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THE EFFICACY OF 3'-AZIDO-3'-DEOXYTHYMIDINE (AZIDOTHYMIDINE) IN THE TREATMENT OF PATIENTS WITH AIDS AND AIDS-RELATED COMPLEX: A DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL.

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ABSTRACT

A double-blind, placebo-controlled trial was conducted in 282 subjects with AIDS manifested by Pneumocystis carinii pneumonia or advanced AIDS-related complex to evaluate the efficacy of oral azidothymidine (AZT). Subjects were stratified according to CD4 cell numbers and randomly assigned to receive 250 mg of AZT or placebo every 4 hours for a total of 24 weeks. One-hundred forty-five subjects received AZT and 137 received placebo. When the study was terminated in September, 1986, 27 subjects had completed 24 weeks of the study, 152 had completed 16 weeks, and the remainder had completed at least 8 weeks. Nineteen placebo recipients and 1 AZT recipient died during the study ($p<0.001$). Forty-five subjects receiving placebo developed opportunistic infections compared to 24 receiving AZT. Baseline Karnofsky performance score and weight gain improved significantly among AZT recipients ($p<0.001$). A statistically significant increase in the number of CD4 cells was noted in subjects receiving AZT ($p<0.001$). After 12 weeks, the number of CD4 cells declined to pretreatment values among AZT recipients with AIDS. Skin test anergy was partially reversed in 29 percent of subjects receiving AZT compared to 9 percent receiving placebo ($p<0.001$). These data demonstrate that AZT administration can decrease mortality and the frequency of opportunistic infections in a specific group of subjects with AIDS and AIDS-related complex at least over the 8 to 24 week period of observation of this study.

INTRODUCTION

The acquired immunodeficiency syndrome (AIDS) is characterized by severe immunodeficiency, life-threatening opportunistic infections, malignancies, and a generally fatal outcome. The underlying immune defect in AIDS is caused by infection with a human retrovirus, human immunodeficiency virus (HIV), previously called human T-cell lymphotropic virus type III/lymphadenopathy-associated virus (1-3). In addition, infection with this virus frequently causes a severe and debilitating condition known as the AIDS-related complex. Strategies for the treatment of patients with AIDS and AIDS-related complex have focused on the development of drugs with activity against HIV *in vitro*, and agents that may produce immunorestoration.

3'-azido-3'-deoxythymidine (azidothymidine, AZT, zidovudine, Retrovir^{R}) is a thymidine analogue which inhibits HIV replication *in vitro* (4). AZT is phosphorylated by cellular enzymes, and as the 5'-triphosphate inhibits reverse transcriptase and terminates viral DNA chain elongation (5,6). In phase I studies, AZT was found to be well tolerated over a six-week period (7). In addition, some subjects had clinical and immunologic improvement characterized by an increase in the number of T helper cells, development of delayed type hypersensitivity reactions, and weight gain (7). Based on these findings, a multicenter double-blind placebo-controlled trial was initiated to evaluate the safety and efficacy of AZT in the treatment of a well defined group of subjects with AIDS or AIDS-related complex. Prior to initiation of the study in February, 1986, an independent efficacy and safety monitoring board was established to review study data during the study for unacceptable toxicity or unequivocal benefit. The study was terminated in September, 1986 because a significant difference in mortality between AZT and placebo recipients was found. The present report presents the clinical and laboratory data collected, demonstrating the efficacy of AZT.

PATIENT POPULATION

The study population consisted of 2 homogeneous groups of subjects with AIDS or AIDS-related complex. Subjects with AIDS were eligible for the study if they were within 120 days of the diagnosis of their first episode of histologically-proven Pneumocystis carinii pneumonia. Subjects with multiple episodes of P. carinii pneumonia or those with any other AIDS-defining opportunistic infection or malignancy were excluded. Subjects with AIDS-related complex were eligible if they had either unexplained weight loss (defined as greater than 6.8 kg or 10 percent loss of total body weight within 90 days prior to enrollment) or documented oral candidiasis and at least one of the following signs and symptoms: unexplained fever, extra-inguinal lymphadenopathy, oral hairy leukoplakia, unexplained night sweats, herpes zoster, or unexplained diarrhea. Eligibility criteria also included hemoglobin $\geq$ 9.5 g/dl, total granulocyte count $\geq$ 1000 cells/mm^3, platelet count $\geq$ 75,000 per mm^3, serum glutamic oxaloacetic transaminase less than 3 times the upper range of normal, serum creatinine less than 2.0 mg/dl, absolute number of cells of the CD4 surface phenotype (CD4) less than 500 cells per mm^3, skin test anergy, serum positive for anti-HIV antibody, and no recent history of therapy with antiretroviral agents, immunomodulators, or systemic antimicrobials. Subjects were instructed not to take any medications without consulting the investigator. Short-term ($\leq$ 72 hours) aspirin or acetominophen was allowed for analgesia or fever. Specific licensed drugs were also permitted after consultation of the investigator with the sponsor. Antimicrobial prophylaxis for the prevention of opportunistic infections was not allowed.

