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A Randomized Clinical Trial of Alternative Stress Management Interventions in Persons With HIV Infection

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Abstract

Research in psychoneuroimmunology suggests that immunosuppression associated with perceived stress may contribute to disease progression in persons with HIV infection. While stress management interventions may enhance immune function, few alternative approaches have yet been tested. This randomized clinical trial was conducted to test effects of three 10-week stress management approaches—cognitive–behavioral relaxation training (RLXN), focused tai chi training (TCHI), and spiritual growth groups (SPRT)—in comparison to a wait-listed control group (CTRL) among 252 individuals with HIV infection. Using repeated measures mixed modeling, the authors found that in comparison to the CTRL group, (a) both the RLXN and TCHI groups used less emotion-focused coping, and (b) all treatment groups had augmented lymphocyte proliferative function. Despite modest effects of the interventions on psychosocial functioning, robust findings of improved immune function have important clinical implications, particularly for persons with immune-mediated illnesses.

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Keywords

stress management; psychoneuroimmunology; tai chi intervention; spirituality intervention; HIV infection

Many persons with HIV infection are known to seek alternative, or nontraditional, treatments, with prevalence rates reported to be between 33% and almost 60% (Agnoletto, Chiaffarino, Nasta, Rossi, & Parazzini, 2006; Hsiao et al., 2003; Tsao, Dobalian, Myers, & Zeltzer, 2005). In order to expand the repertoire of stress management approaches for this group of chronically ill and chronically stressed individuals, we designed a randomized clinical trial to test the effectiveness of two alternative interventions, along with a more traditional cognitive–behavioral approach for stress management.

The overall purpose of the research was to determine whether the three 10-week stress management interventions would improve and sustain improvements 6 months later in the domains of psychosocial functioning, quality of life, and physical health among persons with varying stages of HIV infection. These three outcome domains, along with neuroendocrine and immune mediating variables, were measured by multiple indicators derived from the psychoneuroimmunology (PNI) paradigm. The interventions included cognitive–behavioral stress management focused on enhanced coping skills and relaxation training (RLXN), focused tai chi training (TCHI), and spiritual growth groups (SPRT). Participants were randomly assigned to one of the intervention groups or to a wait-listed control group (CTRL).

Background

The theoretical framework for this research integrates a cognitive–transactional model of the stress process with the PNI paradigm. This stress process model holds that the variety of coping strategies used in response to perceived stress serve to psychologically mediate the adaptational outcomes of psychosocial functioning, quality of life, and physical health (Billings & Moos, 1984; Lazarus & Folkman, 1984). The theoretical framework thus synthesizes multiple indicators of psychosocial, spiritual, neuroendocrine, immunological, and physical health within the context of HIV infection. The psychosocial–spiritual concepts of interest within the framework include (a) perceived stress associated with living with HIV infection; (b) coping patterns; and (c) the adaptational outcomes of psychosocial functioning (including HIV-specific psychological distress, perceived stress level, and social support) and quality of life (including overall and HIV-specific quality of life and spiritual well-being). Neuroendocrine mediation of the stress process is reflected by salivary levels of cortisol and dehydroepiandrosterone (DHEA). Multiple immunological indicators related to HIV pathogenesis—namely, lymphocyte subsets, natural killer cell (NKC) cytotoxicity, and stimulated lymphocyte production of selected Type 1 and Type 2 cytokine levels, as well as lymphocyte proliferative function—indirectly reflect the adaptational outcome of physical health. Physical health is directly reflected by clinical indicators of HIV disease progression status and HIV-specific health status.

In several PNI-related studies with the HIV-infected population, clear associations have been demonstrated between psychological distress and immunosuppression or disease progression (e.g., Antoni, 2003; Herbert & Cohen, 1993; Leserman et al., 2002; Mayne, Vittinghoff, Chesney, Barrett, & Coates, 1996; Patterson et al., 1996). Such relationships could be due to a number of causal factors, including declines in lymphocyte function and numbers, altered expression of immunoregulatory cytokines, changes in neuropeptide or hormone levels (particularly cortisol), and reduced NKC or T-lymphocyte cytotoxicity (Bollinger & Siliciano, 1992; Pitzalis et al., 1997; Rosenberg, Anderson, & Pabst, 1998).

Stress Management in HIV Infection

Cognitive–Behavioral Stress Management—Traditional stress management interventions generally include relaxation strategies and coping effectiveness training. Such strategies may reduce stress levels and enhance psychological functioning by modifying stressor appraisals (perceptions), providing more effective coping strategies (Antoni et al., 2006, 2002; Astin, 1997; Chesney, Chambers, Taylor, & Johnson, 2003; Lutgendorf et al., 1998), and enhancing psychological well-being, as well as supporting the creation of meaning (Folkman, 1997; Ironson et al., 2002). With some techniques, there may be direct relaxation effects on autonomic reactivity that diminish physiological stress-arousal responses (Lehrer & Woolfolk, 1993; Schneiderman et al., 1994; Smith, 1993).

Generally, previous investigators have documented adverse relationships for stress levels and positive relationships for active coping patterns in studies that have included health indicators or immune parameters (e.g., Antoni et al., 2005; Evans et al., 1991; Goodkin et al., 1992). In several studies, psychological distress was directly related to HIV symptomatology (e.g., Hayes, Turner, & Coates, 1992; Pakenham, Dadds, & Terry, 1995; van Servellen et al., 1998). In a recent report of men with HIV infection, Antoni and colleagues (2006) found psychological distress to be positively associated with viral load.

