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Outline for Phase II Clinical Trial
ATEU-06

1.0. INTRODUCTION

1.1 Rationale

The acquired immune deficiency syndrome (AIDS) is a human disease first recognized in the United States in 1981 which is a major epidemic in the United States and many countries throughout the world. It is characterized by profound alterations in immune function predominantly affecting T-cell function and the regulation of cell mediated immunity. AIDS is almost always fatal within one to two years of the first clinical manifestations of illness.

Although AIDS was initially described and characterized in three high risk groups, (homosexual men, hemophiliacs, and intravenous drug abusers), other non-risk individuals have developed the disease. It has been shown to be spread by intimate sexual contact, by the administration of blood products, and occasionally by the maternal-fetal route. Many patients who develop AIDS are asymptomatic when the transmit their disease to contacts because a 1-5 year (or more) latency period exists between infection and clinical manifestations of illness.

In 1983 and 1984 several groups of investigators reported the association of a new virus (HTLV-LAV) with AIDS now known as the Human Immunodeficiency Virus (HIV). Three lines of evidence point to this virus as the etiologic agent of AIDS: (1) it

infects and kills the T+ helper-inducer T cells which are depleted in AIDS, (2) it has been reproducibly isolated from patients with AIDS and the AIDS-related complex (ARC) or diseases which precede frank AIDS, and (3) there is a high (90%) incidence of HTLV-III seropositivity in affected patients.

A long latency or persistent viremic period may precede symptomatic illness. Retrospective studies of recipients of HIV contaminated blood tranfusions indicated a median incubation period of 29 months, range . Studies of the San Francsico cohort indicate a rate of progression to AIDS following seroconversion of 0.5% at 1 year, 1.0% at 2 years, 3.5% at 3 years and % at 4 years. Prospective studies of seropositive homosexual male cohorts (MACS) indicate a rate of progression from asymptomatic seropositive to AIDS/ARC of x %. Recent data suggest that prognosis for progression is worse for seropositives with active HIV viremia.

Azidothymidine has been shown to be a potent inhibitor of HIV retrovirus replication in vitro. Preliminary animal and human data regarding the pharmacology and toxicology of this compound indicate that it is safe at the dose planned for this trialThis study will enable the investigation of this drug on a double blind basis with potential benefit for the treatment of specific HIV patients (patients with asymptomatic HIV infection).

1.2 Animal and In Vitro Toxicity Testing

By the intravenous (IV) route, the LD50 of AZT is greater than 750 mg/kg in rats and mice. No significant alterations were seen when the compound was administered to dogs, intravenously

(IV) at dose levels up to 85 mg/kg/day IV for 2 weeks. Similarly, no changes were noted in rats given AZT IV, at dose levels up to 150 mg/kg/day IV for one month.

In an oral Dose Range-Finding (DRF) study in rats which were given the compound at dose levels up to 500 mg/kg/day, very minimal histologic changes in the liver and kidney of a few animals were observed.

More notable effects were seen in an oral DRF study in Beagle dogs administered 0, 125, 250, or 500 mg/kg/day of AZT daily for 2 weeks. Vomiting and fecal alterations (with blood) were seen in dogs receiving high doses. Moderate to marked leukopenia and thrombocytopenia was noted at all dose levels. Further studies suggest that these changes result from hypocellularity of the bone marrow; hypoactive lymphoid tissues were also noted. One female dog was sacrificed after significant weight loss on day 14. In that dog, alkaline phosphatase, BUN, and creatinine were elevated, perhaps and effect of dehydration. Grossly, hemorrhage in the gastrointestinal tract in the high dose dogs and a mid-dose female, as well as a maturational defect with mucosal atrophy in the intestinal tract of the high dose female were observed.

