The New England Journal of Medicine

VOLUME 335 OCTOBER 10, 1996 NUMBER 15

A TRIAL COMPARING NUCLEOSIDE MONOTHERAPY WITH COMBINATION THERAPY IN HIV-INFECTED ADULTS WITH CD4 CELL COUNTS FROM 200 TO 500 PER CUBIC MILLIMETER

SCOTT M. HAMMER, M.D., DAVID A. KATZENSTEIN, M.D., MICHAEL D. HUGHES, PH.D., HOLLY GUNDACKER, M.S., ROBERT T. SCHOOLEY, M.D., RICHARD H. HAUBRICH, M.D., W. KEITH HENRY, M.D., MICHAEL M. LEDERMAN, M.D., JOHN P. PHAIR, M.D., MANETTE NIU, M.D., MARTIN S. HIRSCH, M.D., AND THOMAS C. MERIGAN, M.D., FOR THE AIDS CLINICAL TRIALS GROUP STUDY 175 STUDY TEAM*

ABSTRACT

Background This double-blind study evaluated treatment with either a single nucleoside or two nucleosides in adults infected with human immunodeficiency virus type 1 (HIV-1) whose CD4 cell counts were from 200 to 500 per cubic millimeter.

Methods We randomly assigned 2467 HIV-1–infected patients (43 percent without prior antiretroviral treatment) to one of four daily regimens: 600 mg of zidovudine; 600 mg of zidovudine plus 400 mg of didanosine; 600 mg of zidovudine plus 2.25 mg of zalcitabine; or 400 mg of didanosine. The primary end point was a ⩾50 percent decline in the CD4 cell count, development of the acquired immunodeficiency syndrome (AIDS), or death.

Results Progression to the primary end point was more frequent with zidovudine alone (32 percent) than with zidovudine plus didanosine (18 percent; relative hazard ratio, 0.50; $P<0.001$), zidovudine plus zalcitabine (20 percent; relative hazard ratio, 0.54; $P<0.001$), or didanosine alone (22 percent; relative hazard ratio, 0.61; $P<0.001$). The relative hazard ratios for progression to an AIDS-defining event or death were 0.64 ($P=0.005$) for zidovudine plus didanosine, as compared with zidovudine alone, 0.77 ($P=0.085$) for zidovudine plus zalcitabine, and 0.69 ($P=0.019$) for didanosine alone. The relative hazard ratios for death were 0.55 ($P=0.008$), 0.71 ($P=0.10$), and 0.51 ($P=0.003$), respectively. For zidovudine plus zalcitabine, the benefits were limited to those without previous treatment.

Conclusions Treatment with zidovudine plus didanosine, zidovudine plus zalcitabine, or didanosine alone slows the progression of HIV disease and is superior to treatment with zidovudine alone. Antiretroviral therapy can improve survival in patients with 200 to 500 CD4 cells per cubic millimeter. (N Engl J Med 1996;335:1081-90.)

ZIDOVUDINE improves survival and decreases the incidence of opportunistic infections among patients with advanced infections with human immunodeficiency virus type 1 (HIV-1) and slows the progression of disease in patients with no or mild symptoms.[1-5] Its beneficial effects, however, wane with time, and a survival advantage is not conferred by prolonged therapy in asymptomatic subjects.[6-8]

Effective treatment of HIV disease will probably require combination therapy.[9] Since high rates of viral replication with rapid turnover of the virus and CD4 cells occur from the onset of the infection, early intervention with the most potent regimens available may prove to be the optimal approach.[10,11] Regimens combining zidovudine with other antiretroviral agents have yielded greater and more durable responses of CD4 cells and viral markers.[12-17] However, a combination of zidovudine and zalcitabine did not produce a clinical benefit.[18]

From Harvard Medical School, Boston (S.M.H., M.S.H.); Stanford University, Stanford, Calif. (D.A.K., T.C.M.); Harvard School of Public Health, Boston (M.D.H., H.G.); the University of Colorado, Denver (R.T.S.); the University of California, San Diego (R.H.H.); the University of Minnesota, Minneapolis (W.K.H.); Case Western Reserve University, Cleveland (M.M.L.); Northwestern University, Chicago (J.P.P.); and the Division of AIDS of the National Institute of Allergy and Infectious Diseases, Bethesda, Md. (M.N.). Address reprint requests to Dr. Hammer at the Division of Infectious Diseases, New England Deaconess Hospital, One Deaconess Rd., Kennedy-6, Boston, MA 02215.

The following were additional authors: Terrence F. Blaschke, M.D. (Stanford University), David Simpson, M.D. (Mt. Sinai Medical Center), Colin McLaren, M.D. (Bristol-Myers Squibb), James Rooney, M.D. (Glaxo–Wellcome), and Miklos Salgo, M.D., Ph.D. (Hoffmann–LaRoche).

*The institutions and investigators participating in AIDS Clinical Trials Group Study 175 are listed in the Appendix.

Responses to antiretroviral therapy may vary according to the stage of the disease and the extent of prior drug exposure, and prolonged clinical benefit from drug intervention has not been demonstrated in patients with less advanced HIV disease. To address these issues, the AIDS Clinical Trials Group Study 175 (ACTG 175) was undertaken.

