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Effects of a Cognitive Behavioral Stress Management Intervention on the Psychological, Endocrinological, and Immunological Health of Minority Women Co-infected with HIV and HPV.

Corina Reyes Lopez
University of Miami, c.lopez26@umiami.edu

UNIVERSITY OF MIAMI

EFFECTS OF A COGNITIVE BEHAVIORAL STRESS MANAGEMENT INTERVENTION ON THE PSYCHOLOGICAL, ENDOCRINOLOGICAL, AND IMMUNOLOGICAL HEALTH OF MINORITY WOMEN CO-INFECTED WITH HIV AND HPV

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Corina Lopez

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Corina Lopez

Approved:

_____	_____
Michael H. Antoni, Ph.D. Professor of Psychology	Terri A. Scandura, Ph.D. Dean of the Graduate School
_____	_____
Frank J. Penedo, Ph.D. Associate Professor of Psychology	Mary Ann Fletcher, Ph.D. Professor of Medicine & Psychology

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Effects of a Cognitive Behavioral Stress Management Intervention on the Psychological, Endocrinological, and Immunological Health of Minority Women Co-infected with HIV and HPV.

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Women infected with HIV are at an increased risk for infection of Human Papillomavirus (HPV), developing cervical lesions, and developing cervical cancer. Prior research has suggested disruptions in the immune system as well as circulating levels of stress and gonadal hormones as possible explanations for the increase of HPV infection in women with HIV. Additionally, psychosocial factors such as symptoms of depression and distress have also been associated with HPV infection, as well as disruptions in immune and endocrinologial systems, suggesting a psychoneuroimmunological pathway to disease progression.

It was hypothesized that HIV+HPV+ women assigned to a Cognitive Behavioral Stress Management (CBSM) intervention will experience improvements in disease status, immune markers, circulating stress hormones, and reductions of depression and distress symptoms. An exploratory investigation of the effects of CBSM in levels circulating reproductive hormones was also tested. Follow-up hypotheses tested whether CBSM effects on immune variables were explained by reductions in symptoms of depression, distress, NE, cortisol, and increases of DHEA-S. Additionally, it was hypothesized that CBSM effects on stress hormones would be mediated by reductions in distress and

depression symptoms. Finally, it was hypothesized that improvements in immune parameters would be correlated with decreases in risk of cervical dysplasia at a 9 month follow-up.

Participants were 71 women co-infected with HIV and HPV that were mostly of African American, Haitian, Latina, and Caribbean descent. Hierarchical regression analyses were performed and showed a significant CBSM effect in decreases on BDI somatic depression subscale scores and increases in NK cell counts. Additionally, there was a marginally significant effect of CBSM on increases in CD4+ T-cells and decreases in urinary NE output. The bootstrapping method evidenced a mediation model, where the relationship between group assignment and CD4+ cell counts was explained by lower BDI somatic scores. More research is necessary to fully elucidate the psychobiological trajectories of disease as immunological changes in our sample did not explain the reduced odds of dysplasia in the women assigned to the CBSM group.

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CHAPTER 1: INTRODUCTION

HIV+HPV+Women

The incidence of Human Immunodeficiency Virus (HIV) infection and Acquired Immunodeficiency Syndrome (AIDS) in the United States is increasing more rapidly among women, specifically in women of color, than in any other defined population at risk for HIV infection (CDC, 2007). Recent studies have found that women infected with HIV have increased prevalence, incidence, and persistence rates of human papillomavirus (HPV) infection (Hankins et al., 1999; Massad et al, 1999). For instance, in a study of Hounduran sex workers, women who were HIV+ had higher HPV prevalence rates than women who where HIV- (Ferrera, 1997). In fact, it is estimated that approximately 40% of women with HIV may develop a neoplastic lesion (Goedert et al., 1998). These lesions represent progressive or uncontrolled proliferations of cells that are significantly preceded by HPV infection, and which can lead to cervical cancer (Tachezy et al., 2003). Additionally, besides a higher frequency of abnormal cervical cytology in HIV+ women, they also have significantly higher HPV DNA cervical shedding (73.2%) when compared to HIV- women (23.7%) (Campos et al., 2005). Multiple factors have been proposed as influencing the progression of cervical intraepithelial neoplasia (CIN), also known as cervical dysplasia, to cervical cancer. These influential factors include cervical screening, education, number of sexual partners, age at first sexual intercourse, male sexual behavior, smoking, immunodeficiency, and parity (Bosch, Munoz, & De Sanjose, 1992; Schiffman et al., 1996; Bosch et al., 1996). To date, HPV has remained the most

significant risk factor for CIN as well as invasive cervical cancer (Kjaer et al., 1996; Danaei et al., 2005).

Cellular Immunity

Although preventative efforts for HPV contraction have made gains, particularly with the development of the new FDA approved HPV vaccine, Guardasil, there is limited treatment and knowledge on the persistence of HPV in women living with HIV (WLWH). Indeed, even with standard treatment, recurrence of CIN persists in women who have HIV, and studies show that the severity of these cervical lesions are inversely correlated to immune function (Boccalon et al., 1996). An HIV impaired immune response may explain HPV occurrence and persistence in women co-infected with HIV and HPV (HIV+HPV+), since a compromised immune system may enhance HPV replication, making them more susceptible to developing CIN, and for some even developing cervical cancer (Palefsky, 2003; Massad et al., 1999; Harris et al., 2005). For instance, it is known that HIV progression is regulated by shared cellular mechanisms of antiviral defense, which includes functions of cytotoxic lymphocytes (CD8+ T-cells) (Bonneau, 1994; Walker & Plata, 1990; Walker et al., 1998; & Bandyopadhyay et al., 1990) and helper T-cells (CD4+ T-cells) (Bonneau, 1994; & Ho et al, 1995). CD8+ T-cells are lymphocytes (a type of white blood cell) that kill target cells that are infected with a virus, while CD4+ T-cells are lymphocytes that direct and activate other cells in maximizing the immune system. Among persons with HIV, a diagnosis of AIDS is made when a CD4+ T-cell count of 200 or below is reached. It is this immunosuppression or low CD4+ T-cell count in WLWH that has shown to be significantly associated with infection of HPV (Grinsztejn et al., 2009). Interestingly, although number of sexual

partners strongly predicts HPV recurrence, HPV risk in immunosuppressed women who are HIV+ still remains, even in women that are not sexually active (Strickler et al., 2005). Moreover, a study examining cellular activity in progression of CIN found that regressors (individuals with baseline gynecological abnormalities that regressed to normal results by follow-up) show an increase of CD4+ T-cell counts at follow-up (Moore et al., 2002). Similarly, results from Woo et al. (2008) suggest that regressors show patterns of increased CD8+ T-cells at baseline, and an increase of CD4+/CD8+ T-cell ratio at follow-up.

Natural Killer (NK) cells, as characterized by CD56+ cells, have also been implicated in the impairment of the immune system of individuals with HIV (Nunes, 2001) as well as in the progression of CIN (Satam, Suraiya, & Nadkami, 1986; Seltzer, Doyle, & Kadish, 1983). NK cells have a unique and important role in killing virally infected cells as they do not need antigen presenting cells to activate them. Studies have shown that NK cell activity is important in preventing lesions from developing in women with HPV (Majewski et al., 1990, Mestecky et al., 2005). It has been proposed that decreased levels of NK cell counts in the subepithelial stroma of the cervix makes the basal cells of the cervix more vulnerable to HPV infection (Tay, Jenkins, & Singer, 1989). For example, patients diagnosed with squamous intraepithelial lesions (SIL) or cervical carcinomas show a decrease of NK cell function against HPV (Malejczyk, Majewski, Jablonska, Rogozinski, & Orth, 1989). Similarly, studies have found that HPV recurrence is associated with decreased NK cell count (Stentella, 1998), and that patients with spontaneous regression of cervical dysplasia show higher levels of NK cell activity (Garzetti, 1995). Conversely, although the majority of research points to

immunosuppression as one of the principal reasons why individuals infected with HIV reveal an increased prevalence of HPV infection and disease, it is important to note that there has also been alternative evidence, such as molecular interactions between HIV and HPV viral genes, as influencing HPV susceptibility (Arany & Tyring, 1998; Dolei et al., 1999; Moscicki, 2000).

Stress Hormones

Catecholamines. Besides cellular dysfunction, there is research suggesting neuroendocrine disturbances in people infected with HIV and in cancer populations. The sympathetic nervous system (SNS) and the hypothalamic pituitary adrenal (HPA) axis are biological systems widely associated with neuro-immune status changes (Pabello & Lawrence, 2006). The SNS regulates a variety of homeostatic mechanisms in the body and releases catecholamines, such as epinephrine (E) and norepinephrine (NE), as a response to stress. Patients who are HIV+ show an earlier NE peak in response to laboratory behavioral challenges when compared to patients who are HIV-, suggesting a physiological dysfunction (Kumar et al., 1991). Additionally, studies have demonstrated that NE plays a significant role in accelerating the rate of HIV replication (Cole et al., 1998; Cole et al., 2001). One study suggests that activation of the SNS stress response releases NE into areas rich in T-lymphocytes, making them more vulnerable to noradrenergic signaling (Shimizu et al., 1994). Although SNS dysfunctions and the role of catecholamines have not been studied much in the HPV literature, work has been conducted in patients with herpes simplex virus (HSV) infections and cancer. Studies reveal that both NE and E impede interferon (cell signaling proteins [cytokines] produced

by cells) activated macrophages in recognizing and killing HSV infected cells (Koff & Dunegan, 1986). Furthermore, studies have proposed a relationship between the neuroendocrine system, immunity, and cancer, wherein the immune system functions as a mediator between the two, and as a consequence of immunosupression tumor progression is enhanced (Shakhar & Ben-Eliyahu, 1998; Reiche & Nunes, 2004). Studies have shown that NE inhibits cytotoxicity of NK cells (Lang et al., 2003), which might explain tumor formation and cancer progression (Palm et al., 2006). Furthermore, of all the neurotransmitters, NE has shown to be the most powerful stimulator for migration of cancerous cells, including breast, colon, and prostate cancer (Masur et al., 2001; Drell et al., 2003; Lang et al., 2004).