In an oral DRF study conducted in Cynomolgus monkeys (a species which metabolizes AZT more like man than the drug disposition patter seen in dog), dose levels of 125, 250, 500 mg/kg/day of AZT were given for 2 weeks. The only changes seen that may have been treatment-related were frequent vomiting in the high dose male, a slight nondose-related decrease (values still within normal limits) in RBC, HCT, Hgb at all treatment

levels, and a slight increase in SGPT (values still within normal limits in treated males and the high dose female.

A 13 week oral toxicity study was conducted in Cynomolgus monkeys given 34, 100 or 300 mg/kg by gavage. The results showed dose-related decreases in RBCs, hemoglobin, and hematocrit at day 21. Throughout the remainder of treatment period, hemoglobin and hematocrit remained stable; RBCs, however, were further reduced until the end of treatment. These values returned to normal limits during the 26-39 day post-dosing recovery period. A 13 week oral toxicity study was conducted in rats given AZT at doses of 56, 167 or 500 mg/kg/day by gavage in distilled water. A control group received water only. Rats were observed for weight changes, food intake, toxicity, ophthalmologic changes, hematology and clinical chemistries. There were no treatment related deaths. Clinically, there was occasional staining of the anogenital area in high dose male rats. A mild increase in glucose was observed only in high dose female rats on day 89. In addition, there was a mild decrease in SGOT in high dose rats at various times. There were no hematologic changes or gross pathologic changes.

In an oral DRF study in pregnant rats given AZT at dose levels up to 500 mg/kg from gestation day 6 through 15, a slight decrease in maternal weight was noted.

In genetic toxicology experiments, the AMES test was negative, whereas the drug was a weak mutagen at the highest concentration tested (1000 to 5000 micrograms/ml) in the mouse

lymphoma assay. In an in vitro cytogenetics assay in cultured human lymphocytes, AZT was clastogenic, with the no-effect level being between 3 and 10 micrograms/ml.

1.3 Human Pharmacokinetics

To date pharmacokinetic data have been analyzed for 19 patients receiving intravenous AZT and for 18 of these patients who have also received oral drug. The number of patients at each dose level is shown below:

	Dosing Schedule (n)	
Group	IV	Oral
A	1.0 mg/kg Q 8 hr (4)	2.0 mg/kg Q 8 hr (3)
B	2.5 mg/kg Q 8 hr (6)	5.0 mg/kg Q 8 hr (6)
C	2.5 mg/kg Q 4 hr (2)	5.0 mg/kg Q 4 hr (4)
D	5.0 mg/kg Q 4 hr (4)	10.0 mg/kg Q 4 hr (2)
E	7.5 mg/kg Q 4 hr (3)	15.0 mg/kg Q 4 hr (3)

AZT exhibits a biexponential decay after the end of infusion indicating two-compartmental pharmacokinetics. The mean AZT half-life at all dose levels following IV and oral dosing was approximately 1.0 hr. AZT concentrations increased proportionally with dose to 5.0 and 10 mg/kg, for IV and oral administration respectrively, indicating dose-independent kinetics up to these dosages. However, a disproportinal increase in peak concentrations (Cmax) and area under the plasma concentration time curve (AUC) occured between the 5.0 and 7.5 mg/kg IV and the 10.0 and 15 mg/kg oral dose levels. AZT Cmax levels are shown below:

	Cmax (microgram/ml)	
Group	IV	Oral
A	0.44 ± 0.14	0.53 ± 0.11
B	1.17 ± 0.49	1.37 ± 0.58
C	1.06 ± 0.03	1.57 ± 0.81
D	2.28 ± 0.31	3.14 ± 0.73
E	4.71 ± 0.79	10.40 ± 3.47

The total body clearance of IV doses from 1.0 to 5.0 mg/kg was approximately 1900 ml/min/70 kg. However, the numbers of patients studies are small, and this observation of dose-dependent kinetics at the highest dose level needs to be confirmed in more patients.

