

P R O T O C O L

UNCONTROLLED CLINICAL TRIAL OF THE LONG TERM
SAFETY OF AZTTM

BURROUGHS WELLCOME CO.

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UNCONTROLLED CLINICAL TRIAL OF THE LONG-TERM SAFETY OF AZT

Burroughs Wellcome Co.

1.0 Introduction:

The Acquired Immunodeficiency Syndrome (AIDS), a recent and internationally recognized health problem, is characterized by a severe and persistent breakdown in the immune system resulting from HTLV-III/LAV (HIV) infection. In some patients, the development of Kaposi's sarcoma (KS) or aggressive lymphomas is the first sign of AIDS as an underlying disorder. In others, opportunistic infections are the first manifestations of the syndrome and they are the most frequent cause of death in AIDS patients. The case fatality rate among patients with AIDS is high. In September 1986, the total number of cases of AIDS diagnosed and reported in the United States exceeded 24,000, 13,000 of whom developed Pneumocystis carinii pneumonia (PCP) at some time during their illness with AIDS; for approximately 60%, PCP is the initial manifestation. Recent projections indicate that as many as 2,000,000 Americans may already be infected with HTLV-III/LAV and be potentially infectious to others through sexual, blood, and perinatal transmission.

1.1 Study Rationale:

AZTTM (3'azido 3' deoxythymidine, also known as azidothymidine) has been shown to be a potent inhibitor of HTLV-III replication in vitro. Preliminary animal data regarding the pharmacology, toxicology and clinical effects of AZT suggested that this agent might be useful in the treatment of HTLV-III infections in man. Studies of the safety and tolerance of AZT administration in AIDS and ARC patients were therefore initiated. Data collected in the early Phase I trial and in the placebo-controlled trial described below indicate that AZT can be administered to patients at the doses specified in the protocol. The toxicity observed to date in patients receiving these treatment regimens has been manageable.

A placebo-controlled trial of AZT in a limited population of HTLV-III infected patients was recently terminated at the recommendation of an independent Data and Safety Monitoring Board. The recommendation to stop the trial was based upon the observation of a significantly higher mortality rate in AIDS patients randomized to receive placebo than in those who received AZT. (See section 1.4) This uncontrolled clinical trial will enable similar patients with AIDS to receive AZT under a Treatment IND and will make AZT more widely available to those patients who have been shown to benefit from treatment.

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 an 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 pattern 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 concentrations 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:

Group	Dosing Schedule (n)	
	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 respectively, indicating dose-independent kinetics up to these dosages. However, a disproportional increase in peak concentrations (C_{max}) and area under the plasma-concentration time curve (AUC) occurred between the 5.0 and 7.5 mg/kg IV and the 10.0 and 15 mg/kg oral dose levels. AZT C_{max} levels are shown below:

Group	C _{max} (microgram/ml)	
	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. At 7.5 mg/kg the mean clearance decreases to 1200 mg/min/70 kg. However, the numbers of patients studied 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 unchanged 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 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 1 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 pruritis.

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 cryptococemia two months after being removed from the study because of anemia. The third patient 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 2 study

Two hundred eighty 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, cryptocococcosis and mycobacteriosis. 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 3½ 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 occurred 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.

Although the preliminary data from this study have not been completely analyzed, mortality figures warrant expanding the availability of AZT to other patients with similar disease at this time.

2.0 Study Purpose

The intent of this protocol is to provide AZT to AIDS patients who are expected to benefit based on data derived from the recently terminated placebo controlled trial described above.

2.1 Objectives

The objective of the study is to provide for the administration of AZT to eligible patients with careful supervision, and to monitor survival, disease progression and toxicity.

2.2 Physicians/Facilities

This study will be conducted under the auspices of the Burroughs Wellcome Co. Physicians prescribing BW-AZT must be licensed to practice medicine in the United States. They should be knowledgeable and experienced in the diagnosis and treatment of AIDS, and be willing to assume the responsibility for supervising the administration of an investigational drug. Hospital pharmacies registered with the BW-AZT Treatment IND Coordinating Center (BW-AZTICC) will transmit the necessary prescription forms to BW-AZTICC and dispense AZT to the patients.

2.3 Type of study

This will be an open-labeled uncontrolled clinical trial of AZT in patients with AIDS who have recovered from PCP.

3.0 Patient Selection

3.1 Inclusion Criteria

- 3.12 AIDS patients who have recovered from one or more episodes of histologically confirmed Pneumocystis carinii pneumonia without AIDS-defining condition(s) (see MMWR May 23, 1986) presently requiring systemic chemotherapy.
- 3.13 All patients must have a Karnofsky performance status ≥ 60 at entry (see appendix I).
- 3.14 Laboratory parameters - All patients will have the following present at entry:
- a. Total granulocyte count ≥ 1000 /cubic millimeter
 - b. Hemoglobin ≥ 9.0 gm/dl.
 - c. Platelet count $\geq 50,000$
 - d. SGOT ≤ 3 times upper limit of normal value.
 - e. Serum creatinine ≤ 1.5 mg/dl. (or upper unit of normal)
 - f. Positive antibody for HTLV-III/LAV confirmed by any federally licensed ELISA test kit.

3.2 Exclusion criteria:

- 3.21 Patients younger than 12 years of age.
- 3.22 Pregnant women, nursing mothers or women of childbearing potential not employing barrier contraception or abstinence.
- 3.23 Patients receiving any potentially myelosuppressive drug (such as trimethoprim-sulfamethoxazole, pyrimethamine-sulfa or DHPG), nephrotoxic agent (such as amphotericin B or aminoglycosides), or cytotoxic or other experimental chemotherapy for any reason.

4.0 AZT: Dosage, Administration, and Concomitant Medication

4.1 Dosage

- 4.11 Patients will initially receive two 100 mg capsules 6 times per day (every 4 hours - if a dose is skipped, do not double up). Maximum daily dose = 1200 mg.
- 4.12 Therapy may be continued indefinitely as long as the Treatment IND remains in effect and the patient meets the specifications of the protocol.

4.2 Prescription Renewal

Upon registration of each patient, medication for one month will be supplied in bottles of 100 mg capsules to the registered pharmacy identified by the requesting physician. The pharmacy will dispense weekly supplies to each patient for the first two months of therapy, and biweekly supplies thereafter. The pharmacy will receive AZT capsules for monthly refills after the Prescription Renewal and Followup Form has been received and reviewed by BW-AZTICC.

4.3 Dosage Alteration for Toxicity

The following dose adjustments are recommended by the sponsor based on a preliminary analysis of the toxicity data from the recently halted placebo controlled trial. The sponsor cannot guarantee that lower dose regimens will have the same efficacy as that seen in the controlled trial, in which uniform dose reduction criteria were not followed.

Future alterations in the dose reduction/discontinuation criteria recommended below may be made based on further analysis of the existing data and on new data as it accumulates. Information regarding changes in doses will be transmitted to physicians participating in this study as soon as they are approved. The prescribing physician should be aware that one possible interpretation of existing data suggests that the hematologic toxicity seen in the first few months of therapy may precede a later suppression of lymphocyte numbers that may not be as readily reversible and may actually increase susceptibility to opportunistic infections. It is not clear at this time what dosage regimen will maximize efficacy with acceptable toxicity for most patients.

WARNING: Approximately 25 percent of the 145 patients who received AZT during the recently halted trial required blood transfusions, usually following 4 to 8 weeks of therapy (at 250 mg every 4 hours). Over the course of extended therapy, even at lower doses, some patients required multiple transfusions. When granulocytopenia occurred, it often appeared later in the course of therapy and required dose adjustment or discontinuation of AZT. Therefore, participating physicians should carefully monitor the hematologic profile of their patients at the specified intervals (weekly X 8 weeks and biweekly thereafter).
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4.31 Dose adjustment for moderate toxicity

The initial dose of 200 mg every 4 hours should be decreased to 100 mg every 4 hours for the following presumptive toxicity:

- 4.311 Hemoglobin: Decrease of ≥ 2 but < 3 gm/dl from study entry value.
- 4.312 Granulocyte count $< 750/\text{mm}^3$ but > 500
- 4.313 Grade III toxicity, see Appendix II.

4.32 Dose adjustment for severe toxicity

AZT will be discontinued for the following:

- 4.321 Hemoglobin - Decrease of ≥ 3 gm from study entry value
- 4.322 Granulocyte count - $< 500/\text{mm}^3$
- 4.323 Grade IV toxicity, see Appendix II

4.33 After drug discontinuation under section 4.32 above, AZT may be restarted at 100 mg every 4 hours when hemoglobin returns to within 1 gm/dl of entry value, granulocytes are $\geq 1000/\text{mm}^3$, and other toxicity becomes $<$ Grade 2. Before restarting AZT, repeat hemoglobin at that time must be greater than 9 gm/dl. (If the patient has required transfusion, one week should elapse before repeat hemoglobin is obtained). If toxicity recurs on the lower dose, AZT must be discontinued and further dose adjustments discussed with a physician at BW-ATZICC. (Telephone 1-800-843-9388)

4.4 Use of Other Medications with AZT

Interactions of AZT and other drugs used in the treatment of AIDS patients have been incompletely studied. Because of the possibility for exacerbation of the potential toxicities of AZT when myelosuppressive, nephrotoxic, cytotoxic or other experimental drugs are used concomitantly for illnesses developing during the study, AZT must be discontinued whenever these agents are required. Even aspirin or acetaminophen may alter the metabolism of AZT and should not be used chronically while the patient is taking AZT.

4.5 Return of Unused Drug

All unused drug supplies will be returned to Burroughs Wellcome Co. if a patient is discontinued. For this purpose the Return Drug List is provided.

5.0 Patient Management

5.1 Enrollment - Prior to administration of the first dose of AZT, a history and general physical exam must be completed and recorded. The patient registration form must be completed and approved by BW-AZTICC. The patient must have signed the informed consent form.

5.2 Management

5.21 Clinical evaluation - All patients must be seen at least once per week for the first two months and then at least once every 2 weeks thereafter for the duration of the study. At each visit, the following items will be assessed and recorded on the patient's medical record.

