

ZIDOVUDINE, DIDANOSINE, OR BOTH AS THE INITIAL TREATMENT FOR SYMPTOMATIC HIV-INFECTED CHILDREN

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ABSTRACT

Background Zidovudine has been the drug of choice for the initial treatment of symptomatic children infected with the human immunodeficiency virus (HIV). This trial was designed to assess the efficacy and safety of treatment with zidovudine alone as compared with either didanosine alone or combination therapy with zidovudine plus didanosine.

Methods In this multicenter, double-blind study, symptomatic HIV-infected children 3 months through 18 years of age were stratified according to age (<30 months or ≥30 months) and randomly assigned to receive zidovudine, didanosine, or zidovudine plus didanosine. The primary end point was length of time to death or to progression of HIV disease.

Results Of the 831 children who could be evaluated, 92 percent had never received antiretroviral therapy and 90 percent had acquired HIV perinatally. An interim analysis (median follow-up, 23 months) showed a significantly higher risk of HIV-disease progression or death in patients receiving zidovudine alone than in those receiving combination therapy (relative risk, 0.61; 95 percent confidence interval, 0.42 to 0.88; $P=0.007$). The study arm with zidovudine alone was stopped and unblinded; the other two treatment arms were continued. At the end of the study, didanosine alone had an efficacy similar to that of zidovudine plus didanosine (median follow-up, 32 months) (relative risk of disease progression or death, 0.98; 95 percent confidence interval, 0.70 to 1.37; $P=0.91$). A significantly lower risk of anemia or neutropenia was seen in patients receiving didanosine alone ($P=0.036$).

Conclusions In symptomatic HIV-infected children, treatment with either didanosine alone or zidovudine plus didanosine was more effective than treatment with zidovudine alone. The efficacy of didanosine alone was similar to that of the combination therapy and was associated with less hematologic toxicity. (N Engl J Med 1997;336:1704-12.)

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ALTHOUGH treatment with zidovudine significantly reduces the likelihood of mother-to-infant transmission of the human immunodeficiency virus (HIV),¹ perinatally acquired infections still account for the majority of new cases of the acquired immunodeficiency syndrome (AIDS) in children.^{2,3} Zidovudine

has been the recommended treatment for these children, but controlled trials have not been conducted to compare it with other antiretroviral agents or combination therapies in children. Recent studies in adults suggest that combination antiretroviral regimens, particularly those including protease inhibitors, may prolong the period of HIV nonprogression,⁴ but comparable studies have not been done in children. In this study, we compared zidovudine or didanosine monotherapy with combination therapy with both agents. Earlier, uncontrolled pediatric therapeutic trials have evaluated antiretroviral efficacy on the basis of clinical assessments.⁵⁻⁹ In this study, clinical end points of HIV disease progression — including changes in weight growth; neurologic development and neurocognitive test scores; the development of opportunistic infections; and death — were used to evaluate therapeutic efficacy.

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METHODS

Study Sample

The study was conducted at 78 hospitals in the United States and Puerto Rico that are affiliated with the AIDS Clinical Trials Group (ACTG) or the National Institute of Child Health and Human Development. HIV-infected children were enrolled from August 19, 1991, through August 31, 1993. In children less than 15 months of age, clinical findings of HIV infection, such as failure to thrive or lymphadenopathy, were required. Immunologic abnormalities, including a CD4+ cell count of less than 1000 per cubic millimeter, a ratio of helper to suppressor cells of 0.9 or less, or hyper- or hypogammaglobulinemia, were required in children less than 15 months of age whose only laboratory abnormality was a positive test for HIV antibody. For children 15 months to 18 years of age, entry criteria included either clinical symptoms of HIV infection or immunologic abnormalities (a CD4+ cell count of less than 500 per cubic millimeter, a helper:suppressor ratio of 0.9 or less, or hyper- or hypogammaglobulinemia).

Patients were excluded from the study if they had received six or more weeks of antiretroviral or specific immunomodulator therapy or had cancer, a history of pancreatitis within the previous year, uncontrolled seizure disorder, severe peripheral neuropathy, or serious hematologic or chemical abnormalities.¹⁰ The protocol was approved by each institution's human-subjects review board. Informed consent was obtained from the patients' parents or guardians and from the children themselves, if appropriate.

Study Design

This study was a randomized, double-blind clinical trial. Study patients were stratified according to age at entry — 3 months to less than 30 months or 30 months to 18 years — and randomly assigned in equal proportions to one of the three treatment regimens: zidovudine (180 mg per square meter of body-surface area every 6 hours, with didanosine placebo), didanosine (120 mg per square meter every 12 hours, with zidovudine placebo), or a combination of zidovudine (120 mg per square meter every 6 hours) and didanosine (90 mg per square meter every 12 hours). The study duration was 104 weeks for the last enrolled patient. The primary end point was length of time to first progression of HIV disease or to death, and was analyzed according to the initial randomized therapy. Disease progression was defined as the development of cancer, weight-growth failure, two or more opportunistic infections, or two or more abnormalities of the central nervous system (neurologic deterioration, a decline in neurocognitive test scores, or brain-growth failure). All cases of potential disease progression were reviewed by a study physician unaware of the treatment assignments. If progression of HIV disease was confirmed in a child assigned to one of the monotherapy arms, that child was crossed over to alternative monotherapy by a blinded method. Children with confirmed disease progression who were receiving combination therapy had their treatment permanently discontinued and were evaluated clinically every 12 weeks.