Cortisol. The HPA axis is a major component of the neuroendocrine system that mediates the body's reaction to stress by producing corticosteroids, including cortisol (Antoni, 2003). There is a substantial amount of literature examining cortisol effects on HIV. For instance, it has been demonstrated that abnormally higher levels of resting cortisol are found in individuals that are HIV+ when compared to individuals that are HIV- (Lortholary et al., 1996; Enwonwu et al., 1996). Moreover, in a study by Markham et al. (1986), cortisol was demonstrated to enhance HIV replication in vitro (Markham et al, 1986). As such, in a study investigating the effects of a bereavement support group for patients with HIV, increased CD4+ T-cell counts were associated with reduced levels of cortisol (Goodkin et al, 1998). In other studies, cortisol was found to up-regulate apoptosis of CD4+ T-cells (Roger et al, 2004; Nair et al., 2000). Cortisol has also been associated with short term reductions of lymphocyte proliferation and NK cells, as well as decreases in CD8+ and CD4+ cells (Petitto et al., 2000; Ullum et al., 1995; Antoni,

2000). This suggests that cortisol may have a detrimental effect on the immune system and other types of immune cells that help fight off viral infections.

Although research has established the negative effects of cortisol on HIV, research is still growing on cortisol's role on other types of viral infections, such as HPV. One study has shown, however, that glucocorticoid elevations increases replication rate and regression of several latent viruses, which include Epstein-Barr, Cytomegalovirus, and Kaposi's Sarcoma related herpes viruses (Scully et al., 1994). This same study also found that corticosteroid therapy makes patients more vulnerable to viral infections and dysplasia. Animal studies add to this literature by demonstrating a direct association between glucocorticoids and HPV activation and progression (Peter et al., 1988; Crook et al., 1988). For example, Bartholomew et al. (1997) found that hydrocortisone treatment interfered with the ability of antigen presenting cells to activate cytolytic T-cells in HPV positive cervical tumor cells. In contrast, this was not found for normal cervical cells, suggesting that HPV infected cells are particularly vulnerable to physiological dysregulations.

DHEA. Dehydroepiandrosterone (DHEA) is another stress hormone produced by the adrenal glands that differs from cortisol in that circulating levels have demonstrated beneficial aspects on immune-mediated illnesses. For instance, DHEA is positively associated with CD4+ T-cells and negatively associated with viral load in patients with HIV (Kannangai et al., 2008). Additionally, DHEA has shown to increase NK cell cytotoxicity (Solerte et al., 1999), as well as improve the function of both immune and endothelial cells (Williams et al., 2004; Khorram et al., 1997). Conversely, individuals who are HIV+ show a decrease in DHEA levels and an increase of cortisol to DHEA

ratio when compared with individuals who are HIV- (Chittiprol et al., 2009). Higher levels of DHEA have shown to be beneficial in cancer populations as well. DHEA has been demonstrated to prevent the development of breast, prostate, and skin cancer (Pashko et al., 1985; Gordon, 1993). In animal studies, increases in DHEA are associated with inhibition of cervical carcinogenesis (Rao, 1989; Green et al., 2001; Ciolino et al., 2003). Notably, one study showed that DHEA is associated with regression of low grade cervical dysplasia in women infected with HPV (Suh-Burgmann et al., 2003).

Sex Hormones

It is well established that long term use of oral contraceptives (OC) increases a woman's risk of HPV infection (Hildesheim, 1990), developing cervical neoplasia (Brinton et al., 1986; Beral et al., 1988), and cervical cancer (Francecshi, 1995). Indeed, OC use has been shown to influence severity of dysplasia as well as influence the progression of malignant cells in the cervix (Stern, 1977; Brinton, 1991). OC's usually contain combinations of synthetic progesterone and estrogen, although there are some that contain only progesterone. Most studies investigating the relationship between estrogen and/or progesterone have found that these sex hormones increase the transcription of HPV oncogenes (genes that help normal cells turn into cancer cells when they are mutated) (Yuan et al. 1999; Yuan et al., 1999b; Mittal et al., 1993). For instance, oestradiol, a type of estrogen, has been shown to up-regulate the transcription of HPV genes and to enhance growth in HPV+ cells (Mitrani-Rosenabum et al., 1989; Chen et al., 1996). Moreover, an increased risk of cervical cancer is associated with use of progesterone only OC's (Herrero et al., 1990; Hildesheim et al., 2001). Conversely, it is important to note that, to date, findings of the relationship between sex hormones and

cervical health are mixed, as studies have also shown indirect or no clear associations (Arbeit et al., 1996; Elson et al., 2000).

Even though studies investigating the influence of synthesized sex hormones on HIV have also been limited, there is one meta-analyses study that found a small but significant association between OC and contraction of HIV as well (Wang et al., 1999). These results remained significant even when taking into account condom use, frequency of partner exchange, concomitant STD, and sexual behavior. Additionally, changes in the menstrual cycle and levels of estrogen and progesterone in women with HIV have been associated with viral load, such that later stages of menses and consequently lower levels of estrogen and progesterone are associated with a higher viral load (Greenblatt et al., 2000). Estrogen has also been shown to induce a humoral immune response rather than a cell mediated immune response, which may be due to the estrogen receptors found in antibody producing B-cells (Gilden, 2003). This could suggest that sex hormones might play a crucial role in women's vulnerability to viral infections, and as such would be of value to examine whether and how they also are related to the progression of viruses. Further research is thus needed to determine the implications of sex hormones on both HIV and HPV progression.

Psychosocial Factors

An important consideration when seeking to understand the relationship between biological systems and disease is the role of psychosocial variables. Studies examining the psychosocial impact of being infected with HIV and HPV have found increased stress reports and depression rates when compared with women with neither diagnosis (McCaffery, 2006; Clarke, 1996; Kabbash, 2008; Siegel & Schrimshaw, 2005). In fact, in

a meta-analysis investigating depression in people with HIV, depression rates were found to be twice as higher when compared with individuals with no HIV diagnosis (Ciesla & Roberts, 2001). Furthermore, Koopman et al. (2002) found that approximately 31% of men and WLWH report levels of acute stress reactions to recent life events that would also meet criteria for an acute stress disorder diagnosis. Interestingly, only 9.4% of the participants in this study described a significantly stressful life event, such as an event that was threatening to the life or physical integrity of themselves or others. This would suggest that a critical subset of individuals with HIV that have experienced non traumatic life events still experience high levels of acute stress, which may put them at risk for developing PTSD. This has been shown in a study by Cohen et al. (2002), wherein PTSD prevalence was found in up to 42% of people infected with HIV. These results have important implications for women who are HIV+HPV+, since both stress and depression are significantly correlated with CIN progression (Dodd et al., 2009; Fang et al., 2008; Pereira et al., 2003). Thus, particular attention needs to be paid to the mental health of individuals who are HIV+HPV+ as they compose a distinct and vulnerable population.

It has been hypothesized that psychosocial factors influence the progression of immunologically-mediated disease by their impact on the immune system. For example, deficits in CD4+ T-cells and NK cells are common in depressed and/or stressed, but otherwise physically healthy individuals (Herbert and Cohen, 1993a; Herbert and Cohen, 1993b). In HIV+ men and WLWH who have a low viral load, defined as one standard deviation above the average viral load (mean= 49,513.50 RNA copies/ml; SD= 102,159.50), those with higher levels of distress show lower levels of helper T-cell and B-cell counts (Motivala et al., 2003). Moreover, people with HIV who report lower life

stress and minor depressive symptoms show less decreases of CD4 T-cells percentages after a 6 month follow-up (Patterson et al., 1995). Furthermore, a study by Leserman et al., (1997), demonstrated that HIV+ men with severe depression and stress symptomatology had decreases in CD8+ T-cells, NK subsets (CD56+ and CD16+) during a 2 year assessment period. Additionally, it has been found that both depression and anxiety symptoms are related to lower levels of NK cell activity and higher activation of CD8+ T-cells and viral load in people with HIV (Evans et al., 2002).

Prior investigations have shown that there are significant associations between adrenal stress hormones and a diagnosis of Major Depressive Disorder (MDD) and PTSD. For instance, higher than average levels of cortisol are associated with a diagnosis of MDD (Plotsky et al., 1998; Yehuda et al., 1993; Yehuda et al. 1996). Over-activity of the SNS has also been linked to MDD, evidenced by higher levels of circulating NE and E in diagnosed patients (Gold & Chrousos, 1999). Patients with PTSD show similar profiles including increased levels of NE (Yehuda et al., 1996; Southwick et al., 1993; Cohen et al., 2001), and cortisol (Cohen et al., 2001). Conversely, DHEA decline is related to both depression (Barrett-Connor et al., 1999) and HIV infection (Jacobson et al., 1991). In fact, DHEA has shown to be effective as a treatment for patients with HIV who are depressed (Rabkin et al., 2006). Beneficial effects of DHEA are seen in patients with PTSD as well, such that DHEA diminishes severity of PTSD symptoms (Rasmusson et al., 2004).

Gonadal hormonal fluctuations have also been shown to covary with negative mood states such as depression and anxiety. For instance, estrogen and progesterone are

two major sex hormones that have been consistently associated with depression (Barret-Connor et al., 1999; Stewart et al., 1993). In childbearing women, estradiol is related to postpartum depression (O'Hara et al., 1991), while progesterone administration after childbirth reduces the chances of postpartum depression (Dalton, 1980; Solthau & Taylor, 1982). Depression is also associated with estrogen shifts in life cycle, such as puberty, premenstrual, postpartum, and perimenopausal stages (Stahl, 2001). Furthermore, women with decreased levels of estrogen and progesterone also report more anxiety, which may explain susceptibility to stress and anxiety disorders (Seeman, 1997). In one study, stress was directly associated with cancer, but only in women who received hormone therapy (Nielsen et al., 2007). This indicates that hormonal changes may put women at risk for cancer related illnesses. Interestingly, as mentioned elsewhere in the paper, increased levels of estrogen and progesterone may contribute to greater vulnerability to HPV infection and progression, as do depression and anxiety symptoms. However, distress has also been shown to be negatively correlated with estrogen and progesterone. This may suggest that dysregulations of the circulating levels of sex hormones may be more crucial in explaining mood and health declines, as opposed to whether these hormones are found in greater or lower amounts. Presently, no study has explored the degree to which variability in negative mood states and gonadal hormone regulation contributes to increased risk for HPV-associated disease activity in women infected with HIV.