- 5.211 Symptoms, weight, vital signs, Karnofsky score
- 5.212 Administration of other medications and/or blood products.
- 5.213 Adverse drug experiences
- 5.214 Documentation of onset of opportunistic infections, other infections, or neoplastic disease.
- 5.215 Record of current AZT dose.

Each month the most recent assessment will be recorded on the Prescription Renewal and Followup Form and submitted to the Pharmacy.

5.22 Laboratory Evaluation - the following laboratory studies must be performed during treatment:

- 5.221 Hematology (CBC with differential, RBC indices, platelet count) - weekly during the first 2 months of therapy and every 2 weeks thereafter.
- 5.222 Chemistries (serum creatinine, BUN, electrolytes, bilirubin, SGOT, alkaline phosphatase, glucose), and urinalysis - every four weeks.

5.23 Prescription Renewal and Patient Followup

- 5.231 Forms - All carefully completed forms will be sent monthly to the BW-AZTICC, PO Box 6042, Rockville, Maryland 20850. A reasonable explanation must be given for any missing information. The physician will save a copy of the original Prescription Renewal and Patient Followup Form.
- 5.232 Final visit - If a patient withdraws from the study for any reason or is lost to followup, a Prescription Renewal and Patient Followup Form should be filed with the last known information and the reason for discontinuation.

6.0 Adverse experiences

6.1 FOR ALL DEATHS, REGARDLESS OF CAUSE:

1. REPORT TO THE AZT INFORMATION LINE (800-843-9388) WITHIN 24 HRS.
2. Submit an ADVERSE REACTION REPORT (FDA FORM 1639) WITHIN 72 HRS.
3. Submit PRESCRIPTION RENEWAL AND PATIENT FOLLOWUP FORM WITHIN 72 HRS.

6.2. For all suspected adverse drug reactions resulting in hospitalization:

Report on a ADVERSE REACTION REPORT (FDA Form 1639) WITHIN 72 hours of the event.

6.3 Other adverse drug experiences not requiring hospitalization:

Report on PRESCRIPTION RENEWAL AND PATIENT FOLLOWUP FORM at the time of renewal.

6.4 Side effects noted in the clinical trials include headache, mild confusion or anxiety, nausea, rash, anemia, and leukopenia. Additional toxicities following extended therapy (AZT use > 6 months) are not known at this time. Side effects may be exacerbated by simultaneous use of any other medication.

7.0 Study discontinuation

Patients will be removed from the study for the following medical or administrative reasons:

7.1 Prescribing physicians judgment that the patient is too ill to continue in the trial.

7.2 Toxicity criteria as specified under Section 4.3 of this protocol.

7.3 Development of an AIDS defining opportunistic infection, neoplasm, or other medical condition requiring systemic treatment with potentially myelosuppressive, nephrotoxic, or cytotoxic agents or experimental drugs for any reason. (refer to Sections 3.23 and 4.4 for examples).

7.4 Patient Non-compliance - a patient who is not taking medication as directed or who is not keeping appointments will not be allowed to continue receiving AZT.

7.5 Physician non-compliance - requests for renewals of AZT will not be approved if forms are not completed as specified.

7.6 Voluntary withdrawal - a patient may remove himself from the trial at any time without prejudice to his medical care.

7.7 Termination of the study by the sponsor or the FDA.

A patient may be restarted in the study if he/she fulfills the original inclusion criteria, and, if discontinuation was due to toxicity, the criteria under Section 4.33 are also met.

AZTTM TREATMENT IND

Appendix I

"PERFORMANCE STATUS" (KARNOFSKY SCALE)

Criteria of Performance Status		
Able to carry on normal activity; no special care is needed	100	Normal; no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; a varying amount of assistance is needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance but is able to care for most of his needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospitalization is indicated although death not imminent
	20	Very sick; hospitalization necessary; active supportive treatment is necessary
	10	Moribund, fatal processes progressing rapidly
	0	Dead

APPENDIX II

ADVERSE EXPERIENCE GRADES

	Grade 0	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Life- Threatening Grade 4
Hematologic (see Section 4.3)					
Platelets (1000/cmm)	-	-	< 50,000	< 25,000	< 10,000
Gastrointestinal					
Bilirubin	<1.25xN*	1.26-2.5xN	2.6-5.0xN	5.1-10.0xN	>10xN
SGOT	<1.25xN	1.26-2.5xN	2.6-5.0xN	5.1-10.0xN	>10xN
Alkaline phosphatase	<1.25xN	1.26-2.5xN	2.6-5.0xN	5.1-10.0xN	>10xN
Nausea/vomiting	none	nausea	transient vomiting	vomiting requiring therapy	intractable vomiting
Renal, bladder					
BUN	<1.25xN	1.26-2.5xN	2.6-5.0xN	5.1-10.0xN	>10xN
Creatinine	<1.25xN	1.26-2.5xN	2.6-5.0xN	5.1-10.0xN	>10xN
Fever-Drug Related	none	Fever ≤ 38.5°C	Fever 38.5-40°C	Fever > 40°C	Fever with hypotension
Allergic	none	Edema	bronchospasm, no parenteral therapy required	bronchospasm parenteral therapy required	anaphylaxis
Cutaneous	none	Erythema	dry desquama- tion vesi- culation, pruritus	moist des- quamation, ulceration	exfoliative dermatitis necrosis, requiring surgical intervention
Neurologic					
State of consciousness alert		transient lethargy	somnolence < 50% of waking hours	somnolence > 50% of waking hours	coma
Headache	none	no therapy required	analgesic required	narcotic required	intractable headache

* N = upper limit of normal

AZT TREATMENT IND

INFORMED CONSENT FOR PATIENTS RECEIVING AZIDOTHYIMIDINE (AZTTM)
UNDER A TREATMENT IND PROTOCOL

Burroughs Wellcome Co invites you to be considered for a research study to determine the safety and tolerance of the investigational drug AZT in AIDS patients who have recovered from Pneumocystis carinii pneumonia (PCP). It is important that you read and understand several general principles that apply to all who participate in the study: (a) taking part in the study is entirely voluntary; (b) direct personal benefit may or may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) you may decline to participate in or withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. Such withdrawal will not jeopardize your future medical care or possible involvement in subsequent clinical studies. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. You are urged to discuss any questions you have about this study with your physician who will explain it to you.

Introduction

HTLV-III/LAV,¹ the virus that is associated with AIDS, infects and inactivates certain blood cells that are part of the body's immune system. The damage to the body's immune system can result in the acquisition of unusual infections and/or unusual forms of cancer. The most common complication in AIDS patients is PCP. While therapies exist for many, but not all, of the infections that might occur, there is no known cure for the immunologic defects caused by the AIDS virus. Although there is no known cure for AIDS, the drug azidothymidine (AZT) has extended the survival of some patients in one study. In this study, 282 patients were studied and 145 received AZT for an average of four-and-a-half months. Patients receiving AZT experienced fewer complications related to their underlying condition than patients who did not receive the drug. However, there are risks, discomforts, and side effects associated with the use of this experimental drug. These are described below.

If you are selected to participate in this study, you will be treated as described below. Be sure to read this document carefully and to ask your doctor any questions that may occur to you about this study.

¹ The International Committee on the Taxonomy of Viruses has recommended the name human immunodeficiency virus or HIV for these viruses (Coffin, J. et al, letter to Science, Vol. 232, page 697, 1986).

Before beginning any treatment, you will be carefully examined by your doctor and have routine tests (complete blood count, blood analyses, and urinalysis) performed. If, on the basis of these studies, there is any evidence of significant kidney disease, liver disease, or other conditions that may make it dangerous for you to participate in this study, or you do not otherwise meet the criteria for participation, your doctor will advise you of other alternatives you may have.

If you are selected to participate in the study, you will receive AZT. AZT will be administered as two 100 mg capsules every four hours, and your care will be under the supervision of your doctor. The dose to be used in this study is lower than the dose used in the recent clinical trial of AZT. This dose was selected to reduce the possibility that adverse side effects might occur. Because this dose was not tested in the clinical trial of AZT, we do not know if it will provide similar benefit. If adverse side effects occur, the dose you receive will be adjusted by your doctor. You will be required to visit your doctor weekly during the first two months of therapy and every other week for the duration of the study. At the followup visits, your physician will assess your disease and monitor for potential side effects. A number of laboratory tests will be used to help determine if you are experiencing side effects. The blood tests will require two to three tablespoons of blood per sample. You will receive the drug for an indefinite period, subject to available supply unless you have severe effects, or wish to withdraw from the study. Additionally, the entire study may be stopped by the Burroughs Wellcome Co., the manufacturer of AZT, if unforeseen adverse effects are noted, or if the drug is approved for marketing. It is planned that the study will end when the drug is sold and available by prescription from a doctor.

Benefit

This study will help determine the safety and tolerance (side effects) of AZT in the treatment of patients with AIDS who have recovered from PCP. This study may also be of direct benefit to you, but it is not expected to produce a cure.

Risks, Inconveniences, and Discomforts

The major risk associated with participation in this study is in receiving a new drug that has had limited use in humans. Limited studies in laboratory animals have been conducted to determine the possible side effects of administering AZT. Vomiting, gastrointestinal bleeding, lowered white blood cell count, lowered red blood cell count, lowered platelet count, and alterations in liver and kidney function were reported among dogs receiving high dosages of AZT.

The side effects in humans of AZT include a loss of red blood cells in your body (anemia), which may be serious enough to require several transfusions. Other side effects that have been reported include headache, mild confusion

or anxiety, nausea, skin rashes and itching. A lowered white blood cell count has also been reported that might further predispose you to other infections or worsen your condition. In general, these effects occur after six weeks of treatment and appear to be reversible when the drug is discontinued. Long-range side effects are not known at this time but may include tumors and birth defects. Interactions of AZT and other drugs used in the treatment of AIDS patients are also incompletely studied. If you are found to be eligible for this study it is because you are infected with the AIDS virus, have recovered from an episode of PCP, and are not taking immunosuppressive or anti-infective drugs.

You will have blood drawn before beginning therapy, and at regular intervals during the course of therapy. Blood will be drawn every week for the first 8 weeks and every other week thereafter. No more than 3 tablespoons of blood will be drawn at any one time and no more than a pint will be drawn over a 6 week period. The risk of blood drawing is minimal. Bruising or bleeding at the site may occur. Rarely, fainting occurs as a result of blood drawing.

