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REDUCTION OF MATERNAL–INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

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Abstract *Background and Methods.* Maternal–infant transmission is the primary means by which young children become infected with human immunodeficiency virus type 1 (HIV). We conducted a randomized, double-blind, placebo-controlled trial of the efficacy and safety of zidovudine in reducing the risk of maternal–infant HIV transmission. HIV-infected pregnant women (14 to 34 weeks' gestation) with CD4+ T-lymphocyte counts above 200 cells per cubic millimeter who had not received antiretroviral therapy during the current pregnancy were enrolled. The zidovudine regimen included antepartum zidovudine (100 mg orally five times daily), intrapartum zidovudine (2 mg per kilogram of body weight given intravenously over a one-hour period, then 1 mg per kilogram per hour until delivery), and zidovudine for the newborn (2 mg per kilogram orally every six hours for six weeks). Infants with at least one positive HIV culture of peripheral-blood mononuclear cells were classified as HIV-infected.

Results. From April 1991 through December 20, 1993, the cutoff date for the first interim analysis of efficacy, 477 pregnant women were enrolled; during the study period, 409 gave birth to 415 live-born infants. HIV-infection status was known for 363 births (180 in the zidovudine group and 183 in the placebo group). Thirteen infants in the zidovudine group and 40 in the placebo group were HIV-infected. The proportions infected at 18 months, as estimated by the Kaplan–Meier method, were 8.3 percent (95 percent confidence interval, 3.9 to 12.8 percent) in the zidovudine group and 25.5 percent (95 percent confidence interval, 18.4 to 32.5 percent) in the placebo group. This corresponds to a 67.5 percent (95 percent confidence interval, 40.7 to 82.1 percent) relative reduction in the risk of HIV transmission ($Z = 4.03$, $P = 0.00006$). Minimal short-term toxic effects were observed. The level of hemoglobin at birth in the infants in the zidovudine group was significantly lower than that in the infants in the placebo group. By 12 weeks of age, hemoglobin values in the two groups were similar.

Conclusions. In pregnant women with mildly symptomatic HIV disease and no prior treatment with antiretroviral drugs during the pregnancy, a regimen consisting of zidovudine given ante partum and intra partum to the mother and to the newborn for six weeks reduced the risk of maternal–infant HIV transmission by approximately two thirds. (N Engl J Med 1994;331:1173-80.)

MATERNAL–INFANT transmission is the primary means by which young children become infected with human immunodeficiency virus type 1 (HIV).[1,2] From 15 to 40 percent of infants born to infected mothers become infected in utero, during labor and delivery, or by breast-feeding.[3-5] Current evidence suggests that most maternal–infant HIV transmission occurs late in pregnancy or during labor and delivery.[5-11]

Despite treatment, pediatric HIV infection remains a fatal disease whose prevention is of paramount importance. Animal models of retroviral infection dem-

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onstrate that zidovudine may prevent or alter the course of maternally transmitted HIV infection.[12-16] Phase 1 studies in pregnant women suggested that this medication is safe when used for short periods and that it crosses the placenta well.[17-21]

To assess the safety and efficacy of zidovudine for the prevention of maternal–infant HIV transmission, the Pediatric AIDS Clinical Trials Group conducted a multicenter clinical trial (Protocol 076) in the United States and France. At the first interim analysis of efficacy, the Data and Safety Monitoring Board recommended that the enrollment of additional patients be discontinued and that all patients receiving a study drug in blinded fashion be offered zidovudine treatment. This recommendation was based on the demonstration of efficacy of zidovudine in reducing the risk of maternal–infant transmission of HIV. We report the results of this trial through December 20, 1993, the date of the data cutoff in the first interim efficacy analysis.

Methods

Trial Design

Our double-blind, placebo-controlled, randomized study enrolled pregnant, HIV-infected women between 14 and 34 weeks' gestation whose CD4+ T-lymphocyte counts were above 200 cells per cubic millimeter and who had no indication for antiretroviral therapy in the judgment of their health care providers. All the women had to meet the following laboratory criteria: hemoglobin concentration, ≥8 g per deciliter; absolute neutrophil count, ≥1000 cells per cubic millimeter; platelet count, ≥100,000 cells per cubic millimeter; serum alanine aminotransferase concentration, ≤2.5 times the upper limit of normal; and serum creatinine concentration, ≤1.5 mg per deciliter (130 μmol per liter), or eight-hour urinary creatinine clearance, >70 ml per minute. Women with any of the following ultrasonographic findings were excluded: life-threatening fetal anomaly or anomaly that might increase the fetal concentration of zidovudine or its metabolites; oligohydramnios in the second trimester or unexplained polyhydramnios in the third trimester; and fetal hydrops, ascites, or other evidence of fetal anemia. Women who had received any antiretroviral treatment during this pregnancy and those who had received immunotherapy, anti-HIV vaccines, cytolytic chemotherapeutic agents, or radiation therapy were excluded.