In summary, from the evidence presented, it appears that women who are HIV+HPV+ form a vulnerable population that experience a variety of psychological stressors that may exacerbate physiological indicators associated with immune system

functioning and susceptibility to disease progression. As mentioned, these women experience higher rates of anxiety and depressive symptoms than women with neither diagnosis. These psychosocial factors have been associated with immunological and endocrinological changes, which in turn have been shown to play a role in HIV disease progression and HPV recurrence. It would be plausible to suggest then that this population, who is dealing with considerable amounts of distress, would benefit greatly from programs designed to lower stress, such as those that help individuals cope and manage their distress.

Psychosocial Interventions

There is growing evidence that stress management interventions are effective and beneficial to distressed medical populations. As described above, individuals who are HIV+HPV+ experience a variety of physiological and psychosocial changes that may influence disease. It is important to note that in the past years studies have investigated the effects of psychosocial interventions on psychological and immunological factors in people infected with HIV. One study found that a mindfulness based stress reduction intervention buffered declines of CD4+ T-cells in patients with HIV from pre to post-intervention (Creswell, Myers, Cole, & Irwin, 2009). This effect was significant even when controlling for medication adherence, elucidating the powerful effects of stress management interventions. In another study, a cognitive behavioral intervention showed decreases in depressed mood and elevations in quality of life in men from Hong Kong who were HIV+ when compared with a waiting list control group (Chan et al., 2004).

Moreover, a review by Crepaz et al. (2008) showed that psychosocial interventions are indeed effective in improving mental health in populations who are HIV+.

Cognitive Behavioral Stress Management (CBSM) intervention has received much attention due to its effectiveness in improving mental and physical health in populations that are HIV +. The CBSM intervention that serves as the basis for this work is a 10 week manualized intervention that incorporates both cognitive behavioral and relaxation training that was designed to build social support and coping self efficacy skills, change distorted cognitive appraisals, reduce perceived stress and improve sense of control (Antoni, Schneiderman, & Ironson, 2007). It has been suggested that stress management interventions that modify psychosocial factors, also modify biological factors, such as endocrine and immune system indicators, and these in turn influence disease status (Antoni, 2003). Figure 1, for example, depicts how CBSM may exert changes in health. One CBSM study looking at depression and anxiety levels in a sample of homosexual men awaiting HIV status notification, showed that men randomized to a CBSM group exhibited stable levels of depression and anxiety when diagnosed as HIV+, while men in the no treatment control group exhibited significant increases in both depression and anxiety when notified that they were HIV+ (Antoni et al., 1991). Moreover, the men who were HIV+ in the CBSM group also showed increases in helper CD4+ T-cells and NK cell counts compared to controls. Other studies have replicated these CBSM findings on depressed mood, anxiety, and distress in gay men with HIV (Lutgendorf et al., 1997; Carrico et al., 2005a). Reductions in depressed mood have also been shown in minority WLWH that have completed a CBSM intervention after a one year follow-up (Laperriere, 2005; Lechner et al., 2003). Importantly, Antoni et al. (2006)

found that HIV+ men on Highly Active Antiretroviral Therapy (HAART) randomized to a CBSM plus medication adherence training (MAT) group displayed significant reductions in HIV viral load over a 15-month follow-up, while men receiving MAT alone demonstrated no changes.

CBSM studies have also shown alterations in adrenal stress hormones in populations that are HIV+. For instance, CBSM has shown to decrease 24 hour urinary free cortisol output, plasma cortisol/DHEA-S ratio, and 24 hour urinary NE in samples of gay men with HIV (Antoni et al., 2000a; Cruess et al., 1999; Antoni et al., 2000b; Cruess et al., 2000). Furthermore, these studies showed that urinary cortisol and plasma cortisol/DHEA-s ratio reductions were associated with decreases in depressed mood, while urinary NE reductions were associated with decreases in anxiety levels. These hormonal changes have been hypothesized to mediate immunological effects of CBSM. For instance, reductions in NE levels have been related to higher levels of CD8+ cytotoxic suppressor T-cells at a one year follow-up (Antoni et al., 2000b), while reductions in urinary cortisol and depressed mood have been associated with higher numbers of naive T-cells at a similar follow-up (Antoni et al., 2005).

Previous CBSM studies have also shown a decrease in HSV 2 IgG antibody titers in gay men with HIV that were assigned to CBSM vs controls (Lutgendorf et al., 1997, Cruess et al., 2000). Reductions in HSV-2 IgG titers over the intervention period were associated with greater perceived social support, increases in relaxation skills, decreases in depressed mood, and decreases in cortisol/DHEA ratio. Additionally, HIV+ men assigned to CBSM have shown reductions in other herpesvirus IgG antibody titers (i.e., Epstein-Barr virus capsid antigen; EBV-VCA) at post-intervention (Esterling et al.,

1992), and up to one year later (Carrico et al., 2005b). Accordingly, there is sufficient evidence that points to psychological and physiological improvements for people with HIV who undergo a CBSM intervention. In spite of this, there are few CBSM studies investigating these effects in minority WLWH, especially in those that are HIV+HPV+. Currently, there is one study that examined CBSM effects on HIV+HPV+ women. This study found that HIV+HPV+ women assigned to a 10-week CBSM intervention showed decreases in life stress and odds of developing persistent cervical dysplasia at a 9 month follow-up (Antoni et al., 2008). The study also found that life stress was not a significant mediator for the effects of CBSM on dysplasia, indicating that other psychosocial variables may be accounting for the effects of the intervention on cervical dysplasia.

Goals and Aims of the Proposed Study

The proposed study sought to investigate whether CBSM improved psychological well-being and physiological indicators in a sample of predominantly African-American or Caribbean-American women (N=71, mean age= 31.23) who are HIV+HPV+. We further proposed to examine whether any of these CBSM intervention effects were associated with the previous findings of a CBSM effect on cervical dysplasia (e.g. CIN). Aims and hypotheses were as follows:

Aim 1 and Hypothesis 1: CBSM effects on depressive symptoms and distress in WLWH and HPV were tested. Specifically, we hypothesized that women in the CBSM condition would show a decrease in depression and anxiety symptoms pre-post intervention, as shown by reports on the Beck Depression Inventory (BDI) and Impact of Events Scale (IES) measures.

Aim 2 and Hypothesis 2: CBSM effects on disease status and immune variables were tested. We hypothesized that women in the CBSM condition would show improvements in immune status (i.e., increased CD4+ T-cells, CD8+ T-cells, NK cells (CD56+CD3-), increased NK cytotoxicity, and decreased viral load) pre to post-intervention.

Aim 3 and Hypothesis 3: CBSM effects on adrenal stress hormones were determined. We hypothesized that women in the CBSM condition would show reductions in urinary cortisol and NE levels and show an increase in serum DHEA-S levels and Cortisol/DHEA-S ratio levels from pre to post-intervention.

Aim 4 and Hypothesis 4: This was an Exploratory Aim. CBSM effects on gonadal hormones, specifically estrogen and progesterone from pre-post intervention were tested.

Follow-up Hypotheses:

Follow-up Hypotheses were proposed if CBSM effects were found for our outcomes of interest.

Hypothesis 5a: We hypothesized that CBSM effects on immune variables would be mediated through cortisol and NE reductions, and increases in DHEA-S levels.

Hypothesis 5b: We hypothesized that CBSM effects on immune variables would be mediated through decreases in depression and anxiety symptoms.

Hypothesis 5c: We hypothesized that CBSM effects on stress hormones were mediated by distress and depressive symptom reduction, such that CBSM-associated reductions in

anxiety and depression would explain decreases in cortisol and NE, and increases in DHEA-S.

Hypothesis 6: We hypothesized that CBSM related increases in immune parameters (CD4, CD8, NK, and NKCC increases and viral load decreases) would mediate the relationship between CBSM and decreases in risk of cervical dysplasia at 9-month follow-up as found in a prior study.

CHAPTER 2: METHOD

Participants

Participants were 71 African-American, Haitian, Jamaican, and Hispanic women living with HIV (WLWH). Women were enrolled in Project C-SMART (Cervical Stress Management, Adherence, and Relaxation Training), which investigated psychological, viral, and immunological risk factors for gynecologic disease and collected data at pre-intervention (T1), post-intervention (T2), 6 month follow-up (T3), and 1 year follow-up (T4). Recruitment was conducted at the Specialty Immunology Clinic at the Department of Obstetrics and Gynecology at the University of Miami/Jackson Memorial Hospitals, where patients received routine gynecological, prenatal, postpartum, family planning, and primary care. OB/GYN personnel informed eligible patients of the present study, and if they were interested introduced them to a psychology student to obtain further information. The psychology graduate student explained the rationale and procedures of the study to the patient. If the patient expressed interest, formal screening procedures were conducted at that time or an appointment was made for a later date at the OB/GYN Research Unit. The C-SMART project was funded by the National Cancer Institute and was conducted in accordance with the rules and regulations of the Human Subjects Committee of the Institutional Review Board at the University of Miami School Of Medicine.

Women eligible to participate in the study were between the ages of 18 to 60, had a history of Papanicolaou smears indicating low-grade squamous intraepithelial lesions (LGSIL) or at least two cervical biopsies indicating atypical cells of undetermined significance (ASCUS) in the two years prior to baseline entry, had a CD4+CD3+ cell

count above 200 cells/mm³, and were fluent in English. Exclusion criteria were designed to increase homogeneity of sample and to reduce confounding factors in physiological and psychological dependent measures. Exclusion criteria included two or more negative Papanicolaou smears in the two years prior to baseline entry, a history of SIL diagnostic or treatment procedure six months prior to baseline entry, any history of high-grade SIL, CIN II, CIN III, or invasive cervical cancer, unless occurring at study entry, on immunotherapy, pregnant or postpartum less than six weeks, or experiencing any major psychiatric illnesses, which may have interfered with providing valid psychosocial assessment data and participation in the intervention, such as suicidality, drug dependence, psychosis, and antisocial/borderline personality disorder. Additional exclusion criteria included a life expectancy less than12 months as determined by the study's research nurse and a reading and writing level below sixth grade.

