Clinical research

One year open trial of naturopathic treatment of HIV infection class IV-A in men

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The potential effectiveness of a comprehensive program of natural therapeutics was evaluated in 30 men with AIDS related complex (ARC) CDC Class IV-A. Therapeutic strategy was three-pronged: 1) administration of botanical anti-viral medicines; 2) enhancement of immune function, and 3) implementation of psycho-neuroimmunology principles. Treatment included botanical medicine, constitutionally prescribed homeopathic medicines, therapeutic nutrition, hyperthermic hydrotherapy treatments and psychological counseling. Twenty eight men completed the intake procedures; 16 of these completed the 12 month regimen. Over 300 variables were measured every 3 months in each patient including blood chemistries, complete blood counts (including CD4, CD8 and B-Cells) and physical exam findings. Neuropsychological evaluations occurred at entry and completion of the trial.

No patient completing the protocol progressed to AIDS during the course of the study and no patients died. Mortality and disease progression rates compare favorably with placebo data in patients in published AZT trials and are similar to disease progression rates in AZT treated patients. Clinical improvement (decreased fatigue, lymphadenopathy and nightsweats), stable or improved neuropsychological status, and effective control of HIV-related complications (oral thrush, diarrhea and herpes zoster) were observed. Although CD8 cell counts decreased, there was only transient rise in CD4 cell count which then fell below baseline levels by the end of the 12 month study. We conclude that this naturopathic protocol for patients with mildly symptomatic immune deficiency may be useful in slowing progression to AIDS and in providing symptomatic relief.

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INTRODUCTION

ALTHOUGH THE ANTIVIRAL AGENT zidovudine (AZT, *Retrovir*) has been demonstrated to be efficacious in increasing survival rates in patients with acquired immune deficiency (1,2), toxicity may be severe and viral resistance to the compound may develop (1,3). There is widespread interest in the development of non-toxic therapeutics which can be administered on an ongoing basis. Additionally, many HIV patients are self-administering untried compounds. It has been said that the one common feature among "long term survivors" of AIDS is that each of them has used some form of natural or alternative therapy.

The goal of this study (Healing AIDS Research Project 1—HARP 1) was to evaluate a protocol of integrated natural products and naturopathic techniques in men with advanced ARC to determine therapeutic potential.

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MATERIALS AND METHODS

Natural products

The 16 subjects were all prescribed a "basic supplement program." The agent, manufacturer, dosage and rationale included:

Ascorbic acid, powder or tablets (*Bronson Vitamin Co* p.o. to bowel tolerance). Vitamin C has demonstrated *in vitro* activity against human retrovirus (4). It is also a potent antioxidant and useful in reducing the tissue destructive action of oxidation reactions associated with immunological responses to viral and bacterial antigens (5,6) as well as having direct antiviral action (7). Ascorbic acid also increases motility of macrophages (8) and neutrophils (9), as well as stabilizing mast cell membranes (10).

Beta carotene "Beta plex" (*Scientific Botanicals,* 300,000 IU/day p.o.). Beta carotene is the precursor for vitamin A but is selectively converted to vitamin A, thus reducing risk of toxicity. A key element in viral pathogenesis involves the production of free radicals capable of lysing the cell membrane. Beta carotene is an effective free radical scavenger and a potent quencher of singlet oxygen (11). Retinoids have been shown to have significant viricidal activity (12).

Vitamin A deficiency has been associated with decreased thymus activity and decreased number of T and B lymphocytes. Oral administration of beta carotene increased the number of CD4 lymphocytes in human blood (13). Moreover, AIDS patients are at high risk for developing malignancies. High intake of beta carotene reduces the rates of cancers involving epithelial cells (14).

Egg Lecithin "Eggsact" (*Source Natural,* 20 g/day p.o.). In 1985, Sarin and Gallo reported that AL721 had prevented human T cells from becoming infected with the AIDS virus (15). This compound, derived from egg yolk, is composed of neutral lipids (70%), phosphatidylcholine (20%) and phosphatidylethanolamine (10%). AL721 removes cholesterol from viral envelope and the lymphocyte lipid bilayer, thus increasing fluidity of membranes. This action has been hypothesized to inhibit the ability of lipid coated viruses (HIV, Epstein Barr virus and members of the Herpes viral family) from attaching to CD4 receptor sites. At the time of the planning of this study, clinical trials conducted in Israel were yielding promising data (16).

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Multiple vitamin and mineral supplement "Spectrum" (*Naturopathic Formulations,* 2 tid cc) A large proportion of AIDS patients are at nutritional risk. There have been reports of hypochlorhydria (17), protein malabsorption, hypoalbuminemia (18), and abnormal zinc status (19,20). Protein calorie malnutrition and hypoalbuminemia may further impair cellular and humoral immunity as well as phagocytic function. As a result of poor nutritional status, the susceptibility of the host to infections such as *Pneumocystis carinii, Candida,* tuberculosis, herpes and bacterial diarrhea is increased (21). A high potency mineral and vitamin supplement was administered in this study in an attempt to reduce the risk of malnutrition and thus reduce host susceptibility to infection.

In addition to the basic supplement package, 11 of the 16 patients were assigned to the "botanical/ natural product group" and received the following:

Glycyrrhiza glabra (*Western Herbs,* three "00" capsules tid between meals) *Glycyrrhiza* (licorice root) is a widely used plant in both oriental and occidental botanical medicine. Numerous studies have demonstrated its ability to enhance macrophage activity and the endogenous production of gamma interferon (22). Glycyrrhizic acid, one of the major active constituents, inhibits *in vitro* growth of several RNA and DNA viruses including vaccinia, Herpes simplex I, Newcastle, and vesicular stomatitis virus (23,24). Glycyrrhizin sulfate, the sulfated polysaccharide constituent, possesses anti-reverse transcriptase activity and demonstrated significant anti-HIV activity *in vitro* (25,26). *Glycyrrhiza* also has broad spectrum antimicrobial action against *Staphylococcus aureus, Streptococcus mutans, Mycobacterium smegmatis* and *Candida albicans* (27).

Glycyrrhiza also has a hepatoprotectant action via its ability to scavenge free radicals (28). Many patients with AIDS and ARC show elevated liver enzymes in serum and present with a past medical history of hepatitis, both A and B. Hepatoprotection is therefore a goal of therapy and prophylaxis.

Another important medical action of *Glycyrrhiza* involves its anti-allergy and anti-inflammatory effects via affinity of glycyrrhinin and glycyrrhetic acid to glucocorticoid receptors (29). *Glycyrrhiza* strongly inhibits beta reductase activity, thus increasing the half life of circulating anti-inflammatory cortisol (30). Given recently published data suggesting an autoimmune component to the pathogenesis of AIDS (31), reducing general inflammation is considered to be a positive step in health maintenance. *Glycyrrhiza* inhibits phospholipase A2 (32) and thus reduces the inflammatory response to experimentally induced allergic reactions (33). Cell mediated immunity is impaired in AIDS and ARC. Nevertheless, these patients often show elevated sedimentation rates and inflammatory skin reactions such as seborrheic dermatitis and eczema suggestive of systemic inflammation. Additionally, glycyrrhizin has been shown to inhibit and protect against the thymolytic activity and thymic involution caused by cortisone, while enhancing cortisone's anti-inflammatory action (34).

Lomatium dissectum **Isolate** (*Eclectic Institute* 3-5 gtts bid between meals). A plant native to the American western states, *Lomatium* has been used widely by practitioners of traditional native American medicine, herbal medicine and naturopathic medicine. Also known as *Leptotaenia,* it was recognized as a medicinal plant by the native people of Nevada, being used most commonly as a tea for upper and lower respiratory infections, including tuberculosis. *In vitro* tests show moderate bactericidal activity against a number of pathogenic bacteria. Gram positive bacteria showed greater sensitivity than gram negative species (35,36). Although more recent scientific literature identifying the active constituents or their mechanism of action on immune system functioning is unavailable, empirical clinical evidence recommends *Lomatium* in any protocol for treatment of virus associated acquired immune deficiency. Since *Lomatium* is high in furanocoumarins, it is reasonable to hypothesize that it is capable of permeating viral coat and cross linking with viral DNA to prevent transcription (37).

"Astra Isatis", "Astra 10" (*Health Concerns,* 3 capsules tid). This patent Chinese medicine contains the following herbs: *Astragalus, Conodopsis, Glycyrrhiza, Atractylodes, Dioscorea, Broussonetia, Isatis, Laminaria, Bupleurum, Lycium,* and *Cynamorium. Astragalus* and *Isatis* are the two major constituents. *Astragalus* has a reputation among western practitioners of traditional Chinese medicine as an immune enhancer. It is purported to elevate the number of macrophages, enhance T cell transformation and increase phagocytosis (37a). In the treatment of people susceptible to the common cold, *Astragalus* increased the amount of IgA and IgG and induced the formation of interferon by peripheral white cells (37a). This herb also enhanced *in vitro* lymphocyte blastogenesis in white blood cells from both normal patients and cancer patients (37b) and improved T cell function in cancer patients (37c). In traditional Chinese herbal medicine, *Astragalus* is classified as a warm, sweet tonic herb that enhances the function of the SPLEEN and the LUNG. Indications in traditional Chinese medicine include edema, night sweats, skin ulcers, eliminating toxins, abscesses and cancer.

Isatis tinctoria has broad spectrum antibacterial and antiviral action. It has marked inhibitory effect on the influenza virus (37d), as well as antibacterial action against *Staphlococus aureus, Diplococcus pneumoniae, alpha Streptococcus, Hemophilus influenza, E. coli, Salmonella typhi, Shigella dysenteriae* and *Neiseria meningitidis* (37e). In open trials, *Isatis* has been shown to be effective in treating encephalitis B, chickenpox, acute and chronic hepatitis, mumps, influenza, infectious mononucleosis, meningitis and diptheria (37f,37g,37h). According to traditional Chinese medical theory, *Isatis* is a cold herb that clears pathogenic HEAT, and has anti-inflammatory, antipyretic and detoxifying properties. It is indicated in WIND HEAT conditions.

Calf Thymus Extract (*Biotic Research,* 2 capsules (125mg) Oral administration of glandular tissues has been used therapeutically for centuries. The preparations used have typically been tablets of whole gland concentrates or crude extracts. Purported mechanism of action include direct hormonal and/or protein precursor stimulation of endocrine function. Radioactive labelling studies have demonstrated that large molecular weight polypeptide constituents of glandular extracts are absorbed whole and accumulate in target tissues (38).

Several clinical studies and review articles have appeared documenting the biological and therapeutic activity of the thymic factors (39,40). Various thymic peptides and extracts are being used to correct congenital immune deficiencies (41,42) and depressed immunity in cancer patients and patients with herpes (43).

Thymic fractions are capable of restoring some aspects of depressed immunity in AIDS patients and may have long-term value in preventing the progression from asymptomatic status to frank AIDS (39). Thymostimulin, a calf thymus extract, enhanced interferon production in vitro by mitogen stimulated human lymphocytes (44). Administration of thymostimulin to patients with HIV infection has been reported to increase CD4 cell percentages (45) and lymphocyte numbers (46). However, a recently published report of a double blind placebo-controlled trial of Thymostimulin in 25 ARC patients showed no therapeutic effect (47).

Monolaurin (*Cardiovascular Research*, 600 mg tid cc) This is a monoglycerol ester of lauric acid, a 12-carbon fatty acid with demonstrated activity against a number of enveloped viruses (48). It has been hypothesized that esters of lauric acid act to solubilize lipids and phospholipids in the viral envelope and prevent viral attachment to host cell. Clinical studies have shown Monolaurin to be effective against Herpes I and II, Epstein-Barr virus, influenza and cytomegalovirus, all of which share lipid envelope characteristics. HIV shares these envelope characteristics as well (49).

