

A CONTROLLED TRIAL OF ZIDOVUDINE IN PRIMARY HUMAN IMMUNODEFICIENCY VIRUS INFECTION

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Abstract *Background.* It is possible that antiretroviral treatment given early during primary infection with the human immunodeficiency virus (HIV) may reduce acute symptoms, help preserve immune function, and improve the long-term prognosis.

Methods. To assess the effect of early antiviral treatment, we conducted a multicenter, double-blind, placebo-controlled trial in which 77 patients with primary HIV infection were randomly assigned to receive either zidovudine (250 mg twice daily; $n = 39$) or placebo ($n = 38$) for six months.

Results. The mean time from the onset of symptoms until enrollment in the study was 25.1 days. Among the 43 patients who were still symptomatic at the time of enrollment, there was no appreciable difference in the mean (\pm SE) duration of the retroviral syndrome between the zidovudine group (15.0 ± 4.1 days) and the placebo group (15.8 ± 3.6 days). During a mean follow-up period of 15 months, minor opportunistic infections developed in eight

patients: oral candidiasis in four, herpes zoster in two, and oral hairy leukoplakia in two. Disease progression was significantly less frequent in the zidovudine group (one opportunistic infection) than in the placebo group (seven opportunistic infections; $P = 0.009$ by the log-rank test). After adjustment for the base-line CD4 cell count, the patients treated with zidovudine had an average gain of 8.9 CD4 cells per cubic millimeter per month (95 percent confidence interval, -1.4 to 19.1) during the first six months of the study, whereas those receiving placebo had an average loss of 12.0 CD4 cells per cubic millimeter per month (95 percent confidence interval, 5.2 to 18.7), for a between-group difference of 20.9 CD4 cells per cubic millimeter per month (95 percent confidence interval, 8.5 to 33.2 ; $P = 0.001$).

Conclusions. Antiretroviral therapy administered during primary HIV infection may improve the subsequent clinical course and increase the CD4 cell count. (*N Engl J Med* 1995;333:408-13.)

CONTROLLED trials have shown that treatment with zidovudine (Retrovir) late in the course of infection with the human immunodeficiency virus (HIV) type 1 results in decreased rates of disease progression and death,^{1,2} but there is no consensus on the benefit of antiretroviral treatment in asymptomatic patients.³⁻⁵ Recent studies demonstrating viral replication throughout the course of infection suggest a possible benefit of early treatment.⁶⁻¹⁰

Primary HIV infection represents the initial stage of

the disease, when there is a burst of viral replication associated with dissemination in lymphoid tissue.^{6,7,11-13} In 50 to 80 percent of patients, primary HIV infection occurs in conjunction with an acute retroviral syndrome, which can be diagnosed, particularly if HIV core (p24) antigenemia is detectable.^{14,15}

We conducted a multicenter, randomized, double-blind, placebo-controlled trial to determine the short- and long-term clinical benefits of early treatment with zidovudine and its effect on immunologic and virologic markers in patients with primary HIV infection.

METHODS

Study Design

Patients 18 years of age or older were enrolled in the study if they met at least one clinical criterion and one laboratory criterion. The clinical criteria were the presence of an acute retroviral syndrome^{14,15} and known exposure to HIV within the previous three months. The laboratory criteria were p24 antigenemia and a negative or low positive result of an antibody test with an indeterminate result of a Western blot. Confirmation of seroconversion was obtained at follow-up visits, with the use of Western blot analysis. All patients gave written informed consent before enrollment. The study was approved by the ethics committees of the participating centers.

Patients were randomly assigned to receive zidovudine (250 mg twice daily) or placebo for six months. The dose was reduced or the drug discontinued if there were serious toxic effects (grade 3 or 4 according to the classification of the World Health Organization). Both patients and physicians were unaware of the treatment assignments. At the end of the trial period, antiviral therapy was administered according to local guidelines. The main end points of the study included the duration of the acute retroviral syndrome, the change in the CD4 lymphocyte count at six months, and the occurrence of opportunistic infections, defined according to the criteria of the Centers for Disease Control and Prevention (CDC).¹⁶ Additional outcome variables were the CD4 lymphocyte counts after the trial period, the CD8 lymphocyte counts, p24 antigenemia, and viremia.