Procedures

Data from T1 (n=71), T2 (n=52), and T3 (39) was utilized from women participating in Project C-SMART. At baseline entry, participants completed an informed consent, colposcopy, and HPV cervical swab to establish cervical health eligibility. After the colposcopy, a psychosocial assessment interview was conducted, which was followed by a peripheral venous blood draw. Participants completed a 60-90 minute psychosocial interview that assessed overall psychiatric and psychological well-being during this assessment and were randomized to a CBSM or one day workshop if eligible. A 2:1 ratio randomization procedure was utilized to ensure that a minimum of six participants were in the 10 week group. Assessments were conducted by female Clinical Health Psychology graduate students or a post-doctoral associate. For follow-up sessions, a staff

member who was not a group or workshop facilitator carried out the assessments in order to reduce potential bias (e.g. demand characteristics).

Participants were compensated financially for completing assessments and for study related accommodations, such as transportation, childcare, and meals. They were also contacted monthly in between study related visits, to update their contact information and to remind them of their next appointment. Before any study related visit, participants were contacted through phone, mail, or in person to discuss any resource issues (e.g. transportation, childcare etc.) or other demands (employment) that could interfere with their ability to attend their appointment.

Measures

Beck Depression Inventory. (BDI; Beck et al., 1961). The BDI is a widely used 21 item multiple choice self report measure designed to assess affective, behavioral, and somatic aspects of depression. The measure is designed for individuals 13 or older, and is composed of items asking about hopelessness, weight loss, fatigue, guilt etc. in order to assess severity of depression. The BDI can be separated into two subscales, the affective and somatic subscale. Examples of items include: “I feel that the future is hopeless and that things cannot improve”, “I blame myself for everything that goes wrong”, and “I am less interested in sex than I used to be”. The inventory is scored by summing the assigned value, from 0-3, for each answer to compose a total score. A cut-off of 0-9 indicates that a person is not depressed, 10-18 indicates mild to moderate depression, 19-29 indicates moderate to severe depression, and 30-63 indicates severe depression. The BDI has a split half Spearman-Brown reliability of .93 for psychiatric patients (Beck, 1970), and a mean alpha coefficient of .81 for non psychiatric patients (Beck, Steer, & Garbin, 1988).

The BDI correlates highly with alternative depression measures such as the Hamilton Rating Scale for Depression (mean= .73 in psychiatric samples) and the Zung Self Reported Depression Scale (mean= .76 in psychiatric samples) and discriminates well between several different groups of both psychiatric and non psychiatric populations (Beck, Steer, & Garbin, 1988). The BDI has been used frequently with individuals infected with HIV and has been shown to respond to changes in dysphoria over the course of the 10 week CBSM intervention (Lutgendorf et al., 1997; Lutgendorf et al., 1998). The mean BDI in the participants was 9.34 *(SD*= 12.80*;* range = 0-44*,* α= .92*)*.

Impact of Events Scale-Revised. (IES-R; Horowitz, Wilner, & Alvarez, 1979; Weiss & Marmar, 1997). The IES-R is a self report measure utilized to assess stress related symptomatology for HIV/AIDS specific intrusive or avoidant thoughts. It is composed of 22 items that measure the coping and stress response of participants to a stressful event and has an intrusion and an avoidance subscale. Examples of intrusive thoughts items include: "I thought about it when I didn't want to", "Pictures about it popped into my mind", and "I had waves of strong feelings about it". Examples of avoidant items include: "I stayed away from reminders of it", "I tried not to think about it", and "I avoided letting myself get upset when I thought about it or was reminded of it". Participants responded to each item by selecting one of five answer choices that best reflected the degree that the statement applies to them (0= Not at all to 4= Extremely). The IES is scored by summing the respective values of all the items to yield a total symptom score (Range 0-110). The IES-R has demonstrated good internal consistency and reliability (alpha=.79 to .92) (Horowitz, Wilner, & Alvarez, 1979). The mean IES score in the participants was 29.97 *(SD*= 11.81*;* range = 15-56*,* α= .93*)*.

Immunologic Measures

Immune measures utilized in this study included HIV viral load, T-helper cells (CD4+), T-cytotoxic cells (CD8+), natural killer cells (CD56+CD3-; NK cells), natural killer cell cytotoxicity Day 1 and Day 2 (NKCC D1; NKCC D2), and interferon stimulated NKCC D1 and D2 (INKC D1; INKC D2). Blood draws were performed by a trained phlebotomist at the Women's Health Initiative Program (WHI) at the UM/JMH campus and were taken to the E.M. Papper Clinical Immunology Laboratory within two hours of draw. Peripheral blood was collected in five tubes; two contained ethylene diamine tetra acetic acid (EDTA), two contained sodium heparin (Vacutainer-EDTA, Becton-Dickinson, Rutherford, NJ, USA) and one did not contain any anticoagulant additive. Plasma were then removed from samples in heparinized tubes and stored at -80 degrees Celsius.

Distribution of lymphocytes was determined by 4-color cytometry as outlined by Ironson et al. (1997). This procedure utilized monoclonal antibodies, specific for lineage, activation, differentiation, and adhesion molecules. Moreover, it also allowed for conjugation with fluorescent dye and photometer to measure the reflective energy given off by cells. A single laser flow cytometer (Coulter XL Cytometer, Coulter Corporation, Hialeah, FL) was used with a whole blood, four color analysis procedure to determine the number and percent of T-cells, NK cells, and the subclasses of these. Cells were incubated with concentrations of monoclonal antibodies infused with fluorescent dye. Four fluorochromes (phycoerythrin, fluorescein isothyocynae, energy couple dye, and PC5) in antibody combinations were used to measure lymphocyte phenotype distribution. One hundred microliters of peripheral whole blood was added to a lysing reagent that

breaks down erythrocytes after a 10 minute incubation period, leaving the leukocytes in place (Coulter Multi Quick Prep System). Positive cells were assayed by direct immunofluorescence using a Coulter XL flow cytometer 488nm laser line to measure the stained samples. The T-cell lymphocytes were accounted for in a large bit map within the lymphocyte area. Mo2 (CD14) surface marker positive cells were accounted by bit maps placed in the monocyte area of the forward angle light scatter against 90 degree light scatter histogram. For the NK1+ cells, bitmaps were placed in the lymphocyte and monocyte area of the forward angle light scatter versus the 90 degree light scatter histogram without a granulocyte area. Positively stained cells and doubled stained cells for each marker pair were found using QuadStat software (Coulter Corporation). The numbers of peripheral lymphocytes were analyzed by multiplying total white blood counts and percentage of lymphocytes. To finish, absolute counts of lymphocytes or mononuclear cells positive for corresponding surface markers were determined by multiplying peripheral lymphocyte or mononuclear cell counts by the percentage of positive cells for each individual surface marker (Klimas et al, 1991).

Natural killer cell cytotoxicity (NKCC) was determined by utilizing the whole blood chromium release assay as described in Baron, Klimas, Fischl, and Fletcher (1985) and Fletcher, Baron, Ashman, Fischl, and Klimas (1987). NKCC assays were completed within eight hours of blood draw when possible, since research suggests that samples held overnight have a significant reduction in NK cell activity against K562 targets (Fletcher et al., 1987). A whole-blood chromium51 release assay was used to determine NKCC to the K562 cell line. Peripheral blood samples were heparanized and dispensed into wells of 96-well flat bottom tissue culture trays (Costar, Cambridge, MA). K562

cells were then incubated with the blood samples for four hours in a humidified 37 degree Celsius environment. After, cell free supernatants were removed and counted on a gamma counter. Number of effector cells was determined by the flow cytometer and defined as CD56+CD3- lymphocytes. NKCC was expressed as cytotoxicity percent at a 1:1 target to effector ratio, which was estimated by a linear regression equation from a computer program developed in house.

Neuroendocrine Measures

Neuroendocrine data was collected through a 15 hour urine collection procedure. Participants were provided with both verbal and written instructions on how to collect their urine. Instructions were to abstain from any caffeine, alcohol, antihistamines, and nicotine beginning before the urine collection began (6pm) and until they had finished collecting their urine (9am). Fifteen hour urine collection was utilized rather than a 24 hr collection since compliance is higher and because it captures the most important time (i.e. overnight) where stress related differences are observed. Participants were instructed to keep their urine samples refrigerated until their next scheduled appointment. Prior to collection, one gram of sodium metabisulfite was added to the urine container as a preservative. After collection, samples were measured for volume and two aliquots of 10ml each (one for cortisol and one for catcholamines) were frozen at -70 degrees Celsius until the time of assay. Finally, 100 µl of 6n CL was added to the catecholamine urine tubes to prevent their breakdown.

Cortisol. Cortisol was measured by a standard solid phase radioimmunoassay procedure using a commercial kit (Coat-A-Count Cortisol, Diagnostic Products Corp., Los Angeles, CA). First, 500 ul of urine samples were extracted in 1 ml of

dichloromethane. In duplicate, fifty microliter aliquots of the extract were deposited into cortisol antibody coated tubes and evaporated to dryness under nitrogen at room temperature. This was followed by an addition of 1 ml of I^{125}-labeled cortisol solution, which competes with the cortisol for antibody sites. Tubes were vortexed and incubated for 45 minutes at 37 degrees Celsius. Tubes were then decanted and radioactivity was counted for 1 minute in a gamma counter (Model KLIN gamma). Calculations were conducted from a calibration curve with percent bound = (net counts/net maximum binding counts) x 100 and percent of binding was converted to ug/dl. This procedure has been shown to be highly specific for cortisol with little cross reactivity to other steroids or compounds that may be present in the samples. A sensitivity of 0.2 ug/dl has been reported by the manufacturer (Diagnostic Products Corp., Los Angeles, CA).

