Safety of Late In Utero Exposure to Zidovudine in Infants Born to Human Immunodeficiency Virus-Infected Mothers: Bangkok

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ABSTRACT. *Background.* **Short-course zidovudine (ZDV) given in the late antenatal period can reduce mother–infant human immunodeficiency virus (HIV) transmission by one half. Because this intervention is being implemented in developing countries, evidence of its safety is needed.**

Methods. **In a randomized, double-blinded, placebo-controlled trial in Bangkok, HIV-infected pregnant women received either ZDV (300 mg twice daily from 36 weeks' gestation until labor, then every 3 hours until delivery) or an identical placebo regimen. Infants were evaluated at birth and at 1, 2, 4, 6, 9, 12, 15, and 18 months of age. Growth, clinical events, and hematologic and immunologic measurements were compared between treatment groups.**

Results. **Of the 395 children born (196 in ZDV group and 199 in placebo group), 330 were uninfected, 55 were infected, and 10 had indeterminate infection status. Overall, 319 children (81%) completed 18 months of follow-up, and 14 (4%) died before 18 months of age. Among uninfected children, the mean hematocrit was lower in the ZDV group at birth (49.1% vs 51.5%) but not at later ages; mean weight, height, head circumference, and $CD4^+$ and $CD8^+$ T lymphocyte counts were similar in both groups at all ages. Five uninfected children in the ZDV group but only one in the placebo group had a febrile convulsion. No other signs suggestive of mitochondrial dysfunction and no tumors were observed. Among infected children, an estimated 62% in the ZDV group and 77% in the placebo group survived free of Centers for Disease Control and Prevention class C disease during the 18-month follow-up.**

Conclusions. **No significant adverse events were associated with short-course ZDV during 18 months of follow-up in this population.** *Pediatrics* **2001;107(1). URL: http://www.pediatrics.org/cgi/content/full/107/1/e5; *zidovudine, vertical HIV transmission, children, disease progression, Thailand.***

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ABBREVIATIONS. ZDV, zidovudine; HIV, human immunodeficiency virus; ACTG, AIDS Clinical Trials Group; PCR, polymerase chain reaction.

The use of zidovudine (ZDV) from 36 weeks' gestation until delivery has been found to reduce the risk for mother–infant human immunodeficiency virus (HIV) transmission by 50% when used with infant formula to replace breastfeeding.[1] This intervention, or modifications of it, is now being implemented throughout Thailand and in other developing countries.[2,3]

The US/French AIDS Clinical Trials Group (ACTG) 076 trial previously studied a longer regimen of ZDV: ~3 months during pregnancy, intravenous treatment during labor, and 6 weeks of treatment for infants. The only short-term adverse event in children attributed to ZDV in this study was mild anemia that resolved rapidly without intervention.[4,5] Moreover, after an additional 4 years of follow-up of 122 ZDV-exposed children in this trial, no additional adverse events clearly associated with ZDV treatment were identified.[6] Nonetheless, concerns have been raised that prenatal ZDV exposure may cause cancer, mitochondrial toxicity, or other problems.[7,8] In addition, in utero exposure to ZDV has been postulated to increase the risk for rapid disease progression among infected infants.[9,10]

Because of the rapid, wide-scale implementation of short-course ZDV in Thailand and elsewhere, there is an urgent need to evaluate its safety. We report the 18-month follow-up of children enrolled in the Bangkok trial, comparing growth, immunologic status, morbidity, and mortality of children born to HIV-infected women who received short-course ZDV with that of children born to women who did not.

METHODS

Population

We conducted a randomized, double-blinded, placebo-controlled trial in 2 large Bangkok hospitals to determine the safety and efficacy of a short course of late antenatal ZDV to prevent mother–infant HIV transmission. Women were enrolled at 36 weeks' gestation and randomly assigned to receive either ZDV (300 mg twice daily from 36 weeks' gestation until labor onset, then every 3 hours until delivery) or an identical placebo regimen. No study drug was given to infants, and infants were not breastfed. The details of the trial procedures and efficacy results are published.[1] Both children of twin births were included in this analysis.