The protocol was approved by the institutional review board at each center in the United States and by the Committee for the Protection of Persons in Biomedical Research in France. Each woman (and the father of the child, when available) gave written informed consent for her participation and that of her child.

The women were stratified according to gestational age (from 14 to 26 weeks or greater than 26 weeks) and were randomly assigned to receive either zidovudine or placebo. The zidovudine regimen consisted of antepartum zidovudine (100 mg orally five times daily) plus intrapartum zidovudine (2 mg per kilogram of body weight given intravenously for 1 hour, followed by 1 mg per kilogram per hour until delivery) plus zidovudine for the newborn (2 mg per kilogram orally every 6 hours for six weeks, beginning 8 to 12 hours after birth).

The women were monitored every 4 weeks until 32 weeks' gestation and then weekly until delivery. Sonograms were obtained before entry into the study and every 4 weeks after the 28th week of gestation. A nonstress test was performed at 34 weeks and repeated weekly thereafter until delivery. Treatment was discontinued if severe preeclampsia, disseminated intravascular coagulation, recurrent thrombocytopenia, life-threatening or recurrent severe toxic effects, or progressive HIV disease requiring treatment with open-label zidovudine developed in the mother, or if fetal death occurred. The women were seen six weeks and six months after delivery.

The infants were evaluated at birth and at 1, 2 or 3, 6, 12, 24, 36, 48, 60, 72, and 78 weeks of age. The study drug was not instituted if an immediately life-threatening condition or any of the following conditions developed: hyperbilirubinemia that required treatment other than phototherapy, an absolute neutrophil count below 750 cells per cubic millimeter, a hemoglobin concentration below 8.0 g per deciliter, a platelet count below 50,000 cells per cubic millimeter, and an alanine aminotransferase concentration more than five times the upper limit of age-adjusted normal values. Newborn therapy was discontinued if any of the above conditions or any type of severe toxic effect developed in the infant, or if the infant received an experimental anti-HIV vaccine or drug.

Peripheral-blood mononuclear cells obtained from infants were cultured for HIV at birth and at 12 and 78 weeks of life. HIV serologic testing (an enzyme immunoassay and a Western blot assay) was performed at 72 and 78 weeks. In September 1992 the protocol was amended to incorporate an additional HIV culture at 24 weeks of age. Infants with at least one positive HIV culture of peripheral-blood mononuclear cells were classified as HIV-infected.

Laboratory Methods

HIV cultures of peripheral-blood mononuclear cells and lymphocyte phenotyping were performed in certified laboratories according to published standard methods.[22,23] The French sites used an equivalent program to ensure quality.[24] Enzyme immunoassays and Western blot assays for HIV antibody were performed in certified laboratories by commercially available methods.

Statistical Analysis

The comparison of efficacy between treatment groups was based on the percentage of infants who were infected at 18 months, as estimated by the Kaplan–Meier method.[25] The P value was determined with a Z statistic calculated from the difference between the Kaplan–Meier estimates at 18 months and their standard errors in the two groups. This approach increased the statistical power of the comparison of treatments by including information from all available HIV cultures without requiring an 18-month follow-up of all infants. The time to the first positive HIV culture was considered as the time to a verified end point for an infant determined to be HIV-infected. Data on all the other infants were censored in the analysis, with their follow-up times set to the latest negative cultures or negative serologic tests. Prognostic factors for the risk of transmission were evaluated and treatment effects adjusted with logistic-regression analyses.[26] The results of intention-to-treat analyses of all available data from eligible subjects are reported. All P values are two-sided.

The target sample was 636 assessable mother–infant pairs. Prospectively, three interim analyses were planned, with the O'Brien–Fleming boundary.[27,28]

Results

Enrollment

From April 1991 through December 1993, 477 pregnant women were enrolled at 59 centers. Of the eligible women, 409 gave birth during this period to a total of 415 live-born infants, including 403 singletons and 6 sets of twins (Table 1). Two women had a history of HIV seropositivity but were later found not to be infected. These two women and an infant born to one of them were excluded from the analysis. Twelve women (one of whom had a creatinine concentration outside the specified range) withdrew from the study before delivery; data on these women were included up to the time of withdrawal.

Characteristics of the Mothers and Infants and Treatment with Study Drugs

There were no significant differences between study groups in the characteristics of the pregnant women and the live-born infants (Table 2). The median ges-

Table 1. Status of Mothers and Infants in the Study, as of December 20, 1993.