Primary End Points

The patients were weighed at the time of enrollment and every four weeks thereafter. Percentiles at base line were calculated as previously described.¹⁰ Weight-growth failure was defined as a weight-growth velocity under the third percentile¹¹ at week 24 or two consecutive 6-month growth velocities under the third percentile after more than 24 weeks of study follow-up.

Neurologic examinations and age-appropriate neuropsychological and neurocognitive tests were performed within 14 days before enrollment and according to an age-appropriate schedule thereafter.¹⁰ Neurocognitive decline was defined as the absence of any increase in raw scores or a decline in normalized scores by 2 SD for children under 30 months of age or by 1 SD for older children. Deterioration in neurologic function was defined as the loss of previously documented motor skills, reflexes, or behavior. Neuroimaging of the head was performed within 30 days of en-

rollment and every 96 weeks thereafter or as indicated. For children under 24 months of age, head circumferences were measured at entry and monthly thereafter. Brain-growth failure was defined as a growth decline that crossed two percentile lines or failed to parallel the fifth-percentile line over three or more consecutive measurements, or as increased cerebral atrophy as measured by sequential imaging studies.

At least two new serious opportunistic infections were required for the disease-progression end point. These included biopsy-proved *Pneumocystis carinii* pneumonia; bacterial meningitis; pneumonia with bacteremia; biopsy-proved esophageal candidiasis or lymphoid interstitial pneumonitis; disseminated viral, fungal, or mycobacterial infection; or two separate episodes of recurrent herpes simplex or varicella-zoster virus infection or bacteremia.

Laboratory Assessments

Hemoglobin, the white-cell count, the platelet count, and blood chemistries were measured before therapy. If total amylase values were elevated, serum samples were fractionated to determine whether the origin was salivary or pancreatic. Lymphocyte-subgroup analysis was performed by using standard flow-cytometric methods.¹² A positive serum p24 antigen test was defined as ≥ 15 pg of p24 antigen per milliliter; all lower values were defined as half that level. The p24 assay was performed according to standard ACTG procedures with commercially available kits as specified by the manufacturer.¹²

Drug Toxicity

Adverse experiences and toxic effects were assessed every 4 weeks until 12 weeks after the discontinuation of the study drugs. Serious toxic effects requiring dose modification included a hemoglobin concentration of less than 7.5 g per deciliter, an absolute neutrophil count of 500 cells or fewer per cubic millimeter, a pancreatic amylase concentration more than three times the upper limit of normal, serious hepatic dysfunction, or clinical gastrointestinal, neurologic, or allergic toxicity.

Statistical Analysis

Base-line characteristics were compared among treatment groups by using the chi-square test for categorical variables, analysis of variance for normally distributed continuous variables, and the Kruskal-Wallis test for ordered scores.¹³ Distributions of the time to first event were estimated by using the Kaplan-Meier method, and pairwise treatment comparisons were made with the log-rank test, with stratification according to age.¹⁴ The intention-to-treat approach was used for analyses of clinical end points, except that eight patients were excluded at base line. Cox proportional-hazards models¹⁴ were used to estimate relative risks and confidence intervals (unadjusted for interim monitoring) and to investigate the role of prognostic factors. Only assessments made while patients were receiving the initial therapy were included in analyses of toxicity, CD4+ counts, and p24 antigen levels. All P values are two-sided and unadjusted for multiple comparisons.

The target sample size of the study was based on the primary treatment comparison of the length of time to progression of HIV-related disease or to death for children of all ages. The study was designed so that if any interim analysis of two treatments showed a difference at a predetermined level, discontinuation of the inferior treatment arm would be considered. The study was reviewed five times by the Data and Safety Monitoring Board before the final analysis. The O'Brien-Fleming boundary¹⁵ was used to account for multiple evaluations of the data, with the Lan-DeMets approach¹⁶ used to allow flexibility in the timing of the interim analyses.

Unblinding of the Zidovudine-Monotherapy Arm

The fifth review by the Data and Safety Monitoring Board, based on data collected through November 16, 1994, resulted in a recommendation that treatment for participants still receiving initial zidovudine monotherapy be unblinded, since a significantly

higher risk of disease progression and toxicity had been observed in this group. Further antiviral therapy in these subjects was at the discretion of the treating physician. For participants receiving initial didanosine therapy, initial combination therapy, or crossover monotherapy, treatment remained blinded until the end of the study (August 31, 1995). Because of the unblinding of the zidovudine arm, two separate analyses were conducted: an interim analysis for all pairwise treatment comparisons involving the zidovudine-monotherapy group (data through November 16, 1994), and a final analysis for pairwise comparisons of didanosine monotherapy and combination therapy (data through study closure).