Tai Chi Training as Stress Management—Tai chi is a fitness exercise developed by Taoist monks. It is often referred to as a “moving meditation” that focuses on the connection of mind and body to facilitate health through breathing, relaxation, and movement (Wanning, 1993). Tai chi has been reported to have multiple beneficial effects, including reduced anxiety, stress, and pain (Adler, Good, Roberts, & Snyder, 2000; Bhatti, Gillin, & Atkinson, 1998); increased balance, strength, and flexibility (Wolf, Coogler, & Xu, 1997); improved psychological states such as depression; and attenuated declines associated with aging and inactivity (D. R. Brown et al., 1995; Jin, 1991; Kutner, Barnhart, Wolf, McNeely, & Xu, 1997; Li et al., 2001; Sandlund & Norlander, 2000). Additionally, tai chi has been shown to enhance immune function in middle-aged and elderly individuals (Irwin, Olmstead, & Oxman, 2007; Yeh, Chuang, Lin, Hsiao, & Eng, 2006).

In the few studies of tai chi as an intervention for individuals with HIV infection, improvements in various domains have been reported. In an 8-week intervention with 38 participants, Galantino, Shepard, and Krafft (2005) found those in the tai chi group (relative to controls) improved in HIV-specific physiological parameters, functional outcomes, and quality of life; qualitative data revealed positive physical changes, enhanced psychological

coping, and improved social interactions. In a smaller qualitative evaluation (n = 11) of an 8-month weekly tai chi intervention for individuals with HIV, Howell (2001) reported that tai chi was energizing, calming, grounding, centering, and enjoyable and that the practice increased patience, acceptance, and spiritual awareness as well as physical, emotional, and mental well-being.

Spirituality as Stress Management—Most studies related to spirituality and HIV infection have been descriptive or exploratory in design, with few intervention studies reported. Regan-Kubinski and Sharts-Hopko (1995) interviewed 38 HIV-infected women from the perspective of the cognitive–transactional stress process and found that effective coping was related to newfound spirituality or new spiritual commitment and reexamination of spiritual beliefs. From a study involving an 8-week stress reduction intervention, Astin (1997) reported decreased physical and psychological symptoms and increased sense of self-control and spiritual awareness among participants. In a recent interventional study, Borman and colleagues (2006) evaluated a psychospiritual intervention of mantra repetition (a word or phrase with spiritual associations repeated silently throughout the day) among 93 HIV-infected adults. Those in the mantra group had reductions in trait anger and intrusive thoughts and increases in quality of life, spiritual connectedness, spiritual faith, sense of meaning or peace, and spiritual well-being in comparison to the control group. In another intervention study (Margolin, Avants, & Arnold, 2005), HIV-infected participants who were using illicit drugs received acupuncture alone or acupuncture plus spiritual group therapy. Those in the group with spiritual therapy benefited more, with reductions in depression and anxiety and greater drug abstinence.

On the basis of this limited but promising empirical background and a well-supported, PNI-based theoretical framework, alternative interventions for stress management warrant further testing. Key indicators of the interactive domains of the PNI model need to be measured simultaneously in order to comprehensively evaluate potential changes in psychosocial functioning, quality of life, and physical health.

Research Design and Method

With a goal of expanding the repertoire of potential stress management interventions, we conducted a randomized clinical trial of three strategies for stress management. In addition to cognitive–behavioral stress management focused on coping and relaxation strategies, two potentially effective alternative stress management techniques derived from the PNI framework—tai chi training and spiritual growth group interventions—were tested. A pretest–posttest design with repeated measures was used to examine the influences of stress management group participation on PNI-based outcomes. Primary study hypotheses were that participants receiving any of the interventions, when compared with the wait-listed control group, would have

1. less HIV-related psychological distress, as measured by the Impact of Event Scale (IES; Horowitz, Wilner, & Alvarez, 1979);

2. more effective coping strategies, that is, reduced emotion-focused and increased problem- and appraisal-focused coping, as measured by the Dealing With Illness Scale (DIS; McCain & Gramling, 1992);
3. higher quality of life, as measured by the Functional Assessment of HIV Infection (Version 4) scale (FAHI; Cella et al., 1996; Peterman, Mo, Cella, & McCain, 1997);
4. lower stress-related neuroendocrine mediation, as reflected by decreased levels of salivary cortisol;
5. attenuated immunological dysfunction, as evidenced by higher lymphocyte proliferative function; and
6. better HIV-specific health status, as measured by the revised HIV Center Medical Staging Scale (rHCMSS; McCain et al., 1998).

To ensure equivalent baseline HIV-specific health status across intervention groups, we stratified gender subgroups by prebaseline $CD4^+$ cell counts into subsets with ≤ 99, 100–199, 200–299, 300–399, 400–499, or ≥ 500 cells/microliter. Within each stratum, participants were randomly assigned following baseline data collection to an immediate intervention or the wait-list group by means of a computer-generated, blocked pattern administered from a blinded list by a project coordinator. Measures were obtained immediately prior to the intervention, upon completion of the 10-week stress management interventions, and at 6 months postintervention. CTRL group measures were obtained at equivalent time periods. Because gender influences both perceptions and experiences of psychosocial stressors as well as group interactions (Chung & McGraw, 1992), men and women were enrolled in separate intervention groups.