Study participants were recruited from 12 medical centers throughout the United States. The study was approved by institutional review boards at each participating center, and all subjects gave written informed consent.

METHODS

Clinical and laboratory evaluations included a medical history, physical examination, neuropsychiatric assessment, and the following laboratory studies: hemoglobin, hematocrit, mean corpuscular volume, white blood cell count, differential white cell count, platelet count, reticulocyte count, erythrocyte sedimentation rate, serum electrolytes, serum glucose, blood urea nitrogen, serum creatinine, bilirubin, serum glutamic oxaloacetic transaminase, alkaline phosphatase, vitamin B12 and folate levels, and serologic tests for hepatitis B, cytomegalovirus, and Epstein-Barr virus. Immunologic assessment included T lymphocyte phenotyping by direct immunofluorescence with monoclonal antibodies or two-color flow cytometry on either whole-blood or Ficoll-Hypaque separated mononuclear cells, quantitative immunoglobulin determination, and measurement of delayed cutaneous hypersensitivity reactions (defined as $\geq$ 10 mm of induration) to 4 antigens (trichophyton, tetanus toxoid, candida, and purified protein derivative). Blood was also collected for pharmacokinetic studies, anti-HIV antibody by enzyme-linked immunosorbent assay (ELISA), and for isolation of HIV from peripheral blood lymphocytes. All subjects were evaluated twice prior to enrollment, weekly for the first 8 weeks of the study, and biweekly thereafter. Neuropsychiatric assessments, immunologic, and virologic studies were repeated monthly.

Response criteria

Drug effects on clinical condition, immune function, and viral replication were monitored. Clinical endpoints used to assess the efficacy of AZT included survival, occurrence and frequency of opportunistic infections, occurrence of AIDS-associated malignancies, Karnofsky performance status (8), body weight, and the number and severity of symptoms. Immunologic parameters included the absolute number of CD4 cells and delayed cutaneous hypersensitivity reactions. Virologic and neuropsychiatric responses are not included in this report.

Treatment regimen

The study design was a double-blind, randomized, placebo-controlled trial intended for a 24-week duration. Subjects were stratified into two groups, according to the absolute number of CD4 cells in peripheral blood. Group A consisted of subjects with CD4 cells equal to or less than 100 cells per mm^3, and group B consisted of subjects with 101 to 499 CD4 cells per mm^3. Using a computer generated code, subjects in each group were randomly assigned to receive either AZT or placebo. A capsule consisting of 250 mg of AZT or placebo was administered orally every 4 hours throughout the 24-hour day. The placebo was indistinguishable in appearance and similar in taste to AZT. Drug therapy was temporarily discontinued or dosing frequency decreased to one capsule every 8 hours or longer if significant adverse experiences were noted. Participants were withdrawn from the study medication if they developed unacceptable toxicity or if they developed an opportunistic infection or malignancy, requiring alternative medical therapy with other experimental drugs or approved treatment regimens thought likely to add to the toxicity of AZT.

Statistical tests

Data were analyzed using the statistical analysis system (SAS), version 82.4 and version 5. Stratified Wilcoxon's Rank Sum Tests were used in the analyses of baseline comparability, number of symptoms, Karnofsky performance status, weight, number of CD4 cells, and clinical data (9). The Mantel-Haenszel method for ordered contingency tables with standardized midranks (modified ridits) as scores implemented in procedure FREQ of SAS was used in the analyses of dose reductions, severity of opportunistic infections, skin test conversions, blood transfusions, and adverse experiences (10). Survival data analysis techniques were used in the analyses of mortality, opportunistic

infections, and Kaposi's sarcoma. Cox's Regression as implemented by SAS procedure COXREG was used (11). In cases where there were too few failures to use this method, an accelerated failure time model was fit using procedure LIFETEST of SAS.

Data were analysed according to treatment group, diagnosis at entry into the study, and pretreatment CD4 stratification.