Catecholamines. Urine samples were thawed and their pH adjusted to 3.00 before analyzing them for catecholamines. Three ml aliquots of urine samples were centrifuged at 15,000 rpm for five minutes at four degrees Celsius. The supernatants were then collected and their pH was adjusted to 6.5 with 0.5 M NaOH. DHBA was added to these samples, which were then applied to Bio-Rex 70 Ion exchange columns (BopRad). After draining the samples completely, the columns were washed three times with 10ml distilled water. Catecholamines were eluted with 6ml 0.6 M boric acid solution and the eluates were used for quantifying the catecholamines, as outlined by Kumar, Kumar, Fernandez, Mellman, and Eisdorfer (1991).

DHEA-S and Reproductive Hormones. Dehydroepiandrosterone sulfate (DHEA-S) and the reproductive hormones used in this study, specifically Estradiol and Progesterone, were measured in the plasma obtained from all participants between

9:00am to 12:00pm during the assessment periods. A sample of 10ml of blood was collected in an EDTA coated tube and centrifuged at 2500 rpm for 5 minutes at a temperature of 4 degree Celsius. After this procedure, plasma was aliquoted into respective freezer tubes and stored at -80 degrees Celsius until they were analyzed. These were assayed using a solid state Radioimmunoassay (RIA) technique, at a sensitivity of 6.5 pg/ml. The intrassay and interassay CV percentages were 3.2 and 9.0 respectively. The RIA competitive binding technique was conducted as described by Yalow and Berson (1971).

Colposcopy and HPV Cervical Swabs. Participants also underwent a colposcopic examination from a registered nurse practitioner with specialized colposcopy training from the American Society for Colposcopy and Cervical Pathology (ASCCP). This consisted of a Papanicolaou smear, colposcopic-guided cervical biopsy, and cervical swab for the detection and subtyping of HPV infection according to ASCCP clinical practice guidelines. The procedure consisted of first inserting a disposable speculum into the vagina and inspecting the vulva, vagina, and cervix. After, excess mucus was removed from the vagina and the cervix was cleaned with cotton tipped disposable applicator soaked in 3% acetic solution. Following this, the surface of the cervix was swabbed with a cervical brush and this was placed in a specimen tube for molecular detection and subtyping of HPV DNA. HPV subtyping analysis was conducted by Ameripath of Miami, FL.

Cervical characteristics such as vascular patterns, color, contour, and clearness of present lesions was assessed in the colposcopy examination. Additionally, leukoplakia, aceto-white epithelium, and lesions of the vulva, anal area, and vagina were assessed. A

schematic picture was then drawn of the woman's cervix. Cervical biopsies were directed by colposcopic findings. Degree of cervical dysplasia was defined by the Bethesda System. Changes seen were divided into three categories: a descriptor of the quality of the smear, if the smear was within normal limits, and if the smear was not within normal limits. Abnormal changes included atypical squamous cells of undetermined significance (ASCUS), low and high grade intraepithelial lesion (LGSIL, HGSIL), and squamous carcinoma and adenocarcinoma. For this study specifically, progression or persistence of SIL was labeled yes (1) or no (0) if the woman had progressed or had persistent abnormal cells on her cervix from the point of study entry at T0 to one year later at T3.

Intervention

Participants were randomized to one of two conditions, a 10-wk CBSM condition or a 1 day CBSM group workshop. Women in the experimental condition participated in a ten week Cognitive Behavioral Stress Management (CBSM) intervention. The "Keeping Hope Alive" study employed a similar format as previous CBSM studies conducted with HIV+ women and men at the University of Miami, but included modifications designed to make the intervention more applicable for low-income minority women who were HIV+HPV+. These changes included education on cervical health, overcoming barriers for gynecological treatment, and utilizing intrapersonal, spiritual, and social resources to negotiate safer sex. Sessions met once a week for 2.5 hours and were conducted according to the training manual by a post-doctoral associate and advanced clinical psychology graduate students. The 2.5 hour sessions consisted of two parts: CBSM and relaxation training. A variety of relaxation techniques were taught to participants so that they would be able to choose among the techniques that they felt

most comfortable with and most comfortable in incorporating into their lifestyle. The specific focus of each of the 10 modules for CBSM and 10 modules for relaxation training are as follows:

CBSM Modules

Week 1: Group members were introduced to one another and were briefed on session expectations, confidentiality, and attendance of group participation. A thorough overview of the 10 week intervention was conducted as part of the session as well. Furthermore, topics on stress and stress management were introduced and discussed, including the association between stress and HIV progression and cervical health.

Week 2: This session focused on the relationship between thoughts, emotions, physical response, and behavior. Women discussed the association between stress and self care behaviors.

Week 3: Concepts included negative thinking, cognitive distortions, and rational thought replacement. Participants identified their own cognitive strategies for dealing with the stress in their lives.

Week 4: Participants learned about productive coping and strategies to match appropriate coping responses to different stressful situations. Specifically, women learned how to distinguish between emotion focused and problem focused coping, to identify situations that are more controllable or uncontrollable, and then match problem-focused strategies to controllable aspects and emotion-focused strategies to more uncontrollable aspects of those situations.

Week 5: This session was a continuation of the prior session, building upon coping strategies and practicing labeling coping responses, and discussing possible scenarios and alternatives.

Week 6: The main focus of this session was sex and sexuality. Women discussed and learned about aspects of sexual behavior, reducing risk of HIV transmission, negotiating condom use, and disclosure of HIV status.

Week 7: Social support was the main topic of this session. Participants learned about differentiating positive and negative social support and building new strategies for accessing more positive social support.

Week 8: Anger management was discussed for this session. The session included anger awareness, patterns of anger, and ways to diffuse and assess one's own anger.

Week 9: Women learned about assertiveness training as a stress management technique, which emphasized understanding different types of interpersonal style and their advantages and disadvantages, barriers to assertiveness, role playing of appropriate assertive behavior and communication.

Week 10: The last session consisted of a review of past topics and discussions, and addressed the women's accomplishments during sessions.

Relaxation Training Modules

Week 1: Participants were informed of the rationale for the use of relaxation as a stress management technique and a seven-muscle progressive muscle relaxation (PMR) technique was introduced.

Week 2: The main highlight of the session was to provide further rationale for the benefits of relaxation training. A four-muscle PMR was demonstrated. Barriers to adherence to homework were discussed.

Week 3: Women were taught diaphragmatic breathing and relaxation imagery.

Week 4: Women continued to practice a four-muscle group PMR as suggested. Breathing skills were evaluated and diaphragmatic breathing was introduced and demonstrated.

Week 5: This session consisted of a continuation of deep breathing practice, as well as an introduction of autogenics training focusing on sensations of heaviness and warmth in the extremities.

Week 6: Autogenics training was continued and included a focus on heartbeat, breathing, and sensations in the stomach and forehead.

Week 7: Autogenics training was practiced with an emphasis on mental suggestion and visualization.

Week 8: Meditation basics were introduced, with a focus on attitude, posture, breathing and personal mantras.

Week 9: Mindfulness or breath counting meditation was introduced with the self suggestion technique.

Week 10: Relaxation techniques of previous sessions were reviewed and the goals were reinforced. Participant's preferred choice of relaxation was practiced.

Control Condition

Women who were randomized to the control condition were invited to attend a one day seminar in where they received a 5 hour compressed version of the CBSM intervention including the mentioned modifications. The session was scheduled during

Week 6 of the 10 week experimental condition and consisted of an informational overview of the topics covered in the complete intervention. The control condition differed from the intervention in having less contact hours, the lack of structured group interactions, and absence of homework or assigned home based practice.

Statistical Analyses

Multiple regression analyses were used to determine differences between the CBSM and control group on our outcome measures (depressed mood, distress, immune status, stress hormones, and sex hormones) using baseline or T1 of our dependent variables (DV's) and other possible variables as covariates. Independent t-tests were conducted between the CBSM and control group on baseline sociodemographic and health variables to determine possible confounders. Candidate covariates included attendance of CBSM group, HIV medications, such as highly active antiretroviral therapy, sleep quality, adherence to medication, illicit drug, number of cigarettes smoked, caffeine, alcohol, antihistamines, and nicotine use, as they have been shown to contribute to mood and hormonal changes (Kuhn, 1989; Sellmeyer, 1996). Dummy codes were utilized (0= control group, 1= CBSM group) as well, with the control group as the reference group so that change can be measured. The regression coefficient of the group allocation reflected the difference in change from T1 to T2 of the groups on our outcome variables. To ensure that our findings are trustworthy and that they don't result in Type I or Type II error, or overestimate or underestimate significance, special attention was be given to testing assumptions of regression. Assumptions for regression as retrieved from Pedhazur (1997) are as follow:

1. Variables have normal distributions. Inspection for outliers were verified by histograms and resolved by either eliminating them or by applying a log or square root transformation.
2. The relationship between the independent and dependent variable is linear in nature. This was met in the present study by use of previous research that informed our current analyses.
3. Variables are measured without error. This assumption was met by use of psychosocial measures with high reliability and use of the most up to date, effective, and available procedures in measuring physiological data.
4. Variance of errors is the same across all levels of the IV (Homoscedasticity). This assumption was examined visually by utilizing a plot of the standardized residuals (errors). If skewness was present, transformation of variables was utilized to ensure homoscedasticity.

Mediation analyses for our follow-up hypothesis were tested by multiple hierarchical regressions. According to Baron and Kenney (1986), mediation is established when the independent variable (IV) no longer affects the dependent variable (as previously determined) once the mediator variable is controlled for in the IV-DV relationship. This is the most often used test for mediation but has some limitations, among them low power, Type I error, not being able to address suppression effects etc. (Mackinnon, Lockwood, Hoffman, & West, 2002; Preacher & Hayes, 2004; Shrout & Bolger, 2002). The Sobel test addresses the limitations of the Baron and Kenny method as it determines the significance of the indirect effect of the mediator by testing the hypothesis of no difference between the total effect and the direct effect. One limitation of this method,

however, is that it assumes the sampling distribution is normal, which has been shown to be commonly violated (Wilcox, 1998).