Sampling

The great majority of participants were recruited from the accessible population of approximately 1,500 patients being treated at a university-affiliated, tertiary medical center clinic. Responses came through study flyers, direct contacts by study personnel, and clinic provider referrals. To be eligible for study inclusion, participants had to be at least 18 years of age, able to read and speak English, previously aware of their diagnoses of HIV infection, and deemed likely to be physically capable of attending the intervention sessions and completing the follow-up requirement, as evidenced by Karnofsky performance scores of at least 60. Potential participants were excluded for (a) significant psychiatric illness (i.e., “psychoses,” dissociative disorders, severe and/or unstable depressive disorders, and organic mental disorders) or (b) significant cognitive impairment (as indicated by scores < 20 on the Cognitive Capacity Screening Examination; Jacobs, Bernhard, Delgado, & Strain, 1977).

To be eligible for immunological measures, participants could not be pregnant or taking steroids or immunomodulatory drugs (including cytokines, thymic derivatives, and antineoplastic agents but excluding antiretroviral drugs). To control for initial effects of antiretroviral drugs on immunological function, we excluded enrolled participants from immunological analyses in the event of significant changes in medication protocols. Prior to study enrollment, otherwise eligible participants were delayed until they had been stable on

antiretroviral drugs for at least one month (cf. Kovacs et al., 1995; Schrager & D'Souza, 1998).

A sample of 387 individuals with HIV infection was recruited between December 2000 and July 2004. A total of 252 participants completed the 10-week intervention, yielding a 65% retention rate, which was equivalent to previous retention rates in studies with our accessible population. All attrition occurred postrandomization. At baseline, there were no significant differences for any demographic, health status, psychosocial, neuroendocrine, or immune variables between those who did and did not complete the intervention. There was no differential loss among the groups. Using an intent-to-treat analysis, we included in the analyses all participants who had any outcome data. No data were imputed for analyses.

Among the study sample of 252, there were 152 men and 100 women; 75.4% were African American, 23.0% were European American, and 1.6% were Hispanic American. The average age of the sample was 42.2 years. Most participants were asymptomatic or had not more symptomatology than fatigue at the time of study entry ($M = 9.167$, $SE = 0.687$, as measured by the rHCMSS; McCain et al., 1998). However, the full range of symptomatology was represented in the sample, with rHCMSS scores ranging from 0 (*asymptomatic*) to 39 (*AIDS with severe complications*). Individuals had known of their HIV-seropositive status for an average of 9 years.

The great majority of participants were being treated with state-of-the-science regimens of highly active antiretroviral treatments (HAART). A total of 219 (87%) were taking multiple antiretroviral medications, including a protease inhibitor. A small percentage of participants (13%) were not taking antiretroviral drugs. As previously noted, immunological measures were not assessed for participants who had categorical changes in drug regimens during study enrollment; this involved only 6% (16) of the sample.

Interventions

Interventions were conducted with groups of 6–10 participants who met in suitably equipped conference rooms in an office setting for 90-min sessions weekly for 10 weeks. Participants who attended less than 8 of the 10 intervention sessions were deemed as having incomplete treatments and classified as withdrawn from the study.

Cognitive–Behavioral Relaxation Training (RLXN)—Structured relaxation training was led by an investigator certified and highly experienced in stress management training. Sessions were conducted following a protocol synthesized from Smith's (1989, 1990, 1993) and Benson and Klipper's (1990) approaches. The intervention consisted of physical and mental relaxation skills training, with a focus on individualized combinations of relaxation techniques, as well as active coping strategies for stress management. Participants were expected to routinely practice relaxation techniques during and following the intervention, and daily practice frequency was recorded each week. Each participant was given a set of eight 30-min audiotapes specifically produced for use in this study.

Focused Tai Chi Training (TCHI)—The focused TCHI group was led by an investigator who had received extensive group and individual training from a tai chi master. Based on

prior research and in consideration of the potential physical limitations of our participants, a focused short form of tai chi involving eight movements was developed for this study. The intervention sequence began with a focus on breathing and balance, both key elements in all tai chi exercises. The sequence of movements taught was focused on developing each individual's skills in balancing, focused breathing, gentle physical posturing and movement, and the active use of consciousness for relaxation. Training videotapes were provided to participants for weekly and ongoing practice of the techniques.

Spiritual Growth (SPRT)—The SPRT groups were led by the investigator who developed the Spirit-10 intervention protocol used in this study (Tuck, 2004). The intervention was designed to facilitate personal exploration of spirituality and to enhance exploration of the spiritual self and awareness of the meaning and expression of spirituality. Each session was designed to explore an aspect of spirituality and included the intellectual process of knowing or apprehending spirituality; the experiential component of interconnecting one's spirit with self, others, nature, God, or a higher power; and an appreciation of the multisensory experience of spirituality. The process of weekly journal entries facilitated increased awareness and the integration of spirituality into daily life.

Data Collection Procedures

Descriptive demographic and cofactor data collected from participants included race, marital/partner status, educational level, risk factors, age, gender, current medications and dates of initiation, use of alcohol or psychoactive drugs, current and usual "healthy" weight, exercise patterns, previous and current experience with stress management or complementary/alternative strategies, and date of participant's first knowledge of HIV-seropositive status. Health status was investigator-evaluated with the Centers for Disease Control (1992) classification system, Karnofsky performance index, and historical as well as concurrent HIV-specific symptom status as measured by the rHCMSS.

