ASSOCIATION OF COMPLEMENTARY AND ALTERNATIVE MEDICINE USE WITH HIGHLY ACTIVE ANTIRETROVIRAL THERAPY INITIATION

Daniel Merenstein, MD; Yang Yang, MS; Michael F. Schneider, MS; Lakshmi Goparaju, PhD; Kathleen Weber, BSN; Anjali Sharma, MD; Alexandra M. Levine, MD; Gerald B. Sharp, DrPH; Monica Gandhi, MD; Chenglong Liu, MD, PhD

Objective • To assess whether complementary and alternative medicine (CAM) use is associated with the timing of highly active antiretroviral therapy (HAART) initiation among human immunodeficiency virus (HIV)-infected participants of the Women’s Interagency HIV Study.

Study Methods • Prospective cohort study between January 1996 and March 2002. Differences in the cumulative incidence of HAART initiation were compared between CAM users and non–CAM users using a logrank test. Cox regression model was used to assess associations of CAM exposures with time to HAART initiation.

Main Outcome and Exposures • Study outcome was time from January 1996 to initiation of HAART. Primary exposure was use of any CAM modality before January 1996, and secondary exposures included the number and type of CAM modalities used (ingestible CAM medication, body practice, or spiritual healing) during the same period.

Results • One thousand thirty-four HIV-infected women contributed a total of 4987 person-visits during follow-up. At any time point, the cumulative incidence of HAART initiation among CAM users was higher than that among non–CAM users. After adjustment for potential confounders, those reporting CAM use were 1.34 times (95% confidence interval: 1.09, 1.64) more likely to initiate HAART than non–CAM users.

Conclusion • Female CAM users initiated HAART regimens earlier than non–CAM users. Initiation of HAART is an important clinical marker, but more research is needed to elucidate the role specific CAM modalities play in HIV disease progression. (Altern Ther Health Med. 2008;14(5):18-22.)

Complementary and alternative medicine (CAM) has been shown to be used with greater frequency in populations with chronic or terminal diseases than in the general population. In the early human immunodeficiency virus (HIV) era, CAM usage was high, due in large part to the virus’s debilitating effects and few effective treatment options. More recently, HIV has been transformed from an acute disease with nearly certain imminent death to a treatable disease, provided that individuals have access to and are adherent to highly active antiretroviral therapy (HAART).

Initiation of HAART as soon as such therapy is clinically indicated leads to an improved prognosis, whereby individuals with higher CD4+ cell counts at initiation are able to achieve immune-reconstitution more effectively than individuals who begin therapy later. Additionally, early initiation of HAART is an effective method to reduce liver-associated mortality in individuals co-infected with the hepatitis C virus. Although it is feasible to successfully treat individuals who present for care at later stages of disease, late presenters have been found to place larger demands on resources, with increased morbidity and mortality at the individual level.

Individuals use CAM for many reasons, but many HIV patients are currently using CAM to help improve their quality of life (QOL). A survey of 191 HIV-positive outpatients found that
METHODS

Study Population

The WIHS is an ongoing multi-center cohort study among HIV-infected and uninfected women sponsored by the National Institutes of Health (NIH). The WIHS is designed to study the natural and treated history of HIV disease, and the main elements of its study design have been described in detail elsewhere. The original recruitment took place in 1994 and 1995 and included 2054 HIV-infected and 569 HIV-uninfected women 6 study sites around the United States (Chicago; Los Angeles; San Francisco; Washington, DC; Brooklyn; and the Bronx). During each semiannual visit, onsite interviews were conducted and data on participant demographics, behaviors, healthcare utilization, medication use, and disease outcomes were collected. In addition, biological specimen collection, physicals, and obstetric/gynecologic examinations were performed. The local institutional review board at each site approved the study protocol and all participants were given written informed consent. In the WIHS, data on comprehensive CAM use was collected annually (at only odd-numbered visits) from study enrollment until March 2002.

In this study, we restricted our analyses to the 2054 HIV-infected participants who did not use HAART in a clinical trial before 1996 and had at least 1 visit during the follow-up period (January 1996–March 2002). The index visit was defined as the semiannual visit that occurred between October 1995 and March 1996. If a participant did not have a visit between October 1995 and March 1996, the visit conducted closest in time to and before October 1995 was used as the index visit. CAM users were defined as those who reported use of CAM at the index visit, and non–CAM users referred to those who never reported CAM use between study enrollment and March 2002.

