ORIGINAL CONTRIBUTION

Lack of Long-term Effects of In Utero Exposure to Zidovudine Among Uninfected Children Born to HIV-Infected Women

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Context With the success of zidovudine chemoprophylaxis for prevention of perinatal transmission of the human immunodeficiency virus (HIV), an increasing number of HIV-exposed but uninfected children will have in utero exposure to zidovudine and other antiretroviral drugs.

Objective To evaluate the long-term effects of in utero exposure to zidovudine vs placebo among a randomized cohort of uninfected children.

Design Prospective cohort study based on data collected during Pediatric AIDS Clinical Trials Group Protocol 076, a perinatal zidovudine HIV prevention trial, and Protocol 219, a long-term observational protocol.

Setting Pediatric research clinics in the United States.

Patients Two hundred thirty-four uninfected children born to 230 HIV-infected women enrolled in Protocol 076 and followed up through February 28, 1997, in Protocol 219 (122 in the zidovudine group and 112 in the placebo group).

Main Outcome Measures Physical growth measurements, immunologic parameters, cognitive/developmental function, occurrence of neoplasms, and mortality data assessed every 6 months for children younger than 24 months and yearly thereafter or as clinically indicated. Baseline echocardiogram and funduscopic evaluations were collected before 36 months of age.

Results Median age of children at time of last follow-up visit was 4.2 years (range, 3.2-5.6 years). There were no significant differences between children exposed to zidovudine and those who received placebo in terms of sequential data on lymphocyte subsets; weight, height, and head circumference *z* scores; and cognitive/developmental function. No deaths or malignancies occurred. Two children (both exposed to zidovudine) are being followed up for abnormal, unexplained ophthalmic findings. One child exposed to zidovudine had a mild cardiomyopathy on echocardiogram at the age of 48 months; the child is clinically asymptomatic.

Conclusions No adverse effects were observed in HIV-uninfected children with in utero and neonatal exposure to zidovudine followed up for as long as 5.6 years. Continued prospective evaluations of children born to HIV-infected women who are exposed to antiretroviral or immunotherapeutic agents are critical to assess the long-term safety of interventions that prevent perinatal HIV transmission.

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SINCE THE RESULTS OF THE SUCcessful perinatal human immunodeficiency virus (HIV) prevention trial, the Pediatric AIDS Clinical Trials Group Protocol 076 (PACTG 076), which included an intensive regimen of zidovudine, were reported in February 1994, use of zidovudine for prevention of mother-to-infant transmission of HIV has become widespread in the United States.[1,2] However, the late effects of perinatal exposure to antiretroviral drugs on the subsequent health of uninfected children are unknown and can be determined only by the long-term follow-up of children exposed in utero.

Zidovudine is a nucleoside analog reverse transcriptase inhibitor that has been extensively studied in adults and children infected with HIV and shown to-

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have moderate antiviral effects for the treatment of persons with HIV infection at all stages of disease. Short-term reversible adverse effects associated with use in adults and children are well documented and include anemia, neutropenia, and elevation of liver enzyme levels.[3,4] In preclinical lifetime animal carcinogenicity studies, high dosages of zidovudine administered to adult rodents have been associated with the development of vaginal epithelial neoplasms in female rodents receiving the highest dosage, a finding that may be explained by the presence of high concentrations of unmetabolized zidovudine in the rodent urine and reflux from the bladder into the vagina.[5]

Although no significant short-term toxic effects were observed in PACTG 076 for those mothers and infants who received zidovudine, the late effects of in utero zidovudine exposure for growing children and adults are unknown. Based on theoretical concerns about the unknown long-term consequences in utero, PACTG 076 infant participants were prospectively monitored for late effects of therapy in an ongoing long-term follow-up study, the Pediatric AIDS Clinical Trials Group Protocol 219 (PACTG 219).

The purpose of the present study was to describe the safety of perinatal zidovudine for prevention of mother-to-child HIV transmission among HIV-uninfected children with in utero zidovudine exposure. Prospective comparative evaluations were made of the growth, immunologic, cognitive/developmental, cardiac, ophthalmologic, neoplasm, and mortality data available to date for the uninfected children from PACTG 076 coenrolled in PACTG 219 who were randomized to zidovudine or placebo prenatally, intrapartum, and during the immediate postnatal period.

