for a difference between the groups was 2.67 (p=0.008). Assuming that all infected children will be detected by their 2-month visit and that the transmission risk among the children whose infection status is pending is as high as 24%, the probability is >98% that the null hypothesis of no treatment effect will be rejected when all results are available.

Reported by: P Vuthipongse, MD, Ministry of Public Health; C Bhadrakom, MD, P Chaisilwattana, MD, A Roongpisuthipong, MD, A Chalermchokcharoenkit, MD, Dept of OB/GYN; S Chearskul, MD, N Wanprapa, MD, K Chokephaibulkit, MD, M Tuchinda, MD, Dept of Pediatrics; C Wasi, MD, R Chuachoowong, MD, Dept of Microbiology, Siriraj Hospital, Mahidol Univ; W Siriwasin, MD, P Chinayon, MD, S Asavapiriyanont, MD, Dept of OB/GYN, Rajavithi Hospital; T Chotpitayasunondh, MD, N Waranawat, MD, V Sangtaweesin, MD, S Horpaopan, MD, Queen Sirikit National Institute for Child Health, Bangkok; The HIV/AIDS Collaboration, Nonthaburi, Thailand. Div of HIV/AIDS Prevention–Surveillance and Epidemiology, National Center for HIV, STD and TB Prevention, CDC.

Editorial Note: This report is the first to describe the efficacy of a short-term regimen of an antiretroviral drug for preventing perinatal HIV transmission. The regimen studied in this trial is more feasible for implementation in Thailand and other developing countries than the regimen now used in the United States (*3*) because it is less expensive (i.e., $50 versus $800) and logistically simpler (i.e., later start in pregnancy, shorter duration, less frequent dosing, oral labor dosing, and no infant treatment). If implemented, thousands of perinatal HIV infections annually could be prevented in Thailand, where an estimated 20,000 HIV-infected women deliver infants each year.

Although this trial was not designed to compare the short-term ZDV regimen to the longer regimen (*2*), the decrease in transmission rate (51%) using the shorter regimen is less than the 66% decrease with the longer regimen. The smaller treatment effect could result from the shorter duration of treatment, oral rather than intravenous administration during labor, lack of treatment for the infant, different study populations, random variation, or a combination of these factors. However, this clinical trial demonstrates that a shorter regimen of ZDV given only during pregnancy can substantially reduce perinatal transmission.

Reasons are unknown for the lower transmission rate in the placebo group (18.6%) than in untreated women (24.2%) studied in the same hospitals during 1993–1994 (*4*). The lower than expected background transmission rate highlights the importance of having included a randomized, concurrently enrolled, untreated control group. Had the test regimen been inactive, a transmission rate of 18.6% may have suggested some efficacy when compared with historical data.

CDC has sponsored another placebo-controlled trial of the same regimen of ZDV in collaboration with the Ministry of Public Health in Côte d'Ivoire in west Africa, where most HIV-infected women breastfeed their infants. Because the trial in Thailand demonstrated that the short-term regimen is efficacious in reducing transmission around the time of birth, and because preliminary data from the trial in Côte d'Ivoire have shown the regimen to be safe in this population, enrollment in the placebo group of the Côte d'Ivoire trial has been stopped. All women enrolled in the study are being offered the short-term ZDV regimen. Because breastfeeding is associated with postnatal HIV transmission from mothers to infants (*5*), follow-up of enrolled infants will continue to determine whether the short-term ZDV regimen results in an overall lower risk for mother-infant HIV transmission in populations where HIV-infected women routinely breastfeed.

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To implement these findings, ministries of health, donor agencies, and other international agencies should develop policies and practices to strengthen access to prenatal care, testing and counseling for HIV infection, and provision of ZDV for HIV-infected pregnant women. Operational research is needed to optimize provision of this intervention to HIV-infected women in resource-poor settings. Further evaluation is needed of the effect of breastfeeding on the efficacy of this regimen.

References

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