

**ZIDOVUDINE ALONE OR IN COMBINATION WITH DIDANOSINE  
OR ZALCITABINE IN HIV-INFECTED PATIENTS WITH THE ACQUIRED  
IMMUNODEFICIENCY SYNDROME OR FEWER THAN  
200 CD4 CELLS PER CUBIC MILLIMETER**

LOUIS D. SARAVOLATZ, M.D., DEAN L. WINSLOW, M.D., GARY COLLINS, M.S., JAMES S. HODGES, Ph.D.,  
CARLA PETTINELLI, M.D., Ph.D., DANIEL S. STEIN, M.D., NORMAN MARKOWITZ, M.D., RANDALL REVES, M.D., M.Sc.,  
MARK O. LOVELESS, M.D., LAWRENCE CRANE, M.D., MELANIE THOMPSON, M.D., DONALD ABRAMS, M.D.,  
AND INVESTIGATORS FOR THE TERRY BEIRN COMMUNITY PROGRAMS FOR CLINICAL RESEARCH ON AIDS\*

**ABSTRACT**

**Background** We compared two combinations of nucleosides with zidovudine alone in patients with advanced human immunodeficiency virus (HIV) infection.

**Methods** A total of 1102 patients with the acquired immunodeficiency syndrome or fewer than 200 CD4 cells per cubic millimeter were randomly assigned to receive zidovudine alone or zidovudine combined with either didanosine or zalcitabine. Disease progression, survival, toxic effects, and the CD4 cell response were assessed.

**Results** After a median follow-up of 35 months, disease progression or death occurred in 62 percent of the 363 patients assigned to zidovudine plus didanosine, 63 percent of the 367 assigned to zidovudine plus zalcitabine, and 66 percent of the 372 assigned to zidovudine alone ( $P=0.24$ ). As compared with zidovudine therapy, treatment with zidovudine plus didanosine was associated with a relative risk of disease progression or death of 0.86 (95 percent confidence interval, 0.71 to 1.03), and treatment with zidovudine plus zalcitabine was associated with a relative risk of 0.92 (95 percent confidence interval, 0.76 to 1.10). Survival was similar in the three groups. In a subgroup analysis, combination therapy delayed disease progression or death in patients who had previously received zidovudine for 12 months or less. Therapy with zidovudine plus didanosine resulted in more gastrointestinal adverse effects, and treatment with zidovudine plus zalcitabine, more neuropathy. The mean increases in CD4 cell counts at two months were higher with combination therapy than with zidovudine alone.

**Conclusions** In patients with advanced HIV infection, combination therapy with zidovudine and either didanosine or zalcitabine is not superior to zidovudine therapy alone. However, these combinations may be more effective than zidovudine monotherapy in patients with little or no previous zidovudine treatment. (N Engl J Med 1996;335:1099-106.)

©1996, Massachusetts Medical Society.

**B**ETTER treatments are needed for patients with human immunodeficiency virus (HIV) infection and a condition characteristic of the acquired immunodeficiency syndrome (AIDS) or severe immune suppression. Prior investigations have found that didanosine or zalcitabine combined with zidovudine acts additively or synergistically against HIV in vitro and increases CD4 lymphocyte counts in vivo, more than does zidovudine alone; that cross-resistance between these agents and zidovudine is uncommon; and that they had different dose-limiting toxic effects from zidovudine.<sup>1-13</sup> As compared with zidovudine alone, combinations of zidovudine with didanosine or zalcitabine might be expected to delay disease progression and prolong survival with acceptable side effects.

We evaluated the rates of disease progression and survival, changes in CD4 lymphocyte counts, and the incidence of adverse events in a randomized comparison of zidovudine alone or in combination with didanosine or zalcitabine.

**METHODS****Study Population**

The patients were enrolled in 15 units of the Terry Beirn Community Programs for Clinical Research on AIDS, a consortium of 21 units in 17 U.S. cities conducting clinical trials in primary care settings. HIV-infected patients 13 years of age or older were eligible if they had had an AIDS-defining condition or had a CD4 cell count below 200 cells per cubic millimeter or 15 percent of the total lymphocyte count. During the study the patients were required to receive prophylaxis for *Pneumocystis carinii* pneumonia and to take no antiretroviral therapy except the study drugs.

From St. John Hospital, Detroit (L.D.S.); the Delaware Community Program for Clinical Research on AIDS, Wilmington (D.L.W.); the Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis (G.C., J.S.H.); the Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md. (C.P.); Albany Medical College, Albany, N.Y. (D.S.S.); Henry Ford Hospital, Detroit (N.M.); the Denver Community Program for Clinical Research on AIDS, Denver (R.R.); the Research and Education Group, Portland, Ore. (M.O.L.); Wayne State University—Detroit Medical Center, Detroit (L.C.); the AIDS Research Consortium of Atlanta, Atlanta (M.T.); and the Community Consortium of San Francisco, San Francisco (D.A.). Address reprint requests to Dr. Lawrence Deyton at the National Institutes of Health, 6003 Executive Blvd., Bethesda, MD 20892.