METHODS

Study Design and Population

ACTG 175 was a randomized, double-blind, placebo-controlled trial to compare monotherapy with zidovudine or didanosine with combination therapy with zidovudine and didanosine or zidovudine and zalcitabine in HIV-1–infected subjects with CD4 cell counts between 200 and 500 per cubic millimeter. The primary study end point was a ≥50 percent decline in the CD4 cell count, an event indicating progression to the acquired immunodeficiency syndrome (AIDS), or death. Secondary end points were an AIDS-defining event or death, death alone, and the occurrence of adverse events (signs, symptoms, or laboratory abnormalities) defined as severe or worse according to the ACTG grading scheme.[19]

We recruited patients from 43 AIDS Clinical Trials Units and 9 National Hemophilia Foundation sites in the United States and Puerto Rico (see the Appendix) who met the following eligibility criteria: age of 12 years or more, laboratory documentation of HIV-1 infection, a CD4 cell count between 200 and 500 per cubic millimeter within 30 days before randomization, no history of an AIDS-defining illness other than minimal mucocutaneous Kaposi's sarcoma, a Karnofsky performance score of at least 70, and acceptable laboratory results. The study was approved by the institutional review boards of participating institutions, and all subjects gave written informed consent.

Patients were randomly assigned to one of four treatments: 200 mg of zidovudine three times daily, 200 mg of zidovudine three times daily plus 0.75 mg of zalcitabine three times daily, 200 mg of zidovudine three times daily plus 200 mg of didanosine twice daily, or 200 mg of didanosine twice daily. Appropriate placebos were provided. A blocked randomization design, carried out with a central computerized system, was used at each study site and was stratified according to the length of prior antiretroviral therapy.

Study End Points

The end point with respect to the CD4 cell count was defined as a count at or below 50 percent of the average of two pretreatment counts (exclusive of the screening count), confirmed by a second count obtained within 3 to 21 days. AIDS-related end points were defined by the 1987 Centers for Disease Control criteria[20] and were reviewed blindly by the cochairs. Patients who reached either type of end point were offered combination therapy with zidovudine and didanosine or zidovudine and zalcitabine in a blinded fashion, without revealing their initial treatment assignment.

Monitoring and Enrollment

Subjects were examined at weeks 2, 4, and 8 and then every 12 weeks thereafter, with CD4 cell counts determined from week 8 onward; such levels were determined even after the premature discontinuation of treatment. Enrollment began in December 1991 and ended in October 1992. The study was reviewed by a data and safety monitoring board on four occasions according to the Lan and DeMets stopping guidelines with O'Brien–Fleming boundaries.[21-23] Patients who did not make a final clinic visit after November 30, 1994, were considered lost to follow-up.

Statistical Analysis

Distributions of times to events were estimated with the method of Kaplan and Meier and compared with the log-rank test and Cox proportional-hazards model, stratified according to the extent of prior antiretroviral therapy.[24] Different relative effects of the treatments among subjects with no prior antiretroviral therapy and those with prior antiretroviral therapy were investigated by including the subgroup–treatment interaction term in proportional-hazards models.[25] Mean changes in CD4 cell counts from base line to week 8 were compared by analysis of variance and two-sample t-tests.[26] An intention-to-treat approach was used for efficacy analyses, except that 28 randomizations (involving 26 patients) were excluded. Analyses of adverse effects were restricted to the period of initial treatment. Separate analyses of the subgroups with no prior antiretroviral therapy and with prior antiretroviral therapy were planned in advance. All P values reported are two-sided and have not been adjusted for multiple comparisons. Global P values were used to assess whether there was evidence against the hypothesis that the measure of interest was identical for all four treatment groups. All other P values are for pairwise comparisons of treatments.

RESULTS

Accrual and Eligibility

There were 2495 randomizations involving 2493 subjects. One subject underwent randomization three times; the second and third randomizations were excluded. Twenty-six other subjects were excluded from all analyses for the following reasons: 24 were not given the study medications and were not followed further, 1 did not have HIV-1 infection, and 1 had a diagnosis of AIDS at entry, violating a major eligibility criterion. Thus, the analyses involved 2467 subjects: 1067 with no prior antiretroviral therapy, and 1400 who had previously received antiretroviral therapy.

Characteristics of the Subjects

Table 1 lists the base-line characteristics of the study population. The characteristics were well balanced among the treatment groups. The subgroup without previous antiretroviral treatment had a higher mean CD4 cell count (372 vs. 338 cells per cubic millimeter), a higher proportion of black subjects (20 percent vs. 14 percent), and a lower proportion with hemophilia (4 percent vs. 11 percent) than the subgroup that had previously received antiretroviral therapy. In the subgroup with previous antiretroviral treatment, 99.6 percent of subjects reported previous zidovudine use (median duration of use, 20 months); only 4 percent reported the use of other antiretroviral therapies.

Duration of Follow-up and Study Treatment

The median duration of follow-up was 143 weeks. Because of more rapid accrual, the median duration of follow-up was longer (147 vs. 135 weeks) and the cumulative follow-up greater (3556 vs. 2430 person-years) in the group with prior antiretroviral therapy than in the group with no prior antiretroviral therapy. The rate of loss to follow-up was 19 percent overall and was higher in the group with no prior antiretroviral therapy than in the group with prior antiretroviral therapy (25 percent vs. 15 percent). With respect

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS ACCORDING TO THE EXTENT OF PREVIOUS EXPOSURE TO ANTIRETROVIRAL AGENTS.*