Data Collection

Children were scheduled for study visits at birth and at 1, 2, 4, 6, 9, 12, 15, and 18 months of age. At each visit, the child's weight, height, head circumference, physical examination findings, illness history, hospitalization and outpatient visit history, and medication use were recorded along with a summary of the child's diagnoses. Venous blood specimens were taken at birth (≤72 hours of life) and at 2, 6, 12, and 18 months of age for complete blood count, lymphocyte immunophenotyping, and viral load measurement, according to published methods.[1]

Each child's infection status was evaluated using HIV DNA polymerase chain reaction (PCR) testing performed at birth and at 2 months and 6 months of life. Children were considered uninfected if their last test at 2 months of age or older was negative, infected if any test was positive, or of indeterminate infection status if neither of these conditions was met. HIV antibody results from all 317 children tested at 18 months of age concurred with the infection status determined by PCR. HIV-1 subtype was determined by peptide enzyme immunoassay serotyping of maternal plasma using synthetic peptides derived from the consensus sequence of the crown of the V3 loop of gp120.[11] Nearly all infants received trimethoprim-sulfamethoxazole for prophylaxis against *Pneumocystis carinii* pneumonia.[12] In general, antiretroviral treatment was started for children with signs of HIV infection.

Analysis

Most analyses compared findings between treatment groups, after stratifying by infection status. We used the χ^2 or Fisher's exact test to compare categorical variables, and we used Student's t test to compare continuous variables. We used the Centers for Disease Control and Prevention classification to categorize children's HIV disease and immunosuppression status.[13] We estimated survival and disease-free survival using the Kaplan-Meier method, compared survival curves using the log-rank test, and adjusted survival estimates using Cox proportional hazards regression.

Weight for age, height for age, and weight for height z scores were calculated using *Epi Info, Version 6*.[14] We compared the mean z score and proportion with z score <-2.0 (lower 2.3% of reference population) at each time point for each treatment group. The average growth rate on each z score was summarized for each infant by a slope estimated from a linear regression, and the mean slopes for the treatment groups were compared.

Children were prospectively monitored for signs of drug-related toxicities, which were graded according to the ACTG adverse events monitoring guide.[15] To further evaluate the possibility of mitochondrial toxicity related to in utero ZDV exposure,[8] we retrospectively reviewed all recorded physical examination findings, clinical diagnoses, hospitalizations, and causes of death among uninfected children. This review was restricted to uninfected children to avoid inclusion of confounding HIV-related conditions. After excluding infectious conditions, rashes, trauma, surgical conditions (eg, hernia), and several miscellaneous diagnoses probably not related to mitochondrial dysfunction (eg, colic and gastroesophageal reflux), we compared the frequency of the remaining diagnoses between the treatment groups. For statistical comparisons, we limited diagnoses to those reported in >5 children (convulsions, developmental delay, hyperbilirubinemia, poor weight gain, hepatomegaly, or splenomegaly).

RESULTS

Between June 1996 and February 1998, 395 children were born to 393 women in the trial, 196 in the ZDV group and 199 in the placebo group. Of these children, 330 were uninfected, 55 were HIV-infected, and 10 had indeterminate infection status. One set of twins was born in each treatment group; all 4 twins were uninfected. Characteristics of the mothers and children are shown in Table 1. Three hundred nineteen children (81%) completed 18 months of follow-up, 14 (4%) died before 18 months of age, and 62 (16%) were lost to follow-up. The total observation time was 3114 child months in the ZDV group and 3268 child months in the placebo group.

Congenital anomalies were noted in 8 children: 5 in the ZDV group (3 cardiac anomalies, 1 pyloric stenosis, and 1 hydrocephalus) and 3 in the placebo group (1 microcephaly, 1 pyloric stenosis, and 1 cleft palate). At birth, 2 children in the ZDV group and 1 in the placebo group had grade 3 anemia (hematocrit, <36%), and 1 infected child in the ZDV group had grade 4 granulocytopenia (<400 cells/μL); all blood abnormalities resolved within 1 week without intervention. Cancer was not diagnosed in any child.

Uninfected Children

Of the 330 uninfected children, 171 were in the ZDV group and 159 were in the placebo group. The follow-up observation times were similar in the 2 groups (Table 2). The mean hematocrit was lower in the ZDV group at birth (49.1% vs 51.5%; $P < .001$) but not at later ages. The mean weight, height, and head circumferences were similar between groups at all study visits (Fig 1A). There was also no statistically significant difference in the proportion of children who were <2 standard deviations for weight or height at any follow-up visit and there was no difference in mean growth velocity overall (data not shown). No significant differences were seen in $CD4^+$ or $CD8^+$ counts or percents between treatment groups (Fig 1B). Overall, 2 uninfected children (.6%) died, 1 presumably of sepsis at 4 months of age (ZDV group) and the other of fever and respiratory distress