The decision was made to stop enrollment in January 1994, after a

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*Dr. Tindall died in August 1994. A complete list of participating institutions and investigators appears in the Appendix.

review of the data (by Drs. J.H. Darbyshire and A. Babiker, Medical Research Council, London) demonstrated the absence of major toxic effects and the necessity of enrolling twice as many patients in order to estimate changes in CD4 counts more accurately. By that time, 77 patients had been enrolled, 68 of whom had completed the six-month treatment regimen. Four opportunistic infections had been diagnosed, and recruitment was rapidly abating, since most physicians were in favor of the intervention. The final analysis (performed on July 10, 1994) included the nine additional patients who had subsequently completed the treatment regimen.

Evaluation of Patients

Clinical assessment and laboratory testing were performed weekly from the day of enrollment until week 6, then every six weeks until the end of the trial period. Subsequent assessments were performed every 2 weeks for 4 weeks after the discontinuation of the trial medication, then every 12 weeks until the end of the first year, and then every 6 months for the next 2 years. Laboratory measurements included routine determinations of blood chemical levels, T-lymphocyte subgroups, p24 antigen, and viremia (the number of HIV RNA copies per milliliter of serum).⁷ Analysis of the HIV reverse transcriptase gene at codon 215¹⁷ was performed at enrollment and at six months. Assessment of viremia was carried out in blood samples obtained from 53 patients (23 in the zidovudine group and 30 in the placebo group) and frozen at -75°C . HIV RNA levels are expressed as the log-transformed number of RNA copies per milliliter of serum.

Statistical Analysis

All analyses were conducted on an intention-to-treat basis. Distributions of categorical variables in the zidovudine and placebo groups were compared with cross-tabulations and chi-square or Fisher's exact tests.¹⁸ Distributions of continuous variables were analyzed with parametric (Student's *t*-test) and nonparametric (the rank-sum test) methods.¹⁸ Two-sided *P* values less than 0.05 were considered to indicate statistical significance. To take into account the lack of independence between repeated measurements in the same person, we used paired *t*-tests to compare two serial measurements. Linear trends in CD4 counts over time were analyzed in two steps: first, linear-regression slopes and corresponding standard errors were computed separately for each patient. Then, the average slopes for the two treatment groups were compared with the use of a weighted least-squares procedure (the weight being the inverse of the variance of each estimated slope). The duration of follow-up free of clinical events was estimated by the Kaplan-Meier method, and the treatment groups were compared with the log-rank test and a Cox proportional-hazards model.¹⁸ Analyses were performed with SPSS for Windows software.

RESULTS

Patients

Seventy-seven patients (39 in the zidovudine group and 38 in the placebo group) were enrolled in the study between April 1991 and January 1994. Data collected up to July 10, 1994, are reported here. Patients were recruited at 27 centers in eight countries: Switzerland (25 patients), France (22), Australia (14), Belgium (4), Italy (4), Denmark (4), Portugal (3), and the United Kingdom (1). The demographic and clinical characteristics of the patients in the two treatment groups were similar at enrollment (Table 1).

Sixty-three patients (81.8 percent; 34 patients in the zidovudine group and 29 in the placebo group) completed the six-month study regimen. The study medication was discontinued in two patients in the placebo group because of neurologic symptoms or immunologic deterioration (a CD4 count of less than 150 cells per cubic millimeter); the patients were offered open-label antiviral treatment. Medication was discontinued in two

Table 1. Characteristics of 77 Patients with Primary HIV Infection Randomly Assigned to Zidovudine Therapy or Placebo.

CHARACTERISTIC	ZIDOVUDINE GROUP (N = 39)	PLACEBO GROUP (N = 38)
Male — no. of patients (%)	35 (90)	33 (87)
Age — yr		
Mean	31	32
Range	19–62	19–57
Risk factors — no. of patients (%)		
Homosexual sex	23 (59)	27 (71)
Heterosexual sex	11 (28)	8 (21)
Injection-drug use	3 (8)	3 (8)
Other	2 (5)	0
Acute retroviral syndrome — no. of patients (%)		
At the start of therapy	21 (54)	23 (61)
Before or at the start of therapy	38 (97)	34 (89)
Detectable p24 antigen — no. of patients (%)		
At the start of therapy	26 (67)	20 (53)
Before or at the start of therapy	35 (90)	27 (71)

patients in the zidovudine group because of persistent nausea. The medication was discontinued in the remaining 10 patients at their request.