	Zidovudine	Placebo	All
	no. of subjects		
Mothers randomized	239	238	477
No confirmed HIV infection	1	1	2
Withdrawal before delivery*	5	7	12
Still pregnant	24	24	48
Loss of pregnancy†	4	2	6
Eligible women who gave birth to live infants	205	204	409
Live-born infants‡	206	209	415
Singletons	204	199	403
Twins	2	10	12
Eligible mother–infant pairs§	205	204	409
Culture data unavailable for infant	25	21	46
Withdrawal before culture	4	2	6
Neonatal death without culture	0	1	1
Infant too young (≤10 wk)	10	10	20
Culture results not yet submitted¶	11	8	19
Included in Kaplan–Meier analysis‖	180	183	363

*The reasons for the mother's withdrawal from the study were as follows. In the zidovudine group, four mothers withdrew before any treatment (one of them was enrolled inadvertently; her creatinine clearance rate was beyond the eligible range), and one mother refused all medications and follow-up after receiving some treatment. In the placebo group, four mothers withdrew before any treatment, and three mothers refused all medications and follow-up after receiving some treatment.

†The reasons for pregnancy loss included an incompetent cervix and inevitable abortion (one in the zidovudine group), death in utero (two in the zidovudine group and two in the placebo group), and stillbirth (one in the zidovudine group).

‡Does not include one infant born to a mother without HIV infection (in the placebo group) who was excluded from the analysis.

§Includes mothers who gave birth to one or more live-born infants; all twins had concordant outcomes, and each set of twins was considered as a single delivery in the efficacy analysis.

¶Eleven of the 19 infants (12 to 33 weeks of age) were from sites in France at which electronic submission of virologic data was not available as of December 20, 1993. The results of subsequent analyses including these infants were the same as those presented here.

‖Pregnancies yielding an infant for whom at least one result of HIV culture was available as of December 20, 1993, were included.

tational age at entry was 26 weeks. Fifty-nine percent of the mothers had CD4+ T-lymphocyte counts greater than 500 cells per cubic millimeter. Only 19 women had received any antiretroviral treatment before the current pregnancy. The median gestational age of the live-born infants was 39 weeks (range, 27 to 43), and the median birth weight was 3160 g (range, 1040 to 5267). Specific intrapartum factors that might be associated with an altered risk of maternal–infant transmission were balanced between the study groups. Only one mother (in the placebo group) reported that she breast-fed her infant; the infant was not infected.

The women received the study drug for a median of 11 weeks (range, 0 to 26) before giving birth. The study groups were balanced with respect to the proportion of women whose dose of the study drug was modified during treatment (26.4 percent in the zidovudine group and 32.0 percent in the placebo group) and with respect to the proportion who received intrapartum infusions of study drug (85.4 percent in the zidovudine group and 84.2 percent in the placebo group). Only 24 women (5 percent) did not complete their treatment as planned, 9 in the zidovudine group and 15 in the placebo group. Open-label zidovudine was prescribed for one woman in each group before delivery.

Twelve live-born infants never started treatment (five in the zidovudine group and seven in the placebo group). The reasons included neonatal death (two infants), the mother's refusal to participate (five), withdrawal from the study (three), and delivery at a non-study hospital (two). Four other infants had their treatment assignments disclosed because they were potential candidates for an initial pharmacokinetics study, and they did not receive placebo. Among the remaining infants, treatment was started within 12 hours for 84 percent and within 24 hours for 96 percent. Forty-six infants (22 in the zidovudine group and 24 in the placebo group) stopped treatment before completing six weeks of therapy; 7 had reached a study end point (1 in the zidovudine group and 6 in the placebo group), and 22 stopped because of toxic effects (11 in each group).

Analyses of Efficacy

The primary analysis of efficacy was based on all 409 eligible deliveries of live infants, and a failure of therapy was recorded if any infant from a given delivery (a singleton or either twin) was found to be infected. Forty-six infants were excluded from the analysis because no data on HIV culture were available in the

Table 2. Characteristics of Women and Infants in the Study.*

Characteristic	Zidovudine	Placebo	All
Mothers			
Median age at entry — yr	25	25	25
Race or ethnic group — no.			
White	48	38	86
Black	107	127	234
Hispanic	71	61	132
Other	6	3	9
History of injection-drug use — no.	40	36	76
Median CD4 count at entry — cells/mm^3	560	538	550
No. with 200–500 cells	93	94	187
No. with >500 cells	136	136	272
Median gestational age at entry — wk	26	27	26
No. with 14–26 wk	120	116	236
No. with >26 wk	112	118	230
Zidovudine before current pregnancy — no.	12	7	19
Sexually transmitted disease — no.			
Syphilis	25	29	54
Other	28	21	49
Infants			
Median gestational age — wk	40	39	39
Median birth weight — g	3147	3160	3160
Premature infants (<36 wk) — no.	16	13	29
Low birth weight — no.			
<1500 g	3	4	7
1500–1999 g	6	8	14
2000–2500 g	19	25	44
Delivery			
Mode of delivery — no.			
Vaginal	142	151	293
Cesarean	59	51	110
Premature rupture of membranes — no.	4	5	9
Abruptio placentae — no.	3	8	11
Fetal-scalp sampling — no.	4	1	5
Fetal-scalp electrodes — no.	13	7	20