Using Salivette kits (Sarstedt, Newton, NC), participants collected saliva samples immediately upon arising in the morning and 30 min later on 3 consecutive days: the 2 days prior to and the day of each data collection. At data collection times, study questionnaires and venipunctures were completed between 3 and 5 p.m. to control for circadian rhythmicity. All laboratory and data entry personnel were blinded to participants' group assignments.

Instrumentation and Measurement

Psychosocial Instruments

Dealing With Illness Scale (DIS; McCain & Gramling, 1992): The DIS, which assesses stress levels and coping patterns, was qualitatively derived with persons with HIV infection and revised in 1994 and 1999 on the basis of empirical evaluations. The DIS is comprised of Stress and Coping subscales. The format for the 20-item Stress subscale, which is modeled after the Life Experiences Survey (Sarason, Johnson, & Siegel, 1978), taps the process of cognitive appraisal by enabling respondents to indicate the level of desirability or undesirability as well as the personal impact of experienced events, thereby reflecting perceived stress. Participants indicate perceived stress specifically related to HIV infection

for two time periods: since the time of their diagnosis and within the past month. The revised 40-item Coping subscale was modeled after the Revised Ways of Coping Checklist (Vitaliano, Maiuro, Russo, & Becker, 1985) and measures problem-focused, emotion-focused, and appraisal-focused coping strategies. Reliability (Stress subscale α = .83, Coping subscale α = .80 to .87) and validity of the DIS for the study population have consistently been supported (Cella, McCain, Peterman, Mo, & Wolen, 1996; McCain et al., 2003). For this sample, the means and standard deviations were as follows: Stress subscale 22.71 (14.37); Coping subscale: Problem-Focused 39.68 (7.50), Emotion-Focused 34.33 (6.59), Appraisal-Focused 47.47 (9.36).

Revised Social Provisions Scale (SPS; Cutrona & Russell, 1987): The SPS was used as a measure of social support. It is a 24-item, 4-point Likert-type measure of six "social provisions," or components of social support. Construct validity of the SPS has been well supported in persons with HIV infection (McCain et al., 2003). For this sample, the mean score was 61.15, with a standard deviation of 0.79.

Impact of Event Scale (IES; Horowitz et al., 1979): The IES was used to measure the subjective impact of living with HIV infection. A 15-item instrument with response options that indicate how frequently within the past 7 days each distressing thought has occurred, the IES has previously shown sensitivity to psychosocial interventions. The IES has excellent psychometric properties, is not confounded with physical symptoms, and yields an index of illness-related psychological distress that can be discriminated from perceived stress in persons with HIV infection (McCain et al., 2003). The mean and standard deviation for this sample were 32.90 and 11.34, respectively.

Functional Assessment of HIV Infection (Version 4) scale (FAHI; Cella et al., 1996; Peterman et al., 1997): The FAHI is a multidimensional measure of quality of life in people with HIV infection. The 44 items are grouped into subscales of physical, functional and global, and social well-being; emotional well-being/living with HIV; and cognitive functioning. Thus, the scale reflects both general health-related and HIV-specific quality of life. The FAHI has demonstrated excellent psychometric performance (α = .85 to .92), including sensitivity to stage of illness and to intervention. The mean and standard deviation in this study were 111.86 and 31.50, respectively.

Spiritual Well-Being Scale (SWBS; Paloutzian & Ellison, 1982): The SWBS is a 20-item Likert-type general measure of spiritual well-being consisting of 11 positively worded and 9 negatively worded statements. Reliability of the scale can be seen in the α range of .78 to . 96. Subscale scores are derived for religious well-being and existential well-being. The scale has been found to be psychometrically sound with persons with HIV infection (Carson & Green, 1992; Carson, Soeken, & Belcher, 1991; Tuck, McCain, & Elswick, 2001). The SWBS mean (standard deviation) was 88.94 (21.34) for this sample.

Neuroendocrine Indicators—To increase the accuracy of the cortisol and DHEA indicators of neuroendocrine mediation, we averaged serial measures of saliva samples collected for 3 consecutive days at each data collection point. Saliva samples have been found to be stable for 5 days without freezing (Clements & Parker, 1998). Thus, participants

brought their prenumbered and -dated saliva containers to their data collection appointments, at which time all samples were frozen. Saliva specimens were later batch-assayed with standardized enzyme-linked immunosorbent assay (ELISA) kits (Salimetrics, State College, PA). For this sample, the mean (standard deviation) was 0.34 (0.55).

Immunological Measures

$CD4^+$, $CD8^+$, and $CD57^+$ T lymphocytes: To explore possible correlations among cytotoxic T lymphocytes as well as natural killer cells (NKCs) with stress levels, we examined a number of lymphocyte subsets. Cell phenotyping was performed in an immune monitoring laboratory; standard, tightly controlled techniques for two- and three-color flow cytometry were used with a Becton-Dickinson FACScan flow cytometer (BD Biosciences, San Jose, CA), FACScan software, and monoclonal antibodies to identify $CD3^+/CD4^+$, $CD3^+/CD8^+$, $CD3^+/CD8^+/CD57^+$, and $CD3^-/CD57^+$ lymphocyte subsets.