Open-Label Antiviral Treatment

Open-label antiviral therapy was initiated in 21 patients during the follow-up period (in 2 patients during the six-month trial period and in 19 patients afterward). The reasons for open-label antiviral treatment during the trial period were a low CD4 lymphocyte count in one case and the patient's preference in another; both patients were in the placebo group. After the trial period, nine patients in the zidovudine group received open-label antiviral therapy because of low CD4 counts (in four patients), recurring p24 antigenemia (in one), or both (in two) or at the patient's request (in two). Ten patients in the placebo group received open-label therapy because of low CD4 counts (in four patients), a low CD4 count and p24 antigenemia (in one), the patient's preference (in one), opportunistic infections (CDC group IV-C1 in one and CDC group IV-C2 in two), or weight loss (in one).

Acute Retroviral Syndrome

The mean (\pm SE) duration of symptoms in 71 symptomatic patients was 31 ± 3.1 days (range, 3 to 180); 5 patients were asymptomatic, and data were incomplete for 1 patient. The most frequent symptoms were fever (reported by 96 percent of the symptomatic patients), skin rash (67 percent), headache (61 percent), malaise (61 percent), and lethargy (61 percent). The mean duration of the acute retroviral syndrome was 27.0 ± 3.3 days (range, 5 to 109) in the zidovudine group and 35.4 ± 5.5 days (range, 3 to 180) in the placebo group.

The average period from the onset of symptoms to the initiation of the trial medication, which could be assessed for 70 patients, was 25.1 days (23.9 in the zidovudine group and 26.6 in the placebo group). The mean duration of symptoms after the initiation of therapy, which could be assessed for 43 of the patients who still had symptoms 1 day after the initiation of the study medication, was 15.0 ± 4.1 days (range, 1 to 84) in the

zidovudine group and 15.8 ± 3.6 days (range, 1 to 64) in the placebo group.

Opportunistic Infections

Eight patients had opportunistic infections (CDC group IV-C2) (seven in the placebo group, one of whom subsequently had the acquired immunodeficiency syndrome [AIDS], and one in the zidovudine group); the mean CD4 count for this group was 310 cells per cubic millimeter (range, 48 to 645). The infections included four episodes of oral candidiasis (at weeks 5, 39, 77, and 100), two episodes of herpes zoster (at weeks 19 and 26), and one episode of oral hairy leukoplakia (at week 55) in the placebo group and one episode of oral hairy leukoplakia (at week 109) in the zidovudine group. Kaplan–Meier curves (Fig. 1) showed a significant difference in the frequency of infections between the two groups ($P=0.009$ by the log-rank test). The relative risk of disease progression in the zidovudine group, as compared with the placebo group, was 0.08 (95 percent confidence interval, 0.01 to 0.76; $P=0.03$).

AIDS subsequently developed in one of the symptomatic patients in the placebo group. Two deaths occurred, both in the absence of detectable HIV-related events. One patient in the zidovudine group died at week 81 (of an intravenous drug overdose), and one patient in the placebo group died at week 14 (by suicide). Data on both patients were censored at the time of the deaths.