TABLE 1. Baseline Characteristics of Children and Their Mothers by Infection Status and Treatment Group

Characteristic	Child's HIV Infection Status						Total
	Infected		Uninfected		Indeterminate		
	ZDV	Placebo	ZDV	Placebo	ZDV	Placebo	
Number of children	171	159	18	37	7	3	395
Mean age of mother in y (SD)*	25 (5)	25 (4)	25 (4)	26 (5)	23 (3)	28 (3)	25 (5)
Mean CD4 count of mother at delivery in cells/μL (SD)*	427 (203)	415 (206)	308 (135)	346 (226)	351 (195)	307 (36)	407 (205)
Mean viral load of mother at delivery in $\log_{10}$ copies/mL (SD)*	3.8 (.8)	4.4 (.7)	4.2 (.7)	4.9 (.6)	4.0 (1.0)	4.5 (.4)	4.2 (.8)
Mean duration on study drug in d (SD)*	26 (10)	26 (12)	27 (9)	28 (14)	19 (7)	28 (6)	26 (11)
Mean birth weight in g (SD)	3046 (384)	2979 (401)	3110 (450)	2945 (458)	2686 (258)	3193 (696)	3007 (404)
Mean gestational age in wk (SD)	39.6 (1.5)	39.7 (1.4)	39.8 (.9)	39.5 (1.6)	39.1 (1.3)	39.7 (2.5)	39.7 (1.4)
Percent boys	53	55	50	43	71	67	53

SD indicates standard deviation.
* Includes mothers of twins ($n = 2$) only once.

TABLE 2. Outcomes of Uninfected Children by Treatment Group

Outcome	ZDV (n = 171)	Placebo (n = 159)	P Value
Observation time (child mo)	2873	2722	
Mean (SD) hematocrit			
Birth (n = 321)	49.1% (6.2)	51.5% (6.5)	<.001
2 mo (n = 315)	31.4% (2.7)	31.4% (2.6)	.8
6 mo (n = 315)	34.5% (2.8)	34.6% (2.6)	.7
18 mo (n = 279)	36.7% (2.3)	36.4% (2.9)	.3
Number (%) hospitalized by 18 mo	41 (24%)	36 (23%)	.8
Mean (SD) outpatient visits in 18 mo	4.3 (2.9)	3.9 (2.5)	.2
Number (%) with convulsions by 18 mo	5 (3%)	1 (<1%)	.2
Number (%) died by 18 mo	1 (<1%)	1 (<1%)	1.0
Number (%) lost to follow-up by 18 mo	22 (13%)	22 (14%)	.8

SD indicates standard deviation.

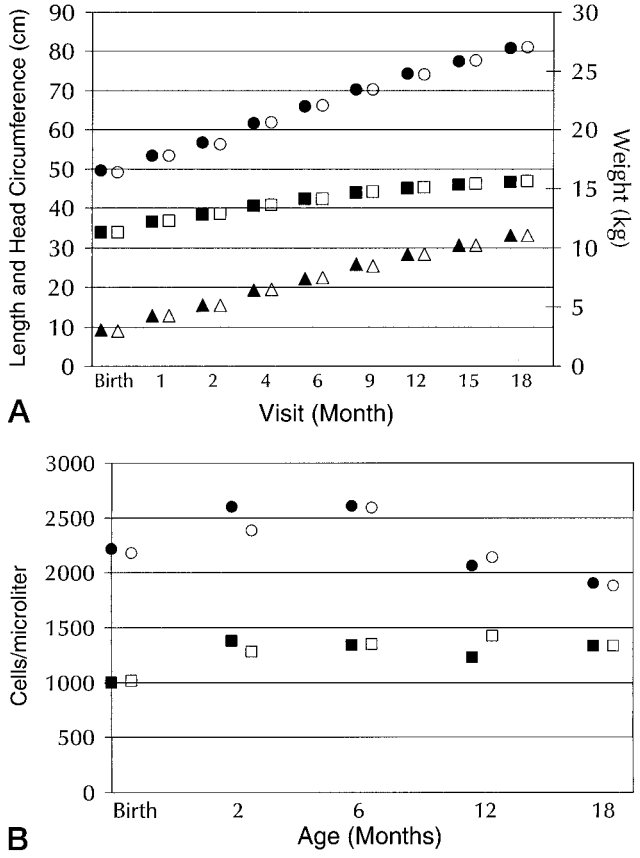

Fig 1. A, Mean weight (triangle), height (circle), and head circumference (square) of HIV-uninfected children, by treatment group. Filled shapes represent zidovudine group; open shapes, placebo group. B, Mean $CD4^+$ (circle) and $CD8^+$ (square) T lymphocyte counts of HIV-uninfected children, by treatment group. Filled shapes represent zidovudine group; open shapes, placebo group.

at 17 months of age (placebo group). Both children died outside study hospitals and neither had an autopsy. There was one death among the 330 uninfected children (3 deaths/1000 live births).