\*Other study participants are listed in the Appendix.

The protocol was approved by each unit's institutional review board, and all patients gave written informed consent.

At entry, patients were required to have a hemoglobin level of at least 8.0 g per deciliter (4.9 mmol per liter), a platelet count of at least 75,000 cells per cubic millimeter, an absolute neutrophil count of at least 1000 cells per cubic millimeter, alanine aminotransferase and alkaline phosphatase concentrations that were no more than five times the upper limit of normal, a total bilirubin concentration that did not exceed 2.5 mg per deciliter (42.75  $\mu$ mol per liter), a total serum amylase concentration that was no more than twice the upper limit of normal, a serum creatinine concentration of no more than 2 mg per deciliter (176.8 mmol per liter), and a serum triglyceride concentration that was no more than 750 mg per deciliter (8.47  $\mu$ mol per liter). Patients were excluded if they had a history or symptoms of pancreatitis or peripheral neuropathy, intolerance to any study drug, or AIDS dementia complex of stage 2 or higher<sup>14</sup>; if they were receiving short-term therapy for any AIDS-defining condition; or if they were pregnant or breast-feeding.

### Study Design

The trial's primary objective was to compare the efficacy of zidovudine alone, zidovudine with didanosine, and zidovudine with zalcitabine in delaying disease progression or death in patients with AIDS or CD4 cell counts below 200 cells per cubic millimeter.

To minimize the number of pills that participants would have to take, the patients were initially randomly assigned in an open fashion to receive, in a 1:1 ratio, zidovudine plus didanosine or zidovudine plus zalcitabine, and then assigned in a double-blind fashion, in a 2:1 ratio, to didanosine or its placebo or zalcitabine or its placebo. Randomization was carried out with a permuted block design stratified according to unit. The sample size and length of follow-up were selected to give the study 80 percent power to detect a 33 percent reduction in the rate of disease progression or death with either type of combination therapy, as compared with zidovudine alone.

Disease progression was defined as the first occurrence of an AIDS-defining condition, defined according to published criteria.<sup>15</sup> Events reported as indicating disease progression were reviewed by a committee unaware of the patients' treatment assignments and were deemed end points if judged confirmed or probable. We used the five-point scale of adverse events devised by the Division of AIDS of the National Institute of Allergy and Infectious Diseases (NIAID), in which a grade of IV indicates a potentially life-threatening event and a grade of V death, to grade adverse events occurring while the patient was taking study drugs and during the eight weeks after their permanent discontinuation. Adverse events were reported if they led to discontinuation of treatment or were grade IV or V.

### Treatment Regimens, Evaluation of Patients, and Follow-up

Zidovudine was prescribed at a dosage of 200 mg three times a day, didanosine at a dosage of 200 mg twice a day, and zalcitabine at a dosage of 0.75 mg three times a day. Placebos for didanosine and zalcitabine were prescribed at the same frequencies. Follow-up evaluations were conducted at weeks 2 and 4, month 2, and then every two months thereafter. At each visit, symptoms were assessed and a blood sample was drawn.

The study drugs were permanently discontinued in the event of unresolved or recurrent peripheral neuropathy, hyperamylasemia (concentrations more than two times the upper limit of normal on retesting or more than five times the upper limit of normal), aphthous ulcers, clinical pancreatitis, a severe cutaneous or allergic reaction attributed to the study drug, a severe or life-threatening toxic reaction, the patient's refusal to continue therapy, or the treating clinician's recommendation. Treatment was also discontinued if the patient was unable or unwilling to take one of the study drugs.

### Statistical Analysis

The investigators were unaware of the interim results. At least quarterly, external monitors visited each unit to check case-report forms against source documents for accuracy. Interim findings were monitored by the NIAID Data and Safety Monitoring Board.

All analyses were performed according to the intention to treat and were stratified according to unit. The three groups were compared for disease progression, survival, and adverse events with Kaplan-Meier estimates, log-rank tests (with 2 degrees of freedom), and proportional-hazards models.<sup>16</sup> The proportional-hazards models were used for adjusted tests of significance; estimates of relative risk, with the group assigned to zidovudine used as the reference group; and 95 percent confidence intervals. Adjusted analyses, including subgroup analyses, included these base-line measures: history of an AIDS-defining condition, CD4 cell count, Karnofsky score, hemoglobin level, and duration of prior zidovudine use, if any. The treatment groups were also compared by combining the relative risks for individual AIDS-defining conditions.<sup>17</sup> All P values were two-tailed; all median times accounted for censoring. Analysis of covariance was used to compare the change in CD4 cell counts from base line to two months. Changes in the CD4 cell count occurring after two months were compared with a random-effects model.<sup>18</sup>

## RESULTS

### Study Population and Follow-up

Between April 1992 and June 1994, 1113 patients were enrolled; 366 received zidovudine plus didanosine, 372 received zidovudine plus zalcitabine, and 375 received zidovudine alone (188 and 187 received didanosine and zalcitabine placebo, respectively). A total of 1102 patients (99.0 percent) who met all eligibility criteria are the basis for this report. The number of patients screened and the reasons for exclusion were not recorded during the trial.