METHODS

Patients and Study Design

The Pediatric AIDS Clinical Trials Group Protocol 076 was a multicenter, randomized, double-blind, placebo-controlled trial of zidovudine for prevention of perinatal HIV-1 transmission conducted in the United States and France. Asymptomatic pregnant women who were infected with HIV and their newborns were randomized to receive either zidovudine or placebo. Women were treated with oral zidovudine prepartum and intravenous zidovudine during the intrapartum period. Infants received the same randomized treatment assignment as their mothers for the first 6 weeks of life. The first subject enrolled in April 1991. The study was closed to new enrollment and unblinded in February 1994, after an interim analysis demonstrated a significant effect of zidovudine in reducing the risk of perinatal HIV transmission.[1]

All caregivers of infants enrolled in PACTG 076 centers in the United States were offered long-term follow-up for their children in PACTG 219, a long-term, prospective, observational study designed to assess late effects of in utero and neonatal exposure to antiretroviral drugs in perinatal HIV clinical trials as well as late effects of antiretroviral treatment in infected children. All children participating in PACTG perinatal prevention or treatment trials are eligible for enrollment. Comprehensive history taking and physical examinations, including growth, cognitive/developmental function, and quality-of-life data, are performed at least annually. Children are scheduled to be followed up until age 21 years. Since 1993, more than 2200 children initially enrolled in PACTG trials have been followed up in PACTG 219, and one quarter of these children had participated in perinatal prevention trials. The study was approved by the review boards for human subject research at each participating institution. Written informed consent was obtained from each child's parent or legal guardian.

The study population chosen for these analyses included children who participated in PACTG 076 and subsequently enrolled in PACTG 219. Data available as of February 28, 1997, from PACTG 076 children who were born on or before January 4, 1994, were included in this analysis. Children born after January 4, 1994, were excluded because they could not have completed 6 weeks of blinded treatment before the PACTG 076 study was unblinded. All analyses are based on the randomized assignment in PACTG 076 and are intent-to-treat analyses. Findings from uninfected children randomized to zidovudine in utero and for 6 weeks postpartum were compared with uninfected children randomized to placebo.

Clinical and Laboratory Monitoring

History, physical examination, growth measurements, and quality-of-life assessments were collected at baseline and every 6 months for children younger than 2 years and every 12 months after age 2 years. Lymphocyte subsets were collected on the same schedule until age 2 years but only as clinically indicated thereafter. Percentages of lymphocyte subsets vary less with age and were used for these analyses.[6,7] Growth and lymphocyte subset data from PACTG 219 were combined with data collected during the initial 18-month follow-up period of the PACTG 076 protocol.

Cognitive/developmental function tests consisted of the Bayley Scales of Infant Development[8] for children 30 months of age or younger and the McCarthy Scales of Children's Ability[9] for children aged 30 months to 6 years. Tests were performed at baseline and every 6 months through 24 months of age and then at age 3 years. Raw data from the tests were individually reviewed by the protocol psychologist (K.O.) to ensure that tests seen as invalid by the site examiner and the protocol psychologist were not included in the analyses and questionable data (eg, widely variable scores from one test to the next) could be verified by a query to the site.

Echocardiograms and ophthalmologic examinations (including visual acuity assessment and funduscopic examination) were required for all children by 36 months of age. Sites were asked to enter all echocardiographic and funduscopic results into the database regardless of whether the examination was performed as part of PACTG 219. Examining cardiologists and ophthalmologists were asked to report the clinical rel-

evance of any abnormal echocardiogram or funduscopic findings, other related clinical findings (if any), and the child's current diagnosis, management plan, and health status.

All data, including deaths, echocardiogram results, funduscopic examination results, and cognitive/developmental function test results, were reviewed by members of the study team who were blinded to PACTG 076 treatment assignment.

Statistical Methods

Comparisons were based on PACTG 076 randomized treatment assignments and performed using *t* tests or Wilcoxon tests for continuous outcomes, the likelihood ratio χ^2 test or Fisher exact test for categorical outcomes, and the Wei-Johnson method on repeated measures over time.[10] All *P* values are 2-sided.