Renal clearance of AZT was estimated to be about 500 ml/min. The 5'-glucuronide of AZT (GAZT) has been identified as a major plasma and urinary metabolite. The plasma levels of this inactive metabolite were approximately 2-3x the corresponding AZT level. GAZT was rapidly cleared from plasma, with a half-life of about 1 hour. Following IV dosing about 25% of the dose is excreted unchanges in the urine as AZT and about 60% as GAZT.

Following oral administration at all dose levels, the bioavailability was about 60-70%. The incomplete bioavailability appears to be due to the first-pass metabolism, rather than reduced absorption. No unexpected drug or metabolite accumulation was observed following chronic IV or oral dosing.

1.4 Summary of Clinical Experience

1.41 Phase I Study

A phase 1 trial to evaluate safety and pharmacokinetics in

humans was conducted in 29 patients with AIDS or AIDS-related complex and HTLV-III/LAV viremia according to the dosage schedules listed in Section 1.3. An initial six-week treatment regimen at the scheduled dosage was followed by a variable observation period. Most patients were then allowed to continue long-term therapy if there had been no serious adverse experiences. Data are now available for treatment for at least 6 months; four patients have been treated for over 1 year (14 months). Headache, the most frequently reported adverse experience, occurred in 8 patients. Three patients experienced mild confusion or anxiety. In one case, this occurred during a febrile episode. A transient erythematous rash occurred in one patient and one other patient reported one episode of generalized pruritus.

Four deaths have occurred during the year since the trial was initiated. One patient with aggressive gastrointestinal Kaposi's sarcoma at entry had continued progression of the disease. He was removed from the protocol after only 3 weeks in order to receive cytotoxic therapy. Death ensued five months later. One patient died of disseminated cryptococcemia two months after being removed from the study because of anemia. The thrid patients died of pneumonia after having stopped therapy of his own accord. The fourth patient required successive dose reductions for hematologic toxicity after 4 months of treatment and died of pneumonia at 8 months.

The most common laboratory abnormalities are hematologic. Although all patients had some decline in hemoglobin by six

weeks, the change was not proportional to the starting dose. Twenty of 28 patients receiving doses greater than 500 mg orally every 4 hours developed anemia which warranted either a dose reduction or temporary interruption of treatment. Anemia has been reversible in most patients when the drug is discontinued. Bone marrow biopsies performed on three patients revealed megaloblastic changes. One of these patients had pernicious anemia responsive to B12 therapy. Neutropenia occurred in 13 patients and appeared to be the dose-limiting toxicity. Neutropenia responded favorably to reduction in dose of AZT.

Five patients had transient elevations in transaminases. In one patient this correlated with presence of hepatitis B antigen. In another patient, hepatitis was observed during simultaneous administration of pentamidine. There was no effect on electrolytes or renal or cardiac function.

1.42 Phase II study

Two hundred eight two (282) patients (AIDS recovered from PCP and late ARC) were entered over a four month period into a placebo controlled study which was scheduled to last six months. Half of the patients were assigned to receive AZT at a dose of 250 mg every 4 hours (1.5 grams daily) and half to receive placebo. Many patients on AZT required a reduction in dosage or interruption of treatment, primarily because of anemia. The groups were comparable at entry for a variety of variables including age, sex, race, weight, mean Karnofsky score, and severity of illness.

As of September 18, 1986 seventeen deaths had occurred: 16

in patients receiving placebo and one in a patient receiving the full dosage of AZT. In general, the deaths were attributed to opportunistic infections, e.g., toxoplasmosis, PCP, CMV, cryptococococcis and mycobateriosis. Because of the marked imbalance in mortality, primarily in AIDS patients, an independent Safety and Data Monitoring Board (DSMB) reviewed the data (on September 18, 1986) and recommended that the study be terminated. Patients had received between 3 1/2 to 7 months of therapy (median of 4.5 months) at the time the placebo group was discontinued.