On the other hand, the Bootstrapping method (Preacher & Hayes, 2008) does not assume that the sampling distribution is normal. Specifically, the Bootstrap method incorporates repeatedly random sampling observations with replacement from the original data, and computes statistics of interest for each resample (Shrout and Bolger, 2002). As a result, an estimate of the distribution of the statistic of interest is obtained. Bootstrapping is the preferred method for testing mediation since it does not violate the assumptions of normality as do the Baron and Kenney method and Sobel test, and is recommended for small sample sizes because it provides a more precise estimate of indirect effects. The Bootstrap method was used to estimate indirect effects and confidence intervals. One advantage to using confidence intervals is that they incorporate the error in an estimate by providing a range of possible values for an effect rather than a single and possibly biased value. As such, since each mediation method described provides unique information, all were used for the present mediation analyses. For our final follow-up hypothesis, logistic regression was conducted for mediation to test whether immune changes at post-intervention mediated the relationship between CBSM and decreased odds of cervical dysplasia at 9 month follow-up. Confounding variables utilized in the previous study were also used for these analyses (Antoni et al., 2008). The statistical package SPSS 16.0 was used for the analyses proposed.

CHAPTER 3: RESULTS

Participant characteristics

Of the 142 women screened for the C-SMART trial, 72 did not meet study criteria, 17 were unwilling to participate, and 2 were missing data on the variables of interest. The final sample consisted of 71 participants; 46 were randomized to the CBSM condition and 25 to the control group. Participants were women co-infected with HIV and HPV and had a mean age of 31.23 (SD=8.4, Range= 18-45). They were predominantly Black/African American (66.2%), with the remainder being Black other (14.1%), Caribbean Islander (8.5%), Hispanic (7%), Caucasian (2.8%), or of another ethnic group (1.4%). Participants considered themselves Christian (57.7%), Catholic (21.1%), of no religion (8.5%), or other (12.7%). More than half of the participants had a high school diploma or greater (58.5%). The majority of women were working full time (67.7%), working part time (16.1%), on disability (3.2%), unemployed (3.2%), or were students (9.7%). Women earned an average of $11, 628.06 (SD=8,464.047) and more than half of the sample had at least one child (59%). Moreover, most of the participants were single/not married (53.5%), followed by married (21.1%), separated (9.9%), divorced (9.9%), or widowed (5.6%). Women had a mean CD4+ T-cell count of 437.27 cells/mm^3 (SD = 288.77; range = 7-1263) and a mean HIV viral load of 26,466.72 copies/mm^3 (SD= 95,175.09; range = 0-750,001). Furthermore, detectable vs. non detectable (<400) viral load for groups were as follow: CBSM- 27 vs. 19, Control- 27 vs. 11. Independent samples t-tests and chi square tests revealed no significant differences on any sociodemographic, health, medication, or outcome variable between women assigned to the CBSM or control group.

Testing Assumptions of Regression

Assumptions of regression were tested to maximize the accuracy of the results. This included inspection for outliers and skewness on the variables of interest. Outliers were removed from the following outcome variables: cortisol, norepinephrine (NE), CD8+ cell count, NK cell count (CD56+CD3-), and natural killer cell cytotoxicity (NKCC) Day 1. Across variables, a minimum of 1 outlier to a maximum of 3 outliers were removed. Homoscedasticity of the data was also examined visually and through skewness value. Progesterone and viral load were found to have skewness values above 2 and were both log transformed to correct for this issue.

Covariates

Testing was done for possible confounders, which included correlation analyses of the outcome variables with candidate covariates and sociodemographic variables (e.g. age, education, income etc). The following correlations were significant: Beck Depression Inventory (BDI) total and Pittsburgh Sleep Quality Index (PSQI) total ($r = .40$, $p = .003$), BDI cognitive-affective subscale and PSQI total ($r = .34$, $p = .02$), BDI somatic subscale and PSQI total ($r = .43$, $p = .001$), Impact of Event Scale (IES) intrusive thoughts and PSQI total ($r = .38$, $p = .008$), and estradiol and PSQI total ($r = .44$, $p = .001$). In addition, all baseline values of our outcome variables were used as covariates in analyses.

Missing data

Given the problematic nature of small samples, mainly the loss of power, missing data was resolved in the present study by utilizing a linear interpolation method (Little & Rubin, 1987). This method is an improvement over mean substitution in that the value

substituted is predicted from other variables. Linear interpolation links the observed values before and after the missing value, such that the missing value at x=x is imputed by the mean value at x=x-1 and x=x+1. It's important to note that although linear interpolation increases sample size and reduces the standard error, the problem of error variance remains. The amount of missing values in the present data ranged from 1-22 values for psychological variables, 6-21 values for endocrine variables, and 4-28 values for immune variables. The majority of missing data was found at post-intervention of the outcome variables and only a minimal amount of missing data was found at baseline.

Descriptive Statistics

Descriptive baseline levels including mean, standard deviation (SD), and standard error of the mean (SEM) of all study variables are shown on Tables 1, 2, and 3.

CBSM Effects

Hierarchical multiple regression analyses were conducted to test the first four hypotheses of group assignment (CBSM vs. Control) predicting changes in psychological, endocrine (stress and gonadal hormones), and immune outcomes in HIV+HPV+ women. In each of the analyses, group assignment served as the predictor variable while psychological and biological variables served as criterion/outcome variables. Baseline collection of the respective criterion variables were entered as covariates in the first step as well as other determined control variables. For the second step, a block with group assignment was entered. Regression analyses thus determined whether the amount of variance explained by the regression equation in step 1 and step 2 differed significantly from zero.

Psychological Outcomes

The first set of analyses tested whether group assignment significantly predicted variance in scores of the BDI total, BDI somatic subscale, BDI cognitive-affective subscale, IES intrusive subscale, and IES avoidance subscale at post-intervention. Only the somatic component of the BDI showed a statistically significant increase in explained variance between the two steps. For BDI Somatic, with all independent variables in step 2, there was a significant increase in explained variance between the two steps ($\Delta R^2 = .05$, $p < .05$), such that group assignment predicted decreases in scores in the BDI somatic at post-intervention. Figure 2 illustrates CBSM effects on BDI somatic scores from pre to post-intervention compared to the control group. Group assignment did not predict variance in scores at post-intervention for the BDI total, BDI cognitive-affective subscale, IES intrusive subscale, or IES avoidance subscale (p's = .33 - .86). Table 4 illustrates Total R^2, standardized coefficients, standard errors, R square change (ΔR^2), and F change (ΔF) of the mentioned psychological outcomes.

Endocrine Outcomes

The second set of analyses tested whether group assignment significantly predicted variance in post-intervention values of cortisol and NE per 15 hour urine sample (Cortisol 15h; NE 15hr; µg/15 hours), cortisol and NE per urine volume (µg/dL), Dehydroepiandrosterone sulfate (DHEA-S) per blood volume (µg/dL), cortisol/DHEA-S ratio (µg/dL), and estrogen and progesterone per blood sample (pg/ml). A tendency was found for the amount of variance explained by the regression equation in step 1 and step 2 for NE, ($\Delta R^2 = .03$, $p = .15$), such that group assignment predicted lower values of NE at post-intervention. Figure 3 illustrates CBSM effects on NE output from pre to post-

intervention compared to the control group. Group assignment did not significantly predict the variance of values at post-intervention for cortisol 15h, cortisol, NE 15H, DHEA-S, cortisol/DHEA-S ratio, estradiol, or progesterone (p's = .39 - .86). Table 5 illustrates Total R^2, standardized coefficients, standard errors, R square change (ΔR^2), and F change (ΔF) of endocrine outcomes.

Immune Outcomes

The third set of analyses tested whether group assignment significantly predicted variance in post-intervention numbers and percentages of CD4+ T-cells, CD8+ T-cells, and NK cells, as well as values of NKCC Day 1, NKCC Day 2, interferon-stimulated NKCC Day 1 and Day 2 (INKC D1 and INKC D2), and viral load. The amount of variance explained by the regression equation in step 1 and step 2 differed significantly from zero for NK cell counts. With all independent variables in step 2, there was a significant increase in explained variance between the two steps ($\Delta R^2 = .06$, $p < .05$), suggesting that those in the CBSM intervention evidenced higher numbers of NK cells post-intervention compared to controls. Additionally, the amount of variance explained by the regression equation in step 1 and step 2 for CD4+ T-cell count was marginally significant, $\Delta R^2 = .03$, $p = .09$, such that women in the CBSM group had higher numbers of CD4+ T-cells after the intervention compared to controls. Figures 4 and 5 illustrate CBSM effects on CD56+ and CD4+ cell counts from pre to post-intervention compared to the control group. Group assignment did not significantly predict post-intervention variance in CD4+ percent, CD8+ percent and cell count, NK percent, NKCC Day 1, NKCC Day 2, INKC D1, INKC D2, or HIV Viral load. Table 6 and 7 illustrates Total R^2, standardized coefficients, standard errors, ΔR^2, and ΔF for all immune variables.

Mediation Analyses

Bootstrapping

The Bootstrap method is the preferred method of testing for mediation for small samples as it does not violate assumptions of normality as do the Baron and Kenney and Sobel tests. In addition, it provides a more accurate estimate of indirect effects. This method incorporates repeatedly random sampling observations with replacement from the original data and computes statistics of interest for each resample. Bootstrapping results revealed that group assignment was marginally significantly associated with higher numbers of CD4+ T-cells (b = 106.27, SE = 56.89, $t(66) = 1.87$, p = .06) as shown in Table 8. Group assignment was significantly associated with lower scores on the BDI somatic subscale (b = -1.29, SE = .67, $t(66) = -1.93$, $p < .05$). The BDI somatic subscale (b = -21.39, SE = 10.12, $t(66) = -2.11$, p = .04), in turn, was inversely associated with higher counts of CD4+T- cells. The direct effect of group assignment on CD4+ T-cells with the BDI somatic subscale in the equation was reduced to b = 78.69, SE = 56.98, $t(66) = 1.38$, *ns*. This suggested that scores on the BDI somatic subscale at post-intervention mediated the relationship between group assignment and increases of CD4+ T-cells at post-intervention.