*Information in the table was derived from data in the data base as of December 20, 1993. Maternal base-line characteristics refer to all HIV-infected women who were randomized, with data submitted by the cutoff date. Infants' base-line characteristics refer to eligible live-born infants only; pregnancy losses were excluded.

data base at the time of this interim analysis (Table 1). The estimated proportions of infants infected were based on the Kaplan–Meier evaluation of 363 births for which at least one HIV culture was performed: 180 infants randomly assigned to zidovudine and 183 randomly assigned to placebo (Fig. 1).

Thirteen children in the zidovudine group had at least one positive HIV culture and were classified as infected, as compared with 40 children in the placebo group. None of the twins were infected. On the basis of the Kaplan–Meier analysis at 18 months, the estimated proportion of infants infected was 8.3 percent in the zidovudine group (95 percent confidence interval, 3.9 to 12.8 percent) and 25.5 percent in the placebo group (95 percent confidence interval, 18.4 to 32.5 percent). The standard errors for these estimates, based on Greenwood's formula, were 2.25 and 3.60 percent, respectively.[29] The estimated absolute difference between the two study groups in the percentage who were infected was 17.2 percent (95 percent confidence interval, 8.9 to 25.5 percent), corresponding to a 67.5 percent relative reduction in the risk of transmission (95 percent confidence interval, 40.7 to 82.1 percent). The difference in 18-month Kaplan–Meier percentages was significant ($Z = 4.03$, two-sided $P = 0.00006$). This result crossed the interim stopping boundary for the monitoring of efficacy ($Z = 3.47$, two-sided $P = 0.0005$).

Two alternative analyses were performed in order to estimate the percentage of infected infants with a simple ratio (Table 3). These analyses were based on a more stringent definition of HIV-infected infants. The estimated probabilities of transmission were consistent with those obtained with the Kaplan–Meier method.

HIV infection was detected by culture within the first six months of life in nearly all the infants. Only

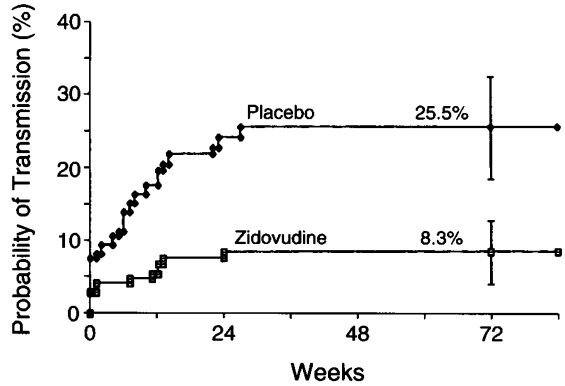

Figure 1. Kaplan–Meier Plots of the Probability of HIV Transmission, According to Treatment Group.

The estimated percentages of infants infected at 72 weeks are shown with 95 percent confidence intervals. The numbers of infants at risk at 24, 48, and 72 weeks are shown below the figure.

Table 3. Alternative Efficacy Analyses.*

Variable	Zidovudine	Placebo	All
Infants >32 wk			
Births (no.)	150	149	299
Infection status (no.)			
Indeterminate	29	22	51
Defined	121	127	248
HIV-infected	9	31	40
Transmission rate (%)†	7.4	24.4	16.1
Infants ≥1 yr			
Births (no.)	95	104	199
Infection status (no.)			
Indeterminate	12	15	27
Defined	83	89	172
HIV-infected	7	20	27
Transmission rate (%)‡	8.4	22.5	15.7

*In these analyses, two positive cultures define HIV infected, and at least two negative cultures (one obtained at ≥24 weeks) and no positive cultures define the absence of HIV infection. P values were determined with the chi-square test.

†$P = 0.002$ for the comparison between groups.

‡$P = 0.03$ for the comparison between groups.

2 of the 53 infants classified as infected (both in the placebo group) had their first positive culture reported after the first 24 weeks. Treatment with zidovudine was not associated with a delay in the detection of HIV by viral culture; the estimated intervals before the first positive culture were virtually identical in the two groups. None of the 105 infants in the zidovudine group who had repeatedly negative cultures before the 24th week of life had evidence of HIV infection after 24 weeks.