If you are selected for the study, you should not take other medications, even medicines like aspirin and acetaminophen, without first talking to your doctor.

Policy Regarding Research-Related Injuries

If injury results from participation in this research, immediate necessary medical care can be obtained from your doctor at your expense. However, there is no provision for free medical care or for monetary compensation for any such injury. If you need financial assistance, you may consult your doctor or social worker regarding resources available in your community.

Policy Regarding Pregnancy

The safety of AZT has not been established during pregnancy or nursing. Therefore, all pregnant or nursing women will be excluded. Any woman of childbearing age will have a pregnancy test performed and evaluated before AZT is started. Female patients must agree to abstain from sexual intercourse, or use barrier contraception (diaphragm, condom, and foam) during treatment, and for four weeks after the end of the treatment.

If you become pregnant while taking AZT, you must tell your doctor immediately. Your doctor will advise you of the possible risks to your unborn child and the options, including abortion, available to you. Because of the possible risks to your unborn child, treatment with AZT will be stopped while you are pregnant.

Confidentiality of Records

Medical records that do not identify you by name will be held by Burroughs Wellcome Co and by the government contractor in charge of data collection (the BW-AZT Treatment IND Coordinating Center). Your medical records, which identify you by name, will be held by the doctor prescribing AZT and by the pharmacy dispensing your AZT. These records may be inspected by the U.S.

Food and Drug Administration (FDA). These records will be kept confidential to the extent permitted by law. Information collected during this study will be submitted to the FDA, and it may also be used for research purposes. However, if this information is used for research purposes, it will not personally identify you nor will you be identified by name in any presentation or publication.

Safeguards

In order to minimize or avoid risks and hazards associated with this study, the following will be performed:

1. AZT will only be given under the close supervision of your doctor who will perform frequent physical exams.
2. In order to safeguard against blood, liver, or kidney damage possibly caused by the treatment with AZT, blood and urine tests will be performed regularly.
3. You should report any side effects that you think may be due to the therapy you are receiving to your physician.
4. If at any time your doctor feels that continued therapy with AZT would be detrimental to your health, you will be withdrawn from the study and AZT will be discontinued. Furthermore, the study may be discontinued for unforeseen reasons.
5. You may withdraw from the study at any time without jeopardizing your future medical care or possible involvement in subsequent clinical studies.

Alternatives to Participation in This Study

If you are not selected or decline to participate in this study, you may qualify for other studies being conducted to evaluate new treatments for the AIDS virus infection. At the present time there are no approved treatments for AIDS.

Circumstances under which your participation may be terminated without your consent:

1. Deteriorating health or other conditions that might occur that would be detrimental to you.
2. Failure to keep appointments or take medications as directed.
3. Failure of your doctor to follow the protocol or submit the necessary documentation to the AZT Treatment IND Coordinating Center.

4. Pregnancy.
5. Termination or suspension of the study.

Cost to You for Participation

Burroughs Wellcome Co. will initially provide AZT free of charge. You will be notified if, in the future, it becomes necessary to charge you for the drug. AZT will not be provided free of charge after this study is concluded and upon general availability of AZT through a prescription by your doctor. You or your insurance company will be responsible for the cost of medical care and laboratory tests associated with this study. However, some insurance companies may not reimburse you for expenses arising from investigational studies.

Significant New Findings

Any significant findings developed during the course of this research, which may bear upon your condition or your willingness to continue participation in the research, will be provided to you through your doctor.

Problems or Questions

Should any problem or questions arise as part of this study, with regard to your rights as a participant in this study, you should contact your doctor.

Name

Phone Number

If you need more information about your rights, about the research or research-related injuries, contact the BW-AZT Treatment IND Coordinating Center at 1-800-843-9388, or write Box 6042, Rockville, Maryland, 20850.

I have read and understand the information in this document and voluntarily agree to participate. I have been given a copy of this consent form.

Patient's Signature
or Patient's Legal Representative
or Guardian, as appropriate

Date

Patient's Name (typed or printed)

Patient's Address

Physician's Signature

Date

Physician's Name (typed or printed)

AZT™ Treatment IND Coordinating Center

Post Office Box 6042
Rockville, Maryland 20850
(800) 843-9388

For Express Mail:
National Institutes of Health
Building 31, Room 7A-05
9000 Rockville Pike
Bethesda, MD 20892

Physician Package

1. Physician Cover Letter With Instructions
2. Statement of Investigator - Form 1573
3. Patient Protocol
4. Informed Consent
5. Patient Registration Form
6. Prescription Renewal and Patient Followup Form
7. Adverse Drug Reaction Report - Form 1639
8. NCI Backgrounder - Azidothymidine
9. NIAID Backgrounder - ATEU Investigators Plan AZT Studies
10. List of AIDS Treatment Evaluation Units
11. Copy of Pharmacy Package
12. Copy of Patient Package

AZTTM Treatment IND Coordinating Center

Post Office Box 6042
Rockville, Maryland 20850
(800) 843-9388

For Express Mail:
National Institutes of Health
Building 31, Room 7A-05
9000 Rockville Pike
Bethesda, MD 20892

Dear Physician:

You are invited to participate in an investigational new drug (IND) exemption treatment protocol for azidothymidine (AZTTM). AZT has recently been identified as a potentially useful therapeutic agent in the management of persons with the acquired immunodeficiency syndrome (AIDS) who meet the minimum criteria of having recovered from Pneumocystis carinii pneumonia.

The Burroughs Wellcome Co, Research Triangle Park, North Carolina, is the IND sponsor for this protocol. The distribution system that has been established requires that AZT be distributed by Burroughs Wellcome Co only through hospital pharmacies that have been registered to participate in this program. Burroughs Wellcome Co has solicited the help of selected pharmacies to expedite the availability of AZT.

Physicians interested in prescribing AZT for their patients should follow the procedures outlined in the accompanying Instructions. In addition, physicians should recognize that AZT is still investigational and must be used under the requirements of the Food and Drug Administration (FDA) regulations for IND drugs. Furthermore, we strongly recommend that physicians be experienced in the diagnosis and treatment of AIDS patients.

Telephone inquiries concerning enrollment in this program may be directed to the Burroughs Wellcome AZT Treatment IND Coordinating Center (BW-AZTICC) at 800-843-9388. Please identify yourself as a physician when you call for this information.

Thank you.

BURROUGHS WELLCOME AZT TREATMENT IND

INSTRUCTIONS FOR PARTICIPATING

PATIENT REGISTRATION

1. Patients must meet all patient eligibility criteria of the protocol. (See BW treatment IND protocol.)
2. The physician must complete a patient registration form for each patient enrolled in the study. The physician should attach a unique patient identification number to the form from the pre-printed labels supplied by BW-AZTICC. This patient registration form should be submitted to a registered pharmacy to initiate the drug distribution system. If the physician does not know where the closest registered pharmacy is located, please call 800-237-2469 for this information.
3. The physician must obtain a informed consent form that has been signed by the patient and the physician for each patient. The patient must also be given a copy.

PHYSICIAN REGISTRATION

1. The physician must have a valid current license to practice medicine in the United States. We strongly recommend that physicians be knowledgeable and experienced in the diagnosis and treatment of AIDS and be willing to assume responsibility for supervising the administration of an investigational drug.
2. The physician must submit a completed FDA-1573 form, his/her medical license number and state of license, patient registration form, and a signed patient informed consent to a participating registered pharmacy.
3. If all registration forms are not accurate and complete, the registered pharmacy will not accept them and they will result in delay of drug distribution.

PHARMACY REGISTRATION

1. The pharmacy must be staffed by at least one licensed full-time pharmacist.
2. The pharmacy must be located in a hospital accredited by the Joint Commission of Accreditation of Hospitals (JCAH). (A copy of the Procedures for Hospital Pharmacies has been included in this packet for your reference.)
3. The hospital must have a medical service.
4. The pharmacy must be located in a hospital that has a locked, secure facility to store AZT.
5. The hospital's director of pharmacy and the appropriate hospital administrator must submit a letter on hospital stationery requesting to participate in the BW treatment IND protocol.

PRESCRIPTION RENEWAL PROCEDURE

1. When the patient is enrolled in the study, a one-month supply of AZT will be sent to the designated pharmacy. The drug will be dispensed to the patient in a one-week supply for the first two months, then in a two-week supply thereafter.
2. In order to continue AZT beyond one month, a prescription renewal and patient followup form must be completed by the physician and provided to the pharmacy two weeks after initial distribution and monthly thereafter. The physician's identification label must be attached to this form.

Burroughs Wellcome Co will not be able to continue distribution of AZT if the completed forms have not been received each month from the physician and the pharmacy at BW-AZTICC.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form approved: OMB No. 0910-0013

Expiration Date: December 31, 1984.

Physician #

STATEMENT OF INVESTIGATOR

Note: No drug may be shipped or study initiated unless a completed statement has been received (21 CFR 312.1(a)(12)).

TO: SUPPLIER OF DRUG (Name, address, and Zip Code)

Burroughs Wellcome Co.
P.O. Box 6042
Rockville, Maryland 20850

NAME OF INVESTIGATOR (Print or Type)

DATE

NAME OF DRUG

Azidothymidine

Dear Sir:

The undersigned, _____
submits this statement as required by section 505(i) of the Federal Food, Drug, and Cosmetic Act and §312.1 of Title 21 of the Code of Federal Regulations as a condition for receiving and conducting clinical investigations with a new drug limited by Federal (or United States) law to investigational use.

1. THE FOLLOWING IS A STATEMENT OF MY EDUCATION AND EXPERIENCE:

a. COLLEGES, UNIVERSITIES, AND MEDICAL OR OTHER PROFESSIONAL SCHOOLS ATTENDED, WITH DATES OF ATTENDANCE, DEGREES, AND DATES DEGREES WERE AWARDED

b. POSTGRADUATE MEDICAL OR OTHER PROFESSIONAL TRAINING. GIVE DATES, NAMES OF INSTITUTIONS, AND NATURE OF TRAINING.

c. TEACHING OR RESEARCH EXPERIENCE. GIVE DATES, INSTITUTIONS, AND BRIEF DESCRIPTION OF EXPERIENCE.

d. EXPERIENCE IN MEDICAL PRACTICE OR OTHER PROFESSIONAL EXPERIENCE. GIVE DATES, INSTITUTIONAL AFFILIATIONS, NATURE OF PRACTICE, OR OTHER PROFESSIONAL EXPERIENCE.

e. REPRESENTATIVE LIST OF PERTINENT MEDICAL OR OTHER SCIENTIFIC PUBLICATIONS. GIVE TITLES OF ARTICLES, NAME OF PUBLICATIONS AND VOLUME, PAGE NUMBER, AND DATE.