The base-line characteristics of the patients were similar among the treatment groups (Table 1). Twenty-three percent had never used zidovudine; among those who had, the median duration of prior use was 12 months. Only 4.4 percent of patients had taken didanosine previously, and 2.5 percent had taken zalcitabine.

The median length of follow-up was 35 months (range, 1 to 44). Attendance at follow-up visits averaged 88 percent. At the close of the study, 2.5, 2.5, and 2.7 percent of patients given zidovudine plus didanosine, zidovudine plus zalcitabine, and zidovudine alone, respectively, had unknown vital status and no reported disease progression.

### Use of Study Drugs

The median length of blinded treatment was 10, 12, and 12 months in the zidovudine-plus-didanosine, zidovudine-plus-zalcitabine, and zidovudine groups, respectively. Of the time between randomization and the occurrence of a primary end point, 57, 62, and 63 percent, respectively, was spent taking the study drug. The most common reasons for discontinuing study drugs were a patient's request to discontinue didanosine, zalcitabine, or placebo (53, 40, and 43 percent), the physician's decision (40, 40,

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE PATIENTS, ACCORDING TO TREATMENT GROUP.\*

CHARACTERISTIC	ZIDOVUDINE PLUS DIDANOSINE (N=363)	ZIDOVUDINE PLUS ZALCITABINE (N=367)	ZIDOVUDINE (N=372)	TOTAL (N=1102)
Age (yr)	37.2±8.2	37.4±8.0	37.9±7.8	37.5±8.0
Female sex (%)	9.1	7.9	7.0	8.0
Race or ethnic group (%)				
Hispanic	9.6	9.3	9.1	9.3
Black	33.9	33.0	33.1	33.3
White	54.8	55.9	55.4	55.4
Other	1.7	1.9	2.4	2.0
Male homosexual contact (%)	70.0	68.1	66.1	68.1
History of injection-drug use (%)	22.9	21.5	23.1	22.5
Karnofsky score	90.7±8.7	90.8±8.9	91.1±8.5	90.9±8.7
Prior AIDS-defining opportunistic infection (%)	30.3	34.6	30.1	31.7
Mean CD4 cell count (cells/mm <sup>3</sup> )	125.3±112.8	113.3±108.2	117.9±110.0	118.8±110.3
Median CD4 cell count (cells/mm <sup>3</sup> )	102.0	87.0	90.0	91.0
Prior zidovudine use (%)	78.0	77.9	75.8	77.2
Median duration of prior zidovudine use (mo)				
All patients	7.0	7.0	6.0	7.0
Patients with prior zidovudine use	12.0	12.0	12.0	12.0

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

and 42 percent), and a patient's request to discontinue zidovudine (36, 32, and 30 percent). These reasons were not mutually exclusive.

After discontinuing the study drugs, many patients did not receive antiretroviral therapy. At 12 months, 45, 37, and 43 percent of the surviving patients in the zidovudine-plus-didanosine, zidovudine-plus-zalcitabine, and zidovudine groups were not receiving antiretroviral therapy; at 24 months, the percentages were 44, 49, and 47 percent. Among patients receiving antiretroviral medications after discontinuing study drugs, far more in all treatment groups received monotherapy than combination therapy. For much of the study period, only zidovudine, didanosine, and zalcitabine were available to patients and physicians.

**Disease Progression or Death**

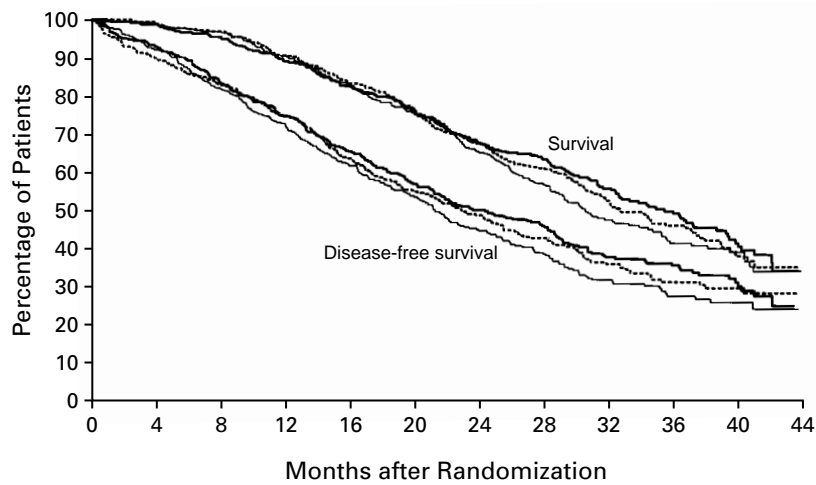
Disease progression or death occurred in 226, 230, and 244 patients in the zidovudine-plus-didanosine, zidovudine-plus-zalcitabine, and zidovudine groups, respectively; the rates per 100 person-years were 34.3, 36.2, and 39.6 (P=0.24). At 12 months 74.8 percent, 74.7 percent, and 71.9 percent, respectively, were alive and disease-free; at 24 months the percentages were 50.2, 48.8, and 44.7 percent; and at 36 months they were 35.7, 31.3, and 27.6 percent (Fig. 1). As compared with zidovudine therapy (Table 2), treatment with zidovudine plus didanosine was associated with a relative risk of disease progression or death of 0.86 (95 percent confidence interval, 0.71 to 1.03; P=0.09) and zidovudine plus