Hypericum perforatum (*Yerba Prima*, three 250 mg tablets qid pc Monday, Tuesday) Hypericin, an active constituent of the plant *Hypericum perforatum* (St. John's Wort) has been long used as a botanical medicine for depression due to its mild monoamine oxidase inhibition (50) and its bactericidal action. In 1988, Meruelo et al. demonstrated, *in vitro* and *in vivo*, the anti-retroviral activity of hypericin (51). Hypericin also blocks HIV syncytia formation (51). The mechanism of antiviral action of hypericin is not known. Unlike AZT and its analogues, it is not a reverse transcriptase inhibitor (52). A Japanese study indicated that an extract of *Hypericum erectum* showed potent antiviral activities against Epstein-Barr virus (53). *Hypericum* also has broad spectrum antimicrobial activity against gram negative and positive bacteria (54).

Other modalities

Hyperthermic hydrotherapy. Artificial fever treatments have long been used to treat viral and bacterial infections. Immersion of patients for 30-40 minutes in whirlpool baths with water temperature at 104° is designed to elevate core temperature to 102°-104° F. Body temperatures above 100° F are viricidal and bacteriostatic. It has been hypothesized that increasing core temperature elevates white blood cell counts and activity, as well as increasing T lymphocyte maturation within the skin. The diaphoresis produced by artifical fever treatments has a detoxifying action which is especially relevant to patients with a history of drug abuse.

Experimental whole body hyperthermia (41-42° C for 1 hr) has been shown to increase the production of cutaneous interleukin-1 in mice(54a). In this study, after a transient fall in IL-1 production, 4 hours after whole body hyperthermic treatment, significant elevations (up to twice control levels) were noted, with a peak at 16-20 hour post treatment. Interleukin-1 represents a family of polypeptides having a pivotal role in the mediation of infectious, inflammatory and immunologic responses, including induction of fever and augmentation of mitogenesis of natural killer lymphocytes, which are involved in both anti-viral and anti-neoplastic responses of the immune system. Whole body hyperthermia has been used experimentally in cancer patients. In one study (54b) of cancer patients, a total of 3 treatments over a 3 wk period, in which core body temperature was elevated by 2° C for 30-60 min with microwave hyperthermia, upregulated the immune system in several ways: Increased the number of peripheral mononuclear cells, increased activity of natural killer T lymphocytes, increased interleukin-1 and interleukin-2 activity and increased CD4/CD8 cell ratios by elevating the number of circulating CD4 cells.

HARP 1 DESIGN & PROTOCOL	
BOTANICAL GROUP	**HOMEOPATHY GROUP**
Basic Supplements (Table 2)	Basic Supplements (Table 2)
Botanical Agents (Table 3)	Individualized constitutional homeopathic prescribing
Twelve hyperthermia treatments (Core temperature to 102 degrees F for 40 minutes; two series of bi-weekly treatments of 3 weeks duration)	Twelve hyperthermia treatments (Core temperature to 102 degrees F for 40 minutes; two series of bi-weekly treatments of 3 weeks duration)
Nutritional counseling and education	Nutritional counseling and education
Psychotherapy (either individual or support group)	Psychotherapy (either individual or support group)

TABLE 1. HARP 1 protocol summary.

HIV is heat labile (55) and has been shown to undergo greater deactivation per unit time at progressively higher temperatures. For example, after 30 min heating in a water bath at 42°C (107.6° F.), 40% deactivation has been reported, and at 56° C (132.8° F.), 100% deactivation (56). Data have suggested that the safe upper limit for hypertheria treatments is 42.0-42.5° C (57). A theoretical basis for predicting HIV inactivation by hyperthermia treatment has been discussed recently in the medical literature (58,59).

Nutrition counseling. Malnutrition is a significant contributory factor in the progression and pathology of AIDS. The immune deficiencies, such as profound depression of cellular immunity and multiple opportunistic infections, are similar to those seen in protein calorie malnutrition. Aside from overall deficiencies in caloric intake, HIV status and AIDS have been associated with deficiencies in vitamin B6 (60) (even in asymptomatic HIV seropositive patients), vitamin B_{12} and folate (61,62). AIDS patients frequently have abnormal Schilling tests indicative of B_{12} malabsorption (63). Long standing vitamin B_{12} malabsorption may begin early in the course of HIV infection and may be related to localization of HIV in cellular reservoirs in the terminal

BASIC SUPPLEMENTS	
NAME (MANUFACTURER)	**DOSAGE**
Ascorbic acid, powder or tablets (Bronson)	To bowel tolerance
Beta Carotene ("Beta Plus" Scientific Botanicals)	5 gtts BID CC 300,000 IU/day
Multiple Vitamin ("Spectrum" NF Formulas; "Optimum" Eclectic Institute)	Spectrum: 2 QID CC Optimum: 2 TID CC
AL-721 Facsimile ("Eggsact" Source Naturals)	20 g. QD with a fat-free meal

TABLE 2. Basic supplement package used in HARP 1.

BOTANICAL GROUP PROTOCOL		
MONTH	**NAME (MANUFACTURER)**	**DOSAGE**
1,2,3	Glycyrrhiza glabra (Western Herb, Seattle, WA)	3 capsules TID between meals
4,5,6	Lomatium isolate (Eclectic Institute, Portland, OR)	3-5 gtts BID between meals
7,8,9	Astra-isatis (Health Concerns, Alameda, CA)	3 capsules TID
10,11, 12	Thymus Extract (Biotic Research, Houston TX)	2 capsules TID cc
	Monolaurin (Cardiovascular Research, Concord CA)	2 capsules TID cc
11,12	Hypericum (Yerba Prima, Oakland, CA)	"pulsed dose" 3 tablets QID after meals Monday and Tuesday

TABLE 3. Natural products used in botanical group protocol.

ileum (64). Additionally, plasma levels of selenium have been shown to be reduced in HIV patients independent of malabsorption (66). Several studies have demonstrated reduced levels of zinc in sera from HIV-infected patients (67).

Malabsorption and diarrhea are significant complications in AIDS (65,68,69). Diarrheal illness occurs in greater than 50% of people with AIDS (65). A recent study of jejunal biopsy specimens showed that 62% of patients with AIDS presenting with chronic diarrhea and weight loss had partial villous atrophy (65). The malabsorption is usually secondary to diarrhea, nonspecific intestinal inflammation of the bowel or intestinal infections which contribute to nutrient deficiencies. However, it has been speculated that HIV alone may affect the structure and function of the small intestine and mucosal immunity (70). HIV has been demonstrated in the cells of the intestinal mucosa by molecular hybridization techniques (64).

There are three sources of malnutrition in AIDS: 1) eating disorders, 2) disturbances in intermediary metabolism and 3) nutrient malabsorption. Supporting evidence for the changes in intermediary metabolism includes the finding of elevated fasting triglyceride levels (71). Hyperlipidemia, with accumulation of very low density lipoproteins has been observed in various acute and chronic infections, while starvation decreases fasting serum triglyceride levels. Hypertriglyceridemia results from decreased lipoprotein lipase activity, increased fatty acid synthesis and esterification, and increased lipoprotein synthesis in the liver. A follow-up study showed that hypertriglyceridemia in AIDS was associated with increased serum concentrations of alpha interferon (72). Elevated triglyceride levels may also be indicative of hypermetabolism as well (72a).

In addition to disordered triglyceride metabolism, studies have documented xylose and fat malabsorption in HIV-infected persons, even in the absence of diarrhea (68). Lactase deficiency is common as well (64).

It has been hypothesized that essential fatty acid deficiency associated with malabsorption may lead to immune dysfunction and increased susceptibility to infections (70). Immune function is tightly coupled to essential fatty acid metabolism and essential fatty acid deficiency leads to immune dysfunction. For example, neutrophil chemotaxis and oxidative metabolism, functions of vital importance in microbial killing, are markedly reduced in essential fatty acid deficiency (73). A recently published open trial demonstrated clinical improvement in 29 patients with ARC and

AIDS who were treated nutritionally for 6 months. Treatment consisted of a balanced nutritional supplement (vitamins, minerals and amino acids), aloe vera juice and essential fatty acids (linoleic acid, gamma linolenic acid, eicosapentaenoic acid, and docosahexaenic acid, with d-alpha tocopherol). Clinical improvement and a decrease in p-24 core antigen activity was observed (74).

Overconsumption of certain nutrients may have a deleterious affect on the immune system. Oral consumption of 100g portions of simple carbohydrate significantly decreases neutrophil phagocytic activity and lymphocyte transformation for up to 5 hours (75,76). High fat diets with increased levels of cholesterol inhibit gastric acid secretion, and increase free fatty acids and triglycerides. These in turn inhibit lymphoproliferative response to infection, response to mitogens, antibody production, neutrophil chemotaxis and phagocytosis (77-80). Alcohol and caffeine are also known immunosuppressants (81,82).

The normal bowel is not completely impermeable to macromolecules. As much as 2% of food protein ingested remains intact and reaches the systemic circulation thereby stimulating antigenic activity (83,84). Impaired protein digestion contributes to the macromolecule load on the gut and increases antigenic stimulation. Intestinal permeability is increased in AIDS patients due to repeated antibiotic treatment for STDs, pathogenic microbes and parasites, nonspecific inflammatory changes, neoplasms and disruption of rectal membranes by anal intercourse.

The Kupffer (reticulo-endothelial) cells of the liver play a crucial role in protection against enteric antigens reaching the systemic circulation. They function by phagocytizing immune complexes and other antigenic material absorbed from the gut and transported via portal circulation to the liver. In chronic liver disease, increased levels of circulating immune complexes pose serious problems (85). HIV seropositive patients have several predisposing factors for liver disease. These included frequent histories of hepatitis, IV drug use and treatment with chemotherapeutic agents for infections and neoplasms (86). Elevated liver enzymes (SGPT and SGOT), alkaline phosphatase and hepatomegaly are common findings in AIDS patients.

The gastro-hepatobiliary picture of the AIDS patient is one of increased gut-derived antigenic load resulting in chronic immune system challenge and stimulation, with its associated chronic stimulation of T cells in particular (87). Replication of the HIV virus in lymphocytes is dependent on chronic or repeated antigenic stimulation. Thus, the gut-derived antigens may be an important susceptibility factor operating in the progression of disease.

Patients were instructed to include the following guidelines in their daily nutritional intake:

Whole foods - more nutritionally dense foods with fewer additives. Emphasize organic and fresh proteins and vegetables.
Reduce simple sugars and replace with complex carbohydrates which have higher zinc levels.
Minimize polyunsaturated and saturated fats while emphasizing mono unsaturated fats with special emphasis on omega 3 essential fatty acids.
Eat numerous small meals throughout the day to maximize absorption of nutrients.
Maintain the following proportions of nutrients: 65% complex carbohydrates, 15% protein, 20% fat.
Fresh fruits and vegetables need to be thoroughly cleaned; steam lightly to kill bacteria and parasites.
Increase variety of foods to decrease antigenic load and secondary mucosal inflammation to insure maximal nutrient absorption.
Eliminate alcohol, caffeine and theophilline intake.

Psychological Counseling

We designed this study to to devote special attention to examining the effects of psychology on immune function. There is evidence that the central nervous system and the immune system are intimately linked. Lymphocyte cell membranes contain receptor sites for diverse neuropeptide neurotransmitters secreted by the brain. Monocytes can chemotax to numerous neuropeptides via processes mediated by distinct receptors indistinguishable from those found in the brain. Neuropeptides and their receptors join the brain, endocrine system and immune system in a complex network of communication between brain and body. Pert et al. have suggested that this complex network may represent the biochemical substrate of the psychosomatic basis of emotion (88,89).

