

COMPLEMENTARY THERAPIES IN HIV DISEASE

Overviews of alternative or complementary therapies were presented at the San Francisco conference by Donald I. Abrams, MD, from the University of California San Francisco, and at the Atlanta conference by Charles Steinberg, MD, of the Beacon Clinic in Boulder. The following summary highlights some of the complementary approaches currently in use and under investigation for HIV disease.

Many approaches outside of mainstream western medicine, including traditional Chinese herbs and acupuncture, foreign pharmaceuticals, vitamin supplements, massage, and spiritual healing, have been explored for the treatment of HIV disease and its associated symptoms. Although little data from formal controlled clinical trials exist, complementary or alternative therapies are widely used by persons with HIV and other diseases or conditions. In a report published by Eisenberg and colleagues in 1993, a survey of 1539 adults in the US revealed that 34% used at least one unconventional treatment in the past year; one third of the 34% made an average of 19 visits to providers of unconventional therapy during the preceding year. In this study, those reporting use of complementary therapies were more likely to be non-African-Americans, 25 to 49 years of age, and to have higher levels of income and education, indicating that they had the access and resources necessary to explore unconventional strategies. It is important to note that 72% of those who reported using complementary therapies had not discussed their use with their primary care physicians.

Studies from around the world on the use of complementary or alternative therapies in persons with HIV disease have revealed an even higher prevalence: 40% to 70% are seeking unconventional treatments in addition to (ie, complementary), or in place of (ie, alternative), conventional treatment. There have been distinct fluctuations in the search for and use of unconventional therapies for HIV disease,

which, according to Dr Abrams, reflect the availability of effective conventional drugs. Through the 1980s, limited options and disappointing data from trials of traditional drugs fueled an upward trend in the use of complementary therapies. With an expanded indication for zidovudine and the availability of didanosine and zalcitabine, interest in alternative compounds leveled off until discouraging results from the Concorde study spurred renewed interest. Now, with the availability of stavudine, lamivudine, and the potent protease inhibitors, the focus in the complementary/alternative therapy movement may be shifting toward investigating therapies for HIV-related symptoms or conditions for which few effective prescription drugs are available.

In addition to introducing a wide variety of nonconventional treatments, the complementary/alternative therapy movement in HIV disease has exerted influence in the political and regulatory arenas. Bans on importing drugs for personal use have been lifted in certain circumstances and buyers' clubs have been established. Widespread use of complementary therapies has also contributed to the modification of trial protocols to in-

clude patients with prior alternative-drug experience, the development of expanded access/parallel track programs for investigational drugs, and the accelerated drug approval policy.

Given the widespread use of complementary therapies and the strength of the complementary/alternative therapy movement in HIV disease, it is important that physicians and other healthcare providers working in mainstream western medicine be aware of these treatments, the risks and benefits associated with their use (see Table 1), and the role they may play in a comprehensive, holistic approach to managing HIV disease.

Selected Complementary Therapies

Vitamins and supplements. At present, there are no formal data from prospective, placebo-controlled, clinical trials evaluating the use of vitamins and supplements in persons with HIV disease.

Antioxidants, including vitamins A, C, E, beta-carotene, zinc, selenium, glutathione, and coenzyme Q-10, may reduce the level of free radicals in the body. A dose-ranging trial of vitamin C (ascorbate) is under consideration at the National Institutes of Health (NIH) to evalu-

Table 1. The Potential Risks and Benefits of Complementary Therapies for HIV Disease.

Potential risks	Potential benefits
<ul style="list-style-type: none">• Immune stimulation or suppression• Interaction with prescribed medication• Exclusion from orthodox clinical trials• Invalidation of clinical trial data• Strain on physician-patient relationship• Financial hardship• Potential for quackery or fraud	<ul style="list-style-type: none">• Evaluation of more potential treatments• Community education on scientific methods and clinical trials• Increased sense of patient hope and empowerment

ate its effect on plasma HIV RNA levels. A pilot study of beta-carotene has shown possibly suggestive short-term but not statistically significant improvement in CD4+ cell counts. In a number of recent trials in older non-HIV-infected adults, the use of beta-carotene supplements appeared to be associated with a higher death rate.