RESULTS

Patient population

Two-hundred eighty-two subjects were enrolled into the study between February and June 1986. All but 13 participants were men. One-hundred sixty had AIDS, and 122 had AIDS-related complex. One-hundred forty-five subjects were randomized to the AZT group and 137 to the placebo group (Table 1). Subjects in both groups were comparable for age, body weight, Karnofsky performance score, number of symptoms, and the mean number of CD4 cells at entry (Wilcoxon's Rank Sum Test). The only statistically significant difference in pretreatment variables between the two groups was the number of days since the diagnosis of *P. carinii* pneumonia in subjects with AIDS (AZT, 77.5 days; placebo, 86.6 days; $p < 0.04$). This difference was not considered consequential because neither mortality nor development of subsequent opportunistic infection were shown in later analyses to be correlated with the number of days since the diagnosis of *P. carinii* pneumonia.

One-hundred ninety-four subjects were still participating in the study when it was terminated in September, 1986 by the recommendation of an independent efficacy and safety monitoring board. Twenty-seven subjects had completed 24 weeks of the study, 152 had completed 16 weeks, and the remainder had completed at least 8 weeks. The mean and median duration of participation were 120 and 127 days, respectively, for the AZT group compared with 116 and

120 days in the placebo group. Sixty-one subjects were discontinued from study prior to its termination. Of these subjects, 21 were in the AZT group, and 40 were in the placebo group. The major reasons for discontinuation included the occurrence of opportunistic infections (19), progressive Kaposi's sarcoma (1), general debilitation (7), adverse experiences (5), patient request (15), or non-compliance (4). Ten placebo recipients died from opportunistic infection while receiving study medication. There was no statistically significant difference between AZT and placebo recipients with regard to the proportion of subjects participating in the study at the time of its termination.

Survival data

Nineteen subjects in the placebo group and one in the AZT group died during the study ($p<0.001$, Cox's Regression model). The immediate causes of death were AIDS-defining opportunistic infections, malignancy, or severe debilitation with wasting. In subjects receiving placebo this included: *P. carinii* pneumonia (8 cases), disseminated *Mycobacterium avium-complex* infection (4 cases), cryptococcosis (2 cases), cerebral toxoplasmosis (2 cases), disseminated cytomegalovirus infection (1 case), B-cell lymphoma (1 case), and severe debilitation with wasting (1 case). The immediate cause of death in the one patient receiving AZT was disseminated cryptococcosis. Of the 20 subjects who died, 10 of the 19 placebo recipients and the one AZT recipient had discontinued study medication 8 to 111 days prior to death. The probability of a 24-week survival for subjects in the AZT group was 0.98 compared with 0.78 in the placebo group ($p<0.001$).

This increased likelihood of survival was comparable for subjects with AIDS and AIDS-related complex who received AZT (Table 2). Two placebo treated subjects with AIDS-related complex died with opportunistic infections during the first 3 weeks of the study. Excluding these two subjects, the probability of a 24-week survival for subjects with AIDS remained unchanged. The

probability of a 24-week survival for subjects with AIDS-related complex was 1.00 in the AZT group compared with 0.83 in the placebo group ($p<0.05$).

The mortality rate was also significantly diminished for subjects receiving AZT when subjects were grouped according to pretreatment CD4 cell numbers ($\leq$ 100 cells per mm^3, $p<0.001$; >100 cells per mm^3, $p=0.028$). Similarly, the probability of a 24-week survival for subjects with pretreatment CD4 cells less than 100 cells per mm^3 was 0.96 for the AZT group and 0.70 for the placebo group ($p<0.001$). For subjects with pretreatment CD4 cells greater than 100 cells per mm^3, the probability of a 24-week survival was 1.00 for the AZT group and 0.91 for the placebo group ($p>0.05$)

Occurrence of opportunistic infections or Kaposi's sarcoma

For the purpose of this study, opportunistic infections were those that met the Centers for Disease Control criteria for the diagnosis of AIDS (12,13). Twenty-four subjects in the AZT group and 45 in the placebo group developed opportunistic infections during the study. One subject in the AZT group and 5 in the placebo group had more than one opportunistic infection. During the first six weeks of the study no significant difference was found in the frequency of opportunistic infections between the AZT placebo group (Figure 1). However, the probability of developing an opportunistic infection during the 24-week study was significantly lower in the AZT group compared with the placebo group, ($p<0.001$, Table 3).

The difference in the probability of developing an opportunistic infection when subjects were grouped by pre-entry diagnosis of AIDS or AIDS-related complex was also statistically significant (AIDS, $p<0.002$; AIDS-related complex, $p<0.002$; see Figure 2). Among 19 subjects with AIDS-related complex who developed opportunistic infections, 5 received AZT and 14 placebo. No opportunistic infection occurred in subjects with AIDS-related complex after 6

weeks of AZT; whereas, 12 episodes of opportunistic infections occurred after 6 weeks in subjects with AIDS-related complex receiving placebo (See Figure 2).