Patients were requested to begin some form of individual or group psychotherapeutic process if not already doing so. Three members of the team (EM,CL,PM) ran a weekly "HARP Healing Circle." This support group focused on open discussion of emotional, physical and spiritual issues as well as meditation and positive affirmation strategies modeled after the work of Louise Hay.

There is a relationship between emotional states, the immune system and rates of progression of disease in cancer patients (90). It is reasonable to hypothesize, based on the emerging data from the field of psychoneuroimmunology, that emotional states and cognitive patterns may have an impact on immune function in patients with acquired immune deficiency. Moreover, because of the immune deficiency which characterizes AIDS, the function of the immune system may be even more heavily influenced by CNS states and their associated neuropeptide secretory patterns.

SPECIFIC INTERVENTION	
Diarrhea	Berberine alkaloids (Hydrastis, Berberis) Garlic (Allium sativa) Lactobacillus acidophilus
Weight loss	Free form amino acids
Oral candidiasis	Sorbic acid mouthrinse (Orithrush), Lactobacillus acidophilus, garlic
Herpes Simplex	Glycyrrhizic acid (Herplic) topically High lysine/ low arginine diet
Compromised liver function	Hepatoprotectant antioxidants (Silymarin, Catechin) Nutritional counselling
Upper respiratory infection	Expectorants (Elecampagne) Immunomodulators (Echinacea)
Herpes Zoster	Glycyrrhizic Acid (Herplic) topically Supplemental vitamin B12
Prostatitis/ UTI	Antibacterials (Hydrastis, Uva ursi, Chimaphilia) Beta-sitosterols (Serenoa)
Skin rashes	Calendula, Comfrey and Echinacea creme Essential Fatty Acid supplementation Homeopathic prescribing Supplemental zinc, retinoids (Vitamin A), or biotin

TABLE 4. Symptom-related intervention.

Based on these psychoneuroimmunological data and principles, we hypothesized that emotional support from group or individual work, stress reduction techniques, meditative states and positive emotional and cognitive states would be beneficial in the optimal functioning of the cellular immune system.

PROCEDURE

Patients

Thirty two men meeting CDC class IV-A definition were enrolled in the study between October 1988 and May 1989. Inclusion criteria included lymphadenopathy in two or more noncontiguous sites either currently or during the 3 months prior to entering the study, and at least one of the following symptoms during the previous 6 months: Herpes zoster, oral candidiasis, fever, night sweats, weight loss of greater than 10 lbs, or chronic diarrhea. Patients currently taking AZT were excluded from the trial. Two patients had previously received a regimen of AZT. All patients were male and at least 18 years of age. Mean age was 34.66 (±6.34). All were homosexual. Of the 28 patients who completed initial intake procedures, 27 were and continued to be employed full time and/or in graduate school. Employment ranged from skilled to professional positions, with approximately equal distributions.

Nine out of 30 patients (30%) presented with oral candidiasis at entry; 19 of 30 patients (63%) presented with chronic diarrhea; 9 out of 30 (30%) had recurrent fevers and 15 out of 30 patients (50%) complained of night sweats. A history of liver disease (hepatitis A or B) was found in the histories of 13 of 30 patients (43%) and 30% of the patients presented with abnormal liver function tests (mean SGOT of 33.8 (±10.6) and mean SGPT of 45.7 (± 23.7). Sixteen of 30 patients (53%) had a history of gonorrhea and 9 of 30 patients (30%) had a history of syphilis.

Immune panels and blood chemistries were completed on all patients at entry. Average CD4 lymphocyte count was 691 (± 346, range 70-1435) and average CD8 lymphocyte counts were 1359 (± 551, range 476-3289). Most patients had normal white and red blood cell counts. Only one patient (A15) showed low RBC counts and only two patients (A1 and A7) showed low WBC counts. Mean corpuscular volumes (MCV) were within normal range for all patients. Four of 30 patients (13%) presented with differential percentages of lymphocytes beyond normal range. While neutropenia was not observed in any patient at entry, 4 patients (13%) presented with abnormally high differential counts of neutrophils. Nine of 30 patients (30%) showed high sedimentation rates at entry as well.

Patients were deemed "evaluated" if they completed the full 12 months of the study. There were 16 such patients. Two patients (A2, A11) died within two weeks of enrolling in the study; A2 of acute liver failure and A11 by suicide. A28 enrolled but did not initiate treatment. Sixteen patients completed the full 12 months of the trial. Of the remaining 13 patients who did not complete the full 12 month trial, 1 patient completed 1 month, 3 completed 2 months, 3 completed 3 months, 1 completed 4 months, 1 completed 5 months, 1 completed 7 months, 2 completed 8 months, and 1 completed 10 months.

Prior to enrolling in the study, patients were screened on the basis of an initial interview, physical exam and HIV

antibody test. Patients who fulfilled entrance criteria signed an informed consent form and were randomly assigned to either the botanical medicine or homeopathic medicine regimen. Two patients who were assigned to the homeopathy group refused to participate unless they received the botanical medicine regimen and were permitted to change to that group. *Table 1* summarizes the medical protocols for patients in the botanical medicine and homeopathy groups respectively. *Tables 2 and 3* present specific doses and sources of supplements and botanical medicines.

Procedure

Prior to initiating treatment each patient underwent a 6 hr neuropsychological assessment of cognitive and emotional status, a complete physical exam, an interview concerning subjective state of health. Blood samples were drawn for a complete blood count and to assess blood chemistry and immune status. These blood tests were repeated every three months while physical exams and interviews were conducted monthly. Neuropsychological assessments were completed at 0 and 12 months.

At each monthly appointment clinical symptoms were assessed by the clinician using a scale from 0 to 5 (0 = no symptom present; 1 = slight, 2 = mild, 3 = moderate, 4 = severe, 5 = debilitating). *Table 5* lists the symptoms assessed in this manner.

At the end of the 12 month study, the medical director of the study conducted exit interviews with each patient, reviewing their medical and emotional progress and current status. During this interview patients were asked to evaluate the impact of their involvement in the study by answering the following question: How do you feel now compared to how you felt when you first began the study one year ago? Using a scale from 1 to 5 (1 = much worse, 2 = worse, 3 = same, 4 = better, 5 = much better). Patients were asked to answer the above question in terms of both emotional and physical well being.

Six month follow up interviews were conducted with 17 patients following completion of the one year regimen in order to determine current health status, numbers of AIDS defining opportunistic infections, current therapies, satisfaction with study results and reasons for completing or dropping out of the study.

Neuropsychological Assessment

Several published studies (91-95) have consistently delineated the areas of neuropsychological involvement subsequent to HIV-1 infection as cognitive, motor and behavioral. Earlier studies have noted impairments in attention/concentration, verbal and non-verbal memory, abstraction abilities, language skills, speed of processing, visuospatial perception/construction abilities, timed psychomotor tasks, and affective states. Although overlapping, the conditions of dementia (AIDS Dementia Complex) and neuropsychological impairment are not identical. As pointed out by Grant & Heaton (96), "The term dementia refers to moderate or severe mental impairment that, by definition, can be detected with clinical diagnostic methods . . ." The term neuropsychological impairment, however, includes mild neurocognitive deficits which may occur in a considerably earlier stage of HIV-1 infection and are usually detectable only with sensitive and comprehensive neuropsychological test batteries.

CLINICAL ASSESSMENT PARAMETERS	
General	Vitals, Weight, Fatigue, Anorexia, Lymphadenopathy, Night sweats Progress in chief complaint Subjective (1-10) • Physical well-being • Emotional well-being
Respiratory	Colds, Sinusitis, Pharyngitis, Bronchitis, Pneumonia, Tuberculosis
Gastro-Intestinal	Thrush, Herpes, Hairy Leukoplakia, Flatulence, Proctitis, Diarrhea/ Constipation
Genito-Urinary	Cystitis, Pyelonephritis, Syphilis, Chlamydia, Herpes Simplex, Condyloma, Candidiasis, Prostatitis, Non-Gonorrheal Urethritis
Skin	Fungi, Herpes Zoster, Herpes Simplex, Kaposi's Sarcoma, Seborrhea, Eczema

TABLE 5. HARP assessment parameters.

In an effort to assess even mild deficits in as broad a spectrum of relevant domains as possible without being unreasonably fatiguing, the battery described below was administered to 28 patients who were accepted into the Project and, again, one year later to the 16 patients who completed the full twelve-month regimen. Although selection of the individual tests was made prior to the autumn of 1988, it is noted that this battery was in accord with the recommendations of the NIMH WORKSHOP ON NEUROPSYCHOLOGICAL ASSESSMENT APPROACHES held in April of 1990 (97,98).

The neuropsychological battery utilized in this study consisted of the following:

Wechsler Adult Intelligence Scale-Revised (WAIS-R) Vocabulary: Standard set of 35 word definitions ranging from very common to moderately uncommon; scaled score correlates highly with verbal IQ and is considered an indicator of premorbid intellectual abilities (99).

Word Fluency Test (FAS): Measures patient's ability to generate orally a number of words beginning with one of three letters within a one-minute time limit for each letter (100).

WAIS-R Digit Span: Brief test of attention and immediate recall; requires the patient to repeat progressively longer sequences of single digits in the order presented by the examiner and then, in the second part, to repeat them in the reverse order (99).

Paced Auditory Serial Addition Test (PASAT): Test of attention and speed of information processing; four sets of randomized digits between 1 and 9 are serially presented via tape recording with patient required to add the current number to the number which preceded it and to respond with the total; the rate at which the digits are presented increases with each set (101).

Rey Auditory Verbal Learning Test (RAVLT): Measures serial learning of verbal material, as well as delayed recall and recognition; five learning trials for a list of 15 words with an interference trial prior to the delayed recall and recognition (102).

Wechsler Memory Scale-Logical Memory: Measure of learning and recall of logically related verbal material; two brief stories are presented and then verbally recalled to the examiner including as many of the 24 elements of each story as possible; recall portion is repeated after a 30-minute period of unrelated testing (103,104).

Wechsler Memory Scale-Figures: Measure of nonverbal learning and memory; on each of three trials, patient must reproduce an increasingly complex geometric figure from memory following a 10-second study period; recall portion is repeated after a 30-minute period of unrelated testing (103,104).

Benton Visual Retention Test (BURT)-Form C, Administration A: Assesses visual perception, visual memory and visuoconstructive abilities; 10 designs, each containing one or more figures; patient is required to reproduce each design from memory following a 10-second study time (105).

Category Test: Nonverbal measure of complex reasoning and abstraction/conceptual skills; involves sequential presentation of 208 stimulus cards, each associated with a number between one and four; patient must develop hypotheses about the way in which sets of visual materials are related and resist the influence of irrelevant information; requires flexibility to develop new hypotheses as new principles are introduced (106,107).

Wisconsin Card Sorting Test- Level of Conceptualization and Perseverative Errors: Measure of abstraction, conceptualization, perseveration; patient required to match a deck of response cards to one of four stimulus cards according to three successive principles while being informed whether each response is right or wrong but not told the current sorting principle (108).

WAIS-R Digit Symbol: Visuo-perceptual and motor task; requires patient to associate single digit numbers with unfamiliar symbols, drawing the correct symbol below each of nine numbers using the given digit-symbol code and completing as many associations as possible in 90 seconds (99).

Finger Tapping Test: Measure of simple motor speed with upper extremities; patient is required to tap on a key counter using the index finger of his/her dominant, and then nondominant, hand for trials of 10 seconds repeated until four trials are obtained within a range of five taps; score is the mean of the trials for each hand (106,107).

Stroop Color and Word Test - Color and Interference: Measure of cognitive flexibility, complexity and resistance to interference from outside stimuli; requires patient to read columns of three color words (red, green, and blue), then columns of colored Xs (red, green and blue), then columns of color words printed in "other color" ink; each task has a 45-second time limit (109).