Dinitrochlorobenzene. Dinitrochlorobenzene (DNCB), a chemical used in color photography, was one of the first unconventional therapies used in HIV disease. A topical sensitizer for anergy testing and the treatment of warts and alopecia areata, DNCB was used at underground clinics in the early 1980s as a topical therapy for Kaposi's sarcoma (KS) lesions. Recently, there has been renewed interest in DNCB, based on anecdotal reports of the ability of the compound to enhance cutaneous—and subsequently—systemic, cellular immune response to HIV. Treatment involves painting a 2- to 4-inch patch of DNCB on the skin; the solution is diluted as sensitivity increases. Severe skin irritations have been observed, and findings from an observational cohort study have proven inconclusive.

Tumor necrosis factor (TNF) inhibitors. Another group of drugs widely available through underground treatment networks are those believed to inhibit TNF, including N-acetylcysteine (NAC), procysteine, pentoxifylline, peptide-T, and thalidomide. High concentrations of TNF in some in vitro systems activate HIV, inducing viral replication and increased destruction of the immune system. In addition, TNF-inhibitors may be useful in treating other cytokine-mediated symptoms of HIV disease, such as fever and wasting. N-acetylcysteine, a cysteine precursor available as a mucolytic agent in Europe, was evaluated by the National Institute of Allergy and Infectious Diseases (NIAID) and was found to have no effect on plasma cysteine levels, CD4+ cell counts, or viral load. Despite disappointing trial results and poor oral bioavailability, NAC remains popular at buyers' clubs. Pentoxifylline was evaluated in an AIDS Clinical Trials Group (ACTG) protocol and was found not to have any beneficial clinical effects.

Thalidomide inhibits TNF by interfering with messenger RNA (mRNA) production; it is being evaluated for the treatment of wasting and aphthous ulcers. Studies in the US and Thailand in persons with HIV and tuberculosis (TB) demonstrated that the addition of thalidomide to anti-TB medications increased weight gain. In an ACTG placebo-controlled study that evaluated thalidomide for the treatment of oral and esophageal ulcers, 95% of patients with oral ulcers had either complete or partial resolution compared with 10% of patients given placebo. The oral-ulcer component of the study was terminated; evaluation of thalidomide for the treatment of esophageal ulcers is ongoing. The primary side effect associated with thalidomide is sedation. The well-documented teratogenic side effects require that women of child-bearing age who are given thalidomide use strict methods of birth control. Based on early promising reports, thalidomide was being widely distributed through the underground buyers' club networks until prohibited by the Food and Drug Administration (FDA). Because of the controversies in the past regarding its use in pregnant women, emotional reactions to the use of thalidomide, particularly in HIV-infected women and minorities, have hampered its evaluation in larger clinical trials.

Complementary Therapies for Wasting

The lack of available effective interventions for HIV-associated wasting has spurred an increased use of complementary therapies in this area. In addition to thalidomide, testosterone, given by injection or patch, testosterone-like agents, and anabolic steroids are also being widely used for their potential to increase lean muscle mass. Efforts are under way to conduct clinical trials on nandrolone and decadurabolin through the ACTG; a study that would compare IM nandrolone with oral oxandrolone has been proposed by the Community Programs for Clinical Research on AIDS (CPCRA). Trials on these and other steroids are needed to examine their potential as immunosuppressants. There have been anecdotal reports from the alternative underground of more rapid HIV disease progression in persons using injected anabolic steroids; specifi-

cally, there is an increasing number of reports of cytomegalovirus (CMV) disease developing in patients with CD4+ cell counts higher than would normally be expected.