Infant length/height, weight, and head circumference measurements were converted to age- and sex-adjusted *z* scores using the Centers for Disease Control and Prevention/World Health Organization international growth standard based on the National Center for Health Statistics and Fels reference databases.[11,12] Group mean scores were calculated for specified nominal ages and expressed as the corresponding percentile.

The statistical power of this follow-up study for each outcome measure is indicated below the width of the 95% confidence interval (CI) for the difference from the placebo group mean, based on the sample sizes available. These CIs were calculated assuming a constant difference over time, based on the Wei-Johnson test.[10] Confidence intervals were also translated into more meaningful metrics, eg, the CI for the difference in *z* scores of weight for age was translated into a difference in SD units (SDU, expressed as a proportion of the SD of the outcome variable) as well as a difference in weight in kilograms.

The 95% CI for a difference between treatment groups over 36 months in weight-for-age *z* scores was ±0.25 *z* scores or ±0.18 SDU (corresponding to a difference of ±0.50 kg from the placebo group mean). The 95% CI for a difference in height-for-age *z* scores over 36 months was ±0.24 *z* scores or ±0.22 SDU (corresponding to a difference of ±1.0 cm from the placebo group mean). The 95% CI for a difference in head circumference-for-age *z* scores over 24 months was ±0.25 *z* scores, or ±0.21 SDU. Similarly, the 95% CI for a difference in $CD4^+$ T lymphocyte percentage over 24 months was ±1.8% (0.25 SDU), and for $CD8^+$ T lymphocyte percentage was ±1.5% (0.27 SDU). The 95% CI for a difference in Bayley scores over 24 months was ±5.0 points (0.28 SDU). With only 1 follow-up at 36 months, the 95% CI for a difference in McCarthy scores was ±8.9 points (0.54 SDU).

RESULTS

Baseline Patient Characteristics

Three hundred thirty-two PACTG 076 uninfected infants (177 in the zidovudine group and 155 in the placebo group) were born at US centers on or before January 4, 1994, and were alive at the time PACTG 219 opened to enrollment in May 1993. Two hundred thirty-four (122 in the zidovudine group and 112 in the placebo group) enrolled in PACTG 219 and met the defined criteria for inclusion in these analyses. One PACTG 076 infant who enrolled at 12 months of age into PACTG 219 was lost to follow-up before infection status was determined. This infant has been excluded from the analyses.

Two hundred thirty-four uninfected children randomized to zidovudine or placebo were born to 230 mothers (1.7% twin births). Characteristics of these mothers and uninfected children were similar to those of the original PACTG 076 study population and did not differ significantly when compared with the mothers and uninfected children who did not enroll in PACTG 219 (**TABLE 1**). As of February 28, 1997, the median age of the children at the time of the last follow-up visit was 4.2 years (range, 3.2-5.6 years) and 86% of the uninfected children enrolled in PACTG 219 were still participating in the study; 26 children

Table 1. Maternal and Infant Characteristics of Uninfected PACTG 076 Infants Including Those Enrolled and Not Enrolled in PACTG 219*

	Children Not Enrolled in PACTG 219			Children Enrolled in PACTG 219		
	All	Zidovudine	Placebo	All	Zidovudine	Placebo
Maternal baseline characteristics						
No. of mothers	**96**	54	42	**230**	122	108
Age at entry into PACTG 076, median, y	26.3	26.6	25.5	25.2	24.9	25.5
$CD4^+$ cell count at entry into PACTG 076, median, $\times 10^9$/L	0.535	0.552	0.495	0.567	0.573	0.547
History of intravenous drug use, %	22	20	24	18	17	19
Race/ethnicity, %						
White, not Hispanic	23	22	24	16	17	15
Black, not Hispanic	53	52	55	49	44	54
Hispanic/Latina	24	26	21	34	36	31
Other	. . .	. . .	. . .	2	3	1
Median gestational age at entry into PACTG 076, wk	27	26.5	28	27	27	28
Infant baseline characteristics						
No. of infants	**98**	55	43	**234**	122	112
Sex, male, %	55	58	51	53	54	51
Gestational age at birth, median, wk	40	40	39	39	40	39
Premature births (<36 wk gestation), %	8	9	7	6	6	5
Low birth weight (<2500 g), %	18	18	19	13	12	14
Apgar scores at 5 min, mean	9	9	9	9	9	9

*PACTG 076 indicates Pediatric AIDS Clinical Trials Group Protocol 076; PACTG 219, Pediatric AIDS Clinical Trials Group Protocol 219; and ellipses, data not applicable.

were lost to follow-up or their caregivers refused further contact.