Beck Depression Inventory: A 21-item self-administered measure of depression in which the patient rates him/herself on a four-point scale for each item (110).

Taylor Manifest Anxiety Scale: Fifty true-false self-administered items dealing with correlates of anxiety; taken from the MINNESOTA MULTIPHASIC PERSONALITY INVENTORY; raw score can be transformed into t-score (111).

Hardiness Scale: Measures a synthesis of commitment, control, and challenge; self-administered inventory is a composite of scales from five existing questionnaires; 48 items require patient to rate him/herself on a four-point scale and 23 items require a forced choice between two alternatives (112).

Clinical interview: Assessment of patient's present mental status, affect, perceived level of stress, etc.; relevant medical and psychological history; present symptoms, especially neuropsychological history; and, at 12-month evaluation, perceived changes and Project assessment. All procedures were administered in the standard manner.*

The time required for each subset of tests was approximately equal. Two patients were evaluated simultaneously with a rest in the middle and an exchange of examiners. Thus, there was a balanced design with one-half of the patients being administered the WAIS-R subtests, PASAT and Category Test first, then the remainder of the procedures; and the other one-half of the patients being evaluated in the reverse order. This arrangement was utilized for both the initial and the 12-month assessments. The self-administered inventories were completed at the end of each session.

All materials for both evaluations were scored by E.M.

RESULTS

Evaluated vs. unevaluated patients

Seventeen of the original 30 patients were able to be contacted for six month follow up interviews. Thirteen of the 16 evaluated patients (81%) were located for telephone interview, but only 4 of the 14 unevaluated patients (29%) were located. Reasons for dropping from the program, in these 4 patients, included inability to pay (1 patient), dissatisfaction with a component of the protocol (2 patients) and desire to initiate AZT treatment (1 patient) subsequent to a drop in CD4 lymphocyte counts (from 70 at entry to 65 at month 3).

Clinically, evaluated and unevaluated patient groups were similar at entry to the study and prior to initiating therapy. Fever was present in 31% of evaluated patients and 29% of unevaluated patients. Oral thrush was present in 67% of evaluated patients and 38% of unevaluated patients.

* E.M. administered the WAIS-R subtests (Vocabulary, Digit Span, and Digit Symbol), the Category Test, the PASAT, and the clinical interview. C.L. administered all of the other procedures.

Chronic diarrhea was a presenting complaint in 56% of evaluated patients and 71% of unevaluated patients. Night sweats were reported at entry by 56% of evaluated patients and 43% of unevaluated patients.

To answer the question of whether evaluated and unevaluated patients differed in their disease progression, mean duration of HIV infection was determined. Patients were asked during the intake interview when they seroconverted or when they first tested seropositive for HIV antibodies. The average number of years since HIV infection using this approximate method was 2.63 years (± 2.08) in the 16 evaluated patients and 1.96 years (± 1.32) in the 14 unevaluated patients.

CD4 lymphocyte counts were 52 cells lower at entry to the study, on the average, in the patients who did not complete the trial (691 cells/mm^3 ± 264 in evalauble patients and 637 cells/mm^3 ± 409 in unevaluated patients) compared with those who did complete the trial. CD8 cell counts were nearly identical (1377 cells/mm^3 ± 352 in evaluated patients and 1359 cells/mm^3 ± 551) in unevaluated patients).

Of the 16 total evaluated patients, 6 were in the homeopathy group and 10 were in the botanical medicine group. Of the 14 unevaluated patients who did not complete the study, 7 were from the homeopathy group and 5 were from the botanical medicine group.

Clinical changes in 16 evaluated patients

For analysis of treatment outcome in the 16 patients who completed one year of naturopathic treatment, patient data from both groups (homeopathy and botanical medicine) were pooled and broadly classified into several groups.

Category A *(Table A, Figures A1, A2)* presents mean changes in fatigue *(Figure A1)*, lymphadenopathy *(Figure A2)*, fever, night sweats and anorexia. Fatigue and lymphadenopathy were common complaints at entry. Although standard deviations are large, these data indicate a decline in both fatigue and lymphadenopathy during the following 12 months. Fevers, night sweats and anorexia were neither common nor severe in this group of patients but showed a decline as well over the 12 month period.

Category B *(Table B, Figure B1)* describes changes in mean total respiratory symptoms. These data reflect the presence and severity of all respiratory symptoms assessed: Colds, sinusitis *(Figure B1)*, pharyngitis, bronchitis and pneumonia. Sinusitis was the most common respiratory complaint and was present at entry in 12 of 16 patients (75%). Resolution of sinusitis occurred in 8 of those 12 patients by the last two months of the trial. Pharyngitis and bronchitis were both rare and mild and no patients developed pneumonia.

Category C *(Table C, Figures C1,C2)* reports changes in mean total symptom severity for a variety of gastrointestinal symptoms over the 12 month trial. Oral thrush (38%), diarrhea (69%) and flatulence (89%) were the most common complaints at entry. While the average severity in diarrhea *(Figure C1)* and flatulence was reduced during the treatment period, oral thrush *(Figure C2)* was resolved in only 3 of the 4 patients who initially presented with this complaint. Three patients were free of thrush initially, developed it during the course of the trial, and were treated into remission *(Table 4)*. Oral herpes simplex lesions were present at entry in 44% of patients; in 3 of those 7 patients lesions did not reappear during the duration of the treatment period. Four of the 7 patients had apparent lesions at the beginning as well as the end of the study. Four out of 16 patients presented with proctitis; improvement was observed in 3 of these 4 patients. Two patients developed proctitis during the study, with resolution in both cases.

Few genitourinary symptoms (cystitis, nephritis, prostatitis, urethritis, chlamydia, herpes simplex, condyloma, gonorrhea or syphilis) were present at entry, nor developed during the study, therefore the data are not presented.

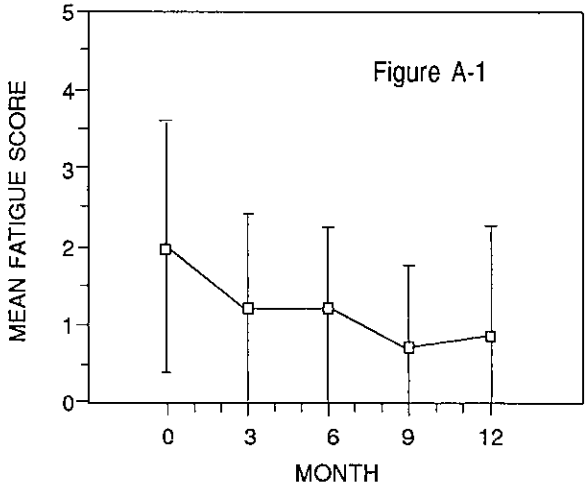
Category D *(Table D, Figure D1, D2)* presents changes in skin symptoms over the course of the study. Acne (69%), skin fungal infections (56%), seborrhea (31%) and eczema (19%) were the most common skin complaints at entry. Two patients presented with Herpes Zoster *(Figure D1)* at entry and four patients developed zoster lesions during the course of the trial. Resolution of zoster lesions occurred in 2 of these 4 patients. Skin fungal infections *(Figure D2)* resolved in 4 of 9 patients who presented with this complaint at entry. One previously asymptomatic patient developed fungal lesions during the course of the study. Seborrhea resolved in only one of 5 patients. Four initially asymptomatic patients developed seborrhea during the study. Every case resolved within 1 month of appearance. *Table 4* lists the specific treatments for a variety of complaints. Acne (4 patients) was the most common skin complaint on entry. An additional 8 patients developed acne during the course of the study. Eczema was present in 3 patients, of which 2 improved during the study. An additional 4 patients developed eczema during the study. Three of these patients had complete resolution before the end of the study. No patients presented with or subsequently developed Kaposi's sarcoma during the trial.

Changes in laboratory values in 16 evaluated patients

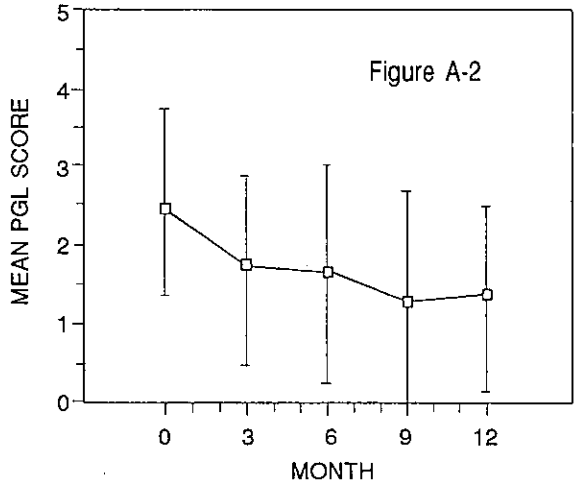
Category E *(Table E, Figures E1-E6)* presents changes in biological markers of immune status (CD4, CD8, CD4/CD8 ratio, WBC, total lymphocyte and total T lymphocyte con-

Interval (Months)

		0	3	6	9	12
Fatigue	MEAN	2.00	1.18	1.19	.75	.94
	S.D.	1.55	1.33	1.17	.93	1.48
PGL	MEAN	2.562	1.75	1.69	1.25	1.31
	S.D.	1.15	1.39	1.45	1.29	1.30
Fever	MEAN	.38	.38	.25	.06	.06
	S.D.	.62	.62	.58	.25	.25
Night sweats	MEAN	1.00	.56	.25	.25	.31
	S.D.	1.32	.73	.45	.45	.79
Anorexia	MEAN	.38	.13	0	.06	.06
	S.D.	1.03	.34	0	.25	.25



CATEGORY A/ Constitutional symptoms. *(Table A)* Mean scores for generalized clinical symptoms. *Figure A1:* Mean fatigue score. *Figure A2:* Mean PGL (persistent generalized lymphadenopathy) score. (n=16). **NOTE:** S.D.=standard deviation.



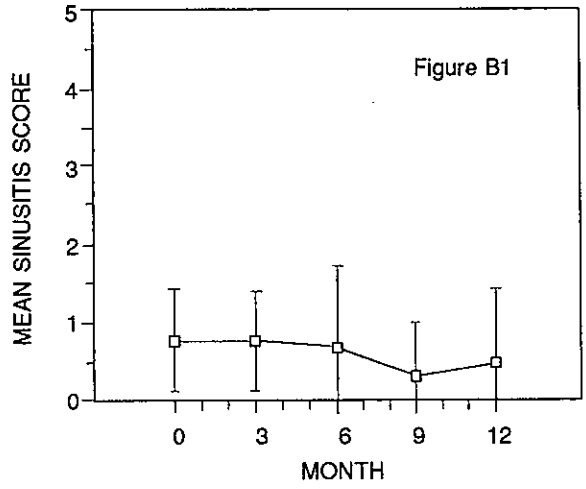
centrations). Mean CD4 cell counts at entry were 691 cells/mm³ (±346). An increase of 84 cells was observed in average CD4 cell counts at 3 months, the average CD4 cell count increasing to 775 (±433, *Figure E1).* However, this rise in CD4 cells was only transient. At 6 months average CD4 cells counts had dropped below baseline and continued falling throughout the duration of the trial. At 12 months average CD4 cell counts were 452 (±293), an average drop of 254 cells over the course of the year. Only two of the 16 evaluated patients showed an increase in CD4 cell count between entry and 12 months (A26, A27). A26 had a CD4 cell count of 181 at entry and 195 at month 12. A27's CD4 cell count was 966 at entry and 1139 at month 12. Mean % CD4 cell counts were 26% at intake and dropped to 22% by month 12. No clear association was seen between rate of decline in CD4 cell counts and STD history (gonorrhea, syphilis, hepatitis B).