Dehydro-3-epiandrosterone (DHEA), an adrenal steroid present in decreased amounts in persons with HIV, has been reported to have antiretroviral and immunomodulatory effects in vitro. In a phase I dose-escalation study, 31 subjects were given the drug in doses ranging from 250 to 750 mg tid for 16 weeks. No changes were observed in CD4+ cell counts, β_2 -microglobulin levels, or p24 antigen levels. A transient decrease in serum neopterin levels was noted. There were no consistent side effects; rare instances of insomnia, fatigue, and nasal congestion were observed. At present, DHEA is the largest selling agent in the San Francisco Buyers' Club, and is used by persons with HIV for wasting and by HIV-negative consumers because of its reputation as a "smart drug," with alleged anti-aging, anti-obesity, and anti-cancer properties.

Ketotifen, an antihistamine widely used in Europe, is a best-selling item in the New York buyers' clubs as another potential treatment for wasting. Interest in ketotifen was sparked by a small German study suggesting decreased levels of TNF- α and a six-pound weight gain in HIV-infected patients with wasting during the 12-week treatment period. In addition to lowering TNF- α levels and stimulating the appetite, ketotifen may also have anti-inflammatory properties. Associated side effects include temporary drowsiness and dry mouth.

Marijuana, either inhaled or ingested in the form of dronabinol capsules, has also been widely used as an appetite stimulant by persons with HIV disease. As of July, the Cannabis Buyers' Club in San Francisco (shut down in August) made this drug available to approximately 8000 people with HIV disease and other life-threatening medical conditions. Based on reports of patients' preferences for inhaled marijuana because of the ability to titrate onset of appetite and duration effect, researchers at the University of California San Francisco designed a clinical trial to compare three strains of inhaled marijuana with dronabinol. Although the

study protocol was approved by the FDA and the institutional review board, questions regarding the source of the marijuana to be used have caused significant delays. An intensive inpatient evaluation of 15 adults using inhaled marijuana has been designed and submitted to the NIAID. Outcome measures will include food intake and impact on the lungs, the immune system, and viral load.

Chinese Medicine

Chinese medicine is used by more than 20% of the world's population. Focusing on the whole person rather than specific pathogens, these ancient methods of healing combine acupuncture and herbal treatment to realign the balance of energy in the body. Although a number of treatments have been evaluated for use in patients with HIV disease, primarily for their effect on constitutional symptoms, formal clinical trials remain a challenge, largely owing to the individualized nature of these approaches.

In studies involving persons with HIV, the use of acupuncture and herbs has been reported anecdotally to yield improvements in symptoms such as fever, night sweats, fatigue, and weight loss. No consistent beneficial effects on laboratory parameters such as CD4+ cell count and viral load have been observed. In a recent study, investigators at San Francisco General Hospital collaborated with practitioners of traditional Chinese medicine at the Quan Yin (a traditional Chinese medicine clinic) to conduct a 12-week randomized, double-blind, placebo-controlled trial using a combination of ENHANCE™ and CLEAR HEAT™. The combination comprised 31 herbal ingredients in a 650-mg tablet. Thirty HIV-positive patients with CD4+ cell counts of 200 to 500/μL and HIV-related symptoms but with no diagnosis of AIDS were given 28 herbal or placebo tablets daily. The results from 29 patients are presented in Table 2. Adherence was high, with patients in both groups taking an average of 26 pills daily. One patient discontinued treatment after two weeks due to diarrhea, one patient had a transient increase in hepatic transaminase levels, and one patient refused to return for follow-up; all three of these patients were in the placebo group.

Table 2. Results from a Placebo-controlled Trial of ENHANCE™ and CLEAR HEAT™.

Outcome measure	Herbal group (n = 15)	Placebo group (n = 14)	P-value
Mean life satisfaction score	0.86	0.20	<.05
Mean change in number of symptoms	-2.2	+0.3	<.05
Mean change in CD4+ count (cells/μL)	-30	-11	NS
Mean increase in weight (lb)	0.04	0.31	NS

NS, not significant.

Data from Burack JH et al. *JAIDS*. 1996.