The development of a new opportunistic infection did not correlate with the number of days from the pre-entry diagnosis of P. carinii pneumonia but did correlate with a low number of CD4 cells prior to therapy (data not shown). The types of opportunistic infection noted during the study did not differ significantly between the AZT and placebo group. The most common infection was P. carinii pneumonia which accounted for more than 50 percent of all opportunistic infections (Table 4).

Sixteen subjects developed Kaposi's sarcoma during the course of the study. Ten occurred in the placebo group (AIDS, 7; AIDS-related complex, 3) and six in the AZT group (AIDS, 3; AIDS-related complex, 3; $p>0.20$).

Clinical Status

The mean pretreatment Karnofsky performance scores for AZT and placebo recipients were the same, 90. Significant changes from baseline performance status scores between the AZT and placebo group were noted as early as 4 weeks ($p<0.05$) and became more prominent during the first 12 weeks of therapy ($p<0.001$). This difference was related predominantly to the progressive deterioration of placebo subjects. By week 16, however, there was no significant difference between the performance scores of the two groups ($p>0.05$). Similar differences between the AZT and placebo group were noted when subjects were grouped according to pre-entry diagnosis of AIDS and AIDS-related complex (data not shown). Subjects in both the AZT and placebo group with pretreatment CD4 cells greater than 100 per mm^3 had no significant changes in performance status from baseline values during the study ($p>0.2$). Subjects who received AZT and had equal to or less than 100 pretreatment CD4 cells per mm^3, however, had sustained increases in performance scores throughout the first 20 weeks of the study compared with subjects receiving placebo who had

equal to or less than 100 CD4 cells (week 4, $p=0.01$; week 8, $p<0.001$; week 12 $p<0.0001$; week 16, $p=0.002$; week 20, $p<0.05$ and week 24, $p<0.2$).

Body weights of AZT and placebo recipients at enrollment were comparable (AZT group, mean=68.9kg; placebo group, mean=68.4kg). Overall, subjects who received AZT gained weight during the study; whereas, subjects in the placebo group lost weight. Statistically significant differences in body weight between the AZT and the placebo group were observed as early as week 4 (mean change in body weight: AZT recipients, +0.5 kg; placebo recipients, -0.1 kg; $p<0.05$). Body weight differences became more prominent during the first 16 weeks of the study (mean change in body weight: AZT recipients, +2.0 kg; placebo recipients, -1.3 kg, $p<0.001$) and less prominent thereafter (week 20, $p<0.04$ and week 24, $p<0.1$). Similar findings were noted when subjects were grouped according to pre-entry diagnosis of AIDS or AIDS-related complex (data not shown). Subjects with pretreatment CD4 cells greater than 100 per mm^3 showed little differences in weight for either the AZT group or placebo group ($p>0.1$), except for week 16 ($p<0.05$); whereas, subjects receiving AZT with pretreatment CD4 cells equal to or less than 100 per mm^3 showed the greatest and most persistent weight gain (weeks 8 through 16, $p<0.001$; week 20, $p<0.005$ and week 24, $p=0.01$).

Immunologic data

There was a statistically significant increase in the number of CD4 cells in subjects receiving AZT compared to those receiving placebo ($p<0.001$, Wilcoxon's Rank Sum analyses). In general, subjects receiving AZT had increases in the number of CD4 cells compared to subjects who received placebo where a decline in the number of CD4 cells was most frequently observed. The earliest difference in the number of CD4 cells was noted at week 4 and differences persisted throughout most of the study (Table 5).

After 12 weeks, a gradual decline in the number of CD4 cells was noted in subjects with AIDS receiving AZT (Figure 3). After 16 to 20 weeks, the number of CD4 cells had returned to baseline values in many of these subjects. The decline in CD4 cell numbers appeared to coincide with the development of neutropenia (data not shown). In subjects with AIDS-related complex receiving AZT, increases in the number of CD4 cells persisted throughout most of the study. Although a slight decline in the number of CD4 cells was noted after 20 weeks of therapy, the mean number of CD4 cells did not decrease to pretreatment levels as noted in many subjects with AIDS (Figure 2).

Thirty-seven of 129 (29%) subjects in the AZT group developed reactivity to at least one skin test antigen as compared to 11 of 117 subjects (9%) who received placebo ($p<0.001$). Similar result were observed when subjects were grouped according to their pretreatment diagnosis or CD4 count (Table 6).