No evidence of cardiomyopathy, encephalopathy, significant developmental delay, or other diagnoses suggestive of mitochondrial dysfunction was found in any uninfected child by clinical history or routine examination. Thirteen children (6 in ZDV group and 7 in placebo group) had developmental delays noted on physical examination, all of which were mild delays in reaching age-appropriate gross motor function. Six children had convulsions; 5 in the ZDV group and 1 in the placebo group (P = .21). One child, who was born to a mother who took ZDV for 46 days, had 2 episodes of convulsions. At birth, the child had low birth weight (2400 g), asphyxia, hypoglycemia, hypocalcemia, and possibly sepsis. On the first day of life, the child had a convulsion that resolved after treatment with glucose, calcium, antibiotics, and anticonvulsants. At 12 months of age, the child had a simple febrile convulsion. The child's development was normal; no other clinical problems were noted. Another child in the ZDV group with convulsions was the child who died at 4 months of age. This child had a convulsion associated with high fever during the hospitalization in which the child died, presumably of sepsis. The other 4 children with convulsions had single episodes of simple febrile convulsions.

Twenty uninfected children had poor weight gain noted during outpatient visits, 14 in the ZDV group and 6 in the placebo group (P = .09). There was no significant difference between groups in the frequency of neonatal hyperbilirubinemia (8 in ZDV group and 7 in placebo group) or hepatosplenomegaly (2 in ZDV group and 6 in placebo group). Fewer uninfected children in the ZDV group than in the placebo group had lymphadenopathy (0 vs 7; P = .005).

Infected Children

Of the 55 infected children, 18 were in the ZDV group and 37 were in the placebo group. Peptide serotyping performed on specimens from 54 of the mothers showed 47 infections (87%) with subtype E and 6 (11%) with subtype B; 1 infection could not be typed. Twenty-two children (40%) had positive HIV PCR test results in the first 72 hours of life; 9 (50%) in the ZDV group and 13 (35%) in the placebo group (P = .30).

There was no significant difference between the 2 treatment groups in mean weight, height, CD4 count, CD8 count, viral load, or proportion who were hospitalized or who started on antiretroviral therapy (Table 3). Seven children developed class C HIV disease during the first 18 months of follow-up; 2 (11%) in the ZDV group and 5 (14%) in the placebo group. Seventeen children developed severe (class 3) immunosuppression; 5 (28%) in the ZDV group and 12 (32%) in the placebo group. Ten children died; 5

TABLE 3. Outcomes of Infected Children by Treatment Group

Outcome	ZDV (n = 18)	Placebo (n = 37)	P Value
Observation time (child mo)	236	545	
6- mo visit (number)	12	32	
Mean weight in kg (SD)	6.8 (1.4)	6.4 (1.3)	.5
Mean height in cm (SD)	64.3 (3.2)	62.6 (4.6)	.3
Mean CD4 count in cells/μL (SD)	1891 (1095)	1923 (828)	.9
Mean CD8 count in cells/μL (SD)	1804 (557)	3105 (2485)	.1
Mean viral load in $\log_{10}$ copies/mL (SD)	6.2 (.4)	6.1 (.6)	.7
18-mo visit (number)	9	26	
Mean weight in kg (SD)	10.9 (1.7)	10.2 (1.3)	.3
Mean height in cm (SD)	78.7 (3.0)	77.5 (3.3)	.3
Mean CD4 count in cells/μL (SD)	1408 (805)	1278 (542)	.6
Mean CD8 count in cells/μL (SD)	2416 (1051)	1996 (681)	.2
Mean viral load in $\log_{10}$ copies/mL (SD)	5.7 (.4)	5.3 (.6)	.1
Number (%) hospitalized by 18 mo	10 (56%)	22 (59%)	.8
Number (%) died by 18 mo	5 (28%)	5 (14%)	.3
Number (%) class C or died by 18 mo	6 (33%)	8 (22%)	.5
Number (%) lost to follow-up by 18 mo	4 (22%)	6 (16%)	.7
Number (%) started PCP prophylaxis by 3 mo	15 (83%)	34 (92%)	.4
Number (%) started PCP prophylaxis by 18 mo	17 (94%)	34 (92%)	1.0
Number (%) started antiretrovirals by 6 mo	7 (39%)	9 (24%)	.3
Number (%) started antiretrovirals by 18 mo	11 (61%)	26 (70%)	.5

SD, standard deviation; PCP, *Pneumocystis carinii* pneumonia.