CHARACTERISTIC	ALL PATIENTS (N=2467)	NO PRIOR EXPOSURE TO ANTIRETROVIRAL AGENTS (N=1067)	PRIOR EXPOSURE TO ANTIRETROVIRAL AGENTS (N=1400)
Male sex — no. (%)	2029 (82)	892 (84)	1137 (81)
Age — yr	34.9±8.7	34.0±8.4	35.6±8.8
Race or ethnic group — no. (%)			
White, non-Hispanic	1730 (70)	707 (66)	1023 (73)
Black, non-Hispanic	409 (17)	214 (20)	195 (14)
Hispanic	291 (12)	131 (12)	160 (11)
Other	37 (1)	15 (1)	22 (2)
Risk factors — no. (%)†			
Homosexuality	1608 (65)	719 (67)	889 (64)
Injection-drug use	355 (14)	154 (14)	201 (14)
Hemophilia	202 (8)	44 (4)	158 (11)
Karnofsky score of 100 — no. (%)	1448 (59)	657 (62)	791 (56)
Symptomatic HIV infection — no. (%)‡	438 (18)	170 (16)	268 (19)
CD4 cell count — cells/mm³§	352±107	372±110	338±103
Median length of prior antiretroviral therapy — mo (lower and upper quartiles)	3 (0, 23)	0 (0, 0)	20 (8, 30)

*Plus–minus values are means ±SD. Because of rounding, not all columns total 100 percent.

†Patients could have more than one risk factor. Only major risk factors are shown here.

‡An infection was considered symptomatic if candidiasis, oral hairy leukoplakia, or herpes zoster was reported within 30 days before randomization.

§The values are the mean of two measurements made at least three days apart. Values obtained at screening, which had to be 200 to 500 cells per cubic millimeter, were excluded.

to treatment, the only significant differences in loss to follow-up were in the subgroup with no prior antiretroviral therapy: the rate was 18 percent among those assigned to didanosine alone, as compared with 27 to 28 percent among those assigned to the other three treatments. Younger ($P<0.001$), black ($P=0.004$), and Hispanic ($P<0.001$) patients and those with a history of injection-drug use ($P<0.001$) had higher rates of loss to follow-up; base-line CD4 cell counts, symptom status, and Karnofsky scores were not associated with loss to follow-up.

The median duration of treatment was 118 weeks, and it was longer in the subgroup with prior antiretroviral therapy than in the subgroup with no prior antiretroviral therapy (median, 124 vs. 106 weeks). As of December 1, 1994, the overall rate of premature discontinuation of treatment was 53 percent; this rate was similar in the subgroup with no prior antiretroviral therapy and the subgroup with prior antiretroviral therapy (54 percent vs. 52 percent). Within the subgroup that had not received previous antiretroviral therapy, the rate of premature discontinuation of treatment was significantly lower among recipients of didanosine alone (46 percent) than in each of the other three treatment groups, explaining the lower rate of loss to follow-up in this subgroup. Among the patients who had previously received antiretroviral therapy, the only significant difference was the lower rate of premature discontinuation of treatment among those given zidovudine and didanosine, as compared with those given zidovudine alone (47 percent vs. 57 percent). Younger patients, those reporting injection-drug use, and those with lower CD4 cell counts, lower Karnofsky scores, and symptoms of HIV infection at enrollment were significantly more likely to discontinue treatment before the study ended.

Only 7 percent (88 of 1306) of the premature discontinuations of treatment were mandated by the protocol because they involved adverse events. The remainder were initiated by the patients for reasons including low-grade toxic reactions (24 percent), declining CD4 cell counts before the study end point was reached, the desire to seek other therapies, and the demands of the study (e.g., the numbers of pills subjects were required to take).

Progression of Disease

Five hundred sixty-five patients reached a primary end point — a ≥50 percent decline in the CD4 cell count, an AIDS-defining event, or death. Sixty-nine percent of these patients were in the subgroup with prior antiretroviral therapy, and 31 percent in the subgroup with no prior antiretroviral therapy. End

TABLE 2. RATES OF DISEASE PROGRESSION AMONG ALL PATIENTS.*

END POINT	ZIDOVUDINE (N=619)	ZIDOVUDINE AND DIDANOSINE (N=613)	ZIDOVUDINE AND ZALCITABINE (N=615)	DIDANOSINE (N=620)	GLOBAL P VALUE
⩾50% decline in CD4 cell count, AIDS, or death — no. (%)	196 (32)	113 (18)	120 (20)	136 (22)	<0.001
Hazard ratio		0.50	0.54	0.61	
95% confidence interval		0.39–0.63	0.43–0.68	0.49–0.76	
Pairwise P value		<0.001	<0.001	<0.001	
AIDS or death — no. (%)	96 (16)	65 (11)	76 (12)	71 (11)	0.021
Hazard ratio		0.64	0.77	0.69	
95% confidence interval		0.46–0.87	0.57–1.04	0.51–0.94	
Pairwise P value		0.005	0.085	0.019	
Death — no. (%)	54 (9)	31 (5)	40 (7)	29 (5)	0.007
Hazard ratio		0.55	0.71	0.51	
95% confidence interval		0.36–0.86	0.47–1.07	0.32–0.80	
Pairwise P value		0.008	0.10	0.003	

*In each case the reference group is the zidovudine group.