A preliminary review of the results prepared for the DSMB indicates that 47 of 145 patients receiving AZT experienced greater than 25% reduction in hemoglobin, compared with 13 of 137 patients receiving placebo. Blood transfusions were required for approximately 25% of the patients receiving AZT and very few of those on placebo. In general, decreases in hemoglobin and neutrophils occureed during the second month of therapy and appeared to be reversible if the dose was decreased or drug discontinued. However, cumulative toxicity manifested as progressive suppression of hematologic parameters may theoretically occur with continued administration of AZT and only a few patients have received the drug for more than 6 months.

1.5 Prognosis in asymptomatic patients

In contrast with patients with AIDS the patients with asymptomatic HIV infection in whom AZT will be evaluated in the present protocol have good near term survival. Excluding patients who have weight loss, diarrhea, thrush, herpes zoster patients

with asymptomatic HIV infection have a 90% survival at 36 months.

1.6 Study Purpose

The purpose of this protocol is to determine whether azidothymidine (AZT) will delay or alter the natural progression of HIV disease in patients with asymptomatic HIV infection. This study will test one drug regimen in a placebo controlled design: 250 mg q 4 hours while awake (five times per day) versus placebo (five times per day). Standard therapy with this drug for AIDS patients with Pneumocystis is 250 mg q4 hrs for six doses per day. This trial will involve skipping the 4 am dose in the "standard" treatment arm. The clinical questions being posed are whether patients who receive chronic AZT will have a delay in the development of AIDS, or symptomatic HIV infection (ARC, minor opportunstic infection). The primary endpoint of this study is to delay the development of both major and minor opportunistic infections, and malignancies in this patient population. Drug effects on clinical signs/symptoms, virus detection, and immune function will be monitored with frequent clinical evaluations. If a study patient develops a major opportunistic infection or AIDS-defining cancer, a study endpoint will have been reached and the patient will discontinue their randomly assigned experimental protocol drug, and will be offered the best available treatments available to them for their opportunistic infection or cancer and for their HIV infection. Such patients will continue to be followed off the study for survival statistics. A Data Safety Monitorineg Board will be established and data reviewed for safety and efficacy every 4 months according to preestablished

criteria.

2.0 STUDY OBJECTIVES

2.1 To evaluate the degree of safety of AZT when used to treat asymptomatic individuals with HIV infection for up to 36 months (156 weeks).

2.2 To evaluate the efficacy of AZT based on the following criteria:

2.21 A decrease in the frequency of and a prolongation in the time to acquisition of AIDS-defining opportunistic infections or malignancy.

2.22 A decrease in the frequency of and prolongation of the time to acquisition of AIDS-related complex defined as:

2.23 A delay in the development of constitutional symptoms, not due to an identifiable opportunistic infection.

2.24 Antiviral effect as measured by a reduction in the ability to detect virus-coded products or disappearance of culturable virus from the blood or other body fluids.

2.25 Restoration of immune response as measured by reactivation of delayed cutaneous hypersensitivity, significant and consistent increase in absolute T4 lymphocyte counts; increase in total lymphocyte counts, and (optional) improvement in the lymphoproliferative

response to recall antigens in vitro.

2.26 Additional observations will include clinical improvements such as stability of weight, and decrease in the frequency of minor opportunistic infections.

3.0 STUDY OUTLINE

3.1 Type of Study

This will be a randomized double-blind placebo-controlled clinical trial of one dose regimen of orally administered AZT in specific populations of asymptomatic HIV infected patients. The trial will continue for 104 weeks (24 months).

4.0 PATIENT SELECTION

4.1 Inclusion Criteria

4.11 Patients with HIV antibody confirmed by Western blot without AIDS, AIDS-related complex or physical signs/symptoms attributable to HIV infection.

4.12 All patients must have a Karnovsky performance status of 100 at entry (Appendix 1).

4.13 Two positive or pending cultures for HIV from blood or semen (if male) obtained at least one week apart prior to entry.

4.14 Positive antibody to HIV confirmed by any federally licensed ELISA test kit and positive antibody to HIV by Western blot.