Primary Outcome

The definition of HAART was guided by the Department of Health and Human Services/Kaiser Panel (DHHS/Kaiser 2004) guidelines and defined as (1) 2 or more nucleoside reverse transcriptase inhibitors (NRTI) in combination with at least 1 protease inhibitor (PI) or 1 non-nucleoside reverse transcriptase inhibitor (NNRTI); (2) 1 NRTI in combination with at least 1 PI and at least 1 NNRTI; (3) a regimen containing ritonavir and saquinavir in combination with 1 NRTI and no NNRTIs; and (4) an abacavir- or tenofovir-containing regimen of 3 or more NRTIs in the absence of both PIs and NNRTIs, except for the 3 NRTI regimens consisting of abacavir, tenofovir, and lamivudine or didanosine, tenofovir, and lamivudine. Combinations of zidovudine and stavudine with either a PI or NNRTI were not considered HAART. The validity of self-reported use of HAART was confirmed using other objective measurements in the WIHS. We defined time to HAART initiation as the time from January 1, 1996, when HAART became available, until either the date of HAART initiation (defined as the midpoint between the date of the last study visit at which HAART was not reported and the date of the first study visit at which HAART was reported) or March 2002, whichever came first. The participants who never initiated HAART and those who started HAART after March 2002 were treated as censored observations in all analyses.

Exposures of Interest

CAM use was divided into 3 categories: ingestible CAM medication (herb medications and non-herb medication), body practice, and spiritual healing. Ingestible CAM medication reported in this study included St John’s wort (hypericin), coenzyme Q10, melatonin, herbs (Chinese/Asian, Native American, South American, Indian/Ayurvedic), cat’s claw, chamomile, combination Chinese herbs, dandelion, echinacea (with or without goldenseal), garlic, ginkgo biloba, ginger, ginseng, goldenseal, milk thistle, valerian, woodroot, evening primrose oil, red clover, black cohosh, DHEA (dehydroepiandrosterone), niacin, NAC (N-acetyl-cysteine), glutamine, acidophilus, alfalfa, algae (blue algae, blue-green algae), aloe vera, astragalus, bee pollen, beta-carotene, chromium, cranberry, megadose vitamins, omega-3-type oils, protein powder, spirulina, thymus glandular, zinc, lecithin, cod Liver oil, L-carnitine, soy, flaxseed (linseed), kerron, thymus extract, peptide T, special diet for health, enzyme therapies (plant or pancreatic), flower remedies, and homeopathic remedies. Multivitamins, folic acid, and antioxidants were not included in our definition of CAM, as HIV primary care providers may routinely prescribe these for their patients. Body practice included acupuncture, acupressure, massage, and reflexology therapy but excluded regular exercise. Spiritual healing consisted of spiritual health therapy, hypnosis, biofeedback, image therapy, and yoga. For analyses, use of any CAM was the primary exposure. Secondary exposures included (1) number of different CAM modalities each participant used, categorized into 1 of 4 groups (0, 1, 2, and 3) and (2) use of any specific CAM modalities, including ingestible CAM medications, body practice, or spiritual healing.

Covariates

On the basis of prior studies and data available in the WIHS, the following covariates were selected as potential confounders in evaluating the association between CAM use and time to HAART initiation. The index visit covariates included age, race/ethnicity (white, black, Hispanic, other), educational level (non-high school graduate, high school graduate only, some college), annual income (≤$12 000 per year vs ≥$12 000), employment, insurance coverage, any illicit drug use (ever used vs never used), perceived that their health was improved due to CAM. However, it is possible that if CAM usage improves patients’ subjective assessment of their QOL, it may also result in the delay of HAART initiation. Indeed, in breast, head, neck, and lung cancer patients, use of CAM has been shown to displace or delay traditional treatments. Using data from the Women’s Interagency HIV Study (WIHS), a large cohort of HIV-infected individuals, we examined the hypothesis that CAM use delays HAART initiation.
depressive symptomatology (measured by the Center for Epidemiologic Studies Depression Scale,29 with a score ≥16 defined as depression), health-related QOL (measured on a scale from 0 to 100 using a modified version of the SF-3631), and use of other antiretroviral therapy (none, monotherapy, or non-HAART combination therapy). As CD4+ T cell counts and HIV RNA level are 2 important laboratory indicators that physicians use to decide whether to initiate HAART, time-varying CD4+ T cell counts and HIV RNA level were also included to adjust their confounding effects.