For 91 infants, results of serologic testing at 72 to 78 weeks were available (47 infants in the zidovudine group and 44 in the placebo group). Among these, all the infants who were counted as uninfected in the Kaplan–Meier analysis had negative serologic results (43 in the zidovudine group and 37 in the placebo group). Two infants classified as infected had negative enzyme immunoassays and Western blot assays; one infant in the placebo group had a single positive culture at birth, and one infant in the zidovudine group had positive cultures at 1 and 21 weeks, but negative serologic results at 78 weeks.

Evaluation of Efficacy in Subgroups

We assessed the influence on the risk of maternal–infant HIV transmission of various factors, including treatment, race and ethnic background, maternal base-line CD4+ T-lymphocyte count, maternal age at entry into the study, gestational age at entry, maternal history of injection-drug use, previous adverse outcomes of pregnancy, history of sexually transmitted diseases, duration of labor, duration of ruptured membranes, intravenous administration of a study drug during labor and delivery, mode of delivery, parity, duration of antepartum therapy, maternal compliance with treatment, ultrasonographic abnormalities, gestational age at delivery, birth weight, and sex of the newborn. The efficacy of zidovudine was observed in all the subgroups. It was impossible to

identify prognostic factors for HIV transmission (other than treatment) in this interim analysis because of the small number of infected infants in the zidovudine group.

Evaluation of Maternal Safety

Adverse Effects

Six women (three in each group) discontinued their treatment because of toxic effects. Thirty-five women (18 in the zidovudine group and 17 in the placebo group) had anemia of more than moderate severity, neutropenia, or thrombocytopenia, and 15 women (8 in the zidovudine group and 7 in the placebo group) had abnormalities of serum electrolytes and liver function of more than moderate severity. Toxic effects were defined according to standard toxicity tables modified for pregnancy and defined in the protocol. The majority of the adverse effects were judged to be related to labor and delivery. None of the mothers died during the study.

Effects on Maternal Health

Changes in CD4+ T-lymphocyte counts from base line could be assessed in 291 women at six weeks post partum and in 168 women at six months post partum. A significant increase in these cell counts was observed in both study groups, but the increase was greater in the zidovudine group. The median increase from base line to six weeks post partum was 141 cells per cubic millimeter in the zidovudine group, as compared with 101 cells per cubic millimeter in the placebo group ($P = 0.02$ by the Wilcoxon test). By six months post partum, the median increase from base line was 53 cells per cubic millimeter in the zidovudine group, as compared with 14 cells per cubic millimeter in the placebo group ($P = 0.12$ by the Wilcoxon test). At six months post partum, the CD4+ T-lymphocyte count was greater than 300 cells per cubic millimeter for 95 percent of the women in both groups; counts for four women (one in the zidovudine group and three in the placebo group) fell below 200 cells per cubic millimeter during the study. Among 189 women for whom data were available from their six-month visit, 40 (19 in the zidovudine group and 21 in the placebo group) were being treated with open-label zidovudine.

Evaluation of Infants' Safety

Deaths

There were eight fetal or neonatal deaths (five in the zidovudine group and three in the placebo group). None of these deaths were considered attributable to the study drug. The causes of death in the zidovudine group were congenital diaphragmatic hernia (one death), Dandy–Walker syndrome (one), premature labor and chorioamnionitis at 24 weeks' gestation (one), inevitable abortion at 18 weeks' gestation in a mother with a history of incompetent cervix (one), and premature labor and abruptio placentae at 28 weeks' gestation (one). The causes of death in the placebo group were cytomegalovirus infection in utero (one death), abruptio placentae associated with cocaine use (one), and hypoplastic right ventricle (one). There were seven deaths in infants who were beyond the neonatal period; six of these (two in the zidovudine group and four in the placebo group) were due to HIV infection, and one (in the zidovudine group) was due to trauma.

Prenatal and Neonatal Evaluation

Serial ultrasonographic examinations and nonstress tests revealed no differences between the study groups. Zidovudine treatment was not associated with premature birth. Examination of the newborns showed normal anthropometric measurements. Length, weight, and head circumference were similar in uninfected infants in the two groups through 18 months of age.

Structural Abnormalities

The incidence of minor and major abnormalities was similar in the two groups. Congenital cardiac anomalies were confirmed in 10 infants (5 in each group). Congenital abnormalities of the central nervous system were reported in five infants (three in the zidovudine group and two in the placebo group). Eighteen other major anomalies were reported, nine in each group. No specific minor or major abnormalities were clustered in either group.