Safety Results

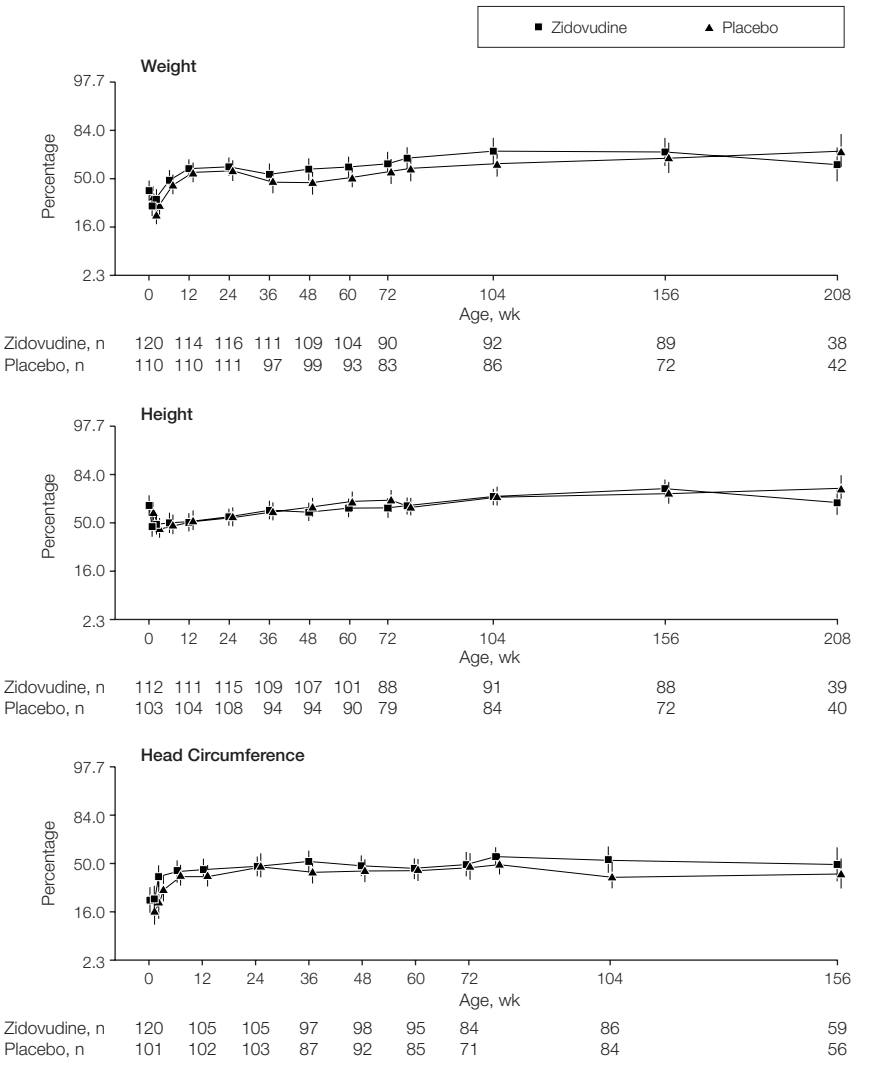
Deaths and Malignancies. There were no deaths or malignancies among the uninfected children.

Growth. Mean age percentiles for weight and height are shown in **FIGURE 1**. The uninfected zidovudine group and placebo group followed similar curves, with normal mean weight and height. There were no observed differences between the groups through 208 weeks. Likewise, no treatment differences in head circumference were noted (Figure 1).

Cognitive/Developmental Function. Five hundred ten Bayley and McCarthy assessments were available from 209 uninfected children (108 in the zidovudine group and 101 in the placebo group). A total of 466 evaluable tests (91%) were included in the analysis.