RESULTS

Accrual and Eligibility

A total of 839 children from 27 ACTG sites (543 children), 26 National Institute of Child Health and Human Development sites (294), and one National Institute of Allergy and Infectious Diseases–National Hemophilia Foundation site (2) in 20 states and Puerto Rico were randomized. Eight children were excluded from analysis: seven because treatment was refused after randomization and one because more

than six weeks of zidovudine therapy before randomization was documented.

Characteristics of the Subjects

Four hundred fifty of the 831 children (54 percent) were less than 30 months of age at the time of enrollment (Table 1). Children were predominantly from minority racial or ethnic groups, and more than 90 percent had acquired HIV perinatally.¹⁰ Only 64 participants (8 percent) were known to have already received antiretroviral therapy; for 59 of those children, this therapy was known to be zidovudine. Only 29 children were born to mothers who had received zidovudine therapy during their gestation.

Children under 30 months of age consistently had more signs and symptoms of HIV infection than older children.¹⁰ Overall, the treatment groups were well balanced with regard to base-line demographic, clinical, and laboratory characteristics, with two exceptions: abnormalities in motor function (global

TABLE 1. BASE-LINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE 831 CHILDREN IN THE STUDY.

CHARACTERISTIC	ZIDOVUDINE	DIDANOSINE	ZIDOVUDINE	TOTAL
			PLUS DIDANOSINE	
Total patients analyzed — no. (%)	276	281	274	831
Age <30 mo	149 (54.0)	153 (54.4)	148 (54.0)	450 (54.2)
Age ≥30 mo	127 (46.0)	128 (45.6)	126 (46.0)	381 (45.8)
Age — yr				
Mean	3.7	3.9	3.7	3.8
25th percentile	0.8	0.8	0.8	0.8
Median	2.1	2.3	2.2	2.2
75th percentile	5.8	5.5	5.2	5.5
Sex — % male	52.2	53.4	51.1	49.9
Race or ethnicity — %				
White, non-Hispanic	11.6	13.1	16.8	13.8
Black, non-Hispanic	56.5	55.9	50.0	54.2
Hispanic	30.4	28.5	31.0	30.0
Other	1.5	2.5	2.2	2.0
Perinatally acquired HIV (suspected)	90.6	88.9	91.5	90.3
— % of 825				
Previous antiretroviral therapy for	8.0	7.7	8.5	8.0
≤6 wk — % of 796				
Birth weight <2500 g — % of 776	27.7	27.4	21.9	25.6
p24 antigen ≥15 pg/ml — % of 747	40.8	35.9	41.7	39.5
HIV+ culture — % of 710	87.5	91.0	86.4	88.3
Median no. of CD4+ cells/mm ³	775	822	808	809
(n = 820)				
Weight for age and sex <5th percentile				
— % of 828				
All patients	27.0	25.0	25.2	25.7
Age <30 mo	42.3	35.3	35.1	37.6
Age ≥30 mo	8.8	12.6	13.5	11.6
Cortical atrophy — % of 797*	13.9	13.1	11.0	12.7
Any known neurologic abnormality	38.4	30.0	36.7	35.0
— % of 818*				
Valid cognitive tests with cognitive score	24.1	20.6	24.2	22.9
<70 — % of 728*				
Previous serious opportunistic infections — %	12.0	17.1	12.4	13.8

*Results of computed tomographic scanning and magnetic resonance imaging and of neurologic and cognitive assessments up to 30 days after the protocol treatment was dispensed were included as base-line assessments in the analysis if these data were not available before study entry.

P=0.04) and tendon reflexes (global P=0.006) were less prevalent among patients randomly assigned to didanosine monotherapy.

Interim Analysis: Pairwise Comparisons of Zidovudine versus Didanosine and Zidovudine versus Combination Therapy

Primary End Points

The median follow-up period for survival and progression of HIV-related disease from entry into the study until November 16, 1994, is summarized in Table 2, as is the median length of time of initial therapy. A total of 686 children (83 percent) were still being studied and 496 (60 percent) were receiving the initial randomized treatment at the time of this interim analysis. The times to first HIV-disease progression or death for the three treatment groups are shown in Figure 1. By the time of the interim analysis, 176 children (21 percent) had reached a primary end point. Primary end points had been reached by 27 percent of the children randomly assigned to receive zidovudine, 19 percent of those randomly assigned to receive didanosine, and 18 percent of those randomly assigned to receive combination therapy. The log-rank P value for zidovudine as

compared with combination therapy, stratified according to age group, was less than that specified by the protocol as indicating that the inferior treatment should be discontinued, and therefore the unblinding of the zidovudine arm was recommended. The difference between didanosine and zidovudine did not reach statistical significance. The relative risk of disease progression or death for children receiving combination therapy as compared with those receiving zidovudine, stratified according to age, was 0.61 (95 percent confidence interval, 0.42 to 0.88), and for those receiving didanosine alone as compared with those receiving zidovudine it was 0.69 (95 percent confidence interval, 0.49 to 0.98). The estimated effects of combination therapy or didanosine as compared with zidovudine were greater within the younger stratum. However, the differences in relative risks between age strata were not statistically significant.