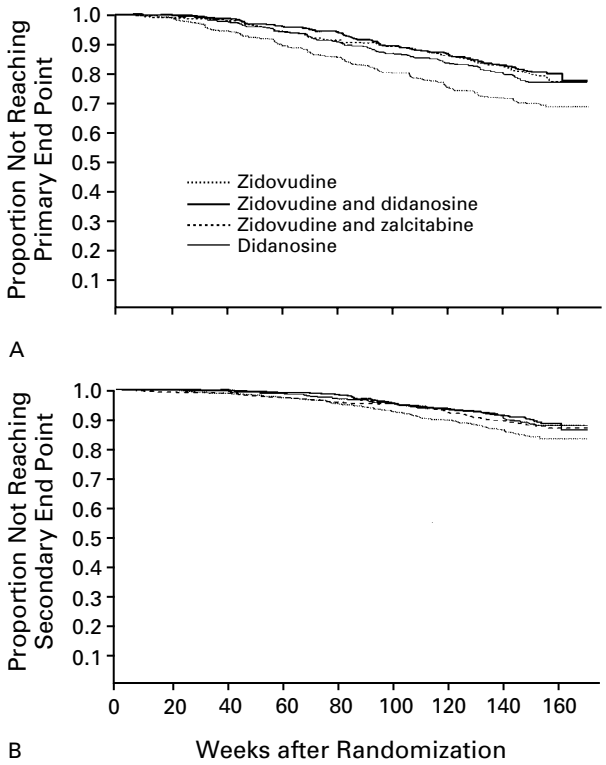

Figure 1. Kaplan–Meier Estimates of the Proportion of Patients Not Reaching the Primary End Point (Panel A) or the Secondary End Point (Panel B).

The primary end point was a ⩾50 percent decline in the CD4 cell count, an AIDS-defining event, or death. The secondary end point was an AIDS-defining event or death.

points related to the CD4 cell count constituted the majority of the first events (399 of 565, or 71 percent). In 75 percent of cases the primary end point was reached during treatment or within three months of its discontinuation; in 15 percent of cases the end point was reached more than one year after treatment was discontinued. Of the clinical (secondary) end points of an AIDS-defining event or death or death alone, 50 and 25 percent, respectively, occurred during treatment or within three months after its discontinuation; 25 and 35 percent, respectively, occurred more than one year after its discontinuation.

All Subjects

The rate of progression to a primary end point was 32 percent among patients assigned to zidovudine alone (Table 2), 18 percent in the group assigned to zidovudine and didanosine, 20 percent in the group given zidovudine and zalcitabine, and 22 percent in the group given didanosine alone, each of which was significantly lower than the rate for zidovudine alone in pairwise comparisons (relative hazard ratio as compared with zidovudine alone, 0.50 [95 percent confidence interval; 0.39 to 0.63]; 0.54 [95 percent confidence interval, 0.43 to 0.68]; and 0.61 [95 percent confidence interval, 0.49 to 0.76], respectively) (Fig. 1A).

The incidence of an AIDS-defining event or death was 16 percent in the zidovudine group and 11 percent, 12 percent, and 11 percent, respectively, in the zidovudine-plus-didanosine, zidovudine-plus-zalcitabine, and didanosine groups (relative hazard ratio, 0.64 [95 percent confidence interval, 0.46 to 0.87]; 0.77 [95 percent confidence interval, 0.57 to 1.04]; and 0.69 [95 percent confidence interval, 0.51 to 0.94]); the differences between the zidovu-

TABLE 3. RATES OF DISEASE PROGRESSION AMONG PATIENTS WITH NO PREVIOUS ANTIRETROVIRAL THERAPY.*

END POINT	ZIDOVUDINE (N=269)	ZIDOVUDINE AND DIDANOSINE (N=263)	ZIDOVUDINE AND ZALCITABINE (N=267)	DIDANOSINE (N=268)	GLOBAL P VALUE
≥50% decline in CD4 cell count, AIDS, or death — no. (%)	63 (23)	37 (14)	27 (10)	46 (17)	<0.001
Hazard ratio		0.55	0.39	0.64	
95% confidence interval		0.37–0.82	0.25–0.62	0.44–0.94	
Pairwise P value		0.003	<0.001	0.023	
AIDS or death — no. (%)	32 (12)	20 (8)	16 (6)	23 (9)	0.074
Hazard ratio		0.61	0.49	0.65	
95% confidence interval		0.35–1.07	0.27–0.89	0.38–1.11	
Pairwise P value		0.082	0.016	0.11	
Death — no. (%)	18 (7)	11 (4)	9 (3)	11 (4)	0.23
Hazard ratio		0.61	0.50	0.55	
95% confidence interval		0.29–1.29	0.22–1.11	0.26–1.16	
Pairwise P value		0.19	0.084	0.11	

*In each case the reference group is the zidovudine group.

TABLE 4. RATES OF DISEASE PROGRESSION AMONG PATIENTS WITH PREVIOUS ANTIRETROVIRAL THERAPY.*

END POINT	ZIDOVUDINE (N=350)	ZIDOVUDINE AND DIDANOSINE (N=350)	ZIDOVUDINE AND ZALCITABINE (N=348)	DIDANOSINE (N=352)	GLOBAL P VALUE
≥50% decline in CD4 cell count, AIDS, or death — no. (%)	133 (38)	76 (22)	93 (27)	90 (26)	<0.001
Hazard ratio		0.48	0.60	0.59	
95% confidence interval		0.36–0.63	0.46–0.79	0.45–0.77	
Pairwise P value		<0.001	<0.001	<0.001	
AIDS or death — no. (%)	64 (18)	45 (13)	60 (17)	48 (14)	0.091
Hazard ratio		0.65	0.91	0.72	
95% confidence interval		0.44–0.95	0.64–1.29	0.49–1.04	
Pairwise P value		0.025	0.60	0.080	
Death — no. (%)	36 (10)	20 (6)	31 (9)	18 (5)	0.023
Hazard ratio		0.52	0.81	0.48	
95% confidence interval		0.30–0.91	0.50–1.31	0.28–0.85	
Pairwise P value		0.019	0.40	0.010	