Adverse Experiences

The hemoglobin concentration at birth of infants in the zidovudine group was significantly lower than that of infants in the placebo group (Fig. 2). Whereas only 4 infants in either group had a hemoglobin concentration of less than 7.0 g per deciliter, 44 infants in the zidovudine group and 24 infants in the placebo group had hemoglobin concentrations below 9.0 g per deciliter. The maximal difference in the mean hemoglobin concentration between the two groups occurred at three weeks of age and was 1 g per deciliter. The lowest mean value for hemoglobin, 10.0 g per deciliter, occurred at six weeks of age in the zidovudine group. By 12 weeks of age, hemoglobin values for

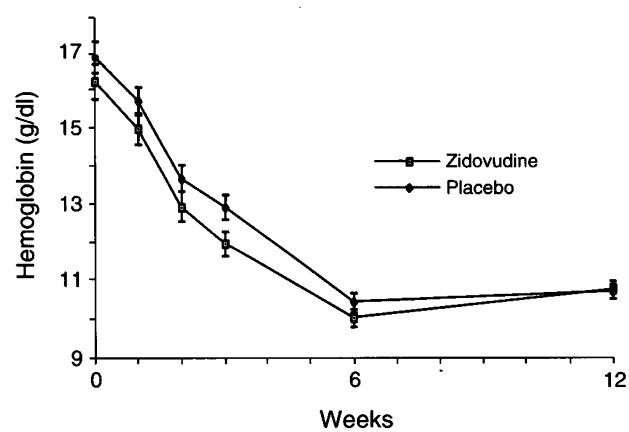

Figure 2. Mean (±SD) Hemoglobin Concentrations at Birth, 6 Weeks, and 12 Weeks in the Two Treatment Groups.

both groups were similar. No significant differences in other safety measures were observed between the study groups.

Discussion

We found that administering zidovudine to the mother during pregnancy and during labor and delivery and giving it to the infant for the first six weeks of life reduced the risk of maternal–infant transmission of HIV by approximately two thirds. We chose to study a regimen that combined antepartum, intrapartum, and neonatal therapy, because the timing of maternal–infant HIV transmission is uncertain. The standard recommended dose and schedule of zidovudine for adults were chosen for maternal antepartum treatment. This dose has been associated with a reduction in circulating levels of HIV and has minimal toxicity.[30,31] Intravenous infusion of zidovudine during labor maintained drug levels and averted the need for oral medication. The intrapartum dosing scheme was derived by pharmacokinetic modeling of data previously obtained in pregnancy.[20] Zidovudine was administered to infants for six weeks at a dose established in studies of zidovudine in newborns,[32] since infected maternal cells may persist in the infant's circulation after birth.

Women were enrolled after the first trimester of pregnancy to avoid fetal exposure to zidovudine during organogenesis, because of the lack of prospective safety data on the use of this medication in humans during the first trimester. In the murine model, zidovudine has been associated with the resorption of preimplantation embryos.[33] In other studies of animal reproduction, low and moderate doses of zidovudine were not associated with teratogenic malformations,[34] but pregnant rats given nearly lethal doses of zidovudine (3000 mg per kilogram) had an increased risk of malformations among their offspring.[35]

A single positive culture was used to define an infant as HIV-infected. In current clinical practice, however, a single positive culture is often confirmed by a second culture or by the polymerase chain reaction. For the study group, adopting more stringent definitions of infection (two positive cultures) and noninfection (at least two negative cultures, one at $\geq$24 weeks of age, and no positive cultures) yielded results similar to those obtained in the primary Kaplan–Meier analysis.

The possibility that zidovudine would delay the detection of HIV infection by culture was a theoretical concern. People with established HIV infection who are treated with zidovudine typically remain culture-positive, but the effect of zidovudine on cultures from people with early (primary) HIV infection is unknown.[30,36] To date, we have no evidence that zidovudine treatment delayed the detection of HIV by culture in this group of infants.

Minimal short-term toxic effects were observed. Few women in either study group discontinued therapy because of toxic effects. At six months post partum, there were no differences between the two groups of women with respect to mean CD4+ T-lymphocyte counts or progression to AIDS. Among infants, the only short-term toxic effect directly attributable to zidovudine was anemia, which was mild and reversible.

The mechanism by which zidovudine reduced the risk of maternal–infant HIV transmission is not established. Maternal zidovudine treatment may have reduced the viral load and diminished the viral exposure of the fetus in utero, of the infant at delivery, or both. Stored samples are being studied to determine whether changes in the maternal viral burden or the virologic characteristics of the infecting strains of HIV can predict the success of the treatment regimen. In addition, there is substantial transplacental passage of zidovudine.[18-20,37] Therapeutic concentrations of the drug in the fetus and the newborn may have prevented HIV infection.

Some infants became infected despite treatment with zidovudine. These infections may have occurred as a result of (1) HIV transmission before treatment, (2) inefficient suppression of maternal viral replication by zidovudine, (3) noncompliance with the treatment regimen, or (4) unique characteristics of the infecting maternal strain of HIV, such as decreased susceptibility to zidovudine. Susceptibility testing of isolates from these mother–infant pairs has not yet been performed. High-level resistance to zidovudine is unlikely, however, considering the relatively short duration of the maternal treatment,[38] the lack of previous maternal exposure to zidovudine in most cases, and the relatively high median CD4+ T-lymphocyte count of the mothers at entry.