The majority of the end points were in children under 30 months of age at randomization (Table 2). Eighty-nine percent occurred while the subjects were receiving the initial randomized therapy. Because of the significant differences in the percentages of children with motor dysfunction and tendon-reflex ab-

TABLE 2. FOLLOW-UP AND PRIMARY END POINTS IN PATIENTS RANDOMLY ASSIGNED TO RECEIVE INITIAL ZIDOVUDINE, DIDANOSINE, OR COMBINATION THERAPY.

	INTERIM ANALYSIS				FINAL ANALYSIS		
	ZIDOVUDINE	DIDANOSINE	ZIDOVUDINE PLUS DIDANOSINE	TOTAL	DIDANOSINE	ZIDOVUDINE PLUS DIDANOSINE	TOTAL
Follow-up							
Total patients analyzed	276	281	274	831	281	274	555
Age <30 mo	149	153	148	450	153	148	301
Age ≥30 mo	127	128	126	381	128	126	254
Median months of follow-up	23	23	23	23	32	33	32
Median months receiving initial therapy	19	20	20	20	28	28	28
Deceased — no. (%)	31 (11)	20 (7)	23 (8)	74 (9)	31 (11)	33 (12)	64 (12)
Lost to follow-up — no. (%)	27 (10)	24 (9)	20 (7)	71 (9)	35 (12)	24 (9)	59 (11)
Prematurely discontinued — no. (%)*	73 (26)	68 (24)	59 (22)	200 (24)	77 (27)	67 (24)	144 (26)
Primary end points — no. (%)							
Weight-growth failure	36 (13)	31 (11)	26 (9)	93 (11)	33 (12)	37 (14)	70 (13)
Age <30 mo	22 (15)	17 (11)	13 (9)	52 (12)	18 (12)	19 (13)	37 (12)
Age ≥30 mo	14 (11)	14 (11)	13 (10)	41 (11)	15 (12)	18 (14)	33 (13)
CNS deterioration (≥2 criteria)†	16 (6)	12 (4)	8 (3)	36 (4)	17 (6)	8 (3)	25 (5)
Age <30 mo	14 (9)	10 (7)	7 (5)	31 (7)	14 (9)	7 (5)	21 (7)
Age ≥30 mo	2 (2)	2 (2)	1 (1)	5 (1)	3 (2)	1 (1)	4 (2)
Other or multiple disease progression‡	5 (2)	4 (1)	4 (1)	13 (2)	8 (3)	11 (4)	19 (3)
Age <30 mo	2 (1)	3 (2)	4 (3)	9 (2)	5 (3)	8 (5)	13 (4)
Age ≥30 mo	3 (2)	1 (1)	0	4 (1)	3 (2)	3 (2)	6 (2)
Death	17 (6)	7 (2)	10 (4)	34 (4)	9 (3)	12 (4)	21 (4)
Age <30 mo	17 (11)	6 (4)	8 (5)	31 (7)	8 (5)	8 (5)	16 (5)
Age ≥30 mo	0	1 (1)	2 (2)	3 (1)	1 (1)	4 (3)	5 (2)
Total primary end points	74 (27)	54 (19)	48 (18)	176 (21)	67 (24)	68 (25)	135 (24)
Age <30 mo	55 (37)	36 (24)	32 (22)	123 (27)	45 (29)	42 (28)	87 (29)
Age ≥30 mo	19 (15)	18 (14)	16 (13)	53 (14)	22 (17)	26 (21)	48 (19)

*Therapy was discontinued for reasons other than death or disease progression.

†CNS denotes central nervous system.

‡Patients had two opportunistic infections, cancer, or more than one disease-progression end point reached on the same date.

normalities at study entry, additional analyses of the primary end points were conducted with adjustments for these base-line neurologic abnormalities. Motor function ($P=0.002$) and tendon reflexes ($P=0.05$) were significantly associated with outcome. The estimated relative risk of disease progression or death for children randomly assigned to combination therapy as compared with zidovudine changed from 0.61 to 0.66 after adjustment for these abnormalities. The relative risk for didanosine as compared with zidovudine changed from 0.70 to 0.78.

No significant differences in survival were noted among treatment groups at the interim analysis. The relative risks of death for the didanosine and combi-

nation-therapy groups as compared with the zidovudine group were 0.63 (95 percent confidence interval, 0.36 to 1.10; $P=0.10$) and 0.75 (95 percent confidence interval, 0.43 to 1.28; $P=0.28$), respectively.

CD4+ Lymphocytes and p24 Antigen

At week 4, CD4+ cell counts were not significantly different in the zidovudine and didanosine groups but were higher in the combination-therapy group as compared with the zidovudine group ($P<0.001$) (Fig. 2). At 96 weeks, CD4+ cell counts were 85 percent higher in the children receiving didanosine and 76 percent higher in the children receiving com-