*In each case the reference group is the zidovudine group.

dine group and each of the two didanosine groups were significant (Fig. 1B). The mortality rate was 9 percent among zidovudine recipients and 5 percent, 7 percent, and 5 percent, respectively, in the zidovudine-plus-didanosine, zidovudine-plus-zalcitabine, and didanosine groups (relative hazard ratio as compared with zidovudine alone, 0.55 [95 percent confidence interval, 0.36 to 0.86]; 0.71 [95 percent confidence interval, 0.47 to 1.07]; and 0.51 [95 percent confidence interval, 0.32 to 0.80]); the differences between the zidovudine group and each of the two didanosine groups were significant.

There were no significant differences in the rate of progression to a primary end point between the zidovudine-plus-didanosine group and the didanosine group. There were also no significant differences between the rate of progression to either a primary or a secondary end point between the zidovudine-plus-didanosine and zidovudine-plus-zalcitabine groups or between the zidovudine-plus-zalcitabine and didanosine groups.

Subgroup Analysis According to Whether There Was Prior Antiretroviral Therapy

Although the incidence of end points was lower in the subgroup with no prior antiretroviral therapy than in the subgroup with prior antiretroviral therapy (Tables 3 and 4), the relative hazard ratios comparing the zidovudine-plus-didanosine group with the zidovudine group were very similar in the two

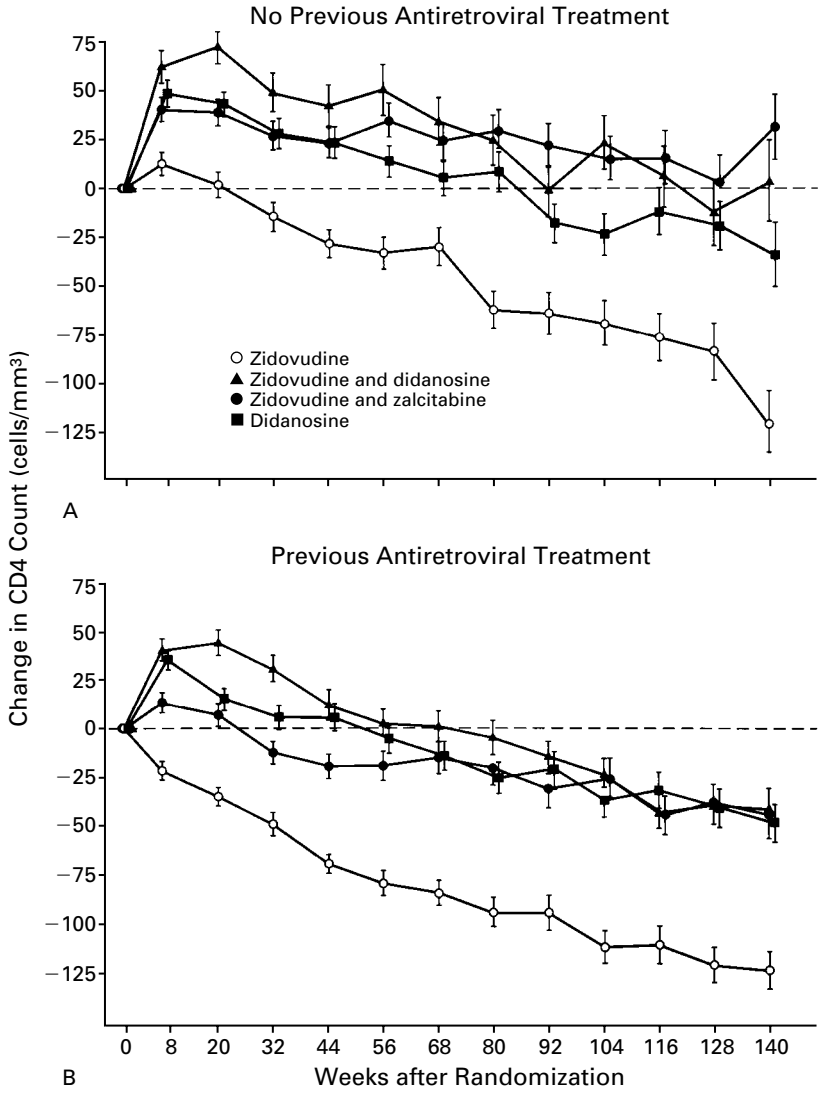

Figure 2. Mean (±SE) Change from Base Line in the CD4 Cell Count among the Patients with No Previous Antiretroviral Treatment (Panel A) and the Patients with Previous Antiretroviral Treatment (Panel B).

subgroups, as were those comparing the didanosine group with the zidovudine group and the zidovudine-plus-didanosine group with the didanosine group (data not shown). In contrast, the effect of zidovudine plus zalcitabine as compared with zidovudine alone tended to be greater in the subgroup with no prior antiretroviral therapy than in the subgroup with prior antiretroviral therapy: for the primary study end point the relative hazard ratio was 0.39 in the previously untreated subgroup and 0.60 in the previously treated subgroup; for the end point of an AIDS-defining event or death, this ratio was 0.49 and 0.91; and for the end point of death, 0.50 and 0.81. In the previously untreated subgroup, zidovudine plus zalcitabine was superior to zidovudine alone in reducing the incidence of both the primary end point and an AIDS-defining event or death; the reduction in deaths was marginally significant (Table 3). In the previously treated subgroup, treatment with zidovudine plus zalcitabine was not significantly superior to treatment with zidovudine alone (Table 4). Despite the apparently different effects of zidovudine plus zalcitabine in the two subgroups, none of the differences in the relative hazard ratios between these subgroups for the comparison of zidovudine plus zalcitabine with zidovudine alone were statistically significant.