Changes in the CD4 Count

Mean changes in the CD4 count are shown in Figure 2A and Table 2. At the beginning of the trial, the mean CD4 count was lower in the zidovudine group than in the placebo group (Table 2). One month after the initiation of the medication regimen, the CD4 counts had increased in both groups, but the increase was almost twice as large in the zidovudine group as in the placebo group. At the end of the trial period, the difference in the mean CD4 counts between the two treatment

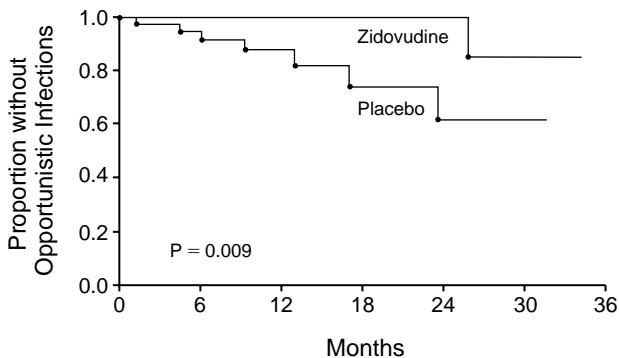
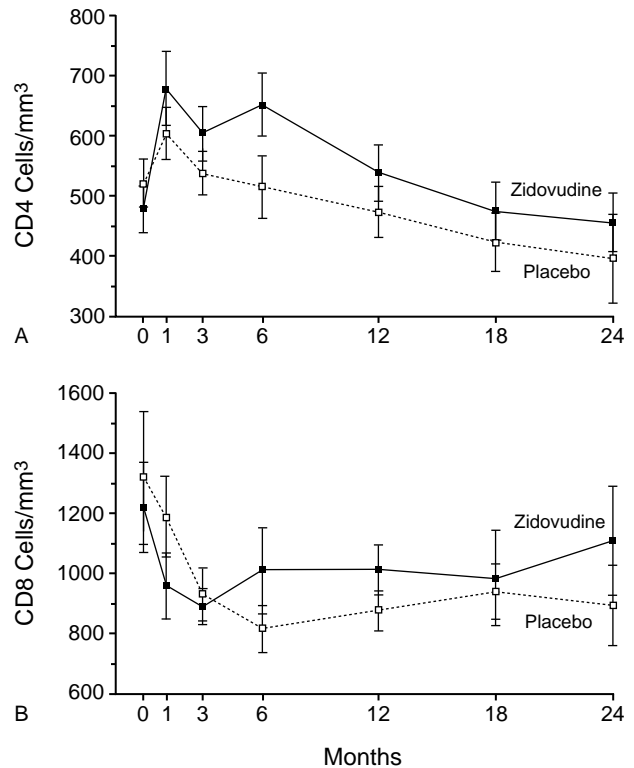


Figure 1. Kaplan–Meier Curves Showing the Proportion of Patients Remaining Free of HIV-Related Opportunistic Infections in the Zidovudine and Placebo Groups.

The curves were compared by the log-rank test.



	0	1	3	6	12	18	24
Zidovudine	36	34	29	27	15	10	
Placebo	38	31	32	30	21	15	11

Figure 2. Mean (\pm SE) CD4 Cell Counts (Panel A) and CD8 Cell Counts (Panel B) in the Zidovudine and Placebo Groups.

groups was 137 cells per cubic millimeter ($P=0.07$) (Table 2).

Linear trends in the CD4 count during the trial period are shown in Table 3. There was a mean monthly gain in CD4 cells in the zidovudine group, as compared with a loss in the placebo group (Table 3). Zidovudine treatment resulted in a mean increase of 17.9 cells per cubic millimeter per month during the first six months. After adjustment for the base-line CD4 count, the zidovudine group had an average increase of 8.9 cells per cubic millimeter per month (95 percent confidence interval, -1.4 to 19.1) during the first six months, as compared with an average loss of 12.0 cells per cubic millimeter per month (95 percent confidence interval, 5.2 to 18.7) in the placebo group. The difference between the two groups amounted to 20.9 cells after adjustment for the base-line CD4 count ($P=0.001$) (Table 3). After the trial period, individual trends in CD4 counts were estimated for 25 patients in the zidovudine group and 27 in the placebo group; in the other patients, the CD4 count was determined on fewer than three occasions after the trial period. The mean CD4 count decreased by 12.1 cells per cubic millimeter per month in the zidovudine group and by 4.9 cells per cubic millimeter per month in the placebo group (Table 3).