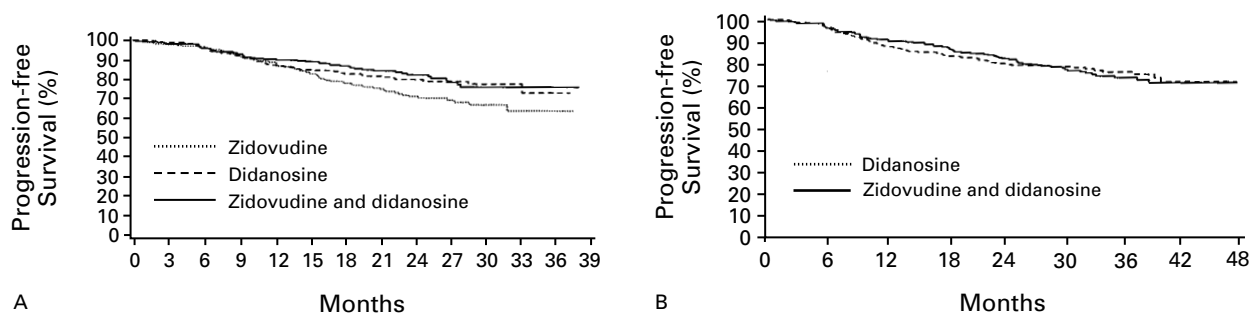
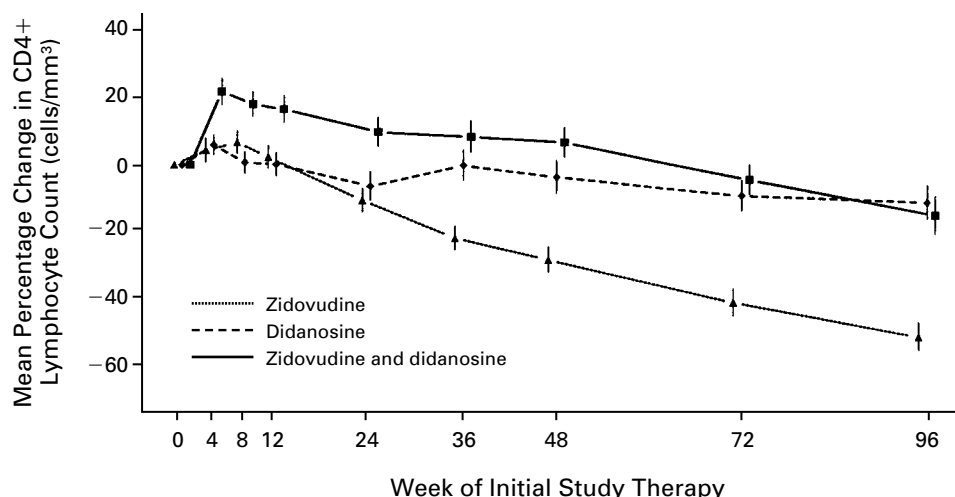


Figure 1. Progression-free Survival at Interim (Panel A) and Final (Panel B) Analyses.

The log-rank P value for the comparison of zidovudine monotherapy with the combination of zidovudine plus didanosine stratified according to age (<30 vs. ≥ 30 months) was 0.007; this was statistically significant when the specified guideline for terminating an inferior treatment was used. The stratified log-rank P value for the comparison of zidovudine monotherapy with didanosine monotherapy was not statistically significant when the prespecified guideline for terminating an inferior treatment was used. The log-rank P value for the comparison of didanosine monotherapy with combination therapy stratified according to age (<30 vs. ≥ 30 months) did not indicate significant differences between treatment groups ($P=0.91$).



	number of patients								
Zidovudine	273	235	232	241	237	225	210	165	107
Didanosine	278	242	245	245	231	216	211	174	115
Zidovudine and didanosine	269	237	226	236	233	219	212	166	117

Figure 2. Mean (\pm SE) Percent Change from Base Line in CD4+ Lymphocyte Counts at Interim Analysis.

combination therapy ($P < 0.001$ for both) than in the children receiving zidovudine alone.

Of the 295 subjects who had detectable p24 antigen at base line, 81 percent became negative for the antigen or had a reduction of their p24 antigen level of 50 percent or more while receiving initial therapy (80 percent of those in the zidovudine group; 75 percent of those in the didanosine group; 88 percent of those in the combination-therapy group). After four weeks of therapy, the mean percent reduction in p24 antigen in children receiving didanosine was smaller than that in those receiving zidovudine ($P = 0.003$), whereas no significant difference was seen between the combination and zidovudine groups. By week 48, p24 antigen levels were more than 40 percent lower for both the combination and didanosine groups than for the zidovudine group ($P < 0.02$ for both). For patients who were p24-negative at entry, the time until the first positive test for p24 antigen while the patient was receiving initial therapy was significantly longer for both those receiving didanosine ($P = 0.007$) and those receiving combination therapy ($P = 0.04$) than for those receiving zidovudine.

Toxic Effects

Toxic effects serious enough to result in the discontinuation of initial treatment were uncommon and were equally distributed among the three groups (24 patients, 2.9 percent). Clinical pancreatitis resulted in the discontinuation of initial therapy for only two children (one receiving zidovudine and one receiving combination therapy). Substantial elevations in pancreatic amylase levels without clinical

pancreatitis led to changes in treatment in two children receiving zidovudine and one receiving combination therapy.

Serious toxic effects on hemoglobin or neutropenia were more common among patients receiving initial zidovudine therapy (32 percent) than among those receiving either didanosine (14 percent) or combination therapy (18 percent) ($P < 0.001$ for both) (Table 3). The relative risk of serious hematologic toxicity for didanosine as compared with zidovudine, stratified according to age, was 0.37; for combination therapy as compared with zidovudine it was 0.49.