In general, the women in this study had mildly symptomatic HIV disease and, with 19 exceptions, no prior treatment with antiretroviral drugs. Women with more advanced disease and those who have had prolonged treatment with zidovudine may have a higher viral burden and may also be infected with zidovudine-resistant strains of HIV. Thus, it is not clear whether the results of this trial can be extrapolated to these groups. In addition, the risks and benefits of initiating zidovudine therapy during the first trimester of pregnancy, after 34 weeks' gestation, or in labor or of treating only the newborn were not assessed. Follow-up of the mothers and infants enrolled in the study will continue to assess the effect of zidovudine in subgroups of women, to try to identify factors (other than treatment) that influence maternal–infant HIV transmission, and to assess long-term safety.

Our study indicates that substantial reduction in the rate of maternal–infant transmission of HIV is possible with minimal short-term toxicity to mother or child. Now it is important to understand the mechanism of protection, to determine whether the treatment regimen can be simplified, and to assess the use of the regimen in women and infants with characteristics other than those of the people we studied.

Note added in proof: Since submitting this paper, we have updated the data on HIV cultures to September 6, 1994. Data were available on at least one HIV culture for each of 400 births in the data base: 200 in the zidovudine group and 200 in the placebo group. Sixteen children in the zidovudine group had at least one positive culture, as compared with 52 children in the placebo group. The Kaplan–Meier estimates of the proportions of children infected at 18 months were 7.9 percent (95 percent confidence interval, 4.1 to 11.7 percent) for the zidovudine group and 27.7 percent (95 percent confidence interval, 21.2 to 34.1 percent) for the placebo group. The difference remained statistically significant ($Z = 5.13$, two-sided $P<0.001$). These updated results support the findings of the interim analysis.

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Appendix

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References

1. Newell ML, Peckham C. Risk factors for vertical transmission of HIV-1 and early markers of HIV-1 infection in children. AIDS 1993;7:Suppl 1: S91-S97.
2. Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report. April 1994.
3. Oxtoby MJ. Vertically acquired HIV infection in the United States. In: Pizzo PA, Wilfert CM, eds. Pediatric AIDS: the challenge of HIV infection in infants, children, and adolescents. 2nd ed. Baltimore: Williams & Wilkins, 1994:3-20.
4. Mofenson L. Epidemiology and determinants of vertical HIV transmission. Semin Pediatr Infect Dis 1994;5:252-65.
5. Mofenson LM, Wolinsky SM. Current insights regarding vertical transmission. In: Pizzo PA, Wilfert CM, eds. Pediatric AIDS: the challenge of HIV infection in infants, children, and adolescents. 2nd ed. Baltimore: Williams & Wilkins, 1994:179-203.
6. de Rossi A, Ometto L, Mammano F, et al. Time course of antigenaemia and seroconversion in infants with vertically acquired HIV-1 infection. AIDS 1993;7:1528-9.
7. Goedert JJ, Duliege AM, Amos CI, Felton S, Biggar RJ. High risk of HIV-1 infection for first-born twins: the International Registry of HIV-exposed Twins. Lancet 1991;338:1471-5.
8. Bryson YJ, Luzuriaga K, Sullivan JL, Wara DW. Proposed definitions for in utero versus intrapartum transmission of HIV-1. N Engl J Med 1992;327:1246-7.
9. Krivine A, Firtion G, Cao L, Francoual C, Henrion R, Lebon P. HIV replication during the first few weeks of life. Lancet 1992;339:1187-9.
10. Rouzioux C, Burgard M, Blanche S, Costagliola D, HIV Infection in Newborns French Collaborative Study. Estimate of the period of perinatal HIV-1 transmission. J Cell Biochem Suppl 1993;17E:100. abstract.
11. Report of a consensus workshop, Siena, Italy, January 17–18, 1992: early diagnosis of HIV infection in infants. J Acquir Immune Defic Syndr 1992;5:1169-78.
12. Shih C-C, Kaneshima H, Rabin L, et al. Postexposure prophylaxis with zidovudine suppresses human immunodeficiency virus type 1 infection in SCID-hu mice in a time-dependent manner. J Infect Dis 1991;163:625-7.
13. Ruprecht RM, O'Brien LG, Rossoni LD, Nusinoff-Lehrman S. Suppression of mouse viraemia and retroviral disease by 3′-azido-3′-deoxythymidine. Nature 1986;323:467-9.
14. Sharpe AH, Jaenisch R, Ruprecht RM. Retroviruses and mouse embryos: a rapid model for neurovirulence and transplacental antiviral therapy. Science 1987;236:1671-4.
15. Sharpe AH, Hunter JJ, Ruprecht RM, Jaenisch R. Maternal transmission of retroviral disease: transgenic mice as a rapid test system for evaluating perinatal and transplacental antiretroviral therapy. Proc Natl Acad U S A 1988;85:9792-6. [Erratum, Proc Natl Acad Sci U S A 1989;86: 2045.]
16. Van Rompay KK, Marthas ML, Ramos RA, et al. Simian immunodeficiency virus (SIV) infection of infant rhesus macaques as a model to test antiretroviral drug prophylaxis and therapy: oral 3′-azido-3′-deoxythymidine prevents SIV infection. Antimicrob Agents Chemother 1992;36:2381-6.
17. Ha JC, Nosbisch C, Conrad SH, et al. Fetal toxicity of zidovudine (azidothymidine) in *Macaca nemestrina:* preliminary observations. J Acquir Immune Defic Syndr 1994;7:154-7.