zalcitabine with a relative risk of 0.92 (95 percent confidence interval, 0.76 to 1.10; P=0.35). As compared with treatment with zidovudine plus didanosine, treatment with zidovudine plus zalcitabine was associated with a relative risk of disease progression or death of 0.93 (95 percent confidence interval, 0.77 to 1.12; P=0.45). Adjusting for base-line covariates had little effect.

No significant differences among the three groups were found in comparisons of the length of time to a first occurrence or recurrence of the specific conditions examined. The results for zidovudine plus zalcitabine did not differ significantly from those for zidovudine monotherapy for any condition. Zidovudine plus didanosine was associated with a lower risk of *P. carinii* pneumonia (relative risk, 0.65; 95 percent confidence interval, 0.44 to 0.96; P=0.03) and a lower risk of *Mycobacterium avium* complex (relative risk, 0.66; 95 percent confidence interval, 0.44 to 0.98; P=0.04) than zidovudine monotherapy. When the analyses for individual conditions were combined, we found that the results for zidovudine plus didanosine differed significantly from those for zidovudine alone (P=0.05), whereas the results for zidovudine plus zalcitabine did not differ significantly from those for zidovudine alone (P=0.51) (Table 2).

**Death**

Death occurred in 176, 182, and 191 patients in the zidovudine-plus-didanosine, zidovudine-plus-zal-



EVENT-FREE SURVIVAL/SURVIVAL				
—	Zidovudine plus didanosine	270/322	164/220	58/83
- - - -	Zidovudine plus zalcitabine	271/330	152/217	50/81
—	Zidovudine	264/333	140/211	40/66

**Figure 1.** Cumulative Disease-free Survival and Survival According to Treatment Group. The numbers of patients at risk at 12, 24, and 36 months are shown below the figure.

**TABLE 2.** THE INCIDENCE AND RELATIVE RISK OF VARIOUS OPPORTUNISTIC DISEASES AND DEATH, ACCORDING TO TREATMENT GROUP.

EVENT	ZIDOVDINE PLUS DIDANOSINE (N=363)	ZIDOVDINE PLUS ZALCITABINE (N=367)	ZIDOVDINE (N=372)	RELATIVE RISK (95% CONFIDENCE INTERVAL)*	
	no. of patients			ZIDOVDINE PLUS DIDANOSINE	ZIDOVDINE PLUS ZALCITABINE
Disease progression or death	226	230	244	0.86 (0.71–1.03)	0.92 (0.76–1.10)
Death	176	182	191	0.88 (0.71–1.08)	0.96 (0.78–1.17)
Pulmonary or extrapulmonary <i>P. carinii</i>	42	51	60	0.65 (0.44–0.96)†	0.79 (0.54–1.15)
Esophageal or pulmonary candidiasis	43	48	42	0.97 (0.63–1.49)	1.16 (0.76–1.75)
Systemic <i>M. avium</i> complex infection	42	52	58	0.66 (0.44–0.98)†	0.85 (0.58–1.24)
Cytomegalovirus disease	49	51	49	0.96 (0.65–1.44)	1.02 (0.69–1.52)
Malignant conditions‡	19	17	27	0.64 (0.36–1.16)	0.58 (0.31–1.06)
Other opportunistic infections§	37	34	38	0.94 (0.60–1.48)	0.88 (0.55–1.40)
Other diseases¶	17	32	26	0.60 (0.33–1.12)	1.13 (0.67–1.90)
All events — first and subsequent (pooled hazard ratios)	454	500	521	0.84 (0.70–1.00)†	0.94 (0.79–1.12)

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

†P=0.05 for the comparison with zidovudine monotherapy.

‡Malignant conditions consisted of Kaposi's sarcoma with visceral involvement, lymphoma, and cervical cancer.

§The opportunistic infections consisted of cryptosporidiosis, isosporiasis, toxoplasmosis, nontuberculosis mycobacterial infection (besides *M. avium* complex), tuberculosis, cryptococcosis, histoplasmosis, salmonella septicemia, herpes simplex, and disseminated herpes zoster.