DISCUSSION

In the present study, AZT was shown to decrease mortality and the frequency of opportunistic infections in a well defined group of subjects with AIDS or AIDS-related complex during at least a period up to 6 months in duration. The most striking difference between AZT and placebo recipients was a significantly lower incidence of death. The immediate causes of death in subjects receiving placebo were due to progressive AIDS-related disorders, demonstrating that the administration of AZT can forestall the progression of HIV related complications at least for the limited duration observed during this study. This effect was most apparent among subjects with AIDS who had recently recovered from their first episode of P. carinii pneumonia and those subjects with AIDS-related complex who had pretreatment CD4 cells equal to or less than 100 cells per mm^3. Further studies will be needed to determine whether similar benefits of AZT will be seen among patients with other AIDS-

defining opportunistic infections or those with less severe HIV infection. Although beneficial effects of AZT were noted, significant hematologic toxicity did occur (14). It is likely that patients with other AIDS-defining opportunistic infections or those with recurrent episodes of P. carinii pneumonia will be debilitated and will more frequently require alternative medical therapy. Therefore, the tolerance and efficacy of AZT may well be different. In addition, HIV infection is a chronic and probably life-long infection. Since the present observations were only 8 to 24 weeks in duration, the long-term benefits and toxicities, as well as optimal regimens of AZT, in this patient population remain unknown until further investigations are completed.

Opportunistic infections did occur less frequently among subjects receiving AZT and is the most likely reason for the decreased fatality rate in this group. No significant difference in the types of opportunistic infections was noted between AZT and placebo recipients. The most common infection was P. carinii pneumonia which accounted for more than half of the opportunistic infections. Since antimicrobial prophylaxis for the prevention of P. carinii pneumonia and other opportunistic infections was not allowed, it is possible that co-administration of AZT and antimicrobial agents could further decrease the incidence of opportunistic infections. Although several drugs including acyclovir, trimethoprim-sulfamethoxazole, aspirin, and acetominophen were administered to AZT recipients during the study, only acetominophen was associated with an increased frequency of toxicity (14). Information about drug interactions with AZT is still limited and caution must be used when administering any concomitant medications.

Although recurrent opportunistic infections were noted in subjects receiving AZT, fatality rate related to opportunistic infections was much lower

compared to patients receiving placebo. Differences in the case fatality rate from opportunistic infection suggest that subjects receiving AZT may have had either less severe episodes of opportunistic infections or a better outcome because of the immunologic enhancement from AZT administration. Whatever the reason, these results support continued use of AZT despite the occurrence of opportunistic infections.

After 6 weeks of AZT therapy, no opportunistic infection occurred in subjects with AIDS-related complex. This low incidence was notably different from the 12 placebo recipients with AIDS-related complex who developed opportunistic infection throughout the period of the study. Based on these findings, it is likely that with continued therapy beyond the 6 month study period the difference between the placebo and AZT groups might have continued to increase. The finding that AZT delayed progression to AIDS in subjects with AIDS-related complex suggests that AZT may have broader value in the treatment of patients with HIV infection. Moreover, the finding that AZT administration was also more likely to be associated with a sustained increase in CD4 cell levels in patients with AIDS-related complex suggests that AZT may be particularly benefical to patients with less severe HIV infection. Early intervention, however, has the potential for unnecessary toxicity occurring after only a few weeks of treatment. The relative benefit to toxicity ratio from early chemotherapeutic intervention in patients with less severe HIV infection is important and further studies will be needed.

Several measures of general clinical improvement, including Karnofsky performance status and body weight, were noted early in the study among AZT recipients. The toxicity of AZT and reduction of dose may have been related to the failure to sustain these positive benefits. The smaller differences between the AZT and placebo groups after 16 to 18 weeks of therapy may also have been in part technical. The number of subjects receiving study medication

after 18 weeks was small. In addition, Karnofsky performance status and body weight were not recorded for subjects who were hospitalized and thus not available for clinic visits. Because this occurred more frequently among subjects receiving placebo, the difference between the two groups were unavoidably reduced.