Fewer patients receiving combination therapy had elevated alanine aminotransferase and total amylase levels than did those receiving zidovudine. The time until the first serious chemical toxic effect was significantly shorter in zidovudine recipients ($P = 0.02$). The estimated relative risk of serious chemical toxicity for combination therapy as compared with zidovudine, stratified according to age group, was 0.60 (95 percent confidence interval, 0.39 to 0.93). No significant difference was noted between didanosine and zidovudine.

Final Analysis: Didanosine versus Combination Therapy

Primary End Points

At study closure, 317 (57 percent) of the 555 children initially enrolled in the didanosine and combination groups were still receiving the initial randomized treatment and 432 (78 percent) had completed the study. The median follow-up for survival and disease progression is shown in Table 2. The lengths of time until progression of HIV disease or death,

TABLE 3. LABORATORY TOXIC EFFECTS IN PATIENTS RECEIVING INITIAL ZIDOVUDINE, DIDANOSINE, OR COMBINATION THERAPY.

TOXIC EFFECT	INTERIM ANALYSIS			FINAL ANALYSIS	
	ZIDOVUDINE	DIDANOSINE	ZIDOVUDINE PLUS DIDANOSINE	ZIDOVUDINE PLUS DIDANOSINE	ZIDOVUDINE PLUS DIDANOSINE
	number of patients (percent)				
Hematologic					
Absolute neutrophil count $\leq 500/\text{mm}^3$	74	28	40	32	51
Hemoglobin $< 7.5 \text{ g/dl}$	26	11	13	13	19
Either	89 (32.2)	38 (13.5)	49 (17.9)	42 (14.9)	63 (23.0)
Chemical*					
ALT $\geq 10 \times \text{ULN}$	18	14	5	14	6
Total bilirubin $\geq 2.6 \times \text{ULN}$	10	9	10	10	12
Hepatic, unspecified type	3	4	2	4	2
Total amylase $> 3 \times \text{ULN}^\dagger$	30	14	20	16	20
Any of the above	52 (18.8)	39 (13.9)	33 (12.0)	42 (14.9)	35 (12.8)

*ALT denotes serum alanine aminotransferase, and ULN upper limit of normal (laboratory-specific).

† Dose modification was not required for elevated total amylase unless there was clinical evidence of pancreatitis or unless pancreatic amylase was found to be > 3 times the upper limit of normal. Pancreatic amylase was not measured routinely in ACTG Study 152.

according to the initial randomized treatment, are shown in Figure 1B. Primary end points were reached by 24 percent of the children receiving didanosine and 25 percent of those receiving combination therapy ($P=0.91$). The relative risk of disease progression or death for children receiving didanosine as compared with combination therapy, stratified according to age, was 0.98 (95 percent confidence interval, 0.70 to 1.37). The relative risk of a primary end point for the patients receiving didanosine as compared with those receiving combination therapy, stratified according to age group, changed to 1.04 (95 percent confidence interval, 0.68 to 1.35) after adjustment for base-line differences in motor function and tendon reflexes.

Eighty-four percent of the primary end points occurred while the children were receiving the initial randomized therapy (88 percent of those in the didanosine group; 81 percent of those in the combination-therapy group). The majority of the 135 end points (52 percent) were weight-growth failures; 84 percent of the central nervous system end points occurred in children under 30 months of age at entry (Table 2). Fewer instances of central nervous system deterioration and more weight-growth failures, cancers, and deaths occurred as primary end points in the combination-therapy group than in the didanosine group. However, a global test comparing the overall pattern of end points showed no significant difference between the two treatment groups.

Similar numbers of deaths occurred in the children receiving didanosine and those receiving combination therapy; the relative risk of death was 0.92 (95 percent confidence interval, 0.56 to 1.50; $P=0.73$).

CD4+ Lymphocytes and p24 Antigen

The mean percent increase in CD4+ cell counts after four weeks of therapy was 22 percent in the children receiving combination therapy and 6 percent in those receiving didanosine ($P<0.001$). This early beneficial effect of combination therapy was not maintained; the mean percent changes in the numbers of CD4+ cells were similar in the two groups by week 96.

For patients who tested positive for p24 antigen at base line, the level at week 4 was 52 percent lower in the combination-therapy recipients than in the didanosine-monotherapy recipients ($P<0.001$). The beneficial effect of combination therapy was not maintained after 24 weeks. For patients who tested negative for p24 antigen at base line, the length of time until a test was positive was similar in both treatment groups.

Toxic Effects

No laboratory or clinical toxic effects resulting in the discontinuation of initial treatment occurred after the interim analysis. Serious anemia or neutrope-

nia developed in more subjects receiving initial combination therapy than subjects receiving didanosine ($P=0.036$ by stratified log-rank test) (Table 3). The relative risk of serious anemia or neutropenia in patients receiving didanosine as compared with those receiving combination therapy, stratified according to age group, was 0.66 (95 percent confidence interval, 0.45 to 0.98). The difference was primarily due to a lower risk of hematologic toxicity in older didanosine recipients. Within the younger stratum, a significant difference was not observed. No significant difference was observed in the length of time until the first serious chemical toxicity.