NKC cytotoxicity: NKC function may be of major prognostic significance in AIDS-related opportunistic infections. These cells spontaneously lyse virally infected cells but become functionally defective as HIV disease progresses (Chehimi et al., 1992; Hu et al., 1995; Zocchi, Rubartelli, Morgavi, & Poggi, 1998). NKC cytotoxicity was evaluated in a standard 4-hr chromium (^{51}Cr) release assay with NKC-sensitive K562 cells (American Type Culture Collection; ATCC, Manassas, VA) as targets. Interassay variability was controlled through batch-processing and cryopreservation of mononuclear leukocytes, which, if carefully frozen at a controlled rate, can be reconstituted without significant loss of cellular activity (Fujiwara et al., 1986). NKC activity levels were expressed as lytic units, indicating the number of patient NKCs required to lyse 20% of the ^{51}Cr-labeled target cells.

Cytokines: To test the hypothesis that stress management enhances cellular production of Type 1 and Type 2 cytokines in the direction of more normal production levels, we measured phytohemagglutinin (PHA)-stimulated cellular production of IFN-γ, TNF-α, and IL-2 (Type 1 cytokines) and IL-4, IL-6, and IL-10 (Type 2 cytokines). The mononuclear cell fraction was collected with Becton-Dickinson serum separator tubes, and samples were then frozen in a Forma Model 700 controlled-rate freezer (Thermo Scientific, Waltham, MA) over the course of 1 hr. Sets of samples were then thawed and batch-processed for a given participant. Standardized ELISA kits (Quantikine; R & D Systems, Minneapolis, MN) were used to measure levels of cytokine production.

Lymphocyte proliferation: To evaluate overall lymphocyte function, we performed lymphocyte proliferation assays using the ^{3}[H]-thymidine incorporation assay. Purified lymphocytes (1×10^6 cells) were incubated with and without PHA in triplicate in a 96-well plate for 72 hr in a CO_2 incubator. Lymphocyte proliferation was calculated as cellular uptake of radioactively labeled thymidine by stimulated cells in comparison to resting cells. Samples for lymphocyte proliferation were cryopreserved and batch-processed. The sample mean and standard deviation were 7,439.29 and 9,139.19, respectively.

Health Status—In the context of an immunologically mediated disease such as HIV infection, symptomatology represents both an indirect measure of immune functioning and a

clinically significant outcome indicator for stress-related impairment. At each research assessment, participants were categorized according to their CDC disease classification. A more complete HIV-specific health status assessment was obtained from clinical evaluations made with the rHCMSS (McCain et al., 1998). This scale addresses only physical illness and thus is not confounded by neurological, psychiatric, or immunological variables. The rHCMSS has demonstrated excellent interrater reliability (r = .90) and construct validity (McCain et al., 2003). It was scored for historical, or cumulative, symptomatology at study enrollment and for concurrent symptomatology at each data collection point.

Statistical Methods

The analytic goal of this clinical trial was to compare changes in each of the intervention groups (RLXN, SPRT, TCHI) with the changes in the CTRL group. While it would have been interesting to evaluate differences among the intervention groups, this clinical trial was sufficiently powered to test only differences between the intervention groups and the control group. The sample size required to test for differences between intervention groups was not feasible for this study. Prior to the study, power analyses indicated the minimum sample size was 55 per group to provide 87%–99% power. Calculations were based on previous research findings and judgments of levels of clinically meaningful changes in the primary study variables.

The changes of interest were for three time periods: (a) pre- to postintervention (immediate effects), (b) postintervention to 6-month follow-up (maintenance effects), and (c) preintervention to 6-month follow-up (total effects). Comparisons of changes in the CTRL group were analyzed for each intervention group at each of these time periods.

In order to make these comparisons and to accommodate for the inherent correlation structure in the repeated measures, we selected the mixed linear modeling method in SAS Version 9.1.3. As noted by H. Brown and Prescott (2006), the mixed linear model is ideally suited for this situation because (a) various effects can be evaluated simultaneously in a single model to accommodate complex treatment contrasts, (b) the model is unaffected by missing data (assuming that data are missing at random), and (c) the model incorporates complex variance–covariance patterns to model correlation patterns.

For each outcome variable, the typical model included main effects for treatment (SPRT, RLXN, TCHI, and CTRL) and time (pre, post, and 6 months), as well as a Treatment × Time interaction. Additionally, the following variables were considered as potential cofactors in the model: gender, known years with HIV infection, and health status (concurrent rHCMSS score). The models were initially fit with a compound symmetric variance–covariance structure to account for within-subject variations in the outcomes. Using a consistent backward elimination strategy, we subsequently removed from the model any cofactors identified as nonsignificant to the fit of the model, as determined by F tests at a significance level of 0.05. Following removal of any nonsignificant cofactors, the unstructured and autoregressive structures were considered as possible variance–covariance structures. If the unstructured or autoregressive structures had a significantly better fit for the model, then the variance–covariance structures were adjusted; otherwise, the compound symmetric variance–covariance structure was used. Once a final model was selected, the test

of the Treatment × Time interaction was an overall test of significance for each of the primary variables. If this overall *F* test was significant at the $\alpha = 0.05$ level, then the nine separate 1 *df* comparisons were tested to determine specific statistically significant differences.

A single primary response variable represented each of the six primary hypotheses. Because each of these hypotheses represented distinct domains within the PNI framework, no adjustment for multiplicity was made for the overall tests of the six primary variables. For the FAHI and IES, subscales were considered to be secondary variables potentially supportive of the interpretation of these primary variables (i.e., psychological distress and quality of life). However, statistical validity decisions allowed these secondary variables to be analyzed only when the primary variable had an overall significance of $p < .05$. Given this representation of distinct conceptual domains, no further adjustment for multiplicity was made. Further, if the overall *F* test was not significant at the $\alpha = 0.05$ level, the nine tests for group differences were not evaluated. This approach to accounting for multiplicity provided conservative tests for intervention effects.