4.15 Absolute T4 cell count less than 600 cells/mm3.

4.16 Laboratory parameters - All patients will have the following present at entry:

4.161 Granulocyte count 1000 cells/mm3

4.162 Platelet count 75,000 platelets/mm3

4.163 Hematocrit 36% (hemoglobin greater than 12.

4.164 Creatinine 1.5x normal or a creatinine clearance of 50 ml/min.

4.165 Transaminases 2.5x the upper range of normal.

4.2 Exclusion Criteria

4.21 Patients with a history of AIDS-defining opportunistic infection or malignancy.

4.22 Patients with any of the constitutional symptoms listed below:

4.221 Temperature greater than 38 for more than one month.

4.222 Watery diarrhea for more than 2 weeks.

4.223 Weight loss (unrelated to dieting) of greater than 10% in the previous 3 months.

4.224 Oral or vaginal candidiasis for more than 2 weeks.

4.225 Herpes zoster in the previous 2 years.

4.226 Patients with a history of other systemic malignancies or lymphomas.

4.227 History of active alcohol or I.V. drug abuse.

4.23 Patients who have received the following agents or therapies prior to entry.

4.231 Anti-retroviral agents, e.g. AZT, ribavirin, HPA-23, rifampin, etc.

4.232 Immunomodulating agents, e.g. steroids isoprinosine, thymic factors, etc. or any other experimental therapy within three months of entry.

4.24 Patients younger than 18 years old.

4.25 Pregnant or lactating females.

4.26 Patients unable or unwilling to practice contraception.

5.0 NUMBER/SOURCE/MANAGEMENT OF PATIENTS

5.1 Number of patients to be studied: A total of 280 patients will be entered into the study (140 patients per arm). Patients who do not complete therapy will be monitored for the duration of the study to ascertain their survival status.

5.2 Study patients will be stratified according to their absolute T4 cell count at entry: Group A = 250/mm3 Group B = 250/mm31; and by at risk group for HIV infection, e.g. transfusion recipients, hemophilics, homosexual/bisexual.

5.3 Source of patients: AIDS clinics within the ATEU study centers.

5.4 Management of patients: This will be an outpatient study and patients will be seen weekly for the first two months, every other week for the next two months, and monthly thereafter.

6.0 BIOSTATISTICAL CONSIDERATIONS

The estimated number of patients eligible for entry into this trial who will experience an adverse event as defined by the development of AIDS or HIV infection with minor opportunistic infection or AIDS-related complex is 30%. We wish to detect in this study a decrease to 25% at 24 months in the proportion of patients with an adverse event who are treated with AZT. To have a power of 0.80 of detecting this difference requires patients per treatment group assuming a 2-sided 0.05 significance level.

7.0 STUDY MEDICATION, DOSAGE AND ADMINISTRATION

7.1 Study Medication

7.11 Patients will receive either one 250 mg capsule of AZT q4 hrs for five doses per day or one placebo capsule q4 hrs for five doses per day

7.12 Medication will be dispensed on a weekly basis for the first month and every other week (a 2 week supply) thereafter.

7.13 The total duration of treatment will be 154 weeks (36 months).

7.14 Medication will be supplied to the study center pharmacy as "blister packages" as required. Neither the investigators nor the patients will know which patient is receiving active drug.

7.15 Each research unit pharmacy will hold envelopes containing the random code with treatment assignment for individual patients; this number

will become the patient identifier. The Coordinating Center will generate and hold the randomization code for the study. A copy of the code will also be held at the NIAID.

8.0 BASELINE EVALUATION

8.1 Enrollment

Once it has been determined that the patient meets the entry criteria of the study, details will be carefully discussed and the patient will be asked to read and sighn a statement of informed consent approved by the Institutional Review Board (IRB).

8.2 Clinical and laboratory evaluation: Prior to randomization into the study, a complete history and physical exam, including chest X-ray and EKG will be performed; findings will be recorded on the data recording forms.