Mean CD8 cell counts*(Figure E2)* also fell: A mean of 1377 (±352) at entry and 1099 (±365) at month 12. The average CD4/CD8 ratio *(Figure E3)* also fell slightly from a mean of .55 at entry to .42 at month 12.

Mean white blood cell counts *(Figure E4)* were within normal limits at entry and remained so throughout the 12 month trial although a trend towards decline in total WBC's was observed. Mean total lymphocyte counts and total T lymphocyte counts were also within normal limits at intake and after 12 months of treatment despite a similar decline over the duration of the study *(Figures E5, E6)* . While average B lymphocyte counts were always within normal range, a slow but steady increase over the 12 month trial was noted.

Category F *(Table F, Figures F1, F2)* presents changes in red blood cell (RBC) counts, hematocrit, mean corpuscular volume, sedimentation rate and complete blood count differential data. Mean RBC counts, % hematocrit and mean corpuscular volume remained steady and well within normal limits throughout the duration of the study. The CBC differential revealed that monocytes, lymphocytes, neutrophils, eosinophils and basophils as well remained within normal limits throughout the trial. A trend towards an increase in % monocytes was observed *(Figure F1)* although values were never outside the normal range. Sedimentation rate, however, showed abnormalities. Mean sedimentation rate *(Figure F2)* was 12.4 (±9) at entry with

		Interval (Months)				
		0	3	6	9	12
Respiratory	MEAN	.40	.39	.30	.09	.30
	S.D.	.30	.37	.25	.14	.19
Sinusitis	MEAN	.75	.75	.69	.31	.50
	S.D.	.68	.68	1.08	.60	.89



CATEGORY B/ Respiratory symptoms. *Table B:* Mean respiratory scores. *Figure B1:* Mean sinusitis score. (n=16)

normal range for men being 0-10. At month 3, sedimentation rate spiked to 39.3 (± 26.6) and in succeeding months dropped from this high value but remained higher than the normal range. At month 12, mean sedimentation rate was 20.1 (± 11.6).

Category G *(Table G, Figures G1-G3)* presents assessment results for a variety of blood chemistries. Kidney, thyroid, electrolyte and cardiovascular function were normal in the 16 evaluated patients. The only abnormal values were liver enzymes and blood triglyceride levels.

Category G presents changes in blood chemistry values which were abnormal either at entry or became abnormal during the study in the 16 evaluated patients.

Liver function tests revealed high but steady mean alanine aminotransferase (SGPT, *Figure G2*) levels. Mean aspartate aminotransferase (SGOT, *Figure G1*) levels were normal at the beginning of the study and remained so throughout. However, 4 patients presented at entry with high SGOT. Two of these four patients showed decreased SGOT during the study. SGOT levels in the other 2 patients remained high, but did not increase. SGPT levels were high at entry in 6 out of 16 patients (mean = 41.8 ± 21). Three of these 6 patients showed improvements in SGPT, while SGPT levels in 3 other patients remained unchanged during the trial. No clear association was found between a history of hepatitis and abnormal liver function tests in this group of patients.

Cholesterol levels at intake were low in 4 of the 16 patients (A13, A15, A18, A30) and high in 2 patients (A20, A26). Of the 4 patients with low entry cholesterol levels, only A18's level increased to within normal limits during the duration of the trial. The two patients presenting with abnormally high cholesterol values (A26 and A28) showed decreases to within normal range during the study period.

Triglyceride levels *(Fig. G3)* were abnormally high in 6 of the 16 patients at entry and in 9 of the 16 patients at month 12. Four of these 9 patients developed hypertriglyceridemia during the study; 4 other patients of the 9 retained their hypertriglyceridemic status during the study, and 1 of the 9 patients with high triglyceride levels at entry showed decreased levels to within the normal range at month 12. Mean value at entry for all patients was 159 (± 119) and 204 (± 140) at month 12.

Blood albumin levels began within normal limits and remained so throughout the duration of the study. However, a trend towards decreased levels was observed during the course of the study. Mean albumin levels at entry were 4.24 (± .22) and 3.89 (± .22) at month 12.

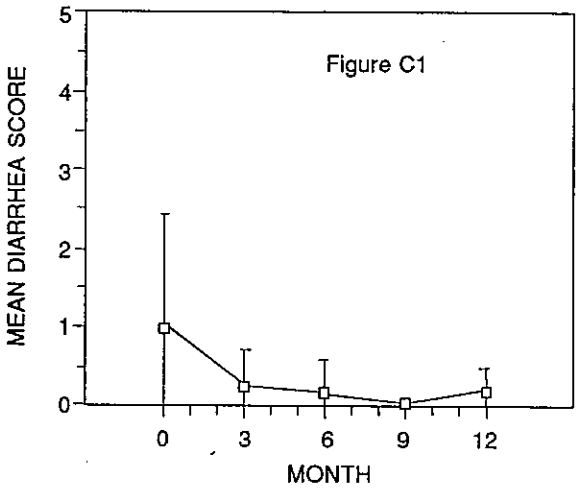
Neuropsychological Assessment

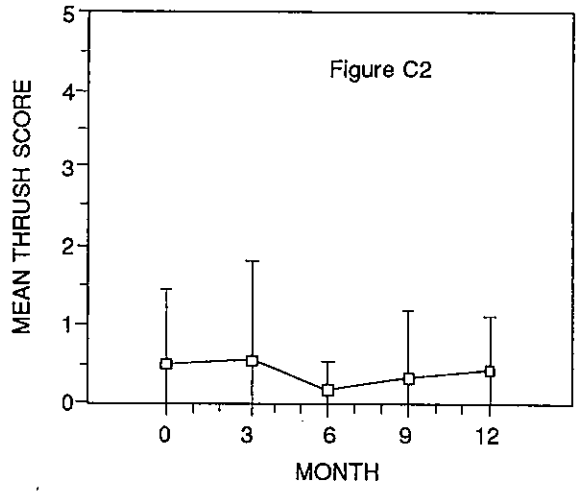
Mean performance on the neuropsychological and psychological measures *(Table 6)* were compared for initial and 12-month assessments. Student's t test was utilized to interpret the significance of differences between means; ratios were computed using the formula for correlated data (113,114). Because there were no a priori hypotheses regarding direction of outcome, a two-tailed test of significance was utilized throughout.

As can be seen from *Table 6*, there was a statistically significant difference between mean performances on 10 of the 21 measures. All 10 - Vocabulary, PASAT (number correct and mean processing rate), BURT (errors), Nonverbal Memory (immediate and delayed), Category Test, and Tapping (preferred hand) - reflect improved performances from initial to final assessment.

Mean performance on the remaining 11 neuropsychological variables evidence improvement, though on 8 of them to a nonsignificant degree. The three exceptions were on measures of immediate and delayed memory for logically related, verbal material and delayed recall on a task

		Interval (Months)				
		0	3	6	9	12
G.I. Symptoms	MEAN	.57	.34	.23	.21	.30
	S.D.	.44	.33	.24	.21	.23
Diarrhea	MEAN	1.00	.25	.19	0	.13
	S.D.	1.41	.45	.40	0	.34
Flatulence	MEAN	1.44	1.06	.81	.56	.81
	S.D.	1.32	1.12	1.22	.89	1.05
Thrush	MEAN	.50	.56	.19	.31	.38
	S.D.	.97	1.32	.54	1.01	.89





CATEGORY C/ Digestive symptoms. *Table C:* Mean gastrointestinal scores. *Figure C1:* Mean diarrhea score. *Figure C2:* Mean thrush score. (n=16)

of serial verbal learning. Nonsignificant improvement can also be seen in the self reports of depression and anxiety but not of hardiness.

Mean performance on all neuropsychological, psychological, and demographic (age, education, and months since first positive HIV test), measures were also compared for initial assessment of those who completed the one-year study (n=16) and those who did not (n=12). Again, Student's t was utilized to interpret significance of differences between means. F-tests for differences between variances were nonsignificant, thereby allowing for the use of pooled variances, for all measures except the WAIS-R Vocabulary and the Stroop Interference. Since the F-tests for those were significant, the standard errors of the two means were used to obtain the standard error of the difference between the means.

No significant difference in the performance of the two groups was found on any of the variables with the exception of depression. On that measure, the 12 patients who did not complete the one-year regimen reported themselves to be more depressed, initially, than the patients who did complete it, to an extent that was statistically significant beyond the $p<.05$ level of probability. In all other respects, the two groups performed the same on all measures and, for purposes of this study, are considered to have been drawn from the same population.

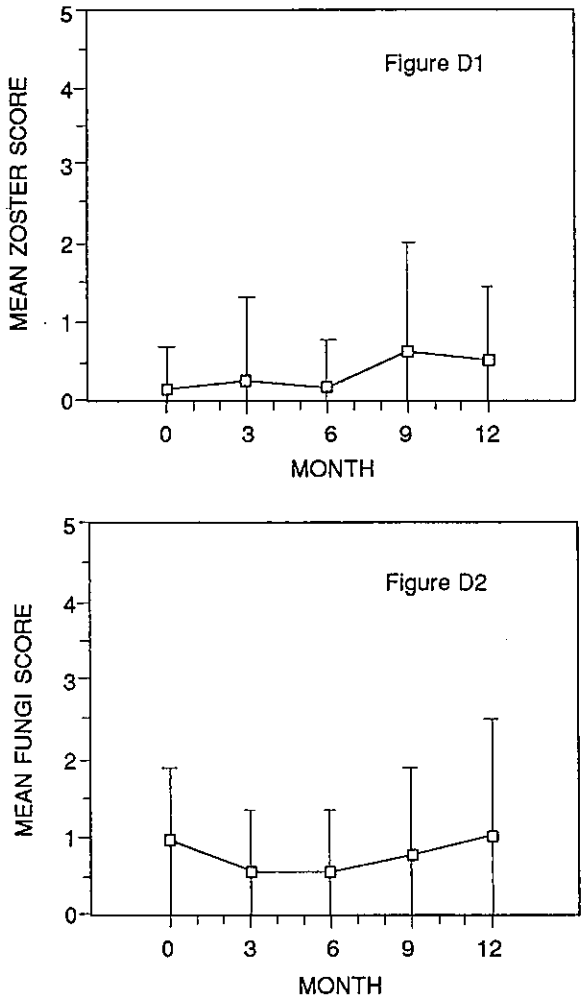
Clinical interviews at the twelve-month evaluation included self reports of changes, if any, in 15 aspects of daily life as well as how each assessed the personal impact of having participated in the study. Responses were grouped according to positive, negative or no change for each aspect. A change was considered positive if it were in a direction viewed by most professional caregivers as promoting/contributing to health, eg. reduction in intake of alcohol, drugs, caffeine, sugar; fewer work absences; better nutrition; more emotional stability, etc.

Patient self-assessment

At the completion of the 12 month participation in the study, each patient was asked to assess both physical and emotional changes since they entered the program on a scale of 1-5. Data were collected for all 16 evaluated patients. All but one patient reported doing either "better" or "much better" both physically and emotionally after one year of participation in the study. A16 reported feeling "worse" physically (score

		Interval (Months)				
		0	3	6	9	12
Skin	MEAN	.29	.21	.28	.31	.36
	S.D.	.31	.18	.19	.28	.34
Acne	MEAN	.44	.56	.75	.56	.44
	S.D.	.81	.89	.93	.73	.73
Fungii	MEAN	.88	.50	.50	.69	1.00
	S.D.	1.03	.89	.89	1.20	1.46
Zoster	MEAN	.13	.25	.19	.56	.38
	S.D.	.50	1.00	.54	1.41	1.03
HSV	MEAN	.25	.06	.13	.19	.19
	S.D.	.58	.25	.50	.75	.75
Seborrhea	MEAN	.31	.25	.50	.38	.31
	S.D.	.60	.68	.82	.72	.79
Warts	MEAN	.25	.13	.25	.25	.38
	S.D.	.45	.34	.58	.78	.72

CATEGORY D/ Skin symptoms. *Table D*: Mean skin pathology scores. *FigureD1*: Mean zoster score. *Figure D2*: Mean fungi score. (n=16)



= 2), but "much better" emotionally. Mean assessment for all 16 patients regarding how each felt at the end of their 12 month treatment, compared to when he first came to the clinic was as follows: "Physically" mean score was 4.44 (± .8); "emotionally" (4.6 ± .5).