AIDS-Related End Points

There were 327 AIDS-defining events (some patients had multiple events): 120 among patients assigned to zidovudine alone, as compared with 61, 76,

and 70 among patients assigned to zidovudine plus didanosine, zidovudine plus zalcitabine, and didanosine alone, respectively. The most common events were infections with *Pneumocystis carinii,* cytomegalovirus, and *Mycobacterium avium* complex (19 percent, 18 percent, and 10 percent, respectively).

Responses of CD4 Cell Counts

At week 8 in the subgroup with no prior antiretroviral therapy, there was a small mean increase in the CD4 cell count of 14 cells per cubic millimeter in the group assigned to zidovudine alone (Fig. 2A). This increase was significantly less than those in the zidovudine-plus-didanosine group (63 cells per cubic millimeter, $P<0.001$), the zidovudine-plus-zalcitabine group (41 cells per cubic millimeter, $P=0.006$), and the didanosine group (49 cells per cubic millimeter, $P<0.001$).

In the subgroup with prior antiretroviral therapy, among those assigned to zidovudine alone, there was a mean decrease of 22 CD4 cells per cubic millimeter by week 8 (Fig. 2B). Among those assigned to zidovudine plus didanosine, zidovudine plus zalcitabine, and didanosine alone, respectively, the mean increases of 40, 13, and 34 CD4 cells per cubic millimeter by week 8 were significantly different from the decrease in the CD4 cell count in the zidovudine group ($P<0.001$ for each comparison).

Adverse Events

In the previously untreated subgroup, the rate of severe or worse signs and symptoms among those assigned to zidovudine alone (22 percent) was higher than the rates among those assigned zidovudine plus didanosine (13 percent, $P=0.004$), zidovudine plus zalcitabine (16 percent, $P=0.056$) or didanosine alone (17 percent, $P=0.022$). This difference was predominantly due to a higher rate of headache and nausea in the zidovudine group. In the previously treated subgroup, the rates of severe or worse signs and symptoms were not significantly different in the four treatment groups (16 percent for zidovudine alone, 20 percent for zidovudine plus didanosine, 22 percent for zidovudine plus zalcitabine, and 22 percent for didanosine alone; global $P=0.58$). The rate of pancreatitis in the entire study population was low (0.5 percent), with the 12 affected subjects distributed among the four treatment groups.

In the subgroup with no prior antiretroviral therapy, the rates of severe or worse laboratory abnormalities ranged from 17 to 22 percent in the four treatment groups (global $P=0.45$). Subjects assigned to zidovudine plus didanosine had the highest rate of elevated hepatic-enzyme levels (9.9 percent, global $P=0.056$). In the subgroup with prior antiretroviral therapy, the rates of severe or worse laboratory abnormalities were 17 percent among those assigned to zidovudine alone, 25 percent among both those assigned to zidovudine plus didanosine and those assigned to zidovudine plus zalcitabine, and 19 percent among those assigned to didanosine alone (global $P=0.062$). The rate of hematologic abnormalities (anemia and neutropenia) was 10 percent among those assigned to zidovudine plus zalcitabine, a rate that was significantly higher than that in the other three treatment groups (global $P<0.001$). The overall rate of pancreatic-enzyme elevations was 1.6 percent (affecting 40 subjects) and did not vary significantly among the treatment groups.

DISCUSSION

In phase 2 trials, combinations of zidovudine and didanosine and zidovudine and zalcitabine showed promise on the basis of the greater and more durable responses of CD4 cells and viral markers that such treatment evoked.[12-14] ACTG 175 was designed to determine whether these results would translate into a clinical benefit in subjects with CD4 cell counts from 200 to 500 per cubic millimeter, regardless of whether they had previously received zidovudine therapy. For the primary end point of a $\geq$50 percent decline in the CD4 cell count, an AIDS-defining event, or death, zidovudine alone was found to be inferior to each of the other three treatment regimens, with risk reductions of 50 percent, 46 percent, and 39 percent for zidovudine plus didanosine, zidovudine plus zalcitabine, and didanosine alone, respectively. The results for the subgroup with no prior antiretroviral therapy and the subgroup with prior antiretroviral therapy were similar. For the clinical end points of an AIDS-defining event or death and death alone, the reductions in the risk of disease progression associated with zidovudine plus didanosine and didanosine alone as compared with zidovudine alone were also similar whether examined in the overall population or in the two subgroups. For example, treatment with zidovudine plus didanosine and didanosine alone reduced the risk of death by approximately 40 to 50 percent in both the overall population and the two subgroups. The extent of the reduction reached statistical significance only in the overall population and in the subgroup with prior antiretroviral therapy, because the greater number of end points reached in this subgroup influenced the overall results.