Subjects receiving AZT showed improvement in at least two measures of immune function which may have contributed to the clinical benefits noted. Statistical differences in both skin test reactivity and in the number of CD4 cells were noted as early as 4 weeks and persisted through 16 weeks of therapy. The absolute number of CD4 cells decreased after 16 weeks, suggesting that the initial beneficial immunological effects of AZT may not be sustained. The decline in CD4 numbers was noted especially among subjects who developed neutropenia, and thus may reflect toxicity of AZT and/or the reduction in dose it required. This was more likely to occur in patients with AIDS; whereas, sustained increases in CD4 cells were more likely to occur in subjects with AIDS-related complex who less frequently demonstrated neutropenia (14). It is possible that varying doses or dosing schedules of AZT may sustain a greater benefit. The need to develop better knowledge about the relative efficacy and toxicity of long term administration of varying doses and dosing schedules of AZT are, therefore, essential.

Data about the ability to recover virus from peripheral blood mononuclear cells are still under analysis. Preliminary data regarding HIV antigenemia, predominantly p24, suggest that changes in antigen levels in serum does correlate with AZT therapy (15). Thus inhibition but not cure of HIV infection accompanied clinical efficacy. This situtation is analogous to the experience with immunocompromised patients from bone marrow transplantation. Functional immune cells (probably CD4 cells) reconstituted as an indirect effect of AZT

may have protected against HIV infection sufficiently to reduce the frequency of opportunistic infections. The fact that the frequency of opportunistic infections was initially similar in the two treatment groups and diverged after six weeks is also analogous to bone marrow transplantation in which immune reconstitution is not immediate but delayed by several weeks. Late declines in CD4 cell numbers, correlating with bone marrow toxicity, could limit the duration of this benefit.

This study demonstrates for the first time that an anti-retroviral agent can confer benefit to patients with HIV infection. AZT is the first step in treating patients with AIDS and related disorders. Although the use of AZT is associated with toxicity in some patients, overall it has been shown to decrease mortality and opportunistic infections and the risk-benefit was in favor of the patient. Further studies will be needed to understand the full range of benefit and toxicity of AZT and how to manage the drug over time in the various groups of patients with HIV infection.

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TABLE 1 **Distribution of patients by diagnosis and CD4 cell stratification at entry into the study**

Diagnosis	Absolute Number of CD4 cells (cells per mm^3)	Number of Patients	
		AZT	Placebo
AIDS	$\leq$100	69	63
	101-499	16	12
AIDS-related complex	$\leq$100	23	27
	101-499	37	35
Total		145	137

TABLE 2 **Projected probability of a 24-week survival**

Patient Group		24-Week Survival Probability	p-Value
All Patients	AZT	0.98	<0.001
	Placebo	0.78	
AIDS Patients	AZT	0.96	<0.001
	Placebo	0.76	
AIDS-related complex Patients	AZT	1.00	0.016
	Placebo	0.81	

TABLE 3 **Projected Probability of Acquiring an Opportunistic infection within a 24-week period**

Patient Group		Probability of Developing an opportunistic infection (Weeks 0-24)	P-Value	Probability of Developing an opportunistic infection (Weeks 7-24)*	P-Value
All Patients	AZT	0.23	<0.001	0.16	<0.001
	Placebo	0.43		0.36	
AIDS Patients	AZT	0.36	0.004	0.30	0.002
	Placebo	0.54		0.45	
AIDS-related complex Patients	AZT	0.09	0.066	0.00	0.002
	Placebo	0.30		0.25	

*Values were calculated eliminating those patients who developed an opportunistic infection during the first six-weeks of the study

TABLE 4 Distribution of Opportunistic Infection in the Study Population

	AZT GROUP n=25 (%)	PLACEBO GROUP n=50 (%)
P. carinii pneumonia	13 (52%)	26 (52%)
M. avium-complex	6 (24%)	8 (16%)
Disseminated cytomegalovirus	0 (0%)	3 (6%)
Chronic mucocutaneous herpes virus infection	0 (0%)	2 (4%)
Candida esophagitis	0 (0%)	5 (10%)
Cryptosporidiosis	1 (4%)	0 (0%)
Toxoplasma encephalitis	2 (8%)	4 (8%)
Cryptococcosis	2 (8%)	2 (4%)
Pneumonia, unknown etiology	1 (4%)	0 (0%)

TABLE 5 **CD4 CELL COUNTS BY WEEK OF STUDY**

Group	Week	AZT GROUP Actual counts N	Median	Mean	PLACEBO GROUP Actual counts N	Median	Mean	P-Value
All patients	Baseline	145	77.0	120.9	136	71.1	121.0	---
	Week 4	123	161.0	198.3	119	66.1	117.6	<0.0001
	Week 8	126	106.8	165.8	108	57.5	107.5	<0.0001
	Week 12	113	112.0	166.1	103	53.0	105.3	<0.0001
	Week 16	82	117.5	168.5	74	70.1	120.7	<0.0001
	Week 20	45	59.0	167.9	36	49.6	114.3	0.0001
	Week 24	19	121.0	167.4	14	74.5	161.9	0.0998