Overall, both the zidovudine and placebo uninfected children demonstrated normal cognitive/developmental function. **TABLE 2** shows the means for the mental development index (MDI) and psychomotor development index (PDI) on the Bayley Scales of Infant Development. There were no significant differences between groups for the Bayley MDI or PDI scores (Wei-Johnson *P* value for MDI scores = .24; for PDI scores, *P* = .84). Among the oldest children studied in the cohort, McCarthy scores were available from 108 uninfected children: 55 children from the zidovudine group and 53 from the placebo group. The General Cognitive Index (from the McCarthy Scales of Children's Ability) means for the zidovudine and placebo groups were 85.2 and 85.3, respectively; there was no significant difference between the groups (Wilcoxon *P* value = .78). The proportion of children with scores lower than 70 (2 SDs below test mean) for both the Bayley and McCarthy tests were equivalent in the zidovudine and placebo groups.

Figure 1. Mean Age Percentiles for Growth Parameters With 95% Confidence Intervals for Uninfected Infants Who Received Zidovudine or Placebo in the Pediatric AIDS Clinical Trials Group Protocol 076



The Wei-Johnson *P* value for weight = .24; for height, *P* = .86; and for head circumference, *P* = .42.

Immunologic Function. Among the uninfected PACTG 076/219 children, mean $CD4^+$ and $CD8^+$ lymphocyte percentages did not differ between treatment groups over time (**FIGURE 2**). There were no statistically significant differences between zidovudine and placebo groups either at each point or when analyzed on an overall basis (Wei-Johnson *P* value = .53 for $CD4^+$; *P* = .38 for $CD8^+$).

Cardiac Observations. One hundred eighty-six uninfected children (80%) had at least 1 echocardiogram result recorded in the database; 97 (80%) were in the zidovudine group and 89 (80%) were in the placebo group. Sixty-six (28%) of 234 children were missing baseline examinations (ie, >36 months of age without baseline echocardiogram results reported).

Twenty-nine uninfected children (16%) had an abnormal echocardiogram result: 16 (16%) in the zidovudine group and 13 (15%) in the placebo group. There was no significant difference between treatment groups in terms of the abnormal echocardiogram results (Fisher exact *P* value = .84). None of these children had required an echocardiogram on the basis of symptoms. All echocardiograms were performed to meet PACTG 219 requirements or because the

child was participating in a natural history study that also required at least 1 echocardiogram.

Only 1 echocardiogram abnormality was considered significant. The echocardiogram of an uninfected child aged 48 months randomized to zidovudine revealed borderline left ventricular function and mild dilatation. The child was reported to have a mild cardiomyopathy of unknown etiology; no previous echocardiograms were performed. The child's mother had received 20 weeks of zidovudine during the antepartum period and the child had received the full 6 weeks of zidovudine during the first 6 weeks of life while enrolled in PACTG 076. The site cardiologist has reported that the child is asymptomatic and healthy; however, repeated attempts to schedule a follow-up echocardiogram have been unsuccessful. In all other cases, follow-up with the site cardiologists revealed that echocardiogram findings reported as abnormal were considered insignificant. All children with abnormal echocardiogram results, other than the child just described, have reported normal cardiac status and are not being followed up in specialty clinics.

Ophthalmologic Observations. One hundred thirty-seven uninfected children (59%) had at least 1 ophthalmologic examination (including funduscopic results) recorded in the database; 72 (59%) were in the zidovudine group and 65 (58%) were in the placebo group. Thirteen children (9%) had results from more than 1 examination in the database. Eighty-eight (38%) of the 234 children were missing baseline examinations (ie, >36 months without baseline results reported). The majority of children with missing examinations had missed their scheduled appointment and will be rescheduled for the evaluation.

The following findings based on general examination were reported: astigmatism (2 children, both from zidovudine group), ptosis (1 child from zidovudine group) and epicanthal folds (1 child from placebo group).

Two children had other abnormal findings recorded on funduscopic examination. A funduscopic examination performed at 51 months of age for 1 child from the zidovudine group revealed bilateral "thinned vessels; discs look slightly pale"; vision was reported as normal. The examining ophthalmologist reported that this was not a significant finding and a 6-month follow-up is planned. Another child from the zidovudine group, aged 33 months, had a reported "copper beaten look" noted on the fundus. The child's mother had received 6 weeks of zidovudine during the antepartum period and the child had received the full 6 weeks of zidovudine during the first 6 weeks of life while enrolled in PACTG 076. The examining ophthalmologist was queried and reported that this was not related to a metabolic disease. The child is scheduled for a follow-up visit. Overall, there was no significant difference between groups in terms of the abnormal ophthalmologic findings (Fisher exact P value >.99).