IF THIS INFORMATION HAS PREVIOUSLY BEEN SUBMITTED TO THE SPONSOR, IT MAY BE REFERRED TO AND ANY ADDITIONS MADE TO BRING IT UP-TO-DATE.

2a. The investigator assures that an IRB that complies with the requirements set forth in Part 56 of this chapter will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator also assures that he/she will report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and that he/she will not make any changes in the research that would increase the risks to human subjects without IRB approval. FDA will regard the signing of the Form FDA 1573 as providing the necessary assurances stated above.

b. A description of any clinical laboratory facilities that will be used. (If this information has been submitted to the sponsor and reported by him on Form FDA 1571, reference to the previous submission will be adequate).

3. *The investigational drug will be used by the undersigned or under his supervision in accordance with the plan of investigation described as follows: (Outline the plan of investigation including approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; clinical uses to be investigated; characteristics of subjects by age, sex and condition; the kind of clinical observations and laboratory tests to be undertaken prior to, during, and after administration of the drug; the estimated duration of the investigation; and a description or copies of report forms to be used to maintain an adequate record of the observations and test results obtained. This plan may include reasonable alternates and variations and should be supplemented or amended when any significant change in direction or scope of the investigation is undertaken.)*

4. THE UNDERSIGNED UNDERSTANDS THAT THE FOLLOWING CONDITIONS, GENERALLY APPLICABLE TO NEW DRUGS FOR INVESTIGATIONAL USE, GOVERN HIS RECEIPTS AND USE OF THIS INVESTIGATIONAL DRUG:

a. The sponsor is required to supply the investigator with full information concerning the preclinical investigations that justify clinical trials, together with fully informative material describing any prior investigations and experience and any possible hazards, contraindications, side-effects, and precautions to be taken into account in the course of the investigation.

b. The investigator is required to maintain adequate records of the disposition of all receipts of the drug, including dates, quantities, and use by subjects, and if the investigation is terminated, suspended, discontinued, or completed, to return to the sponsor any unused supply of the drug. If the investigational drug is subject to the Comprehensive Drug Abuse Prevention and Control Act of 1970, adequate precautions must be taken including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

c. The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the drug or employed as a control in the investigation.

d. The investigator is required to furnish his reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained by various investigators. The sponsor is required to present progress reports to the Food and Drug Administration at appropriate intervals not exceeding 1 year. Any adverse effect that may reasonably be regarded as caused by, or probably caused by, the new drug shall be reported to the sponsor promptly, and if the adverse effect is alarming, it shall be reported immediately. An adequate report of the investigation should be furnished to the sponsor shortly after completion of the investigation.

e. The investigator shall maintain the records of disposition of the drug and the case histories described above for a period of 2 years following the date a new-drug application is approved for the drug; or if the application is not approved, until 2 years after the investigation is discontinued. Upon the request of a scientifically trained and properly authorized employee of the Department, at reasonable times, the investigator will make such records available for inspection and copying. The subjects' names need not be divulged unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual cases studied, or do not represent actual results obtained.

f. The investigator certifies that the drug will be administered only to subjects under his personal supervision and that the drug will not be supplied to any other investigator or to any clinic for administration to subjects.

g. The investigator certifies that he will inform any subjects including subjects used as controls, or their representatives, that drugs are being used for investigational purposes, and will obtain the consent of the subjects, or their representatives, except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects.

h. The investigator is required to assure the sponsor that for investigations subject to an institutional review requirement under Part 56 of this chapter the studies will not be initiated until the institutional review board has reviewed and approved the study. (The organization and procedure requirements for such a board as set forth in Part 56 should be explained to the investigator by the sponsor.)

Very truly yours,

Name of Investigator _____

Address _____

Telephone () _____ State Medical License Number _____

(If you have previously been registered at another pharmacy or by AZT,CC please check here _____.)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

September 30, 1986

WAIVER OF INSTITUTIONAL REVIEW BOARD REVIEW
OF CERTAIN CLINICAL STUDIES OF AZIDOTHYMININE (AZT)

At the request of the Burroughs Wellcome Company, the Food and Drug Administration has granted a waiver from the requirement for Institutional Review Board review of clinical research in the use of azidothymidine (AZT) in the treatment of certain patients with acquired immunodeficiency syndrome. IRBs may, however, elect to review such studies at any time, in which case the waiver will no longer apply, and FDA's IRB regulations will be fully applicable. Even though a waiver has been granted, informed consent must be obtained from each subject who receives AZT for the treatment of acquired immunodeficiency syndrome. Federal law and regulations do not permit a waiver of this requirement.

In its review of Burroughs Wellcome's request for a waiver, FDA had to determine that granting a waiver would be in the best interests of the patients who would receive AZT under a "treatment IND." In view of preliminary findings that the drug significantly prolongs survival, FDA concluded that AIDS patients meeting the inclusion criteria in the Burroughs Wellcome protocol can be expected to benefit from receiving the drug. FDA also determined that adequate mechanisms exist to ensure the protection of human subjects participating in studies of AZT. The Clinical Research Subgroup of the National Institute of Allergy and Infectious Diseases reviewed and approved the treatment protocol and will participate in continuing review under terms of the IND. The Subgroup also approved the model informed-consent form. These factors, together with FDA's review and acceptance of the IND, constitute evidence of acceptable alternate mechanisms to protect the rights and welfare of persons receiving AZT under a "treatment IND."

PLACE PATIENT LABEL HERE

PLACE PHARMACIST STAMP HERE

PLACE PHYSICIAN STAMP HERE

BURROUGHS WELLCOME AZT™ TREATMENT IND PATIENT REGISTRATION FORM

1. Physician Name _____
First Middle Initial Last

2. Office Address _____

City State Zip Telephone

PATIENT INFORMATION

3. Sex: ☐ Male ☐ Female

4. Date of Birth ____/____/____
Month Day Year

5. Race/Ethnic Group

☐ 1. White, not Hispanic

☐ 2. Black, not Hispanic

☐ 3. Hispanic

☐ 4. Pacific Islander, American Eskimo

☐ 5. American Indian

☐ 6. Other (specify _____)

6. Patient characteristic(s) (check all appropriate)

☐ 1. Homosexual/bisexual

☐ 2. I.V. drug user

☐ 3. Hemophiliac

☐ 4. Heterosexual

☐ 5. Blood transfusion recipient

☐ 6. Other (specify _____)

7. Did patient have histologically confirmed *Pneumocystis carinii* pneumonia (PCP)? ☐ Yes ☐ No

8. If "yes," how was the diagnosis of PCP confirmed (check all appropriate)?

☐ 1. Sputum

☐ 2. Bronchoalveolar lavage

☐ 3. Transbronchial biopsy

☐ 4. Open lung biopsy

☐ 5. Other (specify _____)

9. If "yes," mark date clinical specimen was collected confirming diagnosis of PCP.

____/____/____
Month Day Year

10. Has the patient recovered from the most recent episode of PCP? ☐ Yes ☐ No

11. If "yes," what drug was used, how long was it given, and when were treatment doses of antibiotics for PCP discontinued?

Drug _____ Dose _____

Dates of Therapy: Start ____/____/____ Stop ____/____/____
Month Day Year Month Day Year

12. How many total episodes of histologically confirmed PCP has the patient had? (number) _____

13. Is the patient currently receiving prophylactic chemotherapy for PCP? ☐ Yes ☐ No

14. If "yes," what prophylactic agent is the patient receiving (check all appropriate)?

☐ 1. Trimethoprim-sulfa (Dose _____)

☐ 2. Pyrimethamine-sulfadoxine (Dose _____)

☐ 3. Other (Specify _____)

15. Will all drugs listed under protocol exclusion criteria (myelosuppressive, nephrotoxic, cytotoxic, or experimental agents) be discontinued prior to AZT therapy? ☐ Yes ☐ No

(over)

PLACE PATIENT LABEL HERE

PLACE PHARMACIST STAMP HERE

PLACE PHYSICIAN STAMP HERE

16. Has any other AIDS-defining cancer or opportunistic infection been diagnosed? ☐ Yes ☐ No

17. If "yes," list diagnosis(es) and date(s) of initial episode and date of recurrence, if any.

Diagnosis	Date of Diagnosis			Current Clinical Status	
	Month	Day	Year	Active	Inactive
<i>Pneumocystis carinii</i> pneumonia	___	___	___	_____	_____
Toxoplasmosis	___	___	___	_____	_____
CMV Disease	___	___	___	_____	_____
Cryptococcosis	___	___	___	_____	_____
Histoplasmosis	___	___	___	_____	_____
Kaposi's sarcoma	___	___	___	_____	_____
Lymphoma _____ (Specify type)	___	___	___	_____	_____
Mycobacterium avium-intracellulare	___	___	___	_____	_____
Candida Esophagitis	___	___	___	_____	_____
Chronic Herpes Simplex	___	___	___	_____	_____
Chronic Cryptosporidiosis	___	___	___	_____	_____
Other (Specify)	___	___	___	_____	_____
_____	___	___	___	_____	_____
_____	___	___	___	_____	_____
_____	___	___	___	_____	_____
_____	___	___	___	_____	_____

18. Karnofsky score within past 14 days (see protocol) _____ (number between 0 and 100)

19. Is the patient presently hospitalized? ☐ Yes ☐ No

20. Laboratory values within past 14 days: (Please list most recent results of test.)

Test	Result	Normal Range	Date		
			Month	Day	Year
Hemoglobin	_____ gm/dl		___	___	___
Total neutrophil count	_____ /mm ³		___	___	___
Total lymphocyte count	_____ /mm ³		___	___	___
Platelet count	_____ /mm ³		___	___	___
SGOT	_____ iu/dl	_____	___	___	___
Serum creatinine	_____ mgm/dl	_____	___	___	___

FOR WOMEN ONLY:

21. Is the patient of childbearing potential? ☐ Yes ☐ No

22. Is she using a barrier contraceptive or abstaining from sex? ☐ Yes ☐ No

23. Is she pregnant? ☐ Yes ☐ No

Physician Signature

Date _____ / _____ / _____
Month Day Year

COMPLETE FORM AND RETURN TO: BW-AZT TREATMENT IND COORDINATING CENTER
BUILDING 31, ROOM 7A05
9000 ROCKVILLE PIKE
BETHESDA, MD 20892

For help completing the Patient Registration Form, contact 1-800-843-9388.