Botanical medicine vs. homeopathy

Category H *(Figures H1-H6).* Five of the 16 evaluated patients received homeopathic prescriptions with monthly follow up visits with a single physician throughout the study year. Comparison of treatment efficacy between botanical medicine and homeopathy is difficult because only 5 patients were in the homeopathy group and because large differences existed in mean entry CD4 cell count between the two groups. Mean CD4 cell count in the homeopathy group (n=5) was 501 cells/mm^3 (± 283), while mean CD4 cells count at entry in the botanical group (n=11) was 822 cell/nm^3 (± 255). Figure 8 presents the changes in CD4 and CD8 cells in patients receiving homeopathy vs. botanical medicine over the 12 months of the study.

Neither homeopathic nor botanical medical treatment prevented declines in CD4 cell counts. However, there was no transient rise in CD4 cell counts at 3 months in the homeopathic group as there was in the patients receiving botanical medicine. It is possible that this transient rise in CD4 cell counts seen in the botanical medicine group was due to the effects of *Glycyrrhiza glabra*, the botanical medicine administered during the first 3 months of trial. CD8 cell counts were similar at entry between the two groups although they dropped to lower levels in the homeopathic group compared to the botanical medical group.

Symptomatic improvement was similar in the two groups. Category H also shows changes in sedimentation rate and serum levels of SGPT *(Figure H3).* Sedimentation rates were initially higher in the homeopathic group and steadily increased by the same slope as the botanical group *(Figure H6).* Triglyceride levels were similar initially and rose to similar levels by the end of the one year trial in both

groups. While SGPT levels were equivalent at entry in the two groups, they were considerably higher at 12 months in the homeopathy group *(Figure H4)*.

Comparison of results with published zidovudine trials

The efficacy of this naturopathic protocol was determined by comparing previously published clinical trials of zidovudine in similarly ill patients to the result observed with the participants of this study. Unfortunately, there is little current data available on mildly symptomatic class IV-A HIV infected patients with mean CD4 counts >500 mm^3.

A double-blind, placebo-controlled multicenter trial of zidovudine in mildly asymptomatic HIV patients was conducted by the AIDS Clinical Trials Group (115) and published in 1990. Rate of progression to a "critical event" (advanced ARC, AIDS or death) was measured. AIDS related complex was defined as the presence of two or more specified symptoms and a CD4 count< 200mm^3. Of the patients in this AZT trial with CD4 counts between 500-799 mm^3, approximately 3% of those receiving 1200mg AZT daily developed a critical event within an average follow-up interval of 11 months. Approximately 2% of mildly symptomatic patients receiving placebo developed a critical event within that time. The patient population treated in HARP 1 had a 0% progression rate to AIDS and a 0% progression to ARC using the definition in the AIDS Clinical Trials Group study, although 3 of 16 patients developed oral thrush during the course of the trial which was absent at entry. With such a small sample size it would be impossible to determine whether the difference between HARP 1 and the larger placebo-controlled study is meaningful.

A similar 1990 trial (116) of zidovudine in asymptomatic HIV infection in patients with CD4 counts < 500 mm^3 showed a progression rate of 7.7% in patients receiving placebo and reduced progression rates of 2.4% in patients receiving 500mg AZT, and 3.1% in patients receiving 1500mg AZT. While these data are not comparable to the HARP 1 data (CD4 counts were higher in HARP 1 upon entry), it illustrates progression rates to AIDS within 55 weeks of follow-up in initially asymptomatic patients.

Although the numbers in the HARP 1 study are too small to permit a comparision with conventional HIV standard of care, progression rates to AIDS in this small sample of patients was negligible and compares favorably to placebo data in patients in published AZT trials and is, at least, no worse than progression rates with AZT.

DISCUSSION

The data generated by this small open one year trial of natural medical treatment of men with class IV-A AIDS Related Complex suggest amelioration of both specific and constitutional symptoms. The lack of toxic or adverse reactions is demonstrated by stable red and white blood counts and is buttressed by patients' self report of an increase in subjective states of well being. Clinical improvements were attained without the adverse reactions typically associated with AZT administration (macrocytic anemia, neutropenia, elevated liver enzymes, nausea, anorexia).

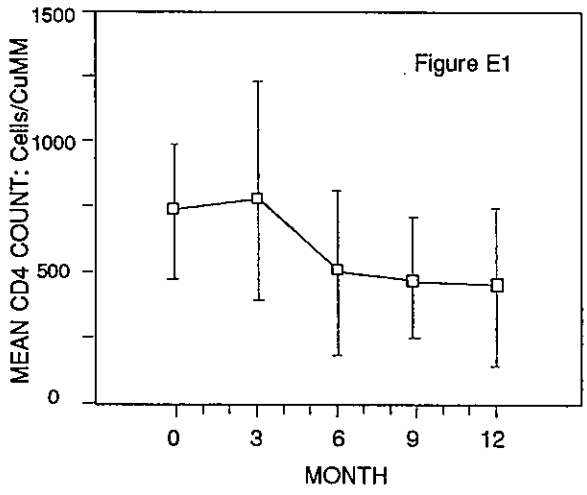
The fact that mean CD4 cell count was elevated only transiently and declined by the end of the one-year trial suggests that immune function was not restored and there was no reversal of disease. CD4 cell counts dropped an average of 248 cells/mm^3 over the course of the year in the 16 evaluated patients. This raises the question of whether this decline was accelerated over the drop of 60-100 cells anticipated by most physicians within a year's time. However, there is some evidence that 2 years prior to the development of AIDS involves a drop from around 500 cells/mm^3 down to 100-200 cells/mm^3 (117). Presently there is insufficient data to assess whether the rate of CD4 cell loss in these patients was greater than patients who are untreated or who are receiving antiviral chemotherapy.

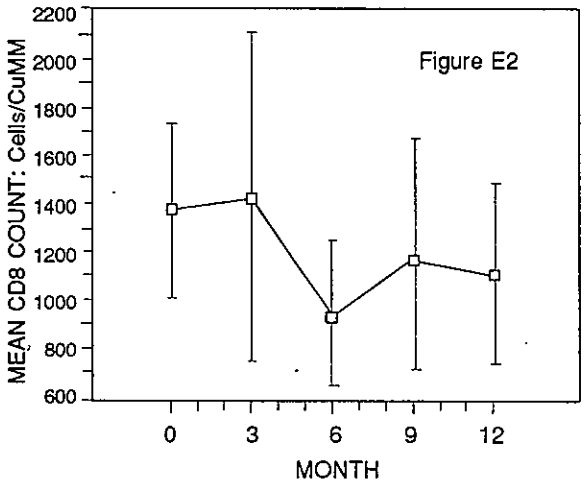
The role of CD4 cells and the human immunodeficiency virus in the genesis and progression of acquired immune deficiency is still not clear. Data have been published that demonstrate that HIV seronegative patients were as likely as seropositives to have abnormal immunological tests (118). Some authors have suggested that the strongest association with prognosis is a recent history of sexually transmitted disease. As high as 10% of HIV seronegative homosexual men have in vitro immunological abnormalities and these are correlated with the number of sexually transmitted infections in the history of the patient (118,119).

Decline in CD4 cell counts following a transient rise at 3 months is a common finding across several published clinical trials using diverse therapeutic agents. This phenomenon may be the result of a placebo effect. If so, it reflects the powerful impact that psychological state can have on immune parameters. However, the transient rise in CD4 cell counts was seen more clearly among the patients receiving botanical medicine. This suggests that the particular botanical medicine used during the initial 3 months, *Glycyrrhiza glabra*, was responsible for this transient rise. A single agent trial utilizing *Glycyrrhiza* solid extract is required to answer this question.

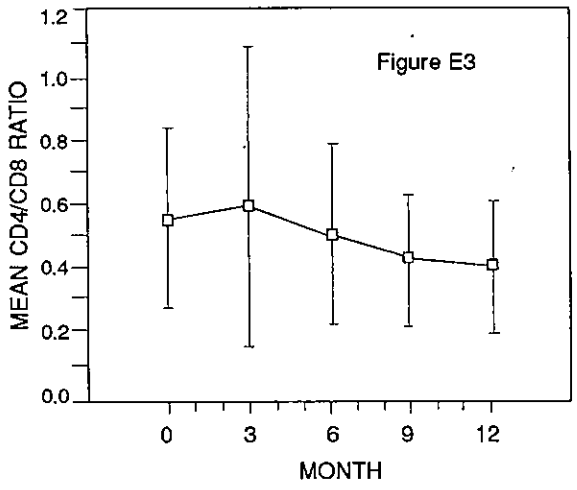
Neuropsychological results were quite favorable, to the extent that they are comparable with other studies in the literature. Most other studies have utilized a cross-sectional design, comparing groups of patients in various stages of HIV-1 infection as classified by the CDC (1987). Although the exact incidence and extent of neurocognitive impairment subsequent to infection is unknown, these studies have

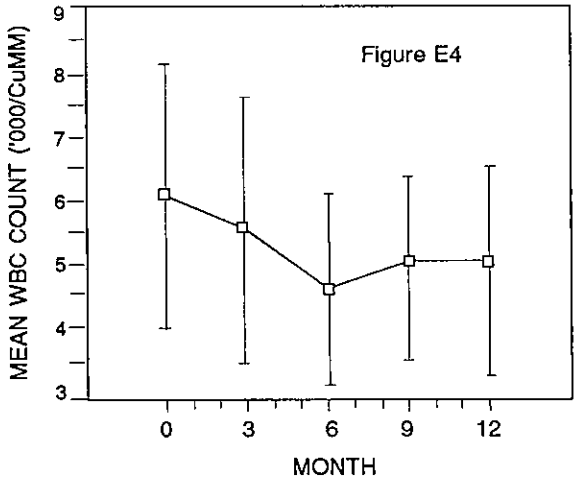
		Interval (Months)				
		0	3	6	9	12
CD4 count	MEAN	691.00	774.50	514.68	466.53	452.19
	S.D.	263.70	432.66	326.84	236.64	293.53
CD8 count	MEAN	1377.40	1431.42	958.80	1168.80	1099.50
	S.D.	351.76	665.27	296.53	453.21	365.17
CD4/ CD8 Ratio	MEAN	.55	.61	.51	.44	.42
	S.D.	.27	.45	.28	.26	.26
WBC count	MEAN	6.13	5.76	4.86	5.07	5.13
	S.D.	2.20	2.03	1.53	1.14	1.15
Total lymphocyte	MEAN	2605.47	2645.00	1839.43	2094.00	1943.63
	S.D.	556.08	1019.94	592.09	685.73	629.31
Total T- lymph	MEAN	2293.40	2369.80	1635.79	1818.71	1690.33
	S.D.	504.46	1041.22	590.38	633.72	563.17
Total B-lymph	MEAN	158.67	209.25	227.87	245.93	231.67
	S.D.	108.55	130.00	242.20	223.46	118.55
% CD4	MEAN	26.00	28.10	24.90	22.10	21.90
	S.D.	9.48	12.14	10.21	9.25	9.87