Statistical Analyses
The cumulative probability of initiating HAART over time was depicted using Kaplan-Meier methods, and possible differences between the 2 groups were evaluated using the logrank test. In addition, we used Cox proportional hazards regression models with time-varying covariates to assess the associations of different CAM exposures with time to HAART initiation. To determine the independent association of each type of CAM modality used with time to HAART initiation, we restricted CAM users to those who used only 1 kind of CAM modality to avoid overlap. Furthermore, a sensitivity analysis was conducted by adding time-varying CAM exposures after HAART was available to the above multivariate model to assess the possible effect of inconsistent CAM use. All analyses were conducted using SAS 9.01 (SAS Institute, Inc, Cary, North Carolina).

RESULTS
Study Population Characteristics
A total of 796 CAM users and 238 non–CAM users were studied and contributed a total of 4987 person-visits between January 1996 and March 2002 (Table 1). The 2 groups had similar QOL scores, CD4+ cell counts, and HIV RNA levels. However, CAM users had more education and higher income and were more likely to be employed than nonusers.

Univariate Analysis
The cumulative incidence of HAART initiation was estimated in order to examine the association of CAM use with time to HAART initiation (Figure). As shown over the duration of follow-up, individuals who used CAM were more likely to have initiated HAART than non–CAM users (P=.012). For example, at 2 years, nearly 50% of CAM users were on HAART compared to approximately 40% of nonusers.

Using a univariate Cox-proportional hazard model, we found that CAM users were 1.27 times more likely to initiate HAART than nonusers (hazard ratio [HR]: 1.27; 95% confidence interval [CI]: 1.05-1.53, Table 2). No dose-response relationship was observed between number of CAM modalities used and HAART initiation (P=.72). Restricting CAM users to those who used only 1 CAM modality, using ingestible CAM medication, body practice, and spiritual healing were all associated with greater likelihoods of HAART initiation, though only the association with spiritual healing was statistically significant.

| TABLE 1 Characteristics of 1034 Women’s Interagency Study Participants at the Index Visit* |
|---|---|---|
| Characteristics | CAM Users (n = 796) | Non–CAM Users (n = 238) |
| Age | 37.0 | 35.0 |
| Ethnicity (%) | | |
| White, non-Hispanic | 24.5 | 13.9 |
| Black, non-Hispanic | 51.2 | 50.6 |
| Hispanic | 21.6 | 35.0 |
| Other | 2.8 | 0.4 |
| Education (%) | | |
| Less than high school | 28.7 | 59.9 |
| High school graduate | 30.2 | 25.3 |
| Some college | 41.0 | 14.8 |
| Income >$12 000 (%) | 43.4 | 24.1 |
| Currently employed (%) | 27.7 | 14.8 |
| Insurance (%) | 81.6 | 69.2 |
| Illicit drug use (%) | 32.4 | 34.6 |
| Type of antiretroviral therapy (%) | | |
| No therapy | 51.3 | 45.3 |
| Monotherapy | 25.7 | 33.5 |
| Combination therapy | 23.0 | 21.2 |
| Quality of life | 61.2 | 62.1 |
| Depression† (%) | 52.3 | 57.5 |
| CD4+ cell count, cells/mm³ | 333.0 | 351.0 |
| \(\log_{10}\) HIV RNA, copies/mL | 4.3 | 4.3 |

*All table entries are medians unless otherwise noted.
†Score of ≥16 on Center for Epidemiologic Studies Depression Scale.
After adjusting for possible confounders, we determined whether different CAM exposures were associated with time to HAART initiation (Table 2). The any CAM user group had a 1.34 times (95% CI: 1.09, 1.64) greater likelihood of initiating HAART than the non–CAM user group. Compared to the non–CAM users, all categories of the number of CAM modalities had similar significant associations with HAART initiation, with no significant dose-response relationship observed (P=.65). Compared to the non–CAM user group, using ingestible CAM medication (HR: 1.18; 95% CI: 0.88-1.59), body practice (HR: 1.34; 95% CI: 0.91-1.96), and spiritual healing (HR: 1.58; 95% CI: 1.22-2.05) were all associated with greater chances of HAART initiation even though only association with spiritual healing reached statistical significance. In the sensitivity analysis among the CAM users, no time-varying CAM exposures after HAART was available were significantly associated with HAART initiation, with the hazard ratio between any CAM use and HAART initiation being 1.14 (95% CI: 0.86-1.52). Additionally, in all 3 models, QOL was not associated with HAART initiation with insignificant confidence intervals.