PLACE PATIENT LABEL HERE

PLACE PHARMACIST STAMP HERE

PLACE PHYSICIAN STAMP HERE

9. (continued)

Diagnosis	Date of Diagnosis			Treatment
	Month	Day	Year	
Mycobacterium avium-intracellulare	___/___/___	___/___/___	___/___/___	_____
Candida Esophagitis	___/___/___	___/___/___	___/___/___	_____
Chronic Herpes Simplex	___/___/___	___/___/___	___/___/___	_____
Chronic Cryptosporidiosis	___/___/___	___/___/___	___/___/___	_____
Other (Specify)	___/___/___	___/___/___	___/___/___	_____
_____	___/___/___	___/___/___	___/___/___	_____
_____	___/___/___	___/___/___	___/___/___	_____
_____	___/___/___	___/___/___	___/___/___	_____
_____	___/___/___	___/___/___	___/___/___	_____
_____	___/___/___	___/___/___	___/___/___	_____

10. Has the patient received a blood transfusion since the last patient followup form was submitted? ☐ Yes ☐ No

If yes, hemoglobin before transfusion _____

Number of units transfused _____

11. Did any adverse drug experience occur during this treatment period? ☐ Yes ☐ NoDate of Event ___/___/___
Month Day Year

If Yes, briefly describe the event. _____

Was treatment with AZT: ☐ Continued at same dose ☐ Reduced in dose ☐ DiscontinuedDid the patient require inpatient hospitalization? ☐ Yes ☐ No

(If the patient required inpatient hospitalization as a result of the adverse drug experience, complete an Adverse Reaction Report.)

12. ALL DEATHS MUST BE REPORTED TO THE AZT INFORMATION LINE (800-843-9388) WITHIN 24 HOURS. IN THE EVENT OF DEATH, COMPLETE THIS FORM AND AN ADVERSE REACTION REPORT AND MAIL BOTH TO THE BW-AZT TREATMENT IND COORDINATING CENTER.

Date of Death ___/___/___
Month Day Year

Cause(s) of death _____

13. Comments: _____

Physician Signature _____

Date ___/___/___
Month Day Year

Pharmacist Signature _____

Date ___/___/___
Month Day Year

COMPLETE FORM AND RETURN TO: BW-AZT TREATMENT IND COORDINATING CENTER
 BUILDING 31, ROOM 7A05
 9000 ROCKVILLE PIKE
 BETHESDA, MD 20892

Burroughs Wellcome AZTTM Treatment IND Coordinating Center

RESPONSIBILITY OF PHYSICIANS TO REPORT
ADVERSE DRUG REACTIONS AND DEATHS

It is the responsibility of the physician to report all deaths, regardless of cause:

- 1) Report to the AZT Information line (800-843-9388) within 24 hours
- 2) Submit an ADVERSE REACTION REPORT (FDA Form 1639) within 72 hours
- 3) Submit PRESCRIPTION RENEWAL AND PATIENT FOLLOWUP FORM within 72 hours

For all suspected adverse drug reactions resulting in hospitalization:

Report on ADVERSE REACTION REPORT (FDA Form 1639) within 24 hours of the event.

Other adverse drug experiences not requiring hospitalization:

Report on PRESCRIPTION RENEWAL AND PATIENT FOLLOWUP FORM at the time of renewal.

Side effects noted in the clinical trials include headache, mild confusion or anxiety, nausea, rash, anemia, and leukopenia. Additional toxicities following extended therapy (AZT use > 6 months) are not known at this time. Side effects may be exacerbated by simultaneous use of any other medication.

If you submit a Drug Experience Report form you must also complete a patient Prescription Renewal Form in order to continue your patient's AZT prescription.

PLACE PATIENT LABEL HERE

PLACE PHARMACIST STAMP HERE

PLACE PHYSICIAN STAMP HERE

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION (HFN-730) ROCKVILLE, MD 20857 ADVERSE REACTION REPORT (Drugs and Biologics)			Form Approved: OMB No. 0910-0230.			
			FDA CONTROL NO.			
			ACCESSION NO.			
I. REACTION INFORMATION						
1. PATIENT ID/INITIALS (In Confidence)	2. AGE YRS.	3. SEX	4-6 REACTION ONSET		8-12. CHECK ALL APPROPRIATE: ☐ PATIENT DIED ☐ REACTION TREATED WITH Rx DRUG ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION ☐ RESULTED IN PERMANENT DISABILITY ☐ NONE OF THE ABOVE	
			MO.	DA		YR.
7. DESCRIBE REACTION(S)						
13. RELEVANT TESTS/LABORATORY DATA						
II. SUSPECT DRUG(S) INFORMATION						
14. SUSPECT DRUG(S) (Give manufacturer and lot no. for vaccines/biologics)					20. DID REACTION ABATE AFTER STOPPING DRUG?	
15. DAILY DOSE		16. ROUTE OF ADMINISTRATION			☐ YES ☐ NO ☐ NA	
17. INDICATION(S) FOR USE					21. DID REACTION REAPPEAR AFTER REINTRODUCTION?	
18. DATES OF ADMINISTRATION (From/To)		19. DURATION OF ADMINISTRATION			☐ YES ☐ NO ☐ NA	
III. CONCOMITANT DRUGS AND HISTORY						
22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (Exclude those used to treat reaction)						
23. OTHER RELEVANT HISTORY (e.g. diagnoses, allergies, pregnancy with LMP, etc.)						
IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER			V. INITIAL REPORTER (In confidence)			
24. NAME AND ADDRESS OF MANUFACTURER (Include Zip Code)			26.-26a. NAME AND ADDRESS OF REPORTER (Include Zip Code)			
24a. IND/NDA NO. FOR SUSPECT DRUG		24b. MFR CONTROL NO.	26b. TELEPHONE NO. (Include area code)			
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE (Check all that apply) ☐ FOREIGN ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ CONSUMER		26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER? ☐ YES ☐ NO			
25. 15 DAY REPORT? ☐ YES ☐ NO	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP		26d. ARE YOU A HEALTH PROFESSIONAL? ☐ YES ☐ NO		Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction	
NOTE: Required of manufacturers by 21 CFR 314.80						

INSTRUCTIONS FOR COMPLETING FORM FDA - 1639

GENERAL

- o Use a separate Form FDA - 1639 for each patient.
- o Additional pages may be attached if space provided on the Form FDA - 1639 is inadequate.
- o Non-manufacturers should send forms to the Food and Drug Administration, Division of Epidemiology and Surveillance, HFN-730, 5600 Fishers Lane, Rockville, MD 20857.
- o For questions call: 301 - 443-4580.
- o Patient and initial reporter identification is held in confidence by the FDA and is not subject to release under the Freedom of Information Act.
- o Reports of serious, suspect reactions are encouraged.

SPECIFIC INSTRUCTIONS

- I. Reaction Information
 - Item 2. Age - For children under 5 years of age, also write date of birth (DOB) in Item 1. For congenital malformations, give the age and sex of the infant (even though the mother was exposed).
 - Item 7. Describe Reaction(s) - Give signs and/or symptoms, diagnoses, course, etc. Underline the single most important descriptive phrase.
- II. Suspect Drug Information
 - Item 14. Suspect Drug - The trade name is preferred. If a generically produced product is involved, the manufacturer should be identified.
 - Item 15. Dose - For pediatric patients, also give body weights.
 - Item 20 and 21. NA - is defined as nonapplicable (e.g. *when only one dose given or outcome was irreversible*).
- V. Initial Reporter
 - Item 26c. Have you also reported this reaction to the manufacturer? Your answer facilitates identification of duplicates in the central adverse reaction file. FDA encourages direct reporting even if a report has been submitted to the manufacturer.

NOTE TO MANUFACTURERS (Refer to 21 CFR 314.80) Detailed instructions are contained in the "Guideline for Postmarketing Reporting of Adverse Drug Reactions."

★ U.S. GPO 1986-0-491-338/55173

disorders developed in 1 in 28. Nevertheless, the possibility of individual misclassification remains and could be resolved only by a review of all 1979 smears.

Further confirmatory evidence comes from the histology reports on the 19 women who had a biopsy within 6 months of the smear. Not all pathologists routinely reported evidence of HPV infection on biopsy specimens, but 13 of 19 (68%) were reported as showing evidence of wart virus infection, and no pathologist specifically commented that there was no evidence of wart virus infection. Only 4 of the 19 samples showed evidence of mild dysplasia. The mild dysplasia may have been missed at the time of the cytology report, but it is also possible that in some subjects it may have developed subsequently.

The number of cases of carcinoma-in-situ in this cohort might have been even greater had not 33 women undergone cervical biopsy and cautery when the histological diagnosis was dysplasia. This procedure may modify the natural history of exposure to wart virus infection. In addition 174 of 846 women (21%) had not had a smear for more than 4 years and carcinoma-in-situ might have developed in some of these women.

In the South Australian Central Cancer Registry the ratio between incidence rates for in-situ and invasive carcinoma of the cervix is 2.9. This ratio is comparable to published data from the United States,^{10,11} but a little lower than that for the UK.¹² Nevertheless, the in-situ incidence rates for South Australia probably under-represent the true population rates, since even today 60–80 cases per year are notified to the Registry at an invasive stage.

This study determined a very highly significant relative risk of 15.6 for the development of cervical cancer after cytological evidence of HPV infection, derived from 30 observed cases and 1.9 expected cases. For reasons outlined above we believe both these figures may be underestimates, but 20 expected cases would be needed for the relative risk to remain significant at $p < 0.05$.⁸ It is unlikely that the incidence figures for the general population are inaccurate to the extent of a 10-fold under-representation.