Results

The 252 participants were evaluated prior to and following the 10-week intervention. A total of 204 participants remained in the sample at 6 months postintervention, yielding a follow-up attrition rate of 19%. Using the mixed linear modeling approach, we tested major hypotheses with 65 participants who completed RLXN, 62 who completed TCHI, 68 who completed SPRT, and 57 who completed a comparable wait-list CTRL period.

Hypothesis Tests

Hypothesis 1 was that participants receiving the interventions, when compared with the CTRL group, would have less HIV-related psychological distress, as indicated by the IES (see Table 1). The overall *F* test for this hypothesis was nonsignificant at $p = .351$.

Hypothesis 2 was that intervention participants would have more effective coping strategies (reduced emotion-focused and increased problem- and appraisal-focused coping), as measured by the Coping subscale of the DIS. With an overall significance of $p = .030$ for emotion-focused coping, the RLXN and TCHI treatment groups showed significant total treatment effects. Concerning frequency in usage of emotion-focused coping between the preintervention and 6-month follow-up visits, whereas an increase was seen in the CTRL group (2.52), declines were found in the RLXN group, −2.74; $\Delta = 5.26$ (*SE* 1.57); 95% confidence interval (CI) = 2.17–8.36, as well as the TCHI group, −1.25; $\Delta = 3.77$ (*SE* 1.60); 95% CI = 0.61–6.93. There also was a significant maintenance effect for the RLXN group, with a decline in emotion-focused coping of −0.79 from postintervention to the 6-month follow-up visit as compared with an increase of 1.92 in the CTRL group, $\Delta = 2.76$ (*SE* 1.32); 95% CI = 0.15–5.37.

Hypothesis 3 was that intervention participants would have higher quality of life, indicated by scores on the FAHI. Overall changes in the total FAHI scores were not statistically significant ($p = .327$).

Hypothesis 4 predicted lower stress-related neuroendocrine mediation, as reflected by decreased levels of salivary cortisol, among intervention participants. However, we found no significant overall changes in salivary cortisol ($p = .187$).

With Hypothesis 5 we anticipated attenuated immunological dysfunction as evidenced by higher lymphocyte proliferative function among those receiving interventions. With an overall $p < .039$, all intervention groups were subsequently found to have significant increases in cellular proliferation capacity—versus a decrease of −3,086 counts/min (cpm) in the CTRL group—between preintervention and the 6-month follow-up visit. The RLXN group had an increase of 1,036 cpm, Δ = 4,122 (*SE* 1,471); 95% CI = 1,220–7,024.0; the SPRT group increased by 1,306 cpm, Δ = 4,392 (*SE* 1,483); 95% CI = 1,466.1–7,318.7; and the TCHI group increased by 646 cpm, Δ = 3,732 (*SE* 1,425); 95% CI = 920.1–6,544.1.

Hypothesis 6 was that those receiving interventions would have better HIV-specific health status (rHCMSS). For health status, there were no significant changes over the study time period ($p = .973$).

Exploratory Analyses

Given the significant findings of reductions in use of emotion-focused coping, we explored possible changes in emotional well-being. There was a total treatment effect noted for the TCHI group in the FAHI subscale of Emotional Well-Being, with an increase of 4.25 versus a control group increase of 0.25, Δ = 4.00 (*SE* 1.66); 95% CI = 0.74–7.26 (see Table 2). The RLXN group also had a 3.85-point increase in Emotional Well-Being scores between the preintervention and 6-month follow-up visits, Δ = 3.60 (*SE* 1.62); 95% CI = 0.43–6.78.

Because the finding of no significant differences in quality of life was not consistent with previous findings by our group and others, we performed additional exploratory analyses. Upon further examination we found significant improvements in the FAHI scores when the intervention groups were compared individually with the CTRL group. For the TCHI group a significant total treatment effect ($p = .017$) was observed in overall quality of life, with an increase in the total FAHI score of 10.18 in contrast to a decrease in the CTRL group of −0.28, Δ = 10.46 (*SE* 4.38); 95% CI = 1.85–19.07. These findings must be viewed as suggestive rather than definitive, given that our multiplicity adjustment rules did not allow for further testing of these differences.

Finally, in the context of the unprecedented changes in lymphocyte proliferation, exploratory analyses of changes in cytokine levels were undertaken. The only clinically and statistically significant change was seen in the SPRT group. A significant total effect was noted in IFN-γ production levels, which increased in the SPRT group by 457.88 pg/ml versus a decrease in the CTRL group of −428.71 pg/ml. The ratio of follow-up median IFN-γ production levels to preintervention IFN-γ production levels was 11.23 times larger for the SPRT group than for the CTRL group (95% CI = 2.21–56.96).