¶Other diseases consisted of AIDS dementia complex, progressive multifocal leukoencephalopathy, and wasting.

citabine, and zidovudine groups, respectively (Table 2); the respective rates of death per 100 person-years were 21.9, 22.7, and 24.1 ( $P=0.44$ ). The survival rate at 12 months was 89.2 percent in the group assigned to zidovudine plus didanosine, 90.9 percent in the group assigned to zidovudine plus zalcitabine, and 90.5 percent in the group assigned to zidovudine alone; at 24 months the rates were 67.5 percent, 67.7 percent, and 65.4 percent; and at 36 months they were 49.4 percent, 46.2 percent, and 41.6 percent (Fig. 1). As compared with zidovudine therapy (Table 2), treatment with zidovudine plus didanosine was associated with a relative risk of death of 0.88 (95 percent confidence interval, 0.71 to 1.08;  $P=0.22$ ) and treatment with zidovudine plus zalcitabine was associated with a relative risk of 0.96 (95 percent confidence interval, 0.78 to 1.17;  $P=0.67$ ). As compared with treatment with zidovudine plus didanosine, therapy with zidovudine plus zalcitabine was associated with a relative risk of death of 0.92 (95 percent confidence interval, 0.74 to 1.13;  $P=0.42$ ). Kaplan–Meier estimates of survival in each treatment group are shown in Figure 1.

**Adverse Events**

The rates of adverse events leading to discontinuation of treatment were 32.9, 32.6, and 26.5 per 100 person-years in the zidovudine-plus-didanosine, zidovudine-plus-zalcitabine, and zidovudine groups, re-

spectively. As compared with zidovudine therapy, treatment with zidovudine plus didanosine was associated with a relative risk of discontinuation of treatment of 1.29 (95 percent confidence interval, 1.01 to 1.64;  $P=0.04$ ) and treatment with zidovudine plus zalcitabine with a relative risk of 1.21 (95 percent confidence interval, 0.95 to 1.54;  $P=0.12$ ) (Table 3).

The numbers of patients with a first occurrence of each type of adverse event are shown in Table 3. Nausea or vomiting, diarrhea, abdominal pain or gastrointestinal distress, and pancreatitis were more common during treatment with zidovudine plus didanosine, whereas neuropathy was more common during treatment with zidovudine plus zalcitabine. Patients taking zidovudine plus zalcitabine had lower rates of diarrhea than those taking zidovudine alone. However, half the patients assigned to zidovudine alone received a didanosine placebo, and these patients had higher rates of some adverse events than the patients who received the zalcitabine placebo; the difference between groups was significant for diarrhea ( $P=0.008$ ). The increased rate of diarrhea with didanosine placebo is related to the buffer used (magnesium hydroxide).

**CD4 Cell Counts**

The mean change in the CD4 cell counts from base line to two months was +19.2, +12.9, and -4.0 cells per cubic millimeter in the zidovudine-

**TABLE 3.** THE INCIDENCE AND RELATIVE RISK OF ADVERSE EVENTS, ACCORDING TO TREATMENT GROUP.\*

ADVERSE EVENT	ZIDOVUDINE PLUS DIDANOSINE (N=363)	ZIDOVUDINE PLUS ZALCITABINE (N=367)	ZIDOVUDINE (N=372)	RELATIVE RISK (95% CONFIDENCE INTERVAL)	
	no. of patients			ZIDOVUDINE PLUS DIDANOSINE	ZIDOVUDINE PLUS ZALCITABINE
Adverse event resulting in permanent discontinuation of study drug regimen	141	151	124	1.29 (1.01–1.64)†	1.21 (0.95–1.54)
Grade IV or V adverse event	64	78	74	1.01 (0.72–1.41)	1.01 (0.73–1.39)
Neutropenia	23	35	28	0.86 (0.49–1.50)	1.17 (0.71–1.94)
Anemia	19	14	15	1.42 (0.72–2.82)	0.90 (0.43–1.89)
Nausea or vomiting	46	17	28	1.79 (1.11–2.87)†	0.60 (0.33–1.11)
Diarrhea	17	4	15	1.14 (0.57–2.30)	0.24 (0.08–0.72)†
Abdominal pain or gastrointestinal distress	37	14	25	1.64 (0.98–2.74)	0.57 (0.29–1.10)
Elevated amylase or lipase level	9	6	6	1.78 (0.63–5.04)	0.93 (0.30–2.90)
Pancreatitis	8	2	2	4.64 (0.98–21.97)	0.97 (0.14–6.91)
Neuropathy	24	56	25	1.06 (0.60–1.86)	2.20 (1.36–3.56)‡

\*In each case the reference group is the zidovudine group. The specific events listed include events that resulted in the discontinuation of study drugs as well as grade IV or V events that occurred during treatment. The following laboratory values were considered to indicate grade IV events: hemoglobin level, less than 6.5 g per deciliter (4.0 mmol per liter); absolute neutrophil count, fewer than 500 cells per cubic millimeter; amylase level, more than five times the upper limit of normal; and lipase level, more than five times the upper limit of normal.

† $P<0.05$ .

‡ $P<0.01$ .

plus-didanosine, zidovudine-plus-zalcitabine, and zidovudine groups, respectively ( $P < 0.001$  for the comparisons of each combination therapy with the monotherapy group). The rate of decline in the CD4 cell count after two months was similar for the three groups.