Furthermore, the indirect effect of group assignment on CD4+ T-cells through the BDI somatic subscale (bootstrap estimated indirect effect =25.92, CI= 3.77, 74.35, $p <$ .001) was significant. The total amount of variance accounted by for the complete model was 34% (Adj. $R^2 = .34$, $p < .001$). These results support the study hypotheses and suggest that a CBSM intervention may be beneficial for women with HIV+HPV+ in increasing CD4+ T-cell count and that this relationship is mediated by reductions in BDI

somatic depression scores. No other proposed mediation models were significant. Table 8 illustrates the results of these additional Bootstrapping analyses.

Baron and Kenny Method

Mediation analyses were also conducted in 4 steps, following the Baron and Kenny (1986) recommendations to compare our bootstrapping results to the most common analyses conducted for mediation. For the Baron and Kenny mediation analyses, both the BDI somatic subscale and NE were used as potential mediators, while NK and CD4+ cell counts were used as outcome variables. As shown in Figure 2, for step 1, path c or standardized total treatment effects were tested and estimated. As shown in our prior analyses, group condition significantly predicted the outcome variable NK cells, and that there was a marginally significant association between group condition and CD4+ cells. Standardized total treatment effects on outcomes, denoted by path coefficients, were β= .25 (95% CI= 1.38, 47.49) for NK cells and β= .17 (95% CI= -17.51, 21.74) for CD4+ cells. This first step established that there was an intervention effect on these immune parameters that may be mediated by candidate mediator variables.

For Step 2, path a coefficients were tested to establish that the intervention condition is correlated with the mediator. Path a coefficients were significant for the association between condition and the BDI Somatic subscale, and showed a marginally significant association between condition and NE. Path a coefficients were β = -.22 (95% CI= -2.71, -.07) for the BDI Somatic subscale and β = -.17 (95% CI= -.31, .05) for NE.

Path b coefficients were estimated in step 3 to show that the mediator affected the outcome variable, while at the same time controlling for the predictor. With NK cells as an outcome variable, neither path b coefficients for the BDI somatic subscale, β = -.03

(95% CI= -4.96, 3.91), nor NE, β -.14 (95% CI= -48.15, 13.06), were significant. With CD4+ cells as the outcome variable, path b coefficients were significant for the BDI somatic subscale, β= -.27 (95% CI= -44.39, -4.80), but not for NE, β= -.15 (95% CI= -26.45, 40.99). To establish that the potential mediators completely mediated the effects of condition on NK cells or condition on CD4+ cells, the effects of group condition on the outcome variable while controlling for the mediator (path c') should be zero. With NK cells as the outcome variable, the path c' coefficient was significant for BDI somatic, β= .27 (95% CI= 2.13, 50.04), but not for NE β= .25 (95% CI= 1.59, 47.19). Similarly, with CD4+ cells as the outcome variable, path c' coefficients were significant for the BDI somatic subscale, β= -.15 (95% CI= -35.07, 192.47), but not for NE, β= .15 (95% CI= -27.25, 200.60). Results revealed that none of our proposed models satisfied Baron and Kenny mediation standards. Figures 6, 7, 8, and 9 show standardized coefficient paths a, b, c, and c' for the proposed mediation models.

Sobel Test

The Sobel test is commonly utilized as a supplement to Baron and Kenny mediation tests. Specifically, the Sobel test is used to examine whether the proposed mediator carries the influence of a predictor variable to outcome variables by determining if the reduction in prediction is statistically significant. In this case, the Sobel test was not calculated given that our proposed mediation models did not satisfy the Baron and Kenny guidelines.

Mediation with dichotomous variables

To test the final hypothesis of potential mediators in the relationship between group assignment and odds of cervical dysplasia at 6 month follow-up, mediation

utilizing logistic regression analyses was tested. Mediation analyses were conducted as previously mentioned and following the Baron and Kenny (1986) recommendations, as bootstrapping analyses are not currently compatible with dichotomous variables. The BDI Somatic subscale, CD4+ cells, and NK cells were used as potential mediators of the relationship between group assignment and odds of dysplasia at 6 month follow-up. For step 1, path c was tested and revealed that the model accounted for a significant amount of variance in cervical dysplasia at 6 month follow-up (χ^2 (6)= 14.52, p= 03). The corresponding logistic coefficient was b= 2.40 (95% CI= .002, .62). This is fully consistent with prior published analyses of this sample (Antoni et al., 2008), showing that women in the CBSM group had lower odds of cervical dysplasia than women in the seminar group (OR= .04, p=.03). For step 2, path a coefficients were significant for the association between group assignment and the BDI Somatic subscale, β= -.22 (95% CI= -2.64, .02, p= .05), group assignment and NK cells, β= .25 (95% CI= 1.38, 47.49, p=.05), and was marginally significant for group assignment and CD4+ cells, β= .17 (95% CI= -17.51, 210.74, p = .09). In step 3, both path b and c' coefficients were estimated simultaneously. Logistic regression coefficients showed no significant associations between BDI Somatic, b= .08 (95% CI= -.738, 1.58; OR=l8; OR= 1.08, p=*ns*), NK cells, b= .003 (95% CI= .99, 1.02; OR= 1.00, p=*ns*), or CD4+ cells, b= -.001 (95% CI= .994, 1.00; OR=1.0, p=*ns*) and odds of dysplasia. Furthermore, the original model with group assignment and odds of dysplasia continued to be significant with the proposed mediators of BDI Somatic, b= 2.31 (95% CI= .935, 107.43; OR= 1.00, p=56) and NK cells, b= 2.47 (95% CI= 1.09, 127.47; OR= 11.80, p=.04), and was marginally significant for CD4+ cells, b= 96.62 (95% CI= -17.51, 210.74; OR= 1.08, p=.06), in the equation. Results

revealed that none of our proposed mediation models satisfied Baron and Kenny mediation standards in explaining the relationship between CBSM and lower odds of cervical dysplasia at 6 month follow-up.

CHAPTER 4: DISCUSSION

The present study examined the effects of a CBSM intervention on psychological, endocrinological, and immunological outcomes in a sample of minority women co-infected with HIV and HPV. The first set of hypothesis predicted that women in the CBSM condition would show improvements in psychological, immunological, and endocrinological parameters from baseline to post-intervention. Results revealed that women assigned to a CBSM intervention reported lower post-intervention scores on the somatic component of the BDI scale and evidenced significantly higher numbers of NK cells compared to controls. Moreover, findings revealed marginally significant higher numbers of CD4+ cells and marginally lower urinary NE output in women assigned to the CBSM group than women in the control group. These results are in accordance with previous studies showing CBSM benefits in attenuating symptoms of depression in heterosexual and homosexual men and minority women infected with HIV (Antoni et al., 1991; Lutgendorf et al., 1997; Carrico et al., 2005a; Laperriere, 2005; Lechner et al., 2003). Moreover, previous findings have also suggested that CBSM may modulate some parameters of immune status and adrenal stress hormone output, such that homosexual men participating in a CBSM intervention have shown decreases in urinary NE values (Antoni et al., 2000b) and increases in CD4+ T-cells and NK cell counts (Antoni et al., 1991).

The present results replicate these findings to some degree but are unique to HIV+HPV+ women in that to date research investigating increases in CD4+ and NK cells from a CBSM intervention have been found mostly in samples of heterosexual and

homosexual men with HIV. These findings are important for the present population given the established relationship between CD4+ T-cells and HIV progression (Bonneau, 1994; & Ho et al, 1995) and the role of CD4+ T-cells in helping the immune system successfully control the HPV virus (Grinsztejn et al., 2009; Moore et al., 2002; Woo et al., 2008). The importance of NK cells in the health of immunosupressed women who are at risk for dysplasia is highlighted by research showing that decreases in NK cell counts are strongly linked to susceptibility to HPV infection and HPV recurrence (Tay, Jenkins, & Singer, 1989; Stentella, 1998).

No significant CBSM effects were found for the BDI total, Cognitive/Affective component of the BDI, or on the intrusion or avoidance subscale of the Impact of Events Scale. Although no significant differences were found on anxiety symptoms, the literature shows that women who are HIV+, report high levels of distress (McCaffery, 2006; Clarke, 1996; Kabbash, 2008; Siegel & Schrimshaw, 2005; Koopman et al., 2002) and also have a high prevalence of anxiety disorders (Cohen et al., 2002). One reason for the lack of intervention effects on depressive and anxiety questionnaires in this sample may be due to the lack of validity of these distress measures in immigrant or minority populations. Indeed, some studies have demonstrated differences in expressions of distress, with immigrant or minority populations expressing physical symptoms or somatization more often than westernized populations (Kirmayer, 2001; Baarnhielm & Ekblad; 2000). This may explain the sole significant intervention effects on the somatic component of the BDI in our largely minority sample, and the lack of findings for the other components of the BDI and the IES. Furthermore, scores on the IES appear to be lower in our sample of women when compared to other HIV+ populations in the

literature (Cruess et al., 2000; Cruess et al., 2003), which may have also contributed to the inability to detect differences.

Results revealed no significant effects for urinary Cortisol, Cortisol 15 h, NE 15h, DHEA-S and DHEA-S/Cortisol ratio as well. Although previous CBSM studies have found changes in urinary cortisol and NE output in samples of men with HIV (Antoni et al., 2000a; Antoni et al., 2000b), our methodology differed from these studies in that our procedure asked for a 15-hour urine collection versus a 24-hour urine collection. Our reasoning behind this was to make collection less invasive while at the same time capturing stress-related differences. Given the multiple stressors experienced by our sample, higher compliance rates were expected in a 15-hour collection versus a possibly perceived intrusive 24-hour collection procedure. For instance, a 15-hour collection procedure does not require subjects to collect urine during busy times such as at work or on the go during the day, which is a time when compliance may be more difficult and activity confounds are more likely (e.g. caffeine consumption, exercise etc.). On the other hand, the disadvantage of a-15 hour urine collection is that total daily estimates of adrenal hormones are not possible as well as values reflecting hormone circadian rhythms. This, of course, may have influenced the lack of findings in changes of adrenal stress hormone output in the present study.