DISCUSSION

The superiority of didanosine monotherapy and combination zidovudine and didanosine over zidovudine alone for the initial treatment of symptomatic HIV-infected children who have never received antiretroviral therapy is a new and important clinical finding. It is supported by recent clinical trials in adults. The ACTG 175 study demonstrated that didanosine monotherapy and combination therapy with zidovudine plus didanosine or zidovudine plus zalcitabine were superior to zidovudine monotherapy in adults who had never taken antiretroviral drugs.¹⁷ In those adults, only the combination of zidovudine and zalcitabine was clinically superior to zidovudine monotherapy; both didanosine monotherapy and didanosine combined with zidovudine were superior when clinical and CD4+ end points were combined. The Delta trial, which compared zidovudine monotherapy with combination therapies of zidovudine plus didanosine and zidovudine plus zalcitabine, also reported that either combination was superior to zidovudine monotherapy.¹⁸ These results, taken together, have led to the licensure of didanosine as monotherapy or in combination with other agents in the initial treatment of HIV-infected patients of all ages.

Study compliance and follow-up in this large multicenter clinical trial were good, with nearly 90 percent of the children initially randomly assigned to didanosine or to combination therapy with zidovudine plus didanosine remaining in the study (i.e., receiving study therapy, being followed while receiving the alternative therapy, or dead) at study closure. The completeness of follow-up in this study compares favorably with that reported in recent studies in adults.^{17,18} In comparison with the children in earlier pediatric antiretroviral trials,⁵⁻⁹ the HIV-infected children in this study were remarkable in their high rate of perinatal HIV acquisition and the wide range of underlying abnormalities in growth, development, and cognitive ability. The stratification of children into two age groups was initially based in part on the neurocognitive tools available and on head-growth measures used to assess clinical end points. Because younger children had significantly higher rates of ab-

normalities in factors relating to weight-growth status, neurologic and neurocognitive function, and brain atrophy,¹⁰ the stratification used in this study also appears to be clinically relevant.

Children were enrolled in this study before the use of antiretroviral therapy during pregnancy became widespread, and the number of subjects exposed to zidovudine before study entry, either in utero or after birth, was low. Thus, exposure to antiretroviral drugs and potential antiretroviral-drug resistance in the mothers' or children's early HIV isolates were unlikely to have had a role in the study outcome. Laboratory assessments of viral load and resistance are under way and may lead to better understanding of clinical disease and the effects of antiviral therapy.

This study demonstrated that the risk of reaching a primary end point was higher in children who received zidovudine monotherapy than in those who received either didanosine monotherapy or zidovudine plus didanosine. Unlike many other antiretroviral agents, zidovudine penetrates well into the central nervous system.¹⁹ Before this study, antiretroviral regimens that included zidovudine were postulated to protect children better from HIV-related neurologic deterioration. Our results do not support this hypothesis. Zidovudine monotherapy was also associated with a significantly higher risk of drug toxicity than the other treatments on the basis of the length of time until the first episode of hematologic toxicity. At the time of the final analysis, fewer patients with serious toxic effects on the hemoglobin concentration and absolute neutrophil counts were found among didanosine recipients than among combination-therapy recipients. It is noteworthy that the dose of zidovudine used for monotherapy was 50 percent higher than that used for combination therapy (180 mg per square meter per day vs. 120 mg per square meter per day).

Despite growing optimism that combination antiviral regimens, particularly those that include a protease inhibitor, can delay disease progression and prolong survival in HIV-infected adults, serious hurdles must be overcome before such therapy can be routinely applied to pediatric patients. Important problems remain, such as the lack of data to ensure safe and effective dosing and the unavailability of these drugs in palatable suspension.^{20,21} The issue of compliance with complex treatment regimens must be considered because of the inability of some patients to adhere to rigid dosing schedules. Although protease inhibitors appear promising, data substantiating the superiority of combinations containing protease inhibitors to nucleoside analogues in children are not yet available.

In summary, zidovudine monotherapy was significantly less efficacious and caused more anemia and neutropenia than combination therapy with zidovu-

dine and didanosine. Didanosine monotherapy had an efficacy similar to that of combination therapy as measured by clinical end points and was associated with significantly less hematologic toxicity. When reviewed in the context of efficacy, toxicity, expense, and ease of administration, the results of this randomized, double-blind trial support the use of didanosine as initial therapy in HIV-infected children who have not previously received antiretroviral therapy.