(28%) in the ZDV group and 5 (14%) in the placebo group (Fig 2). The causes of death and status before death of the 10 children who died are shown in Table 4.

By Kaplan-Meier analysis, the estimated proportions of infected children surviving to 12 and 18 months of age for the ZDV group were 81% and 68%, respectively, and for the placebo group were 89% and 86%, respectively (P = .28). The estimated proportions remaining alive and free of class C disease at 12 and 18 months of age were 75% and 62% in the ZDV group and 83% and 77% in the placebo group (P = .49). Because 18-month disease-free survival differed somewhat by result of the birth PCR test (63% if positive and 77% if negative; P = .30), we adjusted the survival estimates for the early PCR results. After adjustment, the difference remained nonsignificant (P = .49).

Children With Indeterminate Infection Status

Of 10 children with indeterminate infection status, 7 were in the ZDV group and 3 were in the placebo group. Two died: 1 in the ZDV group (no HIV PCR performed) of multiple cardiac anomalies on the day of birth, and 1 in the placebo group (negative HIV PCR at birth; missed 2-month visit) of pneumonia at 3 months of age.

DISCUSSION

Our trial previously demonstrated that a short course of antenatal ZDV can significantly reduce the risk for mother–infant HIV transmission, thus prompting the widespread use of short-course ZDV in Thailand and other developing countries.[1–3] Eighteen months of follow-up of children now shows no major adverse events associated with short-course ZDV.

Our trial design, which included a concurrent, randomly assigned control group, allowed us to compare children who were exposed to short-course ZDV with a control group of children who were not. The only statistically significant difference in adverse events observed between groups was in the mean hematocrit, which was lower in the ZDV group at

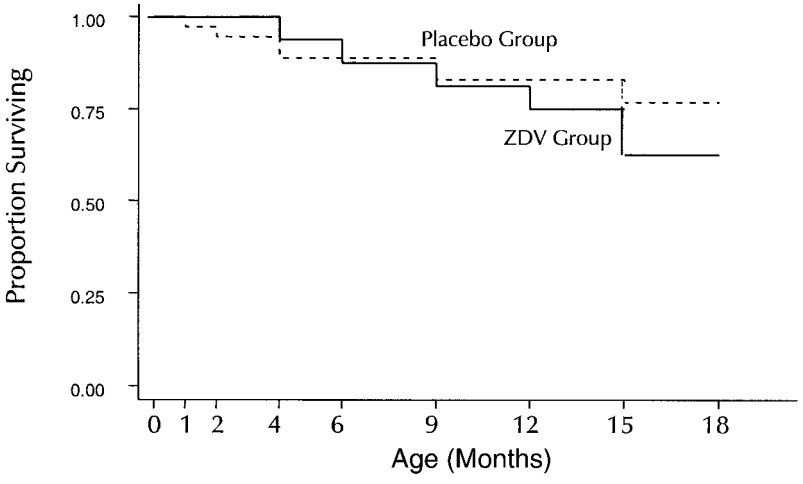

Fig 2. CDC class C disease-free survival, by treatment group, for HIV-infected children.

TABLE 4. Age, Presumed Time of Infection, Treatment Group, Cause of Death, and Last Evaluations for Infected Children Who Died During the 18-Month Follow-Up

Age at Death (Months)	Time of Infection	Treatment Group	Cause of Death	Status at Last Study Evaluation			
				CD4 Count (Cells/μL)	Viral Load (Copies/mL)	Age (Months)	Centers for Disease Control and Prevention Class
1	IU	Placebo	Thrombocytopenia, CNS infection	679	5278	1	C
2	IU	Placebo	Diarrhea, hypoxia, shock	1045	3 550 170	1	N
4	IP	Placebo	Pneumonia	1730	3 294 100	2	A
4	IP	ZDV	CMV pneumonia	503	760 000	4	N
6	IU	ZDV	Pneumonia	844	6 077 840	4	N
9	IP	ZDV	Sepsis	995	6 169 400	6	N
9	IP	Placebo	Diarrhea, shock	618	531 050	9	N
13	IU	Placebo	Respiratory failure	78	1 098 130	12	C
15	IU	ZDV	Febrile illness	103	1 354 760	12	B
17	IU	ZDV	Septicemia, cardiomyopathy	378	3 452 700	12	C

IU indicates in utero (HIV PCR-positive within 72 hours of birth); CNS, central nervous system; IP, intrapartum (HIV PCR-negative within 72 hours of birth); CMV, cytomegalovirus.

birth only, but was not clinically significant. Stratified by infection status, other indicators—death, growth, immunologic status, and number of hospitalizations—were similar between the 2 groups.