Other Laboratory Values

The mean CD8 lymphocyte count at base line was 1210 ± 149 per cubic millimeter in the zidovudine group

Table 2. Changes in CD4 Counts during Treatment with Zidovudine or Placebo in Patients with Primary HIV Infection.*

	ZIDOVUDINE GROUP		PLACEBO GROUP		DIFFERENCE†	
	NO. OF PATIENTS	CD4 COUNT	NO. OF PATIENTS	CD4 COUNT	NO. OF CD4 CELLS	P VALUE
At base line	38	477	36	519	-42	0.45
At one month	31	676	34	601	+75	0.32
Change from base line	30	+199	32	+82	+97	0.09
At six months	30	650	29	513	+137	0.07
Change from base line	30	+173	27	+6	+130	0.07

*Cell counts are expressed as the number of CD4 cells per cubic millimeter.

†The difference between the two groups is expressed as the decrease or increase in the number of cells in the zidovudine recipients, as compared with the number in the placebo recipients. The P values were determined with the independent-sample t-test.

and 1311 ± 223 per cubic millimeter in the placebo group ($P=0.2$). The mean count decreased in both groups during the trial period (Fig. 2B). After the discontinuation of therapy, the mean CD8 count was higher in the zidovudine group than in the placebo group.

At enrollment, p24 antigen was detected in 67 percent of the zidovudine recipients, as compared with 53 percent of the placebo recipients (Table 1), but during follow-up, the proportion of patients with p24 antigenemia was smaller in the zidovudine group than in the placebo group (Fig. 3A). The difference between the two groups was not statistically significant.

Sequential HIV RNA levels were determined in 53 patients (23 in the zidovudine group and 30 in the placebo group). At the initiation of therapy, the mean HIV RNA level was 7.59 ± 0.19 RNA copies per milliliter in the zidovudine group and 6.99 ± 0.17 RNA copies per milliliter in the placebo group ($P=0.02$) (Fig. 3B). At base line, there was a dispersion of values in both groups, ranging from 6.15 to 8.84 RNA copies per milliliter in the zidovudine group and from 4.87 to 8.49 RNA copies per milliliter in the placebo group. At the end of the trial period, the mean HIV RNA level was 6.04 ± 0.23 RNA copies per milliliter in the zidovudine group and 6.14 ± 0.15 RNA copies per milliliter in the placebo group ($P=0.73$). The decline in the HIV RNA level during the treatment period did not differ significantly between the two groups: 1.44 ± 0.32 RNA copies per milliliter in the zidovudine group and 0.93 ± 0.16 RNA copies per milliliter in the placebo group ($P=0.17$).

Among the 58 patients (27 in the zidovudine group and 31 in the placebo group) who were tested for a mutation of the HIV-1 reverse transcriptase gene at codon 215, mutant viruses were detected at base line in 4 patients in the zidovudine group and in 2 patients in the

placebo group. No change in the genotype at codon 215 was seen at six months.

Toxic Effects

Nausea accounted for discontinuation of the trial drug in two patients in the zidovudine group. In both patients the nausea stopped after the drug had been discontinued and recurred when it was reinstated. One patient had grade 3 neutropenia, which may have been related to zidovudine therapy. Measurements of serum creatinine, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase levels revealed no grade 2 or 3 toxic effects on kidney or liver function.

DISCUSSION

The administration of antiviral therapy at the time of primary HIV infection is intended to decrease the viral load, which may shorten the duration of the acute retroviral syndrome, reduce the rate of the clinical progression of disease, and improve survival by delaying the development of AIDS. However, this strategy may inhibit the host's immune response¹⁹ and lead to the emergence of mutant viruses on reintroduction of antiviral treatment at a later stage of the infection.

In this study, treatment with zidovudine during primary HIV infection reduced the frequency of minor opportunistic infections during a mean follow-up period of 15 months and substantially increased the CD4 lymphocyte count during the trial period. Antiviral therapy did not seem to affect the duration of the acute retroviral syndrome.