8.21 Any palpaple lymph nodes will be categorized by size, number and location on standard forms.

8.22 Neurologic assessment will include a standard neurologic exam and neuropsychaitric questionnaire (Appendix 2).

8.23 Hematologic studies: hemoglobin, hematocrit, WBC count, differential, mean corpuscular volume, reticulocyte count, platelet count, and erythrocyte sedimentation rate.

8.24 Chemistries: electrolytes, BUN, creatinine, total protein, albumin, calcium, phosphorus, uric

acid, and glucose.

8.25 Liver function: transaminases, alkaline phospatase, and bilirubin.

8.26 Urinalysis including microscopic exam.

8.27 Virology: At entry, two pending or positive cultures for HIV from blood and/or semen collected at least one week apart.

8.28 Positive antibody to HIV confirmed by a federally licensed ELISA kit.

8.29 Positive antibody to HIV by Western Blot (standard methodology).

8.2A Assessment of immune function.

8.2A1 Delayed hypersensitivity skin test using the Merieux Multitest.

8.2A2 Enumeration of lymphocyte subsets (T4, T8, and T4/T8 ratio) by flow cytometry must be performed twice prior to entry (at least 48 hours apart).

8.2A3 OPTIONAL. In vitro assays of cellular immune fuction (proliferative response of lymphocytes to tetanus toxiod, PHA and pokeweed mitogen) will be performed.

8.2B Assessment of microbiologic status

8.2B1 Oral or vaginal culture for fungus (Candida).

8.3 Concomitant or Recent Medications

Such medications, including blood products, will be documented on the data forms. Please note that since aspirin or acetaminophen may alter the metabolism of AZT, study patients will be instructed not to use these medications on a regular basis, and not to use them beyond 72 hours without contacting the investigator.

The use of any agent which might potentiate the toxicity of AZT, such as drugs causing neutropenia or significant risk of nephrotoxicity, are not to be used while patients are on this study.

Treatment for candidiasis, and localized cutaneous Herpes simplex or zoster infections are allowed under this protocol.

9.0 FOLLOW-UP EVALUATION

9.1 Clinical Evaluation

9.11 Objective signs for each patient will be weight gain or loss, changes in vital signs, development of Candida infections of the Oral mucosa, and cutaneous eruptions including Herpes zoster. Subjective symptoms will include headache, malaise, nausea, appetite, mental acuity, etc. Karnovsky performance status will also be assessed. These observations will be made weekly during the first 4 weeks and every other week for nhe next two months and monthy thereafter.

9.12 A limited physical exam will be performed at weeks 8 and 16 and at months 6, 12, 18 and 24.

Enlarged lymph nodes will be measured and recorded on standard forms.

9.13 Evaluation of Kaposi's sarcoma lesions.

9.131 All new skin lesions will be photographed and examined histologically by punch biopsy.

9.14 Evaluation for the development of opportunistic infections in patients with symptoms suggestive of such an infection:

9.141 In patients with fever/drenching night sweats

i. Blood or stool culture for Mycobacteria avium complex; blood cultures for cytomegalovirus; bone marrow aspirate and culture.

ii. An assessment of the lungs to exclude active Pneumocystis carinii, and other opportunistic pneumonias, including a chest x-ray, resting and excercise arterial blood gas, pulmonary function tests, DLCO, or gallium scan. If indicated, histologic or cytologic confirmation should be obtained.

iii. CT scan of the brain with contrast or magnetic resonance scan to identify toxoplasma encephalitis or other CNS infection.

iv. Lumbar puncture to diagnose cryptococcal meningitis if CT scan is negative. CSF should be sent for India ink, cryptococcal

antigen, fungal/mycobacterial culture and cytology.

v. Serum for cryptococcal antigen.

9.142 In patients with weight loss, diarrhea or dysphagia

i. Blood or stool culture for Mycobacteria avium- complex and blood cultures for cytomegalovirus culture.

ii. Stool for routine parasites, culture, and special stains for cryptosporidiosis.

iii. Radiographic and/or endoscopic studies with biopsy as needed.