Discussion

Major findings indicated by repeated-measures mixed modeling (which consistently included evaluations of the cofactors of gender, known years with HIV infection, and health status) were that, in comparison to the CTRL group, both the RLXN and TCHI groups less frequently used emotion-focused coping strategies, and all three intervention groups had higher lymphocyte proliferative function. Generally, decreased emotion-focused coping can be considered an enhancement in coping strategies; however, there was no concurrent increase in problem-focused or appraisal-focused coping, making interpretation of this change more tenuous. Interestingly, in exploratory analysis the TCHI group was found to have an impressive increase in overall quality of life. This enhancement in quality of life was largely accounted for by an increase in the realm of emotional well-being, and the RLXN group also demonstrated an increase in that component of quality of life. A commonality of the TCHI and RLXN groups was that a component of these interventions focused on guided imagery and meditation, both with emphasis on dwelling in the moment and "letting go" of fears and problems. Effects related to such specificity of focus were not tested in this study, but future studies may reveal finer specifications of effective strategies to reduce distress and enhance perceptions of quality of life.

Compared with the CTRL group, none of the treatment groups had significant changes in levels of salivary cortisol on awakening or 30 min after awakening, averaged over 3 days at each time point. In general, this sample had relatively low levels of perceived stress at the outset of the study (DIS: $M = 22.71$, $SD = 14.39$; IES: $M = 32.90$, $SD = 11.34$). The consistent finding of increased lymphocyte proliferation indicates the interventions were associated with enhancement in immune system functional status. Because HIV infection first manifests in qualitative immune dysfunction (Clerici et al., 1989), functional rather than enumerative immune measures may be more accurate indicators over the illness trajectory. Additionally, functional indicators of immune status may be more sensitive to psychosocial factors than are enumerative immune measures (Kiecolt-Glaser & Glaser, 1992; Schulz & Schulz, 1992). There are limited previous reports of testing these alternative interventions in persons with HIV infection. To our knowledge, this is the first report of enhanced lymphocyte proliferative function in association with psychosocial interventions in this population. However, because there was no significant change in salivary cortisol, the mechanism of increased lymphocyte function is not clear. Ongoing assessment of cytokine activity or patterns of production may ultimately yield insight into other mechanisms involved in immune function changes.

With the exploratory cytokine analyses, an impressive increase in IFN-γ production levels in the SPRT group was noted. While an 11-fold increase in IFN-γ would be clinically important, this finding must be viewed with caution because of the threat of Type 1 error. Additionally, other evidence for changes in cytokine production capacity was minimal. There were no other readily interpretable changes, largely because changes were seen only in single cytokine levels, and the magnitudes of these changes (other than IFN-γ in the SPRT group) were unlikely to have clinical significance. It also could well be that cytokine patterns among persons on effective HAART regimens are essentially normal. Published work related to cytokine dysfunction since the advent of HAART remains limited, and

patterns of cytokine expression have not yet been established. However, indications are that cytokine regulation is less disrupted for those receiving HAART regimens (Aukrust et al., 1999; Herbeuval et al., 2006; Kamga et al., 2005; McCain et al., 2003; Orsilles, Pieri, Cooke, & Caula, 2006; Stylianou, Aukrust, Kvale, Muller, & Froland, 1999). In future studies, measurement of *ex vivo* plasma or serum levels of cytokines, along with pattern analyses, not only will enable more precise assessments but also will be more clinically meaningful than changes in single cytokine levels following *in vitro* cellular stimulation.

Perhaps one limitation of this study is that these participants were not particularly distressed at the outset, thus minimizing the potential to fully detect the stress reduction potential of these interventions. This was an interesting finding given that much of the attrition in this population is believed to be related to significant life stressors. One critical stressor that has changed in this population is the imminent fear of death with the advent of more effective antiretroviral therapies. Treatment advances have transformed HIV infection from a terminal to a chronic disease. Even so, easily learned stress management strategies that are becoming more widely available in our communities may enhance coping, quality of life, and immune function in this population. It is reasonable for clinicians to consider cognitive–behavioral stress management, tai chi training, and enhancement of spirituality for their clients living with HIV infection.

Conclusion

PNI is an integrating paradigm for advancing both theoretical and empirical knowledge of psychosocial and physiological variables and their effects on adaptational health outcomes. In light of mounting evidence of biobehavioral effects, particularly immunosuppression in association with perceived stress, this study was designed to test the effects of alternative stress management approaches in an immunologically vulnerable population. The experimental pretest–posttest design with repeated measures to assess ongoing effects provided a well-controlled approach for evaluating such potential effects. A particular strength of the study was the comprehensive theoretical framework and consequent multifactorial measurement of PNI-based variables. While comprehensive studies provide opportunities for greater understanding of underlying mechanisms and multiple effects, that strength becomes a limitation in the sense of statistical conclusion validity. Even in this context, significant enhancement of immune function was clearly demonstrated for all interventions. Further, the immunological data were controlled for medication effects by restricting the collection of immune-related samples according to antiretroviral regimen stability, a critical control factor in PNI-based research among persons with HIV infection.

Changes in physiological variables in the context of an immunologically mediated disease are difficult to discern. Physiological variables remain a measurement challenge within the natural setting, thus limiting full understanding of those relationships. However, recent advances in technology, such as multiplex instruments and genetic arrays, have enabled more precise physiological measurements. In future studies, such measures will greatly increase the precision for testing the strength of relationships specified by the PNI model.