**Subgroup Findings**

When patients were grouped according to covariates assessed at base line (history of an AIDS-defining condition, Karnofsky score, hemoglobin level, race [nonwhite vs. white], and sex), no significant interactions were found between the subgroups and the treatment effects.

The results were also analyzed according to the extent of zidovudine use before randomization: no prior use, use for 12 months or less, and more than 12 months of use (Table 4). The patients in these subgroups took the study drugs for similar lengths of time (data not shown). The treatment effects in these subgroups differed with respect to disease progression or death ( $P = 0.04$ ) but not with respect to death alone ( $P = 0.39$ ). (Homogeneity was assessed with a test with 4 degrees of freedom, adjusted for other base-line variables; the unadjusted P values were 0.19 and 0.52, respectively.) For both combination therapies, as compared with zidovudine therapy, the adjusted relative risk of disease progression or death increased with increasing prior use of zidovudine. Patients with no prior use and those with 12 months of use or less showed a benefit from combination ther-

apy, whereas patients with more than 12 months of previous use did not. The change in the CD4 cell count at two months showed a similar relation to prior zidovudine use (data not shown): patients with no prior use had significant increases in CD4 cell counts in all three treatment groups.

**DISCUSSION**

In this study of patients with advanced HIV infection, combined treatment with zidovudine and either didanosine or zalcitabine did not delay disease progression or prolong survival, as compared with treatment with zidovudine alone, and patients who received combination therapy had more adverse events. It is unclear why the combination of two antiretroviral medications provided no benefit. Their toxic effects may be more pronounced in patients with advanced disease. About three quarters of the patients had already taken zidovudine before they entered the study; the lack of benefit might be explained by the findings in recent studies that susceptibility to didanosine and zalcitabine decreases when zidovudine resistance occurs<sup>19</sup> and that zidovudine resistance in patients with extensive prior zidovudine use predicts disease progression and death whether they continue to take zidovudine or switch to another medication.<sup>20</sup>

Our study was designed to detect a 33 percent reduction in the rate of disease progression or death with combination therapy as compared with zidovudine therapy alone. Smaller differences may have been

**TABLE 4.** INCIDENCE AND RELATIVE RISK OF DISEASE PROGRESSION AND DEATH ACCORDING TO TREATMENT AND PRIOR ZIDOVUDINE USE.\*

EVENT	ZIDOVUDINE PLUS DIDANOSINE (N=363)	ZIDOVUDINE PLUS ZALCITABINE (N=367)	ZIDOVUDINE (N=372)	RELATIVE RISK† (95% CONFIDENCE INTERVAL)	
	no. of events			ZIDOVUDINE PLUS DIDANOSINE	ZIDOVUDINE PLUS ZALCITABINE
Disease progression or death					
No prior zidovudine	40	42	52	0.57 (0.36–0.90)‡	0.65 (0.42–1.00)
Prior zidovudine					
≤12 mo	99	99	105	0.76 (0.56–1.02)	0.72 (0.54–0.96)‡
>12 mo	87	89	87	1.10 (0.81–1.51)	1.22 (0.89–1.67)
Death					
No prior zidovudine	25	30	37	0.62 (0.35–1.08)	0.82 (0.49–1.36)
Prior zidovudine					
≤12 mo	78	80	83	0.78 (0.56–1.08)	0.80 (0.58–1.10)
>12 mo	73	72	71	1.15 (0.81–1.63)	1.01 (0.72–1.43)

\*In each case the reference group is the zidovudine group. A total of 80, 81, and 90 patients in the zidovudine-plus-didanosine, zidovudine-plus-zalcitabine, and zidovudine groups, respectively, had not previously received zidovudine; 149, 156, and 143 patients had received zidovudine for 12 months or less; and 134, 130, and 139 had received zidovudine for more than 12 months.

†The risks were adjusted for the base-line CD4 cell count, hemoglobin level, Karnofsky score, and prior opportunistic infection.

‡ $P < 0.05$ .

present but undetected; considering the toxicity of the study medications in patients with AIDS or severe immunosuppression, we felt that such differences would not be clinically relevant.

The conclusions of our study may not extend to other nucleoside monotherapies or combination therapies. In particular, it included only zidovudine monotherapy, unlike AIDS Clinical Trials Group Study 175, which included both zidovudine and didanosine monotherapy.<sup>21</sup> The benefit of zidovudine as monotherapy diminishes after two years<sup>22,23</sup>; many of the patients we studied had extensive prior zidovudine use.

Although we did not find an overall benefit of combination therapy, it did appear to be more beneficial than zidovudine alone in the subgroup of patients with no or limited prior zidovudine use.

The optimal time to begin therapy with these medications remains unresolved. Recent studies show that lymph-node destruction and cell death are caused by viral replication after primary HIV infection; early antiretroviral therapy could reduce viral replication and may delay disease progression.<sup>24</sup> Further data from trials with clinical end points are necessary to answer this question.

In summary, we found that combination therapy with zidovudine plus didanosine or zidovudine plus zalcitabine was not superior to zidovudine monotherapy in patients with AIDS or severe immunosuppression and that it produced considerably more side effects. However, subgroup analyses indicate that these combinations may be more effective in patients with little or no prior zidovudine use than in patients with extensive prior use.