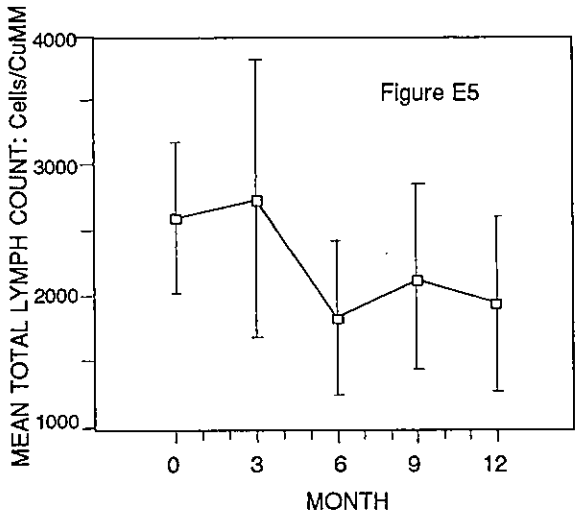


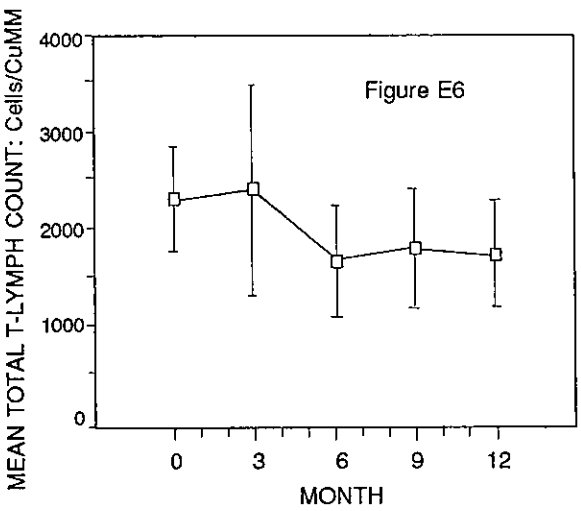


CATEGORY E/ Immune status. *Table E*: Mean scores for biological markers of immune status. *Figure E1*: Mean CD4 counts. *Figure E2*: Mean CD8 counts. **OPPOSITE:** *Figure E3*: Mean T4/T8 ratio. *Figure E4:* Mean WBC count. *Figure E5*: Mean total lymph count. *Figure E6*: Mean total T lymphocyte count. (n=16)







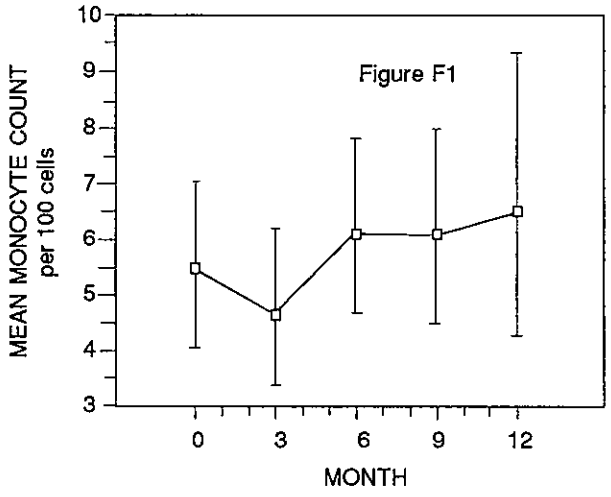


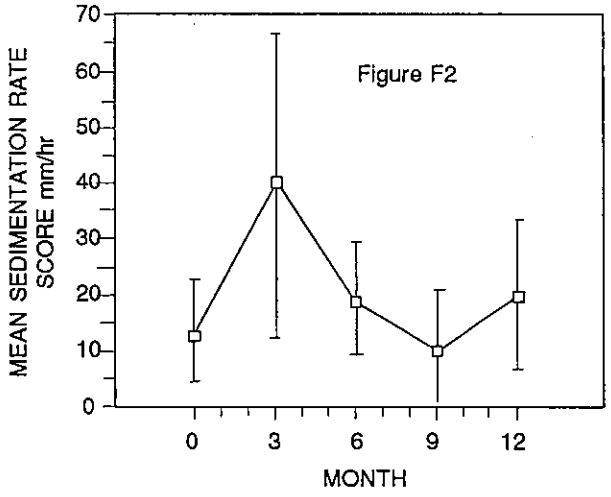
identified deficits in verbal abilities (120); flexibility of thinking, visuocontructional abilities and psychomotor speed (121); and rate of information processing (91,122). Learning and memory impairments have been reported inconsistently in the pre-dementia studies.

Van Gorp et al. (122) found no statistically significant differences between the ARC and HIV seronegative control groups. However, Grant and Heaton (96), on the other hand, are of the opinion that "... CNS involvement with AIDS and ARC is widely acknowledged and noncontroversial, [but] there is much disagreement and divergence of findings ... with regard to the possibility of neuropsychological impairment in the early stages of HIV-1 infection, before significant immunosuppression and other medical symptoms appear." (p. 24) Most recent studies have concentrated, therefore, on elucidating possible deficits in earlier stages. However, as pointed out by Selnes et al. (123), "A somewhat surprising conclusion from review of these cross-sectional studies is that there may be significant variability in the specific domains of cognitive functioning purportedly affected by HIV-1." (p. 207) That conclusion now needs to be examined in the light of longitudinal data.

Two studies have utilized a longitudinal design (123,124). Using a moderately extensive battery, Goethe et al. (124) re-evaluated 15 of the original 83 HIV+ patients after one year and found that three of the patients who had

		Interval (months)				
		0	*3*	*6*	*9*	*12*
RBC	MEAN	4.88	4.79	4.79	4.80	4.88
	S.D.	.41	.51	.43	.35	.39
Hematocrit	MEAN	44.94	43.46	43.83	44.54	44.83
	S.D.	3.69	4.66	3.20	3.45	3.08
MCV	MEAN	92.13	90.64	91.80	92.89	91.93
	S.D.	2.60	2.16	2.81	2.13	2.84
Monocyte	MEAN	5.50	4.73	6.20	6.20	6.75
	S.D.	1.46	1.35	1.37	1.86	2.49
Lymphocyte	MEAN	37.38	39.36	39.73	38.67	36.63
	S.D.	12.44	10.14	9.98	8.17	9.11
Segmented neutrophils	MEAN	54.88	52.18	51.33	52.07	52.88
	S.D.	13.32	12.33	11.37	8.46	11.47
Sed. rate	MEAN	12.43	39.33	18.73	10.33	20.13
	S.D.	9.01	26.58	9.96	10.69	11.66





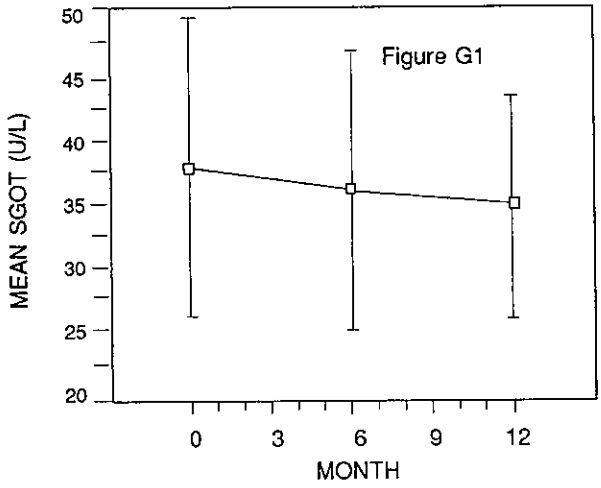
CATEGORY F/ Hematology. *Table F*: Mean score for hematology parameters. *Figure F1*: Mean monocyte count. *Figure F2:* Mean sedimentation rate.

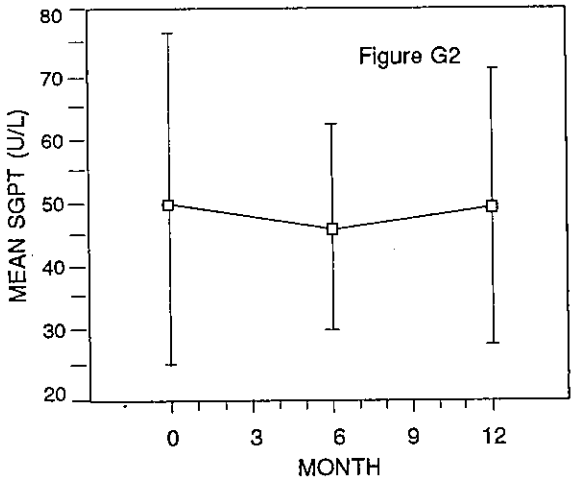
abnormal baseline scores had normal scores on follow-up testing, despite signs of encroaching systemic disease. Selnes et al. (123), using a very brief and less sensitive battery, followed 238 CDC GroupII & III males and 170 uninfected controls in the MACS (MULTICENTER AIDS COHORT STUDY) with neuropsychological testing at semi-annual intervals. The follow-up period (between visits 1 and 4) ranged from 150 to 639 days. They found "... no significant differences between serostatus groups on any of the neuropsychological measures at baseline or at visit 4 testing. Both [groups] showed a trend toward slightly higher scores on the visit 4 testing, consistent with a practice effect." (p. 205-206)

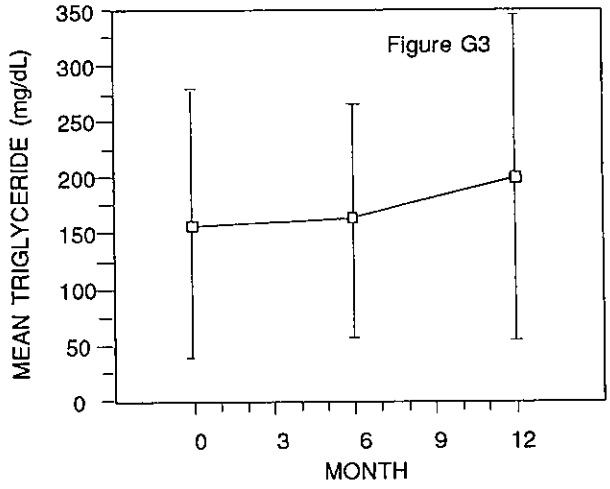
Although practice effects cannot be ruled out in the present study, they are considered unlikely as the testing occurred only twice and the sessions were 11 to 12 months apart with three exceptions; two patients were retested at 10 months and one at 15 months due to scheduling conflicts. Therefore, the differences which are noted on the follow-up testing are considered to be reflections of legitimate differences in performance/present ability.

Unquestionably, most of the improvements, even those which are statistically significant, are not practically significant except in so far as they are indicative of no deterioration. However, given the statement by Grant and Heaton quoted above, and most of the cross-sectional research, this actually is significant in a group of males who have been known to be IV-As for at least one year. Moreover, the differences in scores on the Category Test, the PASAT, and perhaps the WCST are sufficient to suggest genuine improvement in abstraction, conceptualization and speed of processing. By the same token, the consistency of poorer performances on measurements of verbal memory, both immediate and delayed , although not statistically significant, warrants the hypothesis of initial indications of neurocognitive impairment. These results, taken in total, certainly lend support to the comment of Selnes et al. regarding the variability in the specific domains affected by the HIV-1 virus. Hopefully, these patients will be reassessed with the same battery in another 12 to 15 months to shed further light on this point.