COMMENT

This article presents reassuring data regarding longitudinal follow-up through the preschool years of uninfected children exposed to in utero and neonatal zidovudine for the prevention of mother-to-child transmission of HIV. With average follow-up to age 4.2 years (range, 3.2-5.6 years), results so far reveal no adverse outcomes with respect to growth, cognitive/developmental function, immune function, cancers, or mortality for uninfected PACTG 076 children randomized to zidovudine in utero when compared with uninfected PACTG 076 children randomized to placebo. One uninfected, asymptomatic, healthy child randomized to zidovudine was reported to have a mild cardiomyopathy (no previous echocardiograms) of unknown etiology. These are crucial data because zidovudine is now used extensively in the United States and other developed countries for the prevention of mother-to-child HIV transmission.[13,14] Likewise, programs to expand perinatal interventions in developing countries are undergoing consideration.[15]

The findings of this study complement the original PACTG 076 results, in which the infants were followed up through 18 months of age,[16] and are consistent with the limited human data addressing potential effects of perinatal ex-

Table 2. Means, SDs, and Numbers of Children Tested Using Bayley and McCarthy Scales for Uninfected Children by Randomized Treatment Assignment

Age, mo (Range)	Test Scores			
	Bayley Scales of Infant Development*			
	Mental Development Index		Psychomotor Development Index	
	Zidovudine	Placebo	Zidovudine	Placebo
6 (3-9)				
Mean (SD)	109.2 (16.9)	104.7 (15.8)	109.8 (15.1)	104.0 (12.7)
No.	19	17	19	17
12 (9-15)				
Mean (SD)	103.1 (17.2)	102.4 (20.6)	105.0 (13.5)	102.6 (16.0)
No.	34	31	34	31
18 (15-21)				
Mean (SD)	96.2 (14.6)	92.4 (17.9)	97.9 (16.7)	97.4 (14.9)
No.	55	59	55	59
24 (21-30.5)				
Mean (SD)	93.6 (17.1)	89.3 (18.3)	101.2 (16.6)	101.0 (21.1)
No.	65	74	64	73
	McCarthy Scales of Children's Ability (General Cognitive Index)†			
	Zidovudine		Placebo	
36 (28.5-54)				
Mean (SD)	85.2 (15.4)		85.3 (17.3)	
No.	55		53	

*Test mean (SD) = 100 (16). For mental development index, Wei-Johnson P value = .24; for psychomotor development index, Wei-Johnson P value = .84.
†Test mean (SD) = 100 (16). For General Cognitive Index, Wilcoxon P value = .78.

posure to antiretroviral drugs. Birth registry data from the Antiretroviral Pregnancy Registry found no increased risk in the proportion of congenital birth defects among 301 infants exposed to zidovudine monotherapy[17] during the antenatal period. One other study evaluated short-term risk for tumors in 734 infants and children with known zidovudine exposure (including 115 children in the current study and 619 infants and children from the Women and Infants Transmission Study, a natural-history study). In this combined cohort, with 1110.6 person-years of follow-up, no neoplasms have occurred.[18]