Because the data used here were routinely collected by the VCGS, information on some potential confounding variables is not available. However, the degree of risk is much larger than that which confounding would normally induce.

Since 1979 was the first year when wart virus infection was commented on cytologically, we do not know how long this infection may have been present. Before 1979 cytological abnormalities subsequently attributed to HPV infection were likely to have been reported as mild dysplasia. All subjects with a previous report of dysplasia were excluded from the study, and in 1979 dysplasia was not considered to be evident on the smears of the members of the cohort. The follow-up period may be short, but the number of cases of carcinoma-in-situ is large.

The trend shown for an increased relative risk with younger age groups is important. Further research is needed to ascertain the interaction of this risk factor with other established risk factors, such as smoking^{13–15} and use of the oral contraceptive.¹⁶ Identifying such a high-risk population may have important implications for screening policies.

We thank Dr Graham Giles and the staff of the Victorian Cancer Registry for helpful assistance.

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References at foot of next column

ADMINISTRATION OF 3'-AZIDO-3'-DEOXYTHYMIDINE, AN INHIBITOR OF HTLV-III/LAV REPLICATION, TO PATIENTS WITH AIDS OR AIDS-RELATED COMPLEX

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Summary In a 6-week clinical trial 4 dose regimens of 3'-azido-3'-deoxythymidine (AZT), a thymidine analogue with potent anti-viral activity against HTLV-III in vitro, were examined in 19 patients with the acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC). AZT was given intravenously for 2 weeks, then orally for 4 weeks at twice the intravenous dose. AZT was well absorbed from the gut and crossed the blood-brain barrier. Therapeutic levels were maintained with 5 mg given intravenously or 10 mg given orally every 4 h. Treatment was not limited by side-effects, the commonest of which were headaches and depression of white-cell counts. 15 of the 19 patients had increases in their numbers of circulating helper-inducer T lymphocytes ($p < 0.001$) during therapy, 6 who were anergic at entry showed positive delayed type hypersensitivity skin test reactions during treatment, 2

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had clearance of chronic fungal nailbed infections without specific anti-fungal therapy, 6 had other evidence of clinical improvement, and the group as a whole had a weight gain of 2.2 kg. Also, with the highest dose regimen cultures of peripheral blood mononuclear cells for HTLV III became negative.

Introduction

3'-azido-3'-deoxythymidine (AZT), a drug not previously given to man, is a potent inhibitor of the in-vitro replication

and cytopathic effect of HTLV-III/LAV.¹ This drug is a thymidine analogue in which the 3'-hydroxy (-OH) group is replaced by an azido (-N₃) group (fig 1). AZT is converted to a triphosphate form by cellular enzymes and this triphosphate form is utilised by retroviral DNA polymerase (reverse transcriptase).^{2,3} The 3' substitution makes subsequent 5'→3' phosphodiester linkages impossible (AZT can thus act as a chain terminator of DNA synthesis). Cellular DNA polymerase alpha is 100 times less susceptible to inhibition by AZT-triphosphate than is HTLV-III reverse transcriptase.^{2,3}

TABLE 1—CLINICAL AND VIROLOGICAL FEATURES OF PATIENTS RECEIVING AZT

Patient no and diagnosis	Symptoms and findings at entry	Drug toxicity	Clinical course during therapy	Weight change (kg)	HTLV-III isolation*
<i>1 mg/kg IV, then 2 mg/kg PO every 8 h</i>					
1. AIDS—post-PCP	Weight loss, fevers, diarrhoea	None	Fevers ceased, then returned Diarrhoea improved Megaloblastic anaemia with B ₁₂ malabsorption diagnosed Platelets increased from 164 000 to 477 000/ μ l	+4.4	Virus detected while on IV therapy, but not at end of oral
2. AIDS—KS	Fevers, progressive visceral KS	Slight headache	Visceral KS progressed; taken off protocol	+0.8	Virus detected sporadically
3. ARC	Lymphadenopathy, oral candida	Slight headache	No clinical change	-0.6	Decreased virus during initial AZT administration
4. AIDS—post-PCP	Slight oral candida (on oral 'Nystatin')	Abdominal discomfort	Stopped nystatin; oral candidiasis did not recur	+3.6	Virus not detected on day 0 or on AZT
<i>2.5 mg/kg IV, then 5 mg/kg PO every 8 h</i>					
5. ARC	Fevers, weight loss, night sweats	None	Increased sense of well-being Localised herpes zoster; treated with acyclovir	+2.7	Low levels of virus detected early, then negative
6. AIDS—post-PCP	Weight loss, oral candidiasis, fevers	None	Episode of sinusitis Fevers decreased	+3.2	Virus detected throughout
7. ARC	Oral candidiasis, night sweats, fevers	None	Transient febrile episode	+7.2	Virus detected throughout
8. ARC	Peripheral neuropathy, oral candidiasis, malaise	Slight headache	Improved sense of well-being Increased exercise tolerance	+0.7	Virus detected throughout
9. ARC	Oral candidiasis, fevers	None	Fevers decreased Increased ability to concentrate	+0.4	Virus detected throughout
10. AIDS—post-PCP	Malaise	Slight headache	No clinical change	+5.2	Low level of virus at entry, then virus not detectable
<i>2.5 mg/kg IV, then 5 mg/kg PO every 4 h</i>					
11. AIDS—post-PCP	Weight loss, fatigue Appetite loss Severe aphthous ulcers Onychomycosis	Headache	Improved appetite and energy Aphthous ulcers cleared Onychomycosis clearing	+3.6	Virus detected sporadically
12. AIDS—post-PCP	Malaise	Tremors† Headache Confusion Neutropenia Anaemia	Upper lobe pneumonia developed during therapy, treated with trimethoprim/sulphamethoxazole erythromycin; taken off protocol.	-0.9	Not available
13. ARC	Fevers Lymphadenopathy	None	No clinical change	0.0	Virus detected sporadically
14. ARC	Oral candidiasis	None	No clinical change	+4.7	Virus detected sporadically
15. AIDS—KS & post-PCP	Oral candidiasis Onychomycosis	Slight headache	Onychomycosis clearing, KS lesions unchanged	+3.8	Virus detected during first 2 weeks, but not after
<i>5 mg/kg IV, then 10 mg/kg PO every 4 h</i>					
16. ARC	Weight loss Lymphadenopathy Night sweats	Decreased WBC (8700–2600)	Night sweats cleared Oral candidiasis developed	+12.0	Virus detected on day 0 and day 7, but not after
17. AIDS—KS	Cutaneous KS	Slight headache	KS lesions increased	+4.1	Virus not detected on day 0 or on AZT
18. AIDS—KS	Cutaneous KS Oral candidiasis Fevers Lymphadenopathy	Headache Decreased WBC (4000–2300)	Became afebrile 2 new KS lesions appeared	+4.8	Virus detectable on day 0, but not on AZT
19. AIDS—KS	KS	None	No clinical change	+2.8	Virus not detected on day 0 or on AZT

IV = intravenously; PO = orally.

*HTLV-isolation in lectin-stimulated primary cultures of peripheral blood lymphocytes.

†While receiving trimethoprim/sulphamethoxazole for upper lobe pneumonia he had tremors, slight mental confusion, a decrease in haemocrit (from 27.3 on admission to 21.6), and neutropenia (from 2200 on admission to 900), all of which resolved on discontinuation of the three drugs.

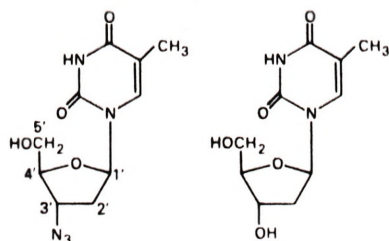


Fig 1—Structures of 3'-azido-3'-deoxythymidine (left) and thymidine (right).

(and Furman PA, personal communication), and this difference may account for the selective antiviral activity of AZT against HTLV-III. AZT exhibits little toxicity in animals even at doses beyond 80 mg/kg/day (Ayers K, personal communication). We have explored the feasibility of giving AZT to patients with HTLV-III/LAV infection.

Materials and Methods

Patients

19 patients with HTLV-III infection (18 males and 1 female) were entered into the study (table 1). Of the 11 AIDS patients 6 had a history of *Pneumocystis carinii* pneumonia (PCP), 4 had Kaposi's sarcoma (KS), and 1 had both PCP and KS. Each of the 8 patients with ARC had either weight loss or oral candidiasis. All 8 had decreased numbers of helper T cells (Leu 3⁺ or OKT4⁺ cells). In addition, 3 of the ARC patients had fever, 3 had lymphadenopathy, and 1 had peripheral neuropathy attributed to HTLV-III infection. Patient 6 was a haemophilic and patient 11 had received several units of blood; the other patients were either homosexual or had had sexual contact with prostitutes. Each of the subjects had circulating antibodies to HTLV-III detectable by enzyme-linked immunosorbent assay (ELISA) and/or western blot, and each had had HTLV-III isolated by primary culture of lectin-activated peripheral blood lymphocytes (see below). Patients 1, 2, 4, 5, 8, 10, 11, 12, 15, 17, and 19 were treated at the Warren G. Magnuson Clinical Center of the National Institutes of Health and the rest at Duke University Medical Center; the protocols were approved by the respective institutional review boards. Each subject gave informed consent for the study.