We chose zidovudine as the treatment drug because it was standard therapy for HIV infection when the study was being planned. Severe toxic effects at an early stage of HIV infection are rarely encountered with the use of this drug, particularly at the dose we used (500 mg daily).²⁰ The few cases in which the drug was withdrawn because of clinical intolerance or serious abnormalities in laboratory tests confirm the low toxicity of zidovudine in primary HIV infection, as previously reported.²¹

The effect of zidovudine on the duration of the acute retroviral syndrome could not be fully assessed because of the delays in enrolling patients and initiating drug therapy. Similar problems were reported during sys-

Table 3. Linear Trends in CD4 Counts during and after the Trial Period in Patients with Primary HIV Infection.*

	ZIDOVUDINE GROUP		PLACEBO GROUP		UNADJUSTED DIFFERENCE		DIFFERENCE ADJUSTED FOR BASE-LINE CD4 COUNT	
	NO. OF PATIENTS	SLOPE (95% CI)	NO. OF PATIENTS	SLOPE (95% CI)	SLOPE (95% CI)	P VALUE	SLOPE (95% CI)	P VALUE
During the trial	38	+6.4 (-4.2 to +16.9)	37	-11.5 (-18.1 to -4.9)	+17.9 (+5.4 to +30.3)	0.006	+20.9 (+8.5 to +33.2)	0.001
After the trial	25	-12.1 (-18.3 to -5.9)	27	-4.9 (-12.2 to +2.4)	-7.2 (-16.7 to +2.4)	0.14		

*The slopes denote the number of cells per cubic millimeter per month. Group averages have been weighted by the inverse of the variance among individual slope estimates. CI denotes confidence interval.

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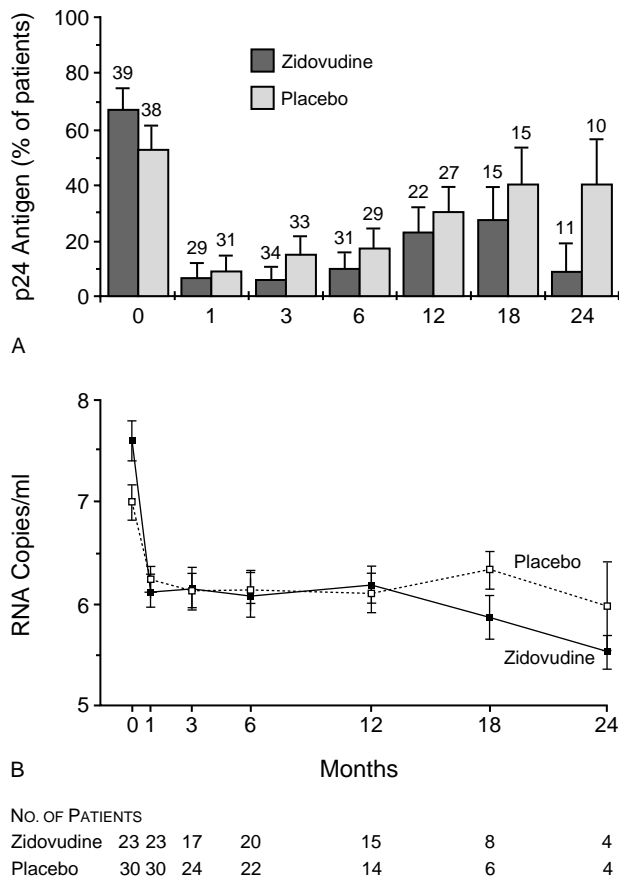


Figure 3. Mean (\pm SE) Proportion of Patients with p24 Antigen (Panel A) and Level of HIV RNA (Panel B) in the Zidovudine and Placebo Groups.

The numbers above the bars in Panel A denote numbers of patients. Levels of HIV RNA are expressed as the log-transformed number of RNA copies per milliliter.

tematic testing for p24 antigen in an emergency department,²² where none of the patients with evidence of seroconversion had received a diagnosis at the time of the acute retroviral syndrome.

The rate of disease progression in our trial was high, considering the short follow-up period. All eight patients with opportunistic infections had documented seroconversion, with a negative HIV test followed by a positive test. The high incidence of minor opportunistic infections is consistent with the poor long-term outcome among patients with symptomatic primary HIV infection.²³⁻²⁷ All opportunistic infections were classified as minor, and seven were diagnosed in the placebo group. The only case of disease progression in the zidovudine group occurred in a patient with a zidovudine-resistant mutation at codon 215; the one case of AIDS was diagnosed in a patient in the placebo group who also had the mutation. Disease progression did not occur in four other patients infected with resistant viral strains. Thus, the prognosis for patients infected with resistant virus remains unclear.