The results of this collaborative trial proved inconclusive, and the methodology used was criticized by practitioners of both western medicine and traditional Chinese medicine. Western concerns included the small sample size, the short duration of the study, and the subjective outcome measures. The practitioners of traditional Chinese medicine also expressed concern about the trial's short duration, as well as the lack of a Chinese diagnosis and of complementary acupuncture, and the use of herbal extracts rather than the herbs themselves. Clinical trials are also under way for Source Qi, an herbal preparation for the treatment of patients with chronic *Cryptosporidium*-negative diarrhea, and for Marrow Plus, an herbal combination treatment for patients with mild-to-moderate anemia. In addition, the CPCRA is conducting a randomized, placebo-controlled study of acupuncture and amitriptyline for the treatment of peripheral neuropathy.

Complementary Therapies with Reported Antiretroviral Activity

An extract of the Boxwood evergreen with purported antiretroviral effects, SPV-30 has recently received much positive publicity. A placebo-controlled study at the Pasteur Institute in Paris demonstrated a modest increase in CD4+ counts in a cohort of about 30 patients with 250 to 500 cells/μL and no previous antiretroviral therapy. In patients given SPV-30, mean CD4+ counts increased by 94 cells/μL compared with a decrease of 43 cells/μL in patients given placebo. No toxicities were reported, and patients

given SPV-30 reported a decrease in fatigue. To date, more than 150 subjects have been enrolled in a larger follow-up phase II/III study in France; results were reported at the International Conference in Vancouver. The group that received a low dose of SPV-30 had fewer therapeutic failures (defined as progression to ARC or AIDS, or a CD4+ cell decline) than the placebo or high-dose SPV-30 groups. The authors concluded that "this trial shows that [SPV-30] slows down progression of disease." However, these results have been considered inconclusive, at best. In the US, an informal, community-based study of SPV-30 enrolled 400 HIV-infected persons with CD4+ cell counts of 0 to 700/μL and plasma HIV RNA levels of 0 to 10⁶ copies/mL. Participants added SPV-30 to their existing antiretroviral therapy, completed questionnaires, and supplied samples for laboratory testing every two months. Preliminary analysis of the study was presented in Vancouver. There was no CD4+ count benefit and only mild plasma HIV RNA activity; hence, these results are similarly considered inconclusive.

Cytolin, a mouse monoclonal antibody directed against the LFA-1 adhesion molecule of CD8+ cells, has been investigated for its ability to down-regulate cytotoxic CD8+ cells. HIV-induced cytotoxic CD8+ cells mediate the destruction of the immune system by killing CD4+ expressing cells. The cytotoxic CD8+ cells are covered with adhesion molecules, which are the primary immunologic lesions. Cytolin, targeted at the LFA-1 adhesion molecule of CD8+

cells, is postulated to block the killing of CD4+ cells. A pilot study conducted by the Search Alliance, a community-based trial group in Los Angeles, demonstrated decreased plasma HIV RNA levels, remission of early disease symptoms, and resolution of refractory molluscum. Additional data are currently being collected. Of concern is the potential for anaphylaxis and for the development of human anti-mouse antibodies (HAMAs) from using a foreign-protein product. In addition, some investigators question the use of LFA-1 as a target molecule. Critical for the attachment of CD8+ cells to virus-infected and cancer cells, blocking expression may promote the development of cancers and the spread of opportunistic viral infections in patients with HIV. Animals injected with anti-LFA-1 have shown markedly decreased cellular immune response.

Sho-Saiko-To (SSKT), a traditional Japanese medicine, is a precise mixture of 7 herbs and has been reported to have in vitro anti-HIV activity via reverse transcriptase inhibition. A trial of this drug conducted at Columbia University using lymphocyte cultures found that the degree of anti-HIV activity correlated with disease stage.

Summary

Given the widespread use of complementary or alternative therapies, it is important that physicians and other health care providers maintain open communication with their patients on issues relating to these unconventional therapies. Awareness of the drugs and compounds being used, the rationales for their use, and their potential toxicities, allows physicians to monitor treatment effects, prevent potential drug interactions, ward off fraud, and educate patients on treat-

ment issues. Such unconventional therapies should be subjected to the same rigorous, systematic assessment of risks and benefits as are the more conventional interventions. Complementary or alternative therapy may be one part of an integrated and individualized treatment program. For the person with HIV disease, seeking information on all available options and making informed treatment decisions are important components of keeping hope alive.

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