Several concerns have been raised about the safety of ZDV treatment during pregnancy. First, as with all drugs taken during pregnancy, the potential for teratogenesis must be considered; however, the incidence of birth defects in ZDV-exposed children does not seem to be increased,[5,16] and the ZDV regimen in our trial began after completion of organogenesis. Second, ZDV can be integrated into infant DNA, and animal data suggest the possibility that in utero ZDV exposure can cause tumors.[17,18] However, follow-up of >700 HIV-exposed infants in the United States has failed to identify any tumors in the first few years of life.[6,19] Third, the potential for mitochondrial toxicity in infants exposed to nucleoside analog antiretroviral medications has been raised recently.[8] Review of several hundred deaths of ZDV-exposed children in the United States, however, has not identified deaths that seem to be related to mitochondrial dysfunction.[20,21] Fourth, ZDV exposure can cause anemia,[4,5] and a direct effect of ZDV on T cells has been postulated.[22,23] Finally, although other unidentified effects could affect the growth and development of ZDV-exposed children, no such effects were seen after 4.5 years of follow-up of children in the ACTG 076 study.[6]

Because of concerns raised about the potential effect on mitochondria of prenatal ZDV exposure,[8] we specifically searched for clinical findings that might suggest mitochondrial dysfunction. Our retrospective review of clinical diagnoses found no evidence of significant cardiomyopathy, encephalopathy, or other organ dysfunction. The incidence of some less severe conditions differed between the groups. For instance, febrile convulsions and reported poor weight gain were more common in the ZDV group; lymphadenopathy and hepatosplenomegaly were more common in the placebo group. The importance of these nonspecific findings is not clear. Although it is possible that they might indicate a subtle effect of ZDV exposure, it is also possible that these findings were attributable to chance alone.

Two reports from uncontrolled observational studies have suggested that children who became infected despite maternal ZDV treatment may have faster disease progression than infected children not exposed to ZDV in utero. The Italian Registry for HIV Infection in Children reported a significantly higher probability of death, severe HIV disease, or severe immunosuppression at 3 years of age among 38 ZDV-exposed children compared with 178 unexposed children.[9] A US study of 325 infected children (82 ZDV-exposed and 243 unexposed) reported that maternal ZDV use was associated with a 1.8-fold increase in risk for AIDS or death within 1 year.[10] In contrast, no increased rate of progression was seen among the 57 infected children (14 ZDV-exposed and 43 unexposed) born in the ACTG 076 study.[24]

In our study, we found a slightly higher risk for disease progression among ZDV-exposed, HIV-infected children during the 18-month follow-up period, although this difference was not statistically significant. Other outcomes related to HIV disease progression—CD4 count, viral load, and frequency of starting antiretroviral treatment—were not significantly different at the end of the 18-month follow-up.

Although our study is greatly strengthened by its use of randomization and high rates of follow-up, it has some limitations. First, our sample size was chosen to determine the efficacy of short-course ZDV and to identify adverse events that occur with high frequency; it was not large enough to detect an increased rate of adverse events that occur rarely. Also, the number of infected children is too small and follow-up too short to draw conclusions about disease progression related to ZDV exposure. Second, our review of clinical conditions potentially associated with mitochondrial dysfunction was retrospective and could not evaluate the incidence of subtle clinical findings or laboratory abnormalities that might suggest mitochondrial dysfunction. Third, as in other studies to date, our follow-up period of 18 months is too short to enable us to evaluate the incidence of conditions, such as cancer, that may take many years to develop.

Whether adverse events will appear with more

widespread use of this regimen or after many years of follow-up remains unknown, and monitoring for late-appearing adverse events will be challenging. Nonetheless, our data suggest that short-course ZDV is safe for infants and that the incidence of adverse effects does not seem, so far, to outweigh the benefits of this regimen in preventing HIV infection in children, particularly in Thailand.

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