In patients with advanced stages of HIV infection, zidovudine prevents the development of major opportunistic infections and improves survival.^{1,2} It also decreases the frequency of disease progression by 50 to 65

percent in initially asymptomatic patients.^{4,5} The clinical benefits of zidovudine in patients with primary HIV infection seem even more pronounced. In our study, the relative risk of disease progression was 0.08 (95 percent confidence interval, 0.01 to 0.76; $P = 0.03$) in the zidovudine group as compared with the placebo group. However, further follow-up of our patients is required to assess the long-term clinical benefit of very early therapeutic intervention with zidovudine.²⁸

The beneficial effect of zidovudine on surrogate markers of HIV infection, such as the CD4 lymphocyte count, has been documented in previous studies of symptomatic and asymptomatic patients,^{1-5,28} but the benefit was smaller than that observed during primary HIV infection. The absolute mean gain of 137 CD4 cells per cubic millimeter in the zidovudine group in our trial is more than four times the increase reported in the Concorde trial.³

The decline in the CD4 counts in both groups after discontinuation of the trial medication raises the issue of the optimal duration of zidovudine therapy at the time of primary HIV infection. The absence of new mutations in the reverse transcriptase at codon 215 at the end of the six-month trial period suggests that antiretroviral treatment may be given for a longer period without the development of drug resistance.²⁹ However, the documented transmission of zidovudine-resistant viruses³⁰ may limit the efficacy of zidovudine as monotherapy.

No dramatic effect of therapy on viral markers was observed. After the first month of therapy, p24 antigen was undetectable in a higher proportion of patients in the zidovudine group than in the placebo group, but the difference was not significant. Similarly, we observed a reduction in viremia in both groups at the end of the trial period, which was more pronounced in the zidovudine recipients than in the placebo recipients, despite a higher viral load in the zidovudine group at base line. However, there was no significant difference in viremia between the two treatment groups, although there was a further mean decrease of approximately 0.5 RNA copy per milliliter in the zidovudine group during the trial period. These data indicate that zidovudine partially inhibited HIV replication. The effect of therapy on the number of latently infected cells or on the main reservoir of virus (i.e., the lymph nodes) has not been evaluated.^{8,31}

In conclusion, these data demonstrate that zidovudine as monotherapy increases the CD4 count and may provide clinical benefits. Future clinical trials should therefore focus on therapy combining zidovudine with new antiviral agents in order to achieve greater antiviral efficacy.³²⁻³⁴ In the meantime, treatment with zidovudine may be considered in patients with primary HIV infection.

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APPENDIX

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CORRECTION

A Controlled Trial of Zidovudine in Primary Human Immunodeficiency Virus Infection

A Controlled Trial of Zidovudine in Primary Human Immunodeficiency Virus Infection . On page 411, Table 2 contained a number of incorrect values. The corrected table appears below.

Table 2. Changes in CD4 Counts during Treatment with Zidovudine or Placebo in Patients with Primary HIV Infection.

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Table 2. Changes in CD4 Counts during Treatment with Zidovudine or Placebo in Patients with Primary HIV Infection.*

	ZIDOVUDINE GROUP		PLACEBO GROUP		DIFFERENCE †	
	NO. OF PATIENTS	CD4 COUNT	NO. OF PATIENTS	CD4 COUNT	NO. OF CD4 CELLS	P VALUE
At base line	38	477	36	519	-43	0.45
At one month	31	676	34	601	+75	0.32
Change from base line	30	+201	32	+104	+97	0.09
At six months	30	650	29	513	+138	0.07
Change from base line	30	+157	27	+27	+130	0.07

*Cell counts are expressed as the number of CD4 cells per cubic millimeter

†The difference between the two groups is expressed as the decrease or increase in the number of cells in the zidovudine recipients, as compared with the number in the placebo recipients. The P values were determined with the independent-sample t-test.