9.143 In patients with altered mental status/neurologic exam

i. CT scan of the brain with double dose contrast or MRI for diagnosis of toxoplasma or other CNS infection.

ii. Lumbar puncture to exclude cryptococcal meningitis or other CNS disease if above is negative. CSF should be sent for India ink, cryptococcal antigen, fungal /myobacterial culture and cytology.

Patients randomized on this study who develop an AIDS defining opportunistic infection (not oral or vaginal thrush or localized zoster) or new malignancy will be discontinued from their randomized treatment regimen, will receive the best available treatments available to

them for HIV and for their opportunistic infection or tumor, and will continue to be followed for survival analysis.

9.2 Laboratory Studies

9.21 Hematologic studies (weekly for two months, every other week for the next two months and monthly therafter: hemoglobin, hematocrit, WBC count, differential, mean corpuscular volume, reticulocyte count, platelet count and erythrocyte sedimentation rate.

9.22 Chemistries (monthly): electrolytes, BUN, creatinine, total protein, albumin, calcium, phosphorus, uric acid, and glucose.

9.23 Urinalysis (monthly): including microscopic.

9.24 Liver function tests (monthly): transaminases, alkaline phosphatase, and bilirubin.

9.25 Virology: Samples for the isolation of HIV from blood and/or semen will be collected at weeks 8 and 24 and every two months thereafter. A standard protocol for virus culture will be followed.

9.26 Microbiology: Oral swab on fungal candida cultures at 4 month intervals.

9.27 Assessment of immune fuction:

9.271 Delayed hypersensitivity skin tests will be performed at 12 and 24 weeks and at study completion using the Merieux Multi-test.

9.272 Enumeration of lymphocyte subsets (T4, T8

and T4/T8 ratio) by flow cytometry at weeks 4, 8, 12 and 24 and at months 9, 12, 18, and 24.

9.273 OPTIONAL: In vitro assays of cellular immune function (proliferative response of lymphocytes to tetanus toxiod, PHA and Pokeweed mitogen antigens) will be performed at weeks 12 and 24 and at months 12, 18 and 24.

9.28 Pharmacokinetic studies: Peak (1.5 hrs after the first dose of the day) and trough (just prior to the first dose of the day) levels of AZT will be determined in serum samples on a subset of patients in the study. These will be collected at weeks 4, 12 and 24 and months 12, 18 and 24. If a severe drug related adverse experience is suspected, serum should be collected for AZT level.

10. MANAGEMENT OF TOXICITY/DOSE MODIFICATION

10.1 Grade 3 toxicity with reference to granulocytes or platelets will have the following dose reductions:

10.11 Patients receiving 250 mg q4 hrs will have drug stopped until toxicity grade returns to grade 1 or 0. Drug should be restarted at 250 mg q8 hrs. Patients with recurrent grade 3 toxicity at this dose will be discontinued from the study.

10.2 Grade 3 hematologic toxicity

Patients with grade 3 toxicity with reference to hemoglobin will have dose reductions as listed above. Patients with persistent grade 3 toxicity at 250 mg q8 hrs will be discontinued from the study.

10.3 Grade 4 toxicity

Patients experiencing grade 4 toxicity, except as defined above, will be removed from the study.

11.0 DISCONTINUATION OF THERAPY

Patients will be removed from the study for any of the following reasons:

11.1 Patient non-compliance as related to the taking of medication as directed or failure to keep appointments.

11.2 any patients may remove themselves from the study at any time without prejudice to their medical care.

11.3 Patients who develop and AIDS defining opportunistic infection or additional neoplasm or progression of Kaposi's lesions (see 12.35) which occurs after two months on study which requires treatment.

11.4 Patients who experience persistent grade 3 toxicity, or grade 4, except as defined above in section 10.

12.0 EVALUATION OF RESPONSE

Patients will be evaluated for response in the following areas: clinical (development of adverse events as defined by development of an AIDS defining opportunistic

infection, minor opportunistic infection (thrush, zoster, vaginal candidiasis, or a new malignancy), and laboratory.