The only tendency for a difference in the results between the overall population and the two subgroups was seen in the comparison of the zidovudine-plus-zalcitabine group with the zidovudine group with respect to the risk of clinical disease progression. In this analysis, zidovudine plus zalcitabine reduced the risk of an AIDS-defining event or death by 51 percent in patients with no prior antiretroviral therapy, with a marginally significant 50 percent reduction in the risk of death alone (Table 3). In contrast, zidovudine plus zalcitabine had no significant

clinical benefit over zidovudine alone in previously treated patients (Table 4).

Thus, with the exception of the apparent lack of clinical benefit of zidovudine plus zalcitabine in patients with prior antiretroviral therapy, the results consistently demonstrate the inferiority of zidovudine monotherapy. On this basis, reasonable choices for initial therapy in patients with no prior antiretroviral therapy could include zidovudine plus didanosine, zidovudine plus zalcitabine, or didanosine alone. In patients who have previously been treated with zidovudine, treatment with zidovudine plus didanosine or didanosine alone is beneficial. The hypothesis that combination therapy would be superior to nucleoside monotherapy was thus only partially borne out in this trial, since the overall clinical results were similar for didanosine alone and zidovudine plus didanosine. Nevertheless, combination regimens are becoming the standard of care.[9,15-17,27-33] The most important message of this trial is that substantial clinical benefits, including effects on the risk of death, can be achieved in a population at a relatively early stage of disease.

The CD4 cell responses generally correlated with the overall study results. In both the subgroup with no prior antiretroviral therapy and the subgroup with prior antiretroviral therapy, zidovudine monotherapy evoked poorer CD4 cell responses than did the other treatments. A complicating factor in the interpretation of the CD4 cell responses is the apparently blunted increase in CD4 cells among patients with no prior antiretroviral therapy who received zidovudine alone. The reason for this difference between our results and those of some prior studies[1-6,28,34] is not clear, since measurements of mean corpuscular volume showed no evidence of major, recent zidovudine use in this group; serum zidovudine levels were in the expected range; and the zidovudine-associated resistance mutation at codon 215 was present only in a small minority of the subgroup.[35]

The 19 percent rate of loss to follow-up is a cause for concern, although certain factors suggest that this does not negate the differences between treatments. First, there was no association between measures of disease status (CD4 cell count, symptoms of HIV infection, and Karnofsky score) at base line and the risk of loss to follow-up, despite the fact that the risk of premature discontinuation of treatment was related to these factors. Second, analyses in which follow-up was censored at earlier times (12, 18, or 24 months) yielded results that were consistent with the overall results. Third, differences among the treatments were reasonably consistent for the various primary and secondary end points, whereas loss to follow-up would be an increasing problem for the end points reached later in the study.

Two trials examining the clinical efficacy of combinations of nucleoside analogues in patients with more advanced disease than was characteristic of our study population have recently been reported. The Delta trial compared zidovudine plus didanosine and zidovudine plus zalcitabine with zidovudine alone in patients with no previous zidovudine treatment and patients with previous zidovudine treatment who had CD4 cell counts below 350 per cubic millimeter.[27] In previously untreated patients, each of the two combinations was superior to zidovudine alone with respect to the end points of an AIDS-defining event or death or death alone. Among previously treated patients, a survival benefit was demonstrated only for those given zidovudine plus didanosine. A trial by Saravolatz et al., reported elsewhere in this issue of the *Journal*,[36] had a design similar to that of the Delta trial and involved patients with CD4 cell counts below 200 per cubic millimeter, 77 percent of whom had previously been treated with zidovudine. For the end points of an AIDS-defining event or death or death alone, no differences were demonstrated between the treatment groups. However, a clinical benefit for zidovudine plus didanosine and zidovudine plus zalcitabine was seen in patients with no or limited previous exposure to zidovudine.

The results of these two trials complement ours and together suggest that in previously untreated patients, combination therapy with zidovudine plus didanosine or zidovudine plus zalcitabine is superior to zidovudine monotherapy; that in patients who have received zidovudine previously, the addition of didanosine to the treatment regimen can be beneficial, although this was most clearly demonstrated in our trial; and that the addition of zalcitabine to the treatment regimen in patients with prolonged exposure to zidovudine does not provide a clinical benefit.

The superiority of didanosine over zidovudine as initial monotherapy in this trial contrasts with the results of ACTG 116A, a study in which zidovudine was found to be clinically superior to didanosine as initial therapy in patients with no previous zidovudine therapy whose CD4 cell counts were less than 300 per cubic millimeter.[37] The reasons for this difference are hard to explain, but in ACTG 116A the population had more advanced disease and the majority of the end points were reached earlier. A recent study in children (ACTG 152) also found zidovudine to be inferior to both didanosine alone and zidovudine plus didanosine.[38]

Given the results of earlier studies of zidovudine monotherapy,[2-4,7] the current results strongly suggest that antiretroviral therapy is beneficial for asymptomatic HIV-infected patients with CD4 cell counts below 500 per cubic millimeter and demonstrate that such therapy can confer a survival benefit in a population with intermediate-stage disease. Since the inception of this trial, a number of other antiretroviral agents have become available, including

stavudine, lamivudine, saquinavir, ritonavir, indinavir, and nevirapine.[15-17,28-30,32,33,39-45] The results of clinical trials with newer combinations of nucleoside analogues, including zidovudine plus lamivudine,[28-32] and the protease inhibitors saquinavir, indinavir, and ritonavir[15,17,42-45] suggest that further progress, in particular greater prolongation of event-free survival, is on the horizon.