Drug Regimens and Monitoring of Patients

AZT was synthesised according to a modification of the method described by Lin and Prusoff.⁴ All patients received test doses of AZT. They were then given AZT intravenously for 14 days according to the following regimens: 1 mg/kg every 8 h for patients 1–4 (regimen A), 2.5 mg/kg every 8 h for patients 5–10 (regimen B), 2.5 mg/kg every 4 h for patients 11–15 (regimen C), and 5 mg/kg every 4 h for patients 16–19 (regimen D). Each dose was administered over a period of 1 h. Patients 1, 2, 3, and 12 received additional intravenous doses for another 7–14 days. Except for patients 2 and 12 who were withdrawn from the study (see below), the patients next received 4 weeks of oral therapy at twice the intravenous dose. Patients were closely monitored for clinical and laboratory changes. They also underwent skin testing for delayed type hypersensitivity at entry, at the end of the intravenous course, and at the end of the oral course of AZT. The antigens used were 0.1 ml of candida extract (Hollister-Stier, Elkhart, New York; 1/100 dilution), intermediate strength (5 TU) purified protein derivative (PPD) (Connaught Labs, Willowdale, Ontario), tetanus toxoid (Lederle Labs, Pearl River, New York; 10 LF/ml), and trichophyton extract (Hollister-Stier; 1/30 dilution). Lymphocyte subsets reacting to Leu 3 or OKT4 (helper-inducer) or to Leu 2 or OKT8 (suppressor-cytotoxic) were analysed by flow cytometry. Patient 19 was monitored for his ability to manifest a secondary in-vitro

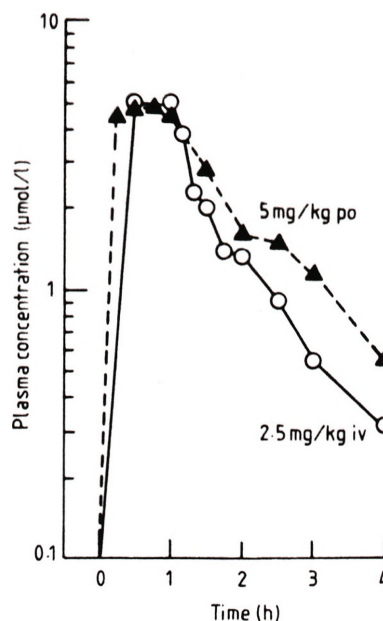


Fig 2—Plasma concentrations of AZT in patient 5 after 2.5 mg/kg of AZT had been infused intravenously over one hour (O) or after 5 mg/kg orally (Δ).

histocompatibility locus-restricted cytotoxic response against influenza-virus-infected autologous lymphocytes as previously described.⁵

Heparinised plasma samples were obtained at various times after intravenous or oral doses of AZT for measurement of AZT levels according to a modification of a procedure recently described for measuring another nucleoside analogue, tiazofurin.⁶ In brief, the beta isomer of azidothymidine was added as an internal standard to 0.5 ml plasma samples. The samples were then passed through C18 extraction and analytical columns and eluted isocratically; the mobile phase for analytical separation was pH 6.5 acetate in 23% methanol. The amount of AZT was measured by comparing ultraviolet absorption at several wavelengths (254, 267, and 280 nm) with that of a known standard; the lowest amount measurable was 0.1 μmol/l.

Peripheral blood mononuclear cells were cultured for HTLV-III as previously described^{7,8} at entry to the study and periodically during treatment. Additional cells from the patients were co-cultivated with a clone of Jurkat known to be susceptible to infection by HTLV-III. Supernatant fluids were sampled twice a week for up to 42 days and assayed for the presence of precipitable reverse transcriptase activity by using dT₁₅-rA_n as the primer-template and Mg⁺⁺ as the divalent cation.^{7,8} In addition, the cells were periodically tested for expression of HTLV-III viral proteins by indirect immunofluorescence.

Statistical Analysis

Immunological variables before and after treatment were logarithmically transformed and compared by the use of the two-tailed Wilcoxon signed rank test for paired samples.

Results

Clinical Pharmacology

Figure 2 shows plasma concentrations of AZT in a representative patient (no 5) after an intravenous infusion of 2.5 mg/kg of AZT over 1 h and after an oral dose of 5 mg/kg mixed with 75 ml of orange juice. The plasma concentration reached a peak of approximately 5 μmol/l after the intravenous dose; plasma disappearance had a half-life of

approximately 1 h. A similar peak level of the drug was attained 1 h after an oral dose of 5 mg/kg; for this subject, the bioavailability of the oral dose (ratio of the area under the curve for the oral *vs* the intravenous dose, corrected for the dose) was approximately 60%. Because of the rapid clearance of this drug, we increased dose frequency to every 4 h for the last two dose regimens (C and D).

Analyses of plasma concentrations of AZT in other patients (nos 1, 2, 4, 8, 10, 11, 17, and 19) yielded peak values of 1.5 to 2 $\mu\text{mol/l}$ after 1 mg/kg given intravenously or 2 mg/kg taken orally, of 4 to 6 $\mu\text{mol/l}$ after 2.5 mg/kg given intravenously or 5 mg/kg given orally, and of 6 to 10 $\mu\text{mol/l}$ after 5 mg/kg given intravenously or 10 mg/kg given orally. The average bio-availability of orally administered drug was 60% with little patient-to-patient variation. Finally, cerebrospinal fluid obtained from patient 19 by lumbar puncture 4 h after the start of an intravenous infusion of 5 mg/kg contained 0.86 $\mu\text{mol/l}$ of AZT; a simultaneously obtained plasma sample contained 1.14 $\mu\text{mol/l}$ of AZT.

Clinical Evaluation (Table 1)

2 patients (nos 2 and 12) were withdrawn from the study, one because of advancing KS and the other of a possible drug reaction (see below); all the other patients completed at least 6 weeks of therapy. 9 of the 19 subjects complained of slight headaches and 1 of mild abdominal discomfort. Haematocrit levels dropped by 5–10% in several patients (this did not seem to be dose related), and by 10–20% in 3 (nos 1, 2, and 12). The pernicious anaemia in patient 1 was incidental and responded to intramuscular vitamin B₁₂ injections. 1 of the

patients on regimen C and 2 of the patients on regimen D had drops in their total white blood cell counts while on AZT. None had thrombocytopenia; 1 even had a progressive rise in platelet counts (table 1). The side-effects that patient 12 seemed to have (table 1) resolved after all drugs were withdrawn. We believe that they were due to the trimethoprim/sulphamethoxazole that he was taking for his pneumonia, but all the same he was taken off the protocol and is considered to be a case of possible drug toxicity. Otherwise, the patients tolerated AZT well, and none showed signs of renal, hepatic, or cardiac dysfunction that could be attributed to the drug.

5 of the patients had KS at entry into the study. 1 of them (patient 2), who was put on the lower dose regimen of AZT, had aggressive gastrointestinal and cutaneous KS before the study. During his 3 weeks on intravenous AZT, his KS lesions progressed and caused oesophageal pain. He was taken off the protocol and given cytotoxic anti-tumour drugs but he died 5 months later. In the other 4 patients with KS, the tumours enlarged in 2 and remained unchanged in the other 2.

Mild infections (localised herpes zoster, sinusitis, or oral candidiasis) developed in 3 of the patients who completed the protocol (nos 5, 6, and 16) and resolved with appropriate therapy, and a transient febrile episode developed in patient 7. In other patients chronic infections improved with AZT—chronic fungal nailbed infections in patients 11 and 15 cleared without specific therapy, as did debilitating ulcerative aphthous stomatitis in patient 11.

On average, patients gained 2.2 kg during the 6–8 weeks of therapy (table 1). This weight gain was not associated with

TABLE II—IMMUNOLOGICAL CHANGES IN PATIENTS RECEIVING AZT

Patient no	Helper-inducer lymphocytes (μl)*		Ratio of helper-inducer/Suppressor-cytotoxic lymphocytes		Total lymphocytes (μl)		Skin tests		Tests converting (mm)‡
	Pre	Post†	Pre	Post	Pre	Post	Proportion positive	Post	
1 mg/kg IV, then 2 mg/kg PO every 8 h									
1.	33	136	0.08	0.14	660	1944	0/4	1/4	PPD (23 mm)
2.	224	264	0.21	0.24	1728	2204	0/4	0/4	..
3.	296	264	0.42	0.37	1508	1764	1/4	1/4	..
4.	<10	<10	<0.02	0.02	378	580	1/4	1/4	..
GM(SEM)§	68(2.23)	99(2.18)	0.11(1.93)	0.13(1.90)	897(1.43)	1456(1.36)	..	..	..
2.5 mg/kg IV, then 5 mg/kg PO every 8 h									
5.	<10	109	0.03	0.26	403	1221	0/4	0/4	..
6.	<10	24	0.25	0.48	108	200	0/4	0/4	..
7.	38	102	0.05	0.16	1290	1088	0/4	1/4	Candida (12 mm)
8.	365	853	1.33	1.79	1015	1984	0/4	1/4	Tetanus (20 mm)
9.	75	118	0.30	0.17	984	1296	0/4	0/4	..
10.	19	91	0.05	0.09	972	1520	0/4	3/4	Candida (15 mm); PPD (20 mm); Tetanus (15 mm)
GM(SEM)	30(1.89)	116(1.59)	0.14(1.81)	0.29(1.54)	615(1.47)	1006(1.40)	..	..	..
2.5 mg/kg IV, then 5 mg/kg PO every 4 h									
11.	12	70	0.05	0.17	594	696	0/4	0/4	..
12.	<10	34	0.03	0.54	396	168	0/4	0/4	..
13.	36	82	0.05	0.11	726	1020	0/4	0/4	..
14.	207	653	0.38	0.53	1161	2688	0/4	0/4	..
15.	31	69	0.04	0.08	1539	1386	0/4	1/4	Candida (20 mm)
GM(SEM)	31(1.71)	97(1.65)	0.06(1.57)	0.21(1.49)	789(1.27)	850(1.59)	..	..	..
5 mg/kg IV, then 10 mg/kg PO every 4 h									
16.	396	231	0.59	0.62	2175	1118	0/4	0/4	..
17.	475	295	0.97	0.43	1440	1476	2/4	2/4	..
18.	52	107	0.12	0.16	720	1334	0/4	0/4	..
19.	114	365	0.21	0.68	950	1218	0/4	1/4	Tetanus (14 mm)
GM(SEM)	183(1.69)	227(1.31)	0.35(1.61)	0.41(1.39)	1209(1.27)	1279(1.06)	..	..	..

*Normal range: helper-inducer lymphocytes, 540–1170/ μl ; ratio of helper-inducer/suppressor-cytotoxic lymphocytes, 0.75–2.5; total lymphocytes 1360–2310.

†Post treatment values are as at end of therapy, except in the case of skin tests. Skin test reactions were measured at the time of first conversion to positive.

‡Average induration at 48 h, measured in mm.