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APPENDIX

The following centers and investigators, listed in order of the numbers of patients enrolled, participated in this study. Columbia University: J. Pitt, B. Tang, and P. La Russa; Children's Hospital of New Jersey/University of Medicine and Dentistry of New Jersey-New Jersey Medical School, and St. Joseph's Hospital and Medical Center: J. Oleske, E. Connor, and N. Hutcheon; Harlem Hospital, New York: S. Champion, D. Calo, and M. Frere; Albert Einstein College of Medicine: L. Bernstein, A. Rubinstein, and M. Sicklick; San Juan City Hospital: M.T. Carrer, L. Ortiz, and M.M. Ramos; University of Massachusetts Medical Center: K. Luzuriaga, B. Stechenberg, and J. Robinson; State University of New York Health Science Center, Brooklyn: H. Moallem, S. Wiltshire, and D. Swindell; Children's Memorial Hospital, Chicago: R. Yogev, E. Chadwick, C. Booth, and D. Johnson; St. Jude Research Hospital: J. Shenep, W. Hughes, P. Flynn, and K. Slobod; Children's Hospital of Philadelphia: H. Lischner, A. Kamrin, R. Rutstein, and S. Starr; Johns Hopkins University and University of Maryland: N. Hutton, R. Livingston, P. Vink, and J. Farley; Children's Hospital, Boston: K. McIntosh, S.I. Pelton, A. Rubin-Hale, and K. Burke; University of California, San Francisco: A. Dorenbaum, A. Petru, and D. Trevithick; Baylor College of Medicine: N. Calles, M.W. Kline, M. Doyle, and W.T. Shearer; Bellevue Hospital: W. Borkowsky; Children's Hospital, Washington, D.C.: T.A. Rakusan; Duke University: M. Valentine and B. Lane; Bronx Lebanon Hospital: A. Wiznia, J. Dobroszycki, P. Cihak, and C. Opedal; Mt. Sinai Medical Center: H.S. Sacks, D. Hodes, and S. Heaton; State University of New York, Stony Brook: S.A. Nachman, D. Hickey, M. Davi, and J. Sigwart; R. Wood Johnson University Hospital: L. Frenkel, S. Gaur, R. Scudder, and K. Stralkus; R. Ruiz Arnau University Hospital: D. Garcia-Tria, R. Aguayo Reyes, and L. Diaz; Kings County Hospital Center: H. Bergin, E. Handelsman, and V. Shah; University of California, San Diego: W.M. Dankner, L. Stangl, and M. Caffery; Howard University: S. Rana, H. Finke, T. Dawkins, and D.C. Mark; Los Angeles County-University of Southern California Medical Center: A. Kovacs, M. Khoury, and J. Ono; Children's Hospital of Michigan: D.D. Harrison, E.C. Moore, and C. Cromer; North Shore University Hospital: S.G. Pahwa, S.S. Bakshi, E.T. Cupelli, and Z. Tagupa; Metropolitan Hospital Center: M. Bamji, S. Inamdar, K. Novita, and G. Kennedy; UCLA Medical Center: P. Krogstad, V. Wong, A. Deveikis, and M. Keller; University of Rochester School of Medicine and Dentistry: F. Gigliotti and G.A. Weinberg; Westchester Hospital: A. Gupta, K. Li, L. Shand, and E. Ahern; Denver Children's Hospital: M.J. Levin, E.J. McFarland, and C. Salbenblatt; State University of New York, Syracuse: L.B. Weiner, C.K. Cunningham, and K.A. Contello; Tulane University School of Medicine: R. Van Dyke, P.A. Sirois, D. Sokol, and T. Alchediak; University of North Carolina, Chapel Hill: W. Lim and V. Dudek; Cornell Pediatric AIDS Clinical Trials Unit: J.S. Cervia, G. Hinds, A.M. Dunn, and D. Pearson; Emory University: S.R. Nesheim, M.K. Sawyer, J.C. Sarver, and L. Meadows; Schneider Children's Hospital: V.R. Bonagura, S.J. Schuval, C. Colter, and R. Rosenthal; Children's Hospital and Medical Center, Seattle: L.M. Frankel, A.J. Melvin, K. Mohan, and J. Ruthberg-Self; Children's Medical Center, Dallas: P. Hicks, A. Finegan, P. Lualien, and M. Mallory; Medical University of South Carolina: G.M. Johnson and G. Connelly; New York Medical College: K. Shah, S. Roa, A. Cintron, and N. Villaria; University of Illinois: K.C. Rich, K. Hayani, C. Everett, and D. Turpin; Yale University: W. Andiman and S. Romano; Case Western Reserve University: P. Toltzis and I. Adkins; Cincinnati Children's Hospital: R. Baker, N. McOwen, P. Daniel, and C. Paulson-White; Hershey Medical Center: J.H. Dossett, M.E. Eyster, and L. Dubble; University of Miami: C.D. Mitchell,

B. Haliburton-Jones, and C. Mendoza; Children's Hospital at Albany Medical Center: N. Wade, M. Lepow, and M.E. Adams; Children's Hospital, Columbus: M.T. Brady, J. Hunkler, K.L. Koranyi, and C. Callaway; Huntington Memorial Hospital; Rhode Island Hospital, Brown University: P. Smith, C. Flynn, C. Kneut, and B.M. Tavares; R. Wood Johnson Hemophilia Center: H.C. Kim; St. Luke's-Roosevelt Hospital; University of Alabama, Birmingham: M. Crain, M. Sturdevant, and M. Cooney; University of Puerto Rico: C. Diaz, L. Lugo, B. Beauchamp, and C. Rivera; Data Management Center: K. Coughlin, B. Cunningham, and B. Lunghofer; and ACTG Operations Center, Social and Scientific Systems: M. Thompson, S. Bradley, and B. Wells.

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