**DISCUSSION**

We have shown that CAM users initiated HAART regimens earlier than nonusers after adjusting for important confounders such as CD4+ T cell counts and HIV RNA level. The effect of CAM use on HAART initiation came mainly from the first year after HAART was available, which was also evidenced by the fact that time-varying CAM exposures after index visit were not significantly associated with HAART initiation in the sensitivity analysis. In addition, number of CAM modalities used did not show a dose-response relationship with initiating HAART, which implied that heavy CAM users might behave the same way as lighter CAM users did in initiating HAART.

Our data are in sharp contrast to the literature on CAM usage in cancer patients, where previous research has shown CAM usage delayed traditional therapies.23-25 We believe part of the explanation for the apparent difference between cancer and HIV+ patients is that most of our cohort had HIV for many years before starting HAART and were already being cared for by physicians, unlike in the case of cancer, where a non-cancer specialist often diagnoses the patient with cancer and then refers the patient to another provider. This gap in care may allow patients to experiment with CAM and delay treatment before visiting the cancer specialist. Further research into these differences might yield important information for providers. Additionally, as was previously discussed, CAM usage has played a significant role in HIV since the beginning of the epidemic, and individuals who use CAM potentially are more likely to use healthcare and seek physician care.

When physicians decide if a patient should initiate HAART, they generally look at empirical data such as CD4+ cell count or viral load; however, patients may take many other factors into account.32-34 We had hypothesized that QOL would be one of these factors, but we found no association between QOL and HAART initiation. Because HAART regimens are the only known successful treatment for HIV, it is important to fully understand and predict what factors influence treatment initiation.
which individuals will start HAART as soon as possible and the role CAM plays in initiation and compliance and treatment of HIV.

Our study has several limitations. Most importantly, CAM use has many different definitions, and we struggled with being inclusive while not considering all CAM modalities. Secondly, our data are self-reported, and it is possible that women who acknowledge partaking in CAM may also report higher HAART initiation rates. However, previous WIHS research has shown self-report of medicines to be consistent with objective measures of HIV outcome, such as CD4+ T cell count, HIV viral load, and self-reported physical functioning. Thirdly, not all CAM users continued to use CAM during study follow-up. However, the prevalence of CAM use has been around 70% over the follow-up period among our CAM users defined at the index visit, which is a reasonably high rate for our intention-to-treat analysis that usually generates a relatively conservative estimate. In addition, our sensitivity analysis with an added time-varying CAM exposure variable did not alter our analysis results. Finally, our study was carried out among women only, and the results obtained may not be generalized to men, as their CAM use pattern might be different from women’s.

Our research found that CAM users initiated HAART sooner than nonusers. This information is relevant for researchers, healthcare providers, and patients. CAM use has a long history in the treatment and care of HIV patients, and it is reassuring that CAM users do not initiate HAART later than nonusers and in fact report an accelerated rate of HAART initiation. Further research into the relationship between specific CAM modalities and the role they play in HIV disease is important for clinicians and patients.

Acknowledgments

Data in this manuscript were collected by the Women’s Intergroup HIV Study (WIHS) Collaborative Study Group with centers (principal investigators) at New York City/Bronx Consortium (Kathryn Anastos); Brooklyn, New York (Howard Minkoff); Washington, DC, Metropolitan Consortium (Mary Young); The Connie Wofsy Study Consortium of Northern California (Ruth Greenblatt); Los Angeles County/Southern California Consortium (Alexandra Levine); Chicago Consortium (Margade Cohen); Coordinates Data Center (Stephen Gange). The WIHS is funded by the National Institute of Allergy and Infectious Diseases with supplemental funding from the National Cancer Institute, the National Institute on Drug Abuse, the National Heart, Lung, and Blood Institute, and the National Institute on Aging (U10-AI-35004, U10-AI-31834, U10-AI-34994, U10-AI-34989, U10-AI-34993, and U10-AI-42598). Funding is also provided by the National Institute of Child Health and Human Development (HD-132632) and the National Center for Research Resources (M01-RR-00071, M01-RR-00079, and M01-RR-00083).

REFERENCES