TABLE 6 **Frequency of Skin Test Conversions During the Study**

Diagnosis	Treatment Group	# Positive/total # ($\geq$ 10 mm induration)	P-Value*
All patients	AZT	37/129	<0.001
	Placebo	11/117	
AIDS	AZT	20/74	<0.001
	Placebo	3/66	
AIDS-related complex	AZT	17/55	0.074
	Placebo	8/51	
CD4 cells $<$ 100 per mm^3	AZT	16/80	0.001
	Placebo	3/76	
CD4 cells $\geq$ 100 per mm^3	AZT	21/49	0.018
	Placebo	8/41	

*Analyzed by Cochran-Mantel-Henszel method

Figure 1. Cumulative frequency of opportunistic infections and Kaposi's sarcoma during treatment.

The number of weeks on study medication is shown along the x axis, and the cumulative number of serious events, defined as opportunistic infections or Kaposi's sarcoma, is shown on the y axis.

Figure 2A. Proportion of patients with AIDS who developed opportunistic infections during the study.

Figure 2B. Proportion of patients with AIDS-related complex who developed opportunistic infections during the study.

Proportion of patients with AIDS and AIDS-related complex who developed opportunistic infections during the study, using the Kaplan-Meier product-limit method. The number of days on study medication is shown along the x axis, and the proportion of patients is shown on the y axis. Closed circles represent AZT recipients with AIDS, closed triangles represent placebo recipients with AIDS, open circles represent AZT recipients with ARC, and closed squares represent placebo recipients with ARC.

Figure 3. Change in the mean CD4 count during treatment.

The number of weeks on study medication is shown along the x axis, and the change in mean CD4 counts is shown on the y axis. Open circles represent AZT recipients with AIDS, open triangles AZT recipients with AIDS-related complex, closed circles placebo recipients with AIDS, and closed triangles placebo recipients with ARC. Data were analyzed using stratified Wilcoxon's rank sum tests and the last observation carried forward technique. No observation was carried forward beyond 24 weeks or beyond the termination date of the study.