Supported by contracts (NO1-AI-04045, NO1-AI-45227, NO1-AI-45231, NO1-AI-45233, NO1-AI-45222, NO1-AI-4040, NO1-AI-45224, NO1-AI-05047, NO1-AI-45230, NO1-AI-05046, NO1-AI-45229, NO1-AI-45220, NO1-AI-45235, NO1-AI-45228, NO1-AI-45234, NO1-AI-55258, NO1-AI-55255, and NO1-AI-55261) with the National Institute of Allergy and Infectious Diseases and by Bristol-Myers Squibb, Glaxo-Wellcome, and Hoffmann-LaRoche.

Dr. Abrams was an ad hoc consultant to Bristol-Myers Squibb during the conduct of this study.

Presented in part at the Terry Beirn Community Programs for Clinical Research on AIDS Group Meeting, Washington, D.C., January 18, 1996; the Third Conference on Retroviruses and Opportunistic Infections, Washington, D.C., January 28–February 1, 1996; and the 11th International Conference on AIDS, Vancouver, B.C., July 7–12, 1996.

We are indebted to the Terry Beirn Community Programs for Clinical Research on AIDS (007) NuCombo protocol team: L. Besch, M.D., B. Brizz, B.S.N., M.H.S.Ed., M. Deblinger, D.N.Sc., L. Deyton, M.S.P.H., M.D., R. Donovan, Ph.D., V. Dratter, R.N., M.S., W. El-Sadr, M.D., M.P.H., A. Martinez, R.Ph., C. McLaren, Ph.D., M.R.C.Path., M. Salgo, M.D., Ph.D., F. Rousseau, M.D., M. Myers, R.N., M. Thurnherr, D. Mayers, M.D., T. Church, Ph.D., P. Gourley, R.N., C. Naus-Karol, Ph.D., R. Swilley, R.N., C.R.N.A., K. Pattishall, B.S., R. Doolittle, R.N., D. McClure, M.S., Ph.D., M. Elkins, J. Warwick, Pharm.D., W. Rida, Ph.D., P. Stampone, M.S., and S. Wakefield.

## APPENDIX

The following centers and investigators also participated in the study: Henry Ford Hospital, Detroit — J. Kumi, B. Al-Ujayli, and D. Mastro-Polak; Denver Community Program for Clinical Research on AIDS — D. Cohn, M. Grodesky, and J. Saldanha; the Research and Education Group — J. Sampson, J. Godbey, and K. Loveless; Wayne State University–Detroit Medical Center — G. Deisinger, K. Mooney, and R. Fakhry; AIDS Research Consortium of Atlanta — S. Thompson, R. Hudson, and M. Tanner; Community Consortium of San Francisco — W.J. Fessel and A. Harris (Kaiser Medical Center), R.C. Scott (Alta Bates Medical Associates, Oakland); Addiction Research and Treatment Corporation, Brooklyn, N.Y. — L.S. Brown, Jr., S. John, and J. Rawls; AIDS Research Alliance, Chicago — R. Luskin-Hawk, R. Slotten, and J. Bonnell-Lucia; Clinical Directors Network of Region II, New York — R.A. Torres; Louisiana Community AIDS Research Programs — J. Osterberger, J. Walker, and S. Pablovich; North Jersey Community Research Initiative, Newark, N.J. — G. Perez; Richmond AIDS Consortium — T.M. Kerkering, E. Fisher, and R. Artz; Washington Regional AIDS Program, Washington, D.C. — F. Gordin; the NIAID Data and Safety Monitoring Board — C. Carpenter, Brown University, Providence, R.I.; B. Brody, Baylor College of Medicine, Houston; D. DeMets, University of Wisconsin Medical School, Madison; T. Fleming, University of Washington, Seattle; K. Mayer, Memorial Hospital, Pawtucket, R.I.; D. Murphy, University of Florida Health Sciences, Gainesville; J. O'Fallon, Mayo Clinic, Rochester, Minn.; J. Rahal, The New York Hospital Medical Center of Queens and Cornell University; M. Sande, San Francisco General Hospital; S. Straus, NIAID, Bethesda, Md.; L. Walters, Georgetown University, Washington, D.C.; R. Whitley, University of Alabama, Birmingham; P. Whitley-Williams, University of Medicine and Dentistry of New Jersey; the Division of AIDS, NIAID — S. Schnittman, W. Duncan, J. Killen, and D.O. Dixon; and the Terry Beirn Community Programs for Clinical Research on AIDS Statistical Center, University of Minnesota — J.D. Neaton.