Supported in part by the AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases and by the General Research Center units funded by the National Center for Research Resources.

Drs. Hammer, Katzenstein, Schooley, Hirsch, and Merigan have served as ad hoc consultants to Bristol-Myers Squibb, Glaxo–Wellcome, or Hoffmann–LaRoche, the pharmaceutical firms whose products were studied.

APPENDIX

The following institutions and investigators participated in ACTG 175: **Harvard University** — C. Crumpacker, D. Craven, B. Chapman, C. Grodman; **Case Western Reserve University** — M. Chance, K. Citraro, A. Davidson; **Northwestern University** — R. Hirschtick, J. Pottage, Jr., J. Pulvirenti; **University of Minnesota** — H. Balfour, N. Reed, S. Swindells, R. Nelson; **Mt. Sinai Medical Center** — D. Mildvan, J. Hassett, B. Simpson, K. Luyks; **University of California, San Diego** — D. Richman, S. Spector, C. Jacobsen; **Stanford University** — V. Tallman, M. Rinki, D. Carroll, G. Van Raalte; **University of California, Los Angeles** — R. Mitsuyasu, G. Beall, W. Hardy, G. Mathisen; **University of Washington, Seattle** — A. Collier, B. Royer, M. Paradise, L. Sacks; **Washington University** — W. Powderly, A. Slack, T. Stiffler, M. Royal; **Ohio State University** — M. Para, N. Stark, C. Jackson, J. Neidig; **University of North Carolina** — J. Eron, T. Lane, J. Horton, D. Ragan; **University of California, San Francisco** — D. Abrams, L. Johnson, K. Dybek, J. Carroll; **University of Rochester** — R. Reichman, C. Greisberger, R. Hewitt, D. Blair; **Indiana University** — K. Fife, M. Goldman, K. Todd, B. Zwickl; **University of Colorado** — D. Kuritzkes, V. Waite, M. Ray; **Charity Hospital** — N. Hyslop, Jr., D. Mushatt, R. Clark, J. Zachary; **University of Cincinnati** — B. Wong, J. Brinkdopke, B. Jackson, D. Dayton; **Albert Einstein Medical Center** — R. Soeiro, D. Stein, J. Schliosberg, B. Zingman; **State University of New York–Stonybrook** — R. Steigbigel, J. Fuhrer, P. Mariuz, C. Wallace; **University of Southern California** — J. Geiseler, J. Leedom, S. Cordina, C. Olson; **University of Miami** — M. Fischl, D. Jayaweera, J. Patrone Reese, E. Dale; **Cornell University Medical Center** — K. Sepkowitz, V. Sharp, D. Shepp; **Johns Hopkins University** — J. Bartlett, R. Becker, D. Baker, D. Wright; **Hershey Medical Center** — W. Ehmann, J. Zurlo, M. Kreher, F. Damianos; **University of Massachusetts** — S. Cheeseman, J. Avato, C. Bova, M. Sands; **St. Luke's–Roosevelt Hospital Center** and **Columbia University** — M. Grieco, G. McKinley, J. Rivera, J. O'Connor; **University of Alabama, Birmingham** — D. Davis, K. Squires, J. Gnann, M. Saag; **University of Texas Medical Branch, Galveston** — R. Pollard, M. Borucki, K. Waterman, G. Casey; **University of Pennsylvania, Philadelphia** — I. Frank, D. Dunbar, I. Matozzo, S. Hauptman; **New York University Medical Center** — V. McAuliffe, V. Rosenwald, F. Valentine; **University of Medicine and Dentistry of New Jersey–University Hospital** — P. Kloser, P. Correll; **Duke University Medical Center** — J. Bartlett, R. Dodge, P. Robinson, K. Shipp; **Yale University** — G. Friedland, E. Cooney, M. Fiellin, B. Griffith; **University of Puerto Rico** — G. Vazquez, M. Cruz-Ortiz, V. Ramirez, I. Lopez; **Howard University** — W. Greaves, J. McNeil, R. Delapenha, V. Holley-Trimmer; **University of Hawaii** — M. Heath-Chiozzi, D. Ogata-Arakaki, S. Bon Akina, M. Millard; **Georgetown University** — P. Pierce, P. Kumar, J. Timpone, L. Green; **Boston Children's Hospital** — K. McIntosh, A. Rubin-Hale, K. Knox-Burke, H. Mahoney-West; **Montefiore Adolescent AIDS Program** — D. Futterman, D. Monte, N. Hoffman; **State University of New York–Brooklyn** — K. Chirgwin, D. Smith, G. Garner, D. Hauck; **Tulane University** — R. Van Dyke, S. Abdalian, C. Degenstein, J. Price; **National Hemophilia Foundation** — D. Brettler, F. Rickles, P. Smith, C. Cornell, S. Seremetis, R. Lipton, L. Cisar, S. Arkin, M. Ragni, J. Steinberg, C. Lessinger, W. Hanna, T. Hadley, J. Penner, S. Adair, E. Czapek, H. Ritter, W. Hoots, M. Cantini, C. Rutherford, D. MacFarlane, R. Stuart, S. Stabler, S. Giambartolomei, M. Ford, G. Gjerset, J. Goldsmith, A. Sosa, N. Sanders; **ACTG Operations Office** — P. Kasdan, J. Cook, B. Landry, L. Nerhood; **Data Management Center** — M. Colon-Ruiz, K. Ojudun; **Division of AIDS, National Institutes of Health** — A. Martinez, C. Pettinelli.

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