All patients randomized will be considered eligible for analysis unless they fail to satisfy the eligibility criteria based on a blinded review of the on study data. Additional analyses will also be performed as described below:

Patients experiencing an adverse event within the first two months of treatment will be considered evaluable for toxicity, but not for efficacy.

Patients experiencing an adverse event after two months will be considered evaluable for toxicity and efficacy.

12.1 Clinical Parameters

12.11 Duration to the development of major and minor opportunistic infections and the frequency of opportunistic infections at different time points.

12.12 Duration to the development of constitutional symptoms as defined in 4.24, not due to an identifiable opportunistic infection.

12.13 Duration to the development of a new malignancy.

12.2 Laboratory Parameters

12.21 Elimination of culturable virus in two successive specimens.

12.22 Sustained normalization of T4 cell numbers.

12.3 Additional minor endpoints

12.31 Clinical parameters: weight gain, inprovement in neurological abnormalities as measured by a standardized neurophsychological examination.

12.32 Laboratory parameters:

12.321 Quantitative decrease in virus without complete elimination of culturable virus.

12.322 Improvement in the number of T4 cells from one subcategory to the next (e.g. subcategory 3: 100 cells/mm3 to subcategory 2: 100-400 cells/mm3) persisting for more than 60 days.

13.0 DATA COLLECTION AND MONITORING

13.1 Data collection

Study data will be collected on standardized case report forms developed by the Coordinating Center. As facilities for distributed data entry by computer terminal become available, data will be transmitted every two weeks to the Coordinating Center.

13.2 Reporting of Adverse Drug Reactions

13.21 Adverse drug reactions shall be reported as described in the Appendix to the AIDS Program Office.

13.22 Adverse reactions or deaths requiring immediate reporting shall be made by telephone to (301) 495-0052 (available 24 hours/day).

13.3 Study monitoring site visits

13.31 Site visits will be performed no less than twice each year by a physician employed by the Coordinating Center to ensure that all regulatory requirements for the use of investigational agents are being met. Records of IRB approvals will be examined.

13.32 Data audit site visits by staff of the Coordinating Center will occur no less than four times each year to monitor the quality of data collected. Patient charts will be examined on a spot check basis to evaluate the accuracy of data entered into the data base.

13.33 Additional instructions concerning the recording of study data or the entry of such data into the computerized data base will be provided by the Coordinating Center.

13.4 Interim monitoring of data

We recognize that this study must be carried out in the most ethical manner possible. Thus, although there is no evidence to demonstrate that AZT is effective in patients with asymptomatic HIV infection (and, in fact, its toxicity must be taken into account when treating these patients), the study will be evaluated once every six months to ensure that no significant differences are emerging with regard to the clinical adverse effects (development of opportunistic infections or malignancy) or toxicity in

the various treatment arms. A special evaluation of the study at such time the NDA for AZT is approved by the FDA will also be considered.

These evaluations will be conducted by an independant Data and Safety Monitoring Board. If it is decided that the placebo-controlled study is unethical due to a statistically significant reduction in the adverse events in the AZT arm, the placebo arm will be discontinued.

14.0 HUMAN SUBJECTS

14.1 IRB Approvals

This protocol must receive approval by the Clinical Research Subpanel of the NIAID and the approval of the institutional review committees of all participating units prior to implementation. All participants must sign an informed consent (copy in Appendix).

14.2 Patient Confidentiality

All records, evaluation forms and reports will be identified by a coded number only to maintain patient confidentiality. All records will be kept in locked files at the participating clinical research units. all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring by the FDA, the Coordinating Center or the NIAID.

15.0 BIOHAZARD CONTAINMENT

As the transmission of HIV can occur through contact with contaminated needles, blood and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and handling of all specimens for this study in a clinical or laboratory setting, as currently recommended by the Centers for Disease Control.