## REFERENCES

- Mitsuya H, Broder S. Inhibition of the *in vitro* infectivity and cytopathic effect of human T-lymphotrophic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2',3'-dideoxynucleosides. *Proc Natl Acad Sci U S A* 1986;83:1911-5.
- Yarchoan R, Perno CF, Thomas RV, et al. Phase I studies of 2',3'-dideoxycytidine in severe human immunodeficiency virus infection as a single agent and alternating with zidovudine (AZT). *Lancet* 1988;1:76-81.
- Yarchoan R, Thomas RV, Pluda JM, et al. Escalating dose phase I study of intravenous and oral 2',3'-dideoxyinosine (didanosine) in patients with AIDS or ARC. In: Proceedings of the Fifth International Conference on AIDS, Montreal, June 4–9, 1989. Ottawa, Ont.: International Development Research Centre, 1989:212. abstract.
- Yarchoan R, Mitsuya H, Thomas RV, et al. *In vivo* activity against HIV and favorable toxicity profile of 2',3'-dideoxyinosine. *Science* 1989;245:412-5.
- Yarchoan R, Mitsuya H, Pluda JM, et al. The National Cancer Institute phase I study of 2',3'-dideoxyinosine administration in adults with AIDS or AIDS-related complex: analysis of activity and toxicity profiles. *Rev Infect Dis* 1990;12:Suppl 5:S522-S533.
- Gottlieb M, Galpin J, Thompkins J, et al. 2',3'-Dideoxycytidine (zalcitabine) in the treatment of patients with AIDS and ARC. In: Proceedings of the Fifth International Conference on AIDS, Montreal, June 4–9, 1989. Ottawa, Ont.: International Development Research Centre, 1989:212. abstract.
- Bozzette S, Skowron G, Arrezo J, et al. ACTG 050: alternating (ALT) and intermittent (INT) zalcitabine and AZT in the treatment of persons with advanced HIV infection and hematologic intolerance to AZT. In: Abstracts of the Sixth International Conference on AIDS, San Francisco, June 20–24, 1990. Vol. 3. San Francisco: University of California, 1990:192. abstract.
- Cooley T, Kunches LM, Saunders CA, et al. Therapy of AIDS and ARC with 2',3'-dideoxyinosine (didanosine) given once daily: results of long-term followup. In: Abstracts of the Sixth International Conference on AIDS, San Francisco, June 20–24, 1990. Vol. 3. San Francisco: University of California, 1990:205. abstract.
- Johnson VA, Merrill DP, Chou TC, Hirsch MS. HIV-1 inhibitory inter-

- actions between 2',3'-dideoxyinosine (didanosine) and either zidovudine (AZT), recombinant soluble CD4 (rsCD4) or recombinant interferon-alpha-A (rIFN-a-A). In: Abstracts of the Sixth International Conference on AIDS, San Francisco, June 20-24, 1990. Vol. 2. San Francisco: University of California, 1990:106. abstract.
- 10.** Merigan TC. Treatment of AIDS with combinations of antiretroviral agents. *Am J Med* 1991;90(4A):Suppl:8S-17S.
- 11.** Meng TC, Fischl MA, Boota AM, et al. Combination therapy with zidovudine and dideoxycytidine in patients with advanced human immunodeficiency virus infection: a phase I/II study. *Ann Intern Med* 1992;116:13-20.
- 12.** Ragni M, Dafni R, Amato DA, et al. Combination zidovudine and dideoxyinosine in asymptomatic HIV(+) patients. In: Abstracts of the Eighth International Conference on AIDS/Third STD World Congress, Amsterdam, July 19-24, 1992. Vol. 1. Amsterdam: CONGREX, 1992:Mo15. abstract.
- 13.** Collier AC, Coombs RW, Fischl MA, et al. Combination therapy with zidovudine and didanosine compared with zidovudine alone in HIV-1 infection. *Ann Intern Med* 1993;119:786-93.
- 14.** Price RW, Brew BJ. The AIDS dementia complex. *J Infect Dis* 1988; 158:1079-83.
- 15.** Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *MMWR Morb Mortal Wkly Rep* 1987;36:Suppl 1: 3S-15S.
- 16.** Lawless JF. Statistical models and methods for lifetime data. New York: John Wiley, 1982.
- 17.** Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. *J Am Stat Assoc* 1989;84:1065-73.
- 18.** Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics* 1982;38:963-74.
- 19.** Mayers DL, Japour AJ, Arduino J-M, et al. Dideoxynucleoside resistance emerges with prolonged zidovudine monotherapy. *Antimicrob Agents Chemother* 1994;38:307-14.
- 20.** D'Aquila RT, Johnson VA, Welles SL, et al. Zidovudine resistance and HIV-1 disease progression during antiretroviral therapy. *Ann Intern Med* 1995;122:401-8.
- 21.** Hammer SM, Katzenstein DA, Hughes MD, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. *N Engl J Med* 1996;335:1081-90.
- 22.** Concorde Coordinating Committee. Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet* 1994;343:871-81.
- 23.** Volberding PA, Lagakos SW, Grimes JM, et al. The duration of zidovudine benefit in persons with asymptomatic HIV infection: prolonged evaluation of protocol 019 of the AIDS Clinical Trials Group. *JAMA* 1994; 272:437-42.
- 24.** Ho DD. Time to hit HIV, early and hard. *N Engl J Med* 1995;333: 450-1.