18. Sperling RS, Roboz J, Dische R, Silides D, Holzman, I, Jew E. Zidovudine pharmacokinetics during pregnancy. Am J Perinatol 1992;9:247-9.
19. Watts DH, Brown ZA, Tartaglione T, et al. Pharmacokinetic disposition of zidovudine during pregnancy. J Infect Dis 1991;163:226-32.
20. O'Sullivan MJ, Boyer PJ, Scott GB, et al. The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women infected with human immunodeficiency virus and their infants: phase I acquired immunodeficiency syndrome clinical trials group study (protocol 082). Am J Obstet Gynecol 1993;168:1510-6.
21. Sperling RS, Stratton P, O'Sullivan MJ, et al. A survey of zidovudine use in pregnant women with human immunodeficiency virus infection. N Engl J Med 1992;326:857-61.
22. Hollinger FB, Bremer JW, Myers LE, Gold JWM, McQuay L. Standardization of sensitive human immunodeficiency virus coculture procedures and establishment of a multicenter quality assurance program for the AIDS Clinical Trials Group. J Clin Microbiol 1992;30:1787-94.
23. Calvelli T, Denny TN, Paxton H, Gelman R, Kagan J. Guidelines for flow cytometric immunophenotyping: a report from the National Institute of Allergy and Infectious Diseases, Division of AIDS. Cytometry 1993;14:702-15.
24. Rouzioux C, Puel J, Agut H, et al. Comparative assessment of quantitative HIV viraemia assays. AIDS 1992;6:373-7.
25. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
26. Cox DR. The analysis of binary data. London: Methuen, 1970.
27. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
28. Kim K, Tsiatis AA. Study duration for clinical trials with survival response and early stopping rule. Biometrics 1990;46:81-92.
29. Greenwood M. A report on the natural duration of cancer. Reports on public health and medical subjects no. 33. London: Her Majesty's Stationery Office, 1926:1-26.
30. Ho DD, Moudgil T, Alam M. Quantitation of human immunodeficiency virus type 1 in the blood of infected persons. N Engl J Med 1989;321:1621-5.
31. Volberding PA, Lagakos SW, Koch MA, et al. Zidovudine in asymptomatic human immunodeficiency virus infection: a controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. N Engl J Med 1990;322:941-9.
32. Boucher FD, Modlin JF, Weller S, et al. Phase I evaluation of zidovudine administered to infants exposed at birth to the human immunodeficiency virus. J Pediatr 1993;122:137-44.
33. Toltzis P, Mourton T, Magnuson T. Effect of zidovudine on preimplantation murine embryos. Antimicrob Agents Chemother 1993;37:1610-3.
34. Sieh E, Coluzzi ML, Cusella De Angelis MG, et al. The effects of AZT and DDI on pre- and postimplantation mammalian embryos: an in vivo and in vitro study. AIDS Res Hum Retroviruses 1992;8:639-49.
35. Comprehensive information for investigators: retrovir (1993). Research Triangle Park, N.C.: Burroughs Wellcome Co., 1993.
36. Coombs RW, Collier AC, Allain J-P, et al. Plasma viremia in human immunodeficiency virus infection. N Engl J Med 1989;321:1626-31.
37. Pons JC, Taburet AM, Singlas E, Delfraissy JF, Papiernik E. Placental passage of azathiothymidine (AZT) during the second trimester of pregnancy: study of direct fetal blood sampling under ultrasound. Eur J Obstet Gynecol Reprod Biol 1991;40:229-31.
38. Blanche S, Mayaux M-J, Rouzioux C, et al. Relation of the course of HIV infection in children to the severity of the disease in their mothers at delivery. N Engl J Med 1994;330:308-12.