§ GM(SEM)—Geometric mean (standard error of the mean).

oedema or fluid retention but with increased appetite and waist size. Patient 8, who had peripheral neuropathy with weakness and dysaesthesia attributed to HTLV-III, noted considerable improvement in these symptoms while he was on AZT. Finally, 6 patients (nos 5, 6, 8, 9, 11, and 18) noted cessation of fevers or night sweats or marked improvement in their sense of well-being while they were on AZT. Patient 1 recently had PCP, which responded to pentamidine, patient 2 died from progressive visceral KS, patient 6 recently had cryptococcal meningitis, and patient 10 recently had herpes zoster (localised to a dermatome) and PCP, which responded to trimethoprim-sulphamethoxazole; otherwise the patients are alive and stable at the time of this report, 4-8 months after entry to the study.

Immunological and Virological Changes

There was no clear trend in the absolute lymphocyte counts or lymphocyte subsets in the patients receiving the lowest dose regimen (1 mg/kg intravenously; 2 mg/kg orally every 8 h) of AZT (table II). By contrast, 14 of the 15 patients receiving the higher three dose regimens had rises in their absolute numbers of helper-inducer T cells by the end of their course of intravenous AZT ($p < 0.001$ compared with numbers at entry) and 13 of the 15 had rises by the end of their course of oral therapy ($p < 0.001$ compared with numbers at entry) (table II; fig 3). With regimens B, C, or D the number of helper-inducer T cells rose by a mean 2.5 times. Of the entire group of 19 patients, 15 had increases in their helper-inducer T cells at the end of therapy ($p < 0.001$ mean 2.2-fold increase). There were also improvements in other immunological variables—15 patients had increases in their ratio of helper-inducer to suppressor-cytotoxic T cells ($p < 0.02$) and 15 patients had increases in their absolute lymphocyte count ($p < 0.02$).

Only 3 of the 19 patients had positive delayed type cutaneous hypersensitivity skin tests to at least one antigen upon entry; the other 16 patients were anergic (had no measurable reactivity to any of the four test antigens at 48 h). 6 of the 16 anergic patients gave positive skin tests (induration of 10 mm or greater present at 48 h) to at least one of the four test antigens during the course of treatment (table II and fig 3). Patient 1 showed a positive skin reaction of 5 TU PPD

2 weeks after starting on 1 mg/kg intravenously; 2 weeks later he reacted again to low strength (1 TU) PPD, but 6 weeks after completion of therapy, he was again anergic. Of the other anergic patients who gave positive skin reactions during treatment, 3 were on regimen B, 1 on regimen C, and 1 on regimen D. In addition, during therapy 1 anergic patient (patient 11) reacted with erythema but no induration to tetanus, and another (patient 13) with 8 mm induration to candida. All anergic patients who gave positive skin tests while on AZT also had increases in the number of circulating helper-inducer T lymphocytes.

The cytotoxic T-cell response to influenza-virus-infected autologous cells requires both helper-inducer T cells and cytotoxic effector T cells, and has been absent in each of 30 untreated AIDS patients tested so far⁵ (and Shearer GM, unpublished). At entry, peripheral blood cells from patient 19 did not show a detectable cytotoxic response (0% cytotoxicity at 40:1 effector:target ratio). After 2 weeks of intravenous therapy, a response was detectable (11% cytotoxicity), and after the course of oral therapy it was in the normal range (38% cytotoxicity). Thus, the patient's increase in the number of helper-inducer T cells (from 114 to 365/ μ l) was accompanied by a restoration of cytotoxic effector function.

For most of the patients on regimens A-C, virus continued to be detected in cultures established during therapy but virus was not detected in cultures established from any of the 4 patients on regimen D after 2 weeks of therapy. In 2 of these patients (nos 16 and 18) virus cultures established at entry had been positive, which suggests that the failure to isolate virus was related to the administration of AZT. 1 patient (no 15) on regimen C also became virus negative while on AZT.

Discussion

The results of this study show that treatment of AIDS or ARC patients with 2 weeks of AZT intravenously (up to 30 mg/kg/day), followed by 4 weeks of AZT orally (up to 60 mg/kg/day), was not limited by toxicity, and that except for the depression of white blood counts, the side-effects did not appear to be dose related. On the highest dose regimen tested (regimen D), plasma drug levels were maintained above 1 μ mol/l (a minimum level for an in-vitro antiviral effect) for 3

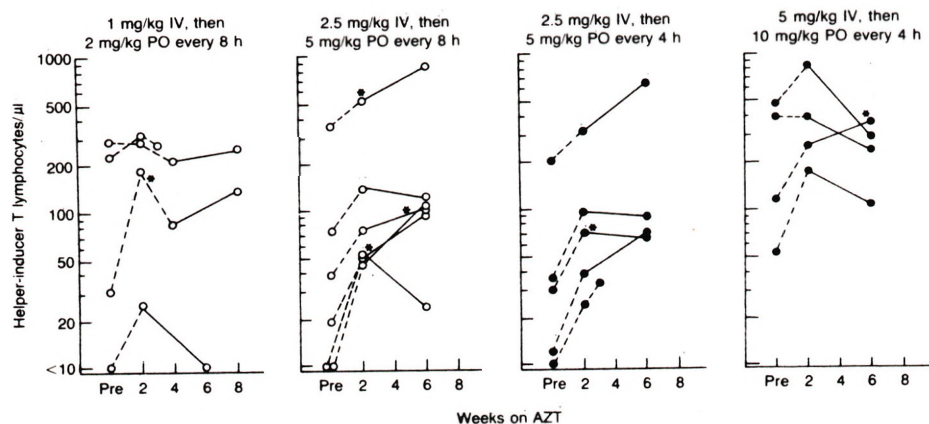


Fig 3—Absolute number of helper-inducer (Leu 3⁺7 or OKT4⁺) lymphocytes in subjects receiving AZT.

Broken lines (---) depict intravenous AZT and solid lines (—) oral AZT. Open circles (○) depict 8 hourly administration and closed circles (●) 4 hourly doses. Asterisks denote times when previously anergic patients first gave positive skin tests.

out of every 4 h. We also found that, administered orally, AZT is well absorbed. Moreover, AZT enters the cerebrospinal fluid, as has been shown in rhesus monkeys (Poplack D, personal communication). The ability of the drug to penetrate the cerebrospinal fluid is important because HTLV-III can infect the nervous system.⁹⁻¹¹

The dual aim of our trial was to determine the safety and feasibility of administering a DNA-chain terminating thymidine analogue to patients with AIDS or ARC (ie, to do a phase I study). However, the results also suggest that at least some immunological reconstitution occurred in most of the patients (particularly those in the three highest dose regimens), and that a clinical response was obtained in some. In particular, 15 of the 19 patients had increases in numbers of their circulating helper-inducer T lymphocytes, 6 previously anergic patients gave positive skin test during treatment, and the 1 patient in whom it was tested showed restoration of a virus-specific cytotoxic T-cell response. Furthermore, 2 patients showed a clearing up of chronic fungal nailbed infections, 13 patients had weight gains of 2 kg or greater, and 6 patients had other clinical improvement.

We have to ask whether our findings were related to the administration of AZT or whether they were due to variable and spontaneous improvement. Moreover, entry into a clinical trial may have a strong placebo effect in influencing such factors as appetite and sense of well-being, and it is even possible that improved nutrition may then induce changes in immune function. Similar improvements, however, were not observed when suramin was given to patients with HTLV-III infection.¹² Another concern is that repeated skin testing may lead to an increase in the size of positive tests in normal persons.^{13,14} This is unlikely to be responsible for all the observed skin test conversions since (1) positive reactions rarely develop in previously anergic individuals as a result of repeated skin testing, especially in the case of PPD;¹³ (2) patient 1, who became a positive skin test reactor while on AZT, was anergic again 2 months after treatment; and (3) loss of anergy occurred only in patients who had increases in their numbers of helper-inducer T lymphocytes.

Although our findings suggest that AZT is virustatic at the highest dose examined, it should be recognised that only a small proportion of circulating cells in patients with ARC or AIDS express the HTLV-III virus⁹ and that present technology does not permit precise measurement of the viral load, nor does it distinguish between cells bearing spontaneously replicating virus and cells producing virus only upon exogenous stimulation in vitro. Virus is more likely to be isolated from patients with ARC than from patients with fulminant AIDS and low numbers of helper-inducer T cells,² and consistent culture results are not always obtained on repeat testing of an individual patient. Moreover, recent studies suggest that HTLV-III can infect T cells,¹⁵ EBV-infected B cells,¹⁶ and macrophages (Popovic M, personal communication) without killing them. Viral isolation from patients who have improved in other ways with AZT may theoretically reflect the presence of such long-lived HTLV-III-infected cells. Thus, although our findings suggest that an antiviral effect was responsible for the improvement observed, one must be aware of the limitations in interpreting the viral cultures. Another possibility is that AZT reduces levels of a virus-related toxic lymphokine that is responsible for certain immunological and clinical abnormalities in AIDS at doses that do not completely suppress viral replication.

Although our findings suggest partial immunological reconstitution in certain patients given AZT, it must be

stressed that the increases in numbers of helper-inducer T cells were often small and were most substantial during the first 2 weeks of intravenous therapy; we cannot be sure that starting with an oral course of therapy will yield similar results. Also, decreases in helper-inducer T cells or total white blood cells in 3 of the patients on the highest dose tested suggest that this dose may be lymphotoxic. Recent observations suggest that the accumulation of phosphorylated AZT within cells may cause a substantial depression of thymidine triphosphate (Balzarini J, Broder S, unpublished); long-term toxicity of AZT may theoretically be reduced by regimens designed to limit the depression of thymidine triphosphate concentrations.

Thus, although the results of present study indicate that some of the patients treated with AZT improved over 6 weeks, we cannot say whether AZT can be tolerated over a long time, whether immunological improvements will be sustained, whether viral drug resistance will develop, or ultimately whether AZT will affect disease progression or survival in patients with HTLV-III-induced disease. These are issues which can be resolved only by appropriately controlled long-term studies.

We thank Mr L. Edward Kirk, Dr Joan Drucker, Ms Jean F. Jenkins, Ms Rose V. Thomas, Ms Susan Tapson, Dr Jerome F. Groopman, Dr Robert R. Redfield, Dr Michael S. Gottlieb, Dr Annette E. Maluish, Mr Roy Overton, Mr Keith Veren, Mr Atul Patel, Dr Robert W. Makush, and the clinical staffs of the National Cancer Institute and Duke University Medical Center for their help.

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