Generally, study findings support use of the PNI-based model for stress management in individuals living with HIV infection. Despite modest effects of the interventions on

psychosocial functioning in this sample, the robust finding of improved immune function with these stress management approaches has important clinical implications, particularly for persons with immune-mediated illnesses. Given that as many as 60% of individuals living with HIV disease are seeking nontraditional therapies, clinical guidance is important. Findings of this study indicate that immune function and possibly coping and quality of life may be enhanced with cognitive–behavioral stress management, tai chi, and spirituality-based interventions. While further research is needed to examine specific effects of various stress management interventions and to expand the repertoire of alternative approaches that might be effective in enhancing adaptational outcomes, this study contributes to a growing body of well-designed research that generally lends support to the integration of stress management strategies into the standard care of individuals living with HIV infection.

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Table 1

Means and Significance for Mixed Model Tests of Primary Outcome Variables

Measure and group	Least–square mean (*SE*)			*p*		
	Preintervention	Postintervention	6-month follow-up	Immediate	Maintenance	Total
Impact of Event Scale (possible range: 0-60)						
RLXN	34.45 (1.38)	32.01 (1.38)	33.05 (1.50)			
SPRT	33.70 (1.35)	31.68 (1.36)	32.75 (1.48)			
TCHI	33.96 (1.43)	30.56 (1.45)	28.96 (1.58)			
CTRL	30.15 (1.48)	29.41 (1.51)	30.26 (1.57)	Overall $p = .351$		
Emotion-Focused subscale of Coping (possible range: 0-48)						
RLXN	35.90 (0.81)	33.95 (0.77)	33.16 (0.86)	*ns*	0.038	< 0.001
SPRT	34.11 (0.78)	33.22 (0.75)	35.20 (0.84)	*ns*	*ns*	*ns*
TCHI	35.11 (0.82)	33.90 (0.81)	33.86 (0.91)	*ns*	*ns*	< 0.020
CTRL	33.08 (0.86)	33.63 (0.84)	35.60 (0.89)	Overall $p < .030$		
Cortisol μg/dL (detection range: 0.012-3.00)						
RLXN	0.310 (0.073)	0.437 (0.210)	1.450 (0.446)			
SPRT	0.365 (0.075)	0.216 (0.204)	0.250 (0.462)			
TCHI	0.349 (0.077)	0.647 (0.199)	0.346 (0.430)			
CTRL	0.277 (0.081)	0.266 (0.228)	0.260 (0.471)	Overall $p = .187$		
Total FAHI (possible range: 0-176)						
RLXN	103.81 (3.82)	113.46 (3.78)	111.84 (3.97)			
SPRT	116.93 (3.72)	124.53 (3.69)	122.07 (3.90)			
TCHI	112.93 (3.95)	121.33 (3.96)	123.11 (4.14)			
CTRL	110.74 (4.14)	114.46 (4.12)	110.46 (4.21)	Overall $p = .327$		
Lymphocyte proliferation in counts/ min (sample range: 0-41,533)						
RLXN	6,790 (1,252)	7,797 (1,185)	7,826 (1,191)	*ns*	*ns*	< 0.006
SPRT	8,888 (1,191)	9,356 (1,132)	10,194 (1,205)	*ns*	*ns*	< 0.004
TCHI	6,872 (1,199)	6,656 (1,144)	7,518 (1,137)	*ns*	*ns*	< 0.010
CTRL	6,550 (1,282)	5,163 (1,211)	3,464 (1,214)	Overall $p < .039$		
rHCMSS (possible range: 0-39)						
RLXN	11.47 (1.26)	9.58 (1.25)	10.15 (1.38)			
SPRT	8.65 (1.23)	7.06 (1.23)	5.89 (1.38)			
TCHI	7.73 (1.30)	5.05 (1.29)	5.52 (1.43)			
CTRL	8.57 (1.35)	6.66 (1.35)	5.79 (1.44)	Overall $p = .973$		

Note. RLXN = cognitive–behavioral relaxation training; SPRT = spiritual growth; TCHI = focused tai chi training; CTRL = control; FAHI = Functional Assessment of HIV Infection (Version 4) scale; rHCMSS revised HIV Center Medical Staging Scale.

Table 2

Means and Significance for Exploratory Analyses

Measure and group	Least square mean (*SE*)			*p*		
	Preintervention	Postintervention	6-month follow-up	Immediate	Maintenance	Total
FAHI: Emotional Well-Being subscale (possible range: 0-40)						
RLXN	22.56 (1.18)	26.91 (1.18)	26.41 (1.26)	*ns*	*ns*	0.026
SPRT	24.20 (1.16)	27.80 (1.16)	27.22 (1.25)	*ns*	*ns*	*ns*
TCHI	23.25 (1.23)	27.61 (1.22)	27.50 (1.32)	*ns*	*ns*	0.016
CTRL	23.20 (1.29)	25.38 (1.29)	23.45 (1.34)			
IFN–γ pg/ml (detection range: 15.6-1,000; sample *M* = 109.12; *SE* = 8.11)						
RLXN	343.32 (19.44)	466.44 (25.98)	420.63 (30.76)	*ns*	*ns*	*ns*
SPRT	208.31 (11.64)	450.82 (23.64)	666.19 (52.19)	*ns*	*ns*	0.004
TCHI	181.34 (10.24)	212.81 (12.03)	164.74 (11.88)	*ns*	*ns*	*ns*
CTRL	599.51 (38.66)	366.94 (23.31)	170.80 (13.80)			

Note. FAHI = Functional Assessment of HIV Infection (Version 4) scale; RLXN = cognitive–behavioral relaxation training; SPRT = spiritual growth; TCHI = focused tai chi training; CTRL = control; NKC = natural killer cell.