		Interval (months)		
		0	***6***	***12***
SGOT	MEAN	37.88	35.93	34.73
	S.D.	11.35	10.83	8.08
SGPT	MEAN	49.88	45.00	49.00
	S.D.	26.14	15.76	21.76
Triglyceride	MEAN	158.50	164.00	203.80
	S.D.	118.93	97.35	140.43
Albumin	MEAN	4.24	4.06	3.89
	S.D.	.22	.28	.22





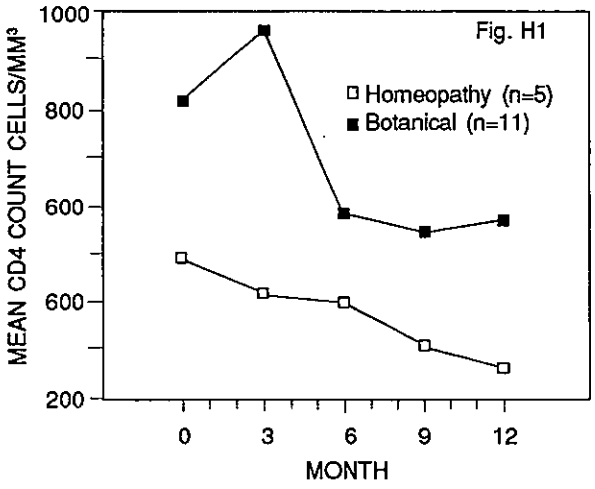


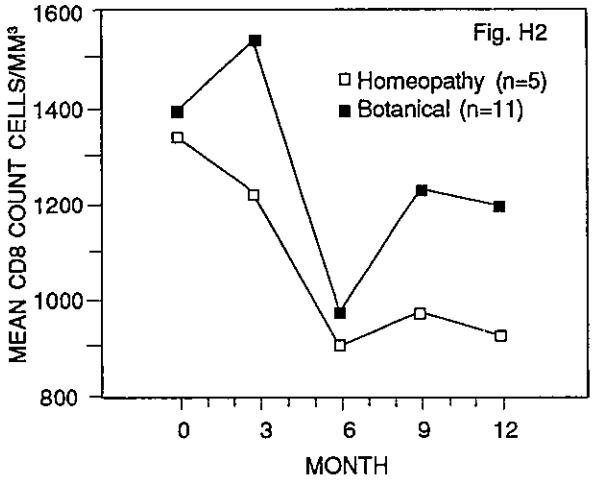
CATEGORY G/ Chemistries. *Table G:* Mean blood chemistries; *Figure G1:* Mean SGOT; *Figure G2:* Mean SGPT; *Figure G3:* Mean triglycerides.

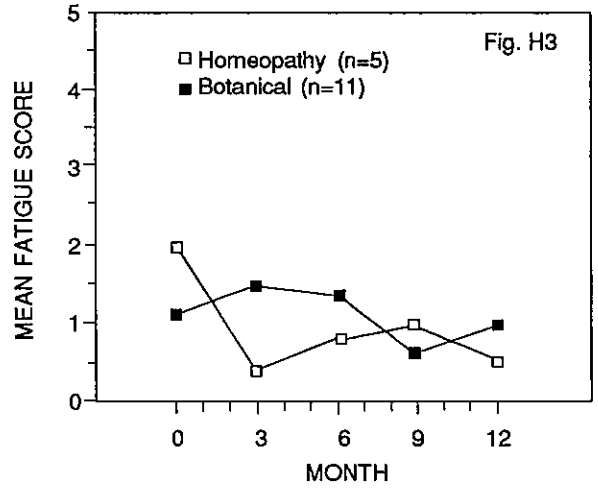
As mentioned above, CD4 cells increased in some of the patients over the first three months of the Project, and then declined. Some researchers have tried to assess the impact of the CD4 cell count on cognitive changes. As reviewed by Perry (125): "A correlation between neuropsychological impairment and lymphocyte subset has been found in some studies but not others. Even when a relationship between immunosuppression and neuropsychological impairment has been found, the correlation coefficients were generally low. These data would suggest that reduced total CD4 is not a reliable indicator of impaired mental functioning . . ." (p. 703) This is further buttressed in the present study by the fact that there was a mean decrease of 248 cells over the Project year in these patients; yet they reported feeling better (*Table 7* and the depression and anxiety scales in *Table 6*) and performed better in all neuropsychological areas except that of retention and recall of verbally presented material. They continued to be employed and/or in graduate school with few absences due to illness.

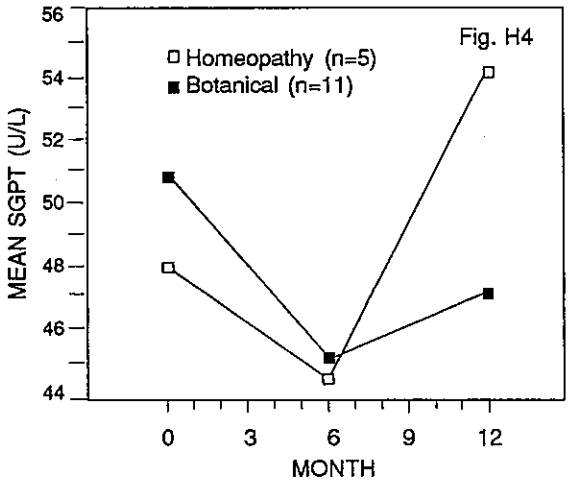
The fact that mortality and morbidity rates were so low suggests the possibility that progression to more serious immune dysfunction and AIDS defining illness was slowed, and perhaps even halted. Careful follow up on these patients over the next decade will be necessary to determine the long term outcome on disease progression.

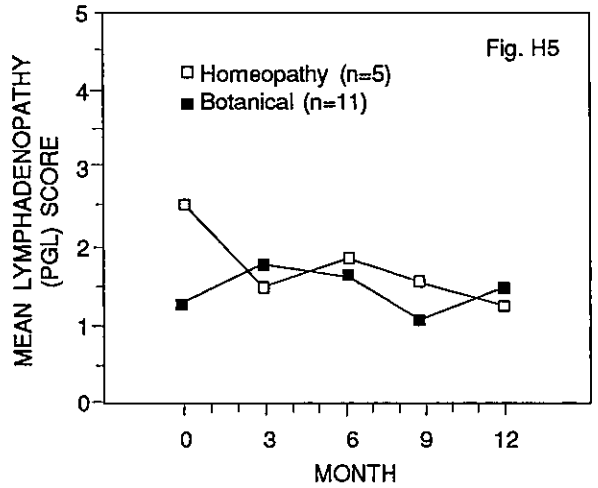
The interpretation of data from this study is limited by the lack of control data, the small sample size and by the fact that these patients enrolled in this study had higher CD4 cell counts at entry compared to both past and current NIAID's

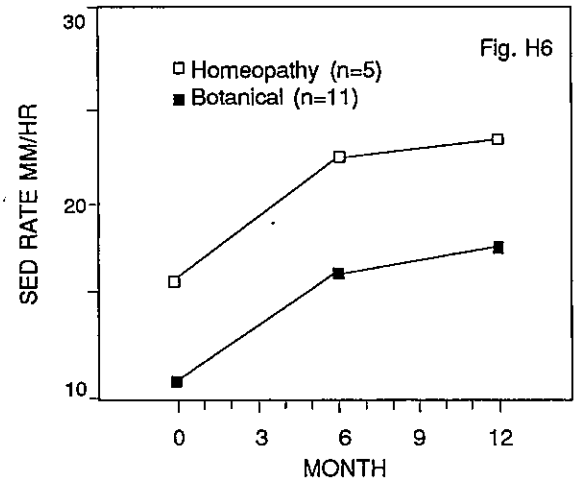












NEUROPSYCHOLOGICAL TEST PERFORMANCE						
VARIABLE		INTAKE MEAN	S.D.	12 MONTH MEAN	S.D.	t
LANGUAGE	WAIS-R Vocabulary	11.00	1.26	11.56	1.03	2.33
	Verbal Fluency (FAS)	43.62	10.27	45.62	8.73	1.02
ATTENTION	WAIS-R Digit Span	9.00	1.97	9.81	2.37	1.76
SPEED OF PROCESSING	PASAT Total Correct	126.62	19.38	136.81	21.36	2.54
	PASAT Mean Rate	3.55	0.52	3.30	0.55	2.25
VERBAL MEMORY	WMS Stories Immediate	10.77	1.97	10.22	2.85	-0.86
	WMS Stories Delayed	9.70	2.15	8.66	2.64	-2.11
	RAVLT Trial 5	13.50	1.46	13.94	1.53	1.16
	RAVLT Trial 6	12.75	3.00	12.12	2.60	-1.44
NON-VERBAL MEMORY	WMS Figures Immediate	10.09	2.40	11.75	1.61	3.02
	WMS Figures Delayed	9.56	2.46	11.09	1.90	3.19
	BVRT Correct	8.00	1.10	8.12	1.20	0.44
	BVRT Errors	2.75	1.57	2.38	1.67	2.42
ABSTRACTION	Categories Test	45.56	21.60	28.56	15.85	4.00
	WCST LOCC (%)	0.71	0.19	0.83	0.05	2.40
	WCST Persev. Errors (%)	0.13	0.10	0.07	0.02	3.00
VISUOSPATIAL	WAIS-R Digit Symbol	10.00	2.58	10.56	2.13	1.65
MOTOR ABILITIES	Finger Tapping (PH)	50.43	8.43	53.05	6.71	2.39
	Finger Tapping (NPH)	45.34	7.71	48.60	5.50	1.78
COGNITIVE FLEXIBILITY	Stroop Color	47.00	7.66	47.19	7.18	0.19
	Stroop Interference	50.75	8.32	51.25	6.62	0.42
PSYCHOLOGICAL ASSESSMENT	Depression	7.12	6.25	5.44	6.62	1.21
	Anxiety	52.38	14.82	48.75	14.94	1.82
	Hardiness	125.44	15.71	125.06	19.85	-0.13

OPPOSITE/ CATEGORY H: Homeopathy/ Botanical comparisons. Comparison of CD4 counts *(Figure H1)*, CD8 counts *(Figure H2)*, Fatigue *(Figure H3)*, SGPT *(Figure H4)*, PGL *(Figure H5)* and sedimentation rate *(Figure H6)* between homeopathy cohort (n=5) and botanical cohort (n=11)

ABOVE: TABLE 6/ HARP neuropsychological results. df=15; p values <.05 (t=2.131) are shaded grey. P values <.01 (t=2.947) are shaded black.

VARIABLE	IMPROVED	NO CHANGE	WORSE
Cognitive symptoms	6.0	8.5	1.5
Use of alcohol	8.5	7.0	0.5
Use of non-prescription drugs	9.0	7.0	0.0
Use of caffeine	12.0	4.0	0.0
Use of sugar	8.5	7.5	0.0
Quality/quantity of sleep	7.0	8.5	0.5
Amount of exercise	8.0	3.5	4.5
Stress reduction techniques	11.0	5.0	0.0
Work absences	5.0	10.0	1.0
Sexual activity	3.5	6.5	6.0
Use of safe sex	0.0	16.0	0.0
Quality of nutrition	11.0	5.0	0.0
General attitude	12.0	4.0	0.0
Emotional lability	14.0	2.0	0.0
Social support system	8.0	6.0	2.0
Effect of project participation	14.0	2.0	0.0
X=	8.59	6.41	1.00

TABLE 7 (OPPOSITE): *Self-report for patient completing the study (n=16).* Number of patients reporting improvement, no change or worsening for 16 identified variables.

AIDS Clinical Trial Group protocols. Further clinical research in the natural medical treatment of AIDS will require adequate control groups. Cooperation with Seattle's AIDS Clinical Trial Unit at University of Washington/ Harborview Hospital will provide a matched sample control group for the next prospective trial. Patients enrolled in such trials will provide antiviral research with a non drug treated control group. Patients seeking out "alternative medicine" and refusing AZT and other antiviral drugs are quickly becoming a reservoir for the "non-drug treated controls" needed for AZT, ddI, ddC and other antiviral research.

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