Figure #1

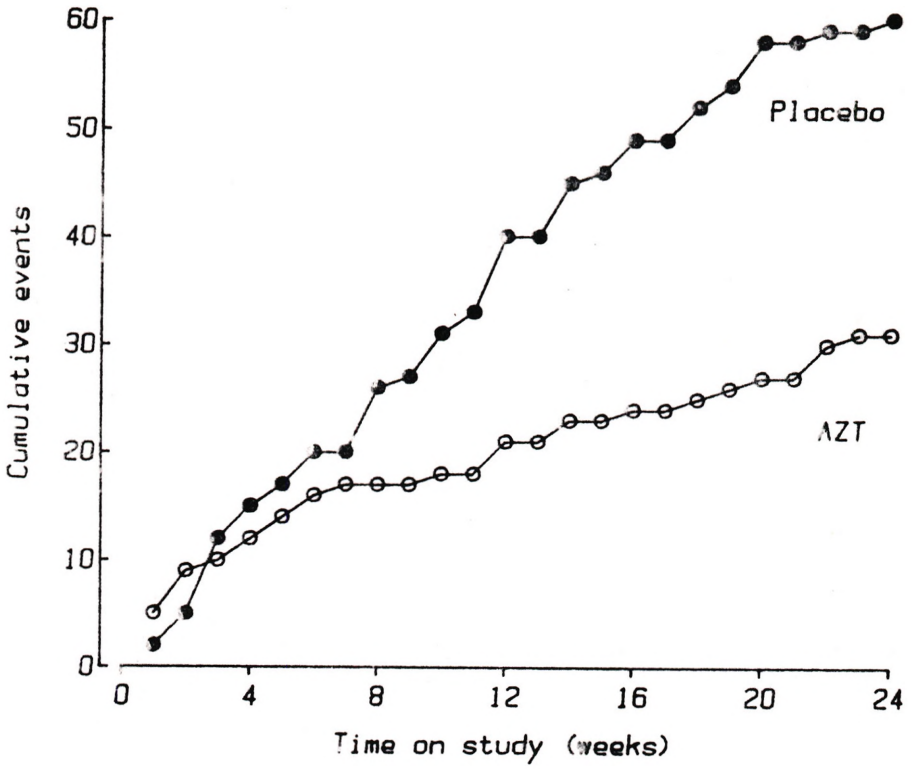

Figure #3

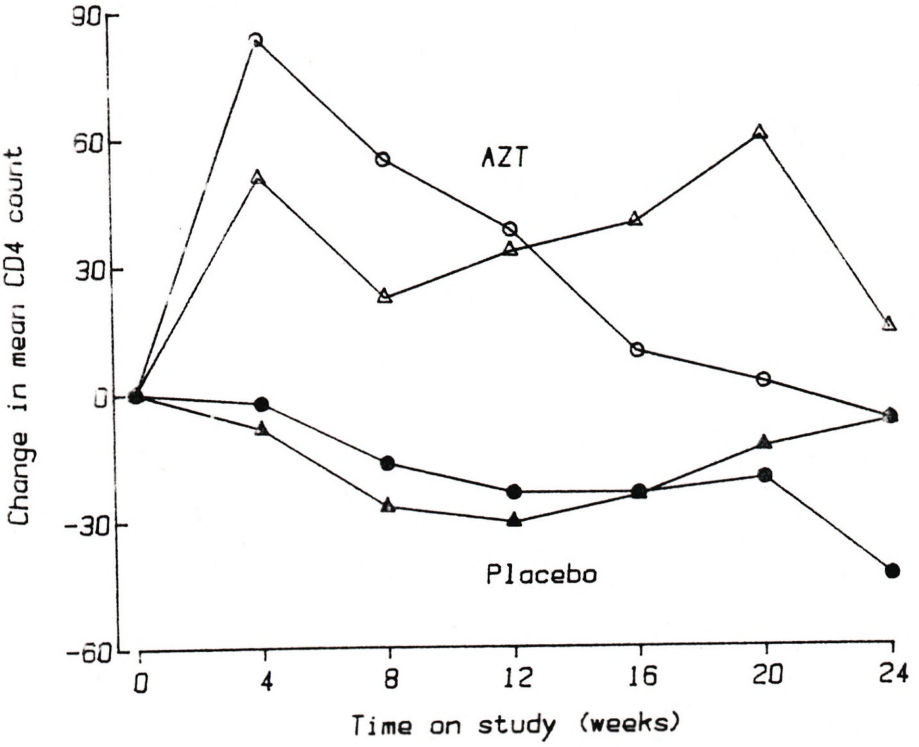

Figure #2A

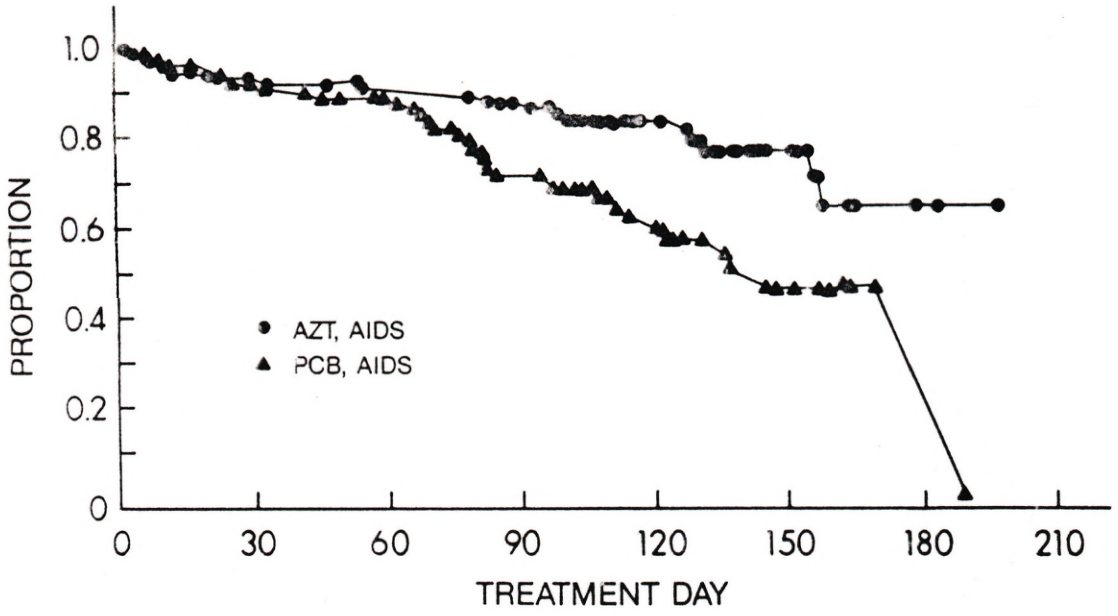

Figure #2B