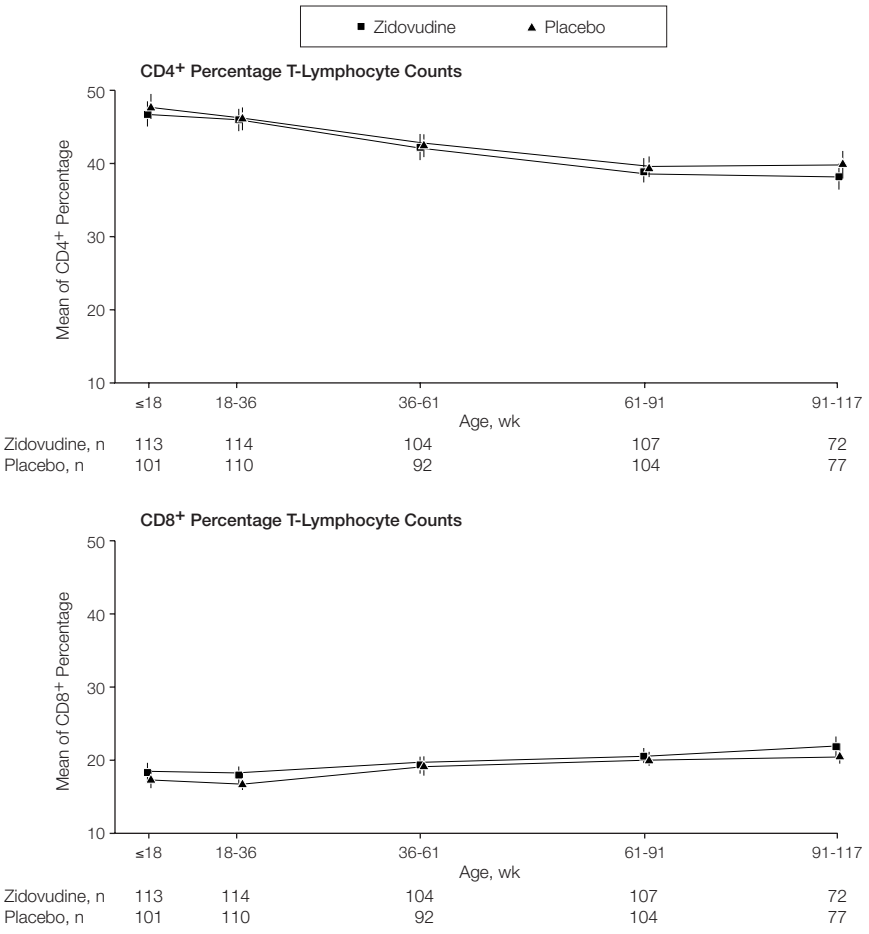
There are caveats to the data presented. Only two thirds of the children enrolled in the original PACTG 076 protocol are currently being followed up in this late-effects protocol. Maintaining uninfected children in longitudinal study will be difficult; because of risk factors associated with HIV in their families, many will eventually be placed in foster care or adoptive settings. Loss to follow-up is estimated to be about 10% per year.

A critical strength of this study is the randomized design and substantial follow-up rates. The primary end points of long-term growth, cognitive/developmental function, cardiac and ophthalmologic toxic effects, and assessment of cancers and mortality provide an ongoing opportunity to address potential late adverse effects. With a sample size of 120 per arm, there is limited power to detect very rare adverse events, but the sample size allows for adequate statistical power to detect any clinically relevant differences between treatment groups for growth, immunologic parameters, and cognitive/developmental function. The study is positioned to clarify whether perinatal zidovudine use is safe in the long-term to early adulthood and may be able to address issues raised by 2 recently published but conflicting animal studies about the potential transplacental carcinogenic effects of zidovudine.[19,20]

Early initiation of aggressive combination antiretroviral therapy is now the standard of care for treatment of all HIV-infected individuals, including pregnant women. Increasing numbers of uninfected children will have prolonged in utero exposure to multiple antiretroviral agents used for treatment of their mother's HIV infection.[21] These trends highlight the need for long-term surveillance of perinatally exposed children. Protocol 219 is a surveillance mechanism within the framework of the PACTG trial network for children who have been exposed to antiretroviral drugs in utero. However, there is currently no surveillance in place for long-term tracking of children exposed to antiretroviral drugs perinatally who are not part of the PACTG framework. Approaches that have been proposed in the United States include national or regional passive tracking systems, with registries of those exposed to perinatal interventions being linked in future years to cases from cancer registries. Building innovative approaches to look for late effects will be necessary as these interventions become widely implemented.

Although theoretical concerns about late effects of in utero/neonatal antiretroviral exposure exist based on animal models, the findings from this comparative follow-up study of uninfected PACTG 076 children exposed to zidovudine vs placebo suggest no evidence of adverse effects through the preschool years. A critical public health goal is the development and implementation of long-term tracking strategies to assess potential late effects of perinatal antiretroviral exposure among the vast majority of children exposed to perinatal antiretroviral

Figure 2. Mean Values for Lymphocyte Subset Parameters for Uninfected Infants Who Received Zidovudine or Placebo in the Pediatric AIDS Clinical Trials Group Protocol 076



The Wei-Johnson *P* value for CD4+ cell counts = .52; for CD8+ cell counts, *P* = .38.

drugs in clinical care settings but not followed in cohort studies.

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