The exploratory investigation on the effects of CBSM on estradiol and progesterone, produced no significant findings as well. While the most up to date endocrine measurements and assays were conducted at the time of collection, there remains a need for standardization of hormonal tests, which may threaten the validity of

results and may point to a lack of sensitivity in measuring hormones for common tests (Stanczyk et al., 2007). To date, no gold standard test is available to ensure maximum quality control that allows for objective validation and comparisons among different assays. However, the RIA method used in our study has been commonly used in various studies and has provided valuable results in the past (Yalow and Berson, 1971; Stanczyk et al., 2007). It is also possible that other factors not measured in the present study may have a larger influence on estradiol and progesterone levels than our psychological variables of interest. Although careful attention was given to ensuring that women's blood draws were conducted around the same time (before noon peaks; 9am-12pm) and that if medications were correlated with reproductive hormones they were controlled for in the present analyses, common factors, such as body weight, age, time of day, disease status, and use of prescribed medication may influence women's hormonal levels (Crave, 1995; Feigelson, 1998; Schunkert et al., 1997). As such, use of birth control and prescribed medication were also examined in our sample but only 3 women reported using birth control and only a range of 1.4% to 8.5% of women reported taking prescription medications.

Another goal of this study was to explore a psychoneuroimmunological model that may explain the trajectory of disease progression in an HIV+HPV+ population. As previously mentioned, it has been proposed that psychosocial interventions that modify psychosocial factors may also modify biological systems, which may in turn influence disease progression (Antoni, 2003). This follows along with the second set of hypothesis in the present study, which predicted that CBSM effects on immune variables would be mediated by decreases in Cortisol, NE, and depression and anxiety symptoms. Moreover,

it was proposed that CBSM effects on adrenal stress hormones would be mediated by decreases in depression and anxiety symptomatology as well. Findings revealed a marginally significant mediation model explaining the relationship between CBSM and immunological changes. Specifically, bootstrapping analyses, which are the most appropriate method for analyzing mediation in small samples, showed that the relationship between group assignment and higher counts of CD4+ cells were explained or mediated by women's decreases in the somatic component of the BDI. This provides further support to previous CBSM studies demonstrating a relationship between reductions in depressive symptoms and improvement in immune indices (Antoni et al., 1991) and appears to be a consistent finding even in a relatively small and diverse sample such as ours. Since our outcome measurements of psychological and immunological variables occurred at post-intervention and thus at the same time, there is a possibility that the relationship between depression and immune changes may be reversed. However, there is longitudinal research supporting a sequential relationship of depressive symptoms and immune changes (Leserman et al., 1997; Cruess et al., 2005). No other mediation models were found using the Baron and Kenny method, sobel test, or bootstrapping in our sample. Future work should utilize longitudinal designs with various time points that would allow for a clearer picture in the sequential relationship between depressive symptoms and immunological changes, such as looking at reductions in depressive symptomatology at one time point and looking at immunological changes occurring at future time points.

For the final hypothesis, we tested whether significant immunological changes and psychological changes at post-intervention predicted odds of cervical dysplasia at a 6

month follow-up for women in the CBSM condition. Regrettably, none of our proposed mediators were found to explain the lower odds of dysplasia in women assigned to the CBSM intervention. This was surprising given the extant literature strongly linking immunity with prevalence of HPV and recurrence of HPV (Grinsztejn et al., 2009; Strickler et al., 2005; Moore et al., 2002; Woo et al., 2008) but is also understandable given the high attrition rates that occurred at later follow ups. Future research should incorporate larger samples and investigate alternative factors that may explain the lower risk of dysplasia in women assigned to a CBSM intervention. This may include post-intervention changes in levels of condom use or other STD reduction behavior learned from the CBSM intervention.

Overall, results suggest that CBSM is beneficial in improving both psychological and immunological outcomes in a vulnerable minority population dealing with multiple infectious diseases. It is important to note that this is one of few studies showing benefits of a CBSM intervention in a population that is HIV+ and is also at risk for cervical dysplasia. Thus far, previous studies have shown CBSM effects in decreasing perceptions of life stress and lowering odds of cervical dysplasia in this particular population (Antoni et al., 2008). Given the dearth of research in this area, there is a need for future research investigating the psychobiological relationship and its influence on disease status and risk of dysplasia in HIV+HPV+ populations.

Limitations

As with all studies utilizing small samples with missing data, interpretation of results should be made with caution. Given our small sample and the limited statistical

power it is also not surprising that other significant effects did not emerge. To determine the extent to which non-significant results were due to a lack of statistical power, post hoc analyses using GPower were conducted (Erdfelder, Faul, & Buchner, 1996). Power (1-β) was set at .90, α=.05, with 2 groups and 2 different time points entered for the present analysis. Analyses showed that in order for group differences to reach statistical significance at the .05 level, the sample size would have to increase up to N=158. This would mean an increase of more than double our present sample in order to detect minimum effects. Indeed, high attrition rates and the management of missing data contribute to methodological limitations, which may have affected the ability of statistical tests to detect effects in the present study.

The present study has other limitations that should be noted. Although there were no significant differences between groups, it is possible that because of low sample size relevant associations between clinical variables in our sample and our outcome variables were not detected thereby masking possible interactions or covariates. In addition, an untreated control group may also pose a limitation in regards to the equivalence of patient contact between groups, creating a marked difference in attention time between conditions. This raises possible ethical dilemmas to consider in utilizing no treatment control groups as participants should receive the best standard therapy available (Schwartz et al., 1997). The generalizability of results is also in question since our sample was small and was composed of diverse ethnicities.

Future Research

It is important to take into account the uniqueness of the present sample, which was mostly composed of low-income minority women with multiple infectious diseases,

as it may speak to differences in factors influencing health and wellbeing, and differences in distress manifestations. For example, studies have found that higher rates of depressive symptoms in minority group members may be explained by socioeconomic status, lack of basic resources, and lack of education (Plants & Sach-Ericsson, 2004; Sachs-Ericsson et al., 2005). Future studies should thus, pay particular attention to alternative psychological and ecological variables that are more relevant to this population. Additionally, inclusion of spiritually and culturally pertinent factors may provide researchers with a better understanding of the experiences of minority women dealing with deteriorating health and lack of basic resources. For instance, the importance of spirituality and social support in health and healing in minority cultural groups has been well established (Brome et al., 2000; Potts, 1996; Hodge et al., 2000; Galvan et al., 2008). Moreover, the importance of such variables has been established as well for particular health populations dealing with HIV and/or cancer (Crawford et al., 2002; Lagos et al., 2008; Avants & Margolin, 2004; Yanez et al., 2009). Importantly, inclusion of these variables within the framework of psychosocial interventions may enhance their effectiveness and therapeutic influence.

Future studies should also make an effort to prepare and plan for high attrition rates if they cannot be avoided, such as by recruiting a larger sample and conducting extensive screening of eligible participants. Unfortunately, attrition is not uncommon in longitudinal studies, which are necessary to effectively investigate PNI correlates and models influencing health and disease trajectories. It is recommended that future research continue to investigate possible trajectories of wellness and disease progression in minority populations as there is a dearth of information in this area. Given the high rates of sexually transmitted diseases such as HIV and HPV in the United States and the global

impact of infectious diseases, it is imperative that proper attention be given to biological and psychological mechanisms of disease susceptibility and progression.

The present study examined CBSM effects on the mental health, immunity, disease status, and hormonal changes in a sample of low-income minority women with HIV and HPV. Our results suggested that CBSM was beneficial in ameliorating somatic symptoms of depression and to a lesser extent in modulating immune status by increasing CD4+ and NK cells at post-intervention. A PNI model was significant in illustrating a course where the effects of CBSM on psychological changes may have preceded immunological changes found at post-intervention. However, given the results observed here, this model must be viewed as tentative until a larger sample can be collected. More research is necessary to fully elucidate the psychobiological trajectories of disease since immunological changes in our sample did not explain the lower odds of dysplasia in the women assigned to the CBSM group. A consideration of culturally and ecologically relevant variables should be incorporated in future studies with marginalized or minority populations, especially in the growing population of women living with HIV and HPV.

Table 1. *Baseline levels of psychosocial outcome variables.*

Variable	Condition	N	Mean	SD	SEM
BDI Total	Control	26	9.85	9.45	1.85
	CBSM	45	8.98	10.07	1.50
BDI Cognitive-Affective	Control	26	7.55	7.74	1.52
	CBSM	45	6.08	7.68	1.15
BDI Somatic	Control	26	2.29	2.15	.42
	CBSM	45	3.04	3.34	.50
IES Intrusive	Control	26	12.75	6.62	1.30
	CBSM	45	12.86	5.54	.83
IES Avoidance	Control	26	16.81	7.32	1.44
	CBSM	45	17.18	6.08	.91

SD= Standard Deviation; SEM= Standard Error Mean

Table 2. *Baseline levels of endocrine outcome variables.*

Variables	Condition	N	Mean	SD	SEM	Condition	N	Mean	SD
Cortisol 15H µg/15 hours	Control	26	33.08	32.72	6.42	Control	26	33.08	32.72
	CBSM	45	32.74	24.37	3.63	CBSM	45	32.74	24.37
Cortisol µg/dL	Control	26	.62	.53	.10	Control	26	.62	.53
	CBSM	45	.64	.36	.05	CBSM	45	.64	.36
Norepinephrine 15H µg/15 hours	Control	26	145.97	226.89	44.50	Control	26	145.97	226.89
	CBSM	45	188.13	306.93	5.75	CBSM	45	188.13	306.93
Norepinephrine µg/dL	Control	26	.77	.42	.08	Control	26	.77	.42
	CBSM	45	.77	.54	.08	CBSM	45	.77	.54
DHEA µg/dL	Control	26	87.95	53.04	10.40	Control	26	87.95	53.04
	CBSM	45	7.25	67.61	10.08	CBSM	45	97.25	67.61
DHEA/cortisol ratio µg/dL	Control	26	1.64	5.40	1.06	Control	26	1.64	5.40
	CBSM	45	.80	2.14	.32	CBSM	45	.80	2.14
Estradiol pg/ml	Control	26	67.99	39.84	7.81	Control	26	67.99	39.84
	CBSM	45	73.11	44.66	6.66	CBSM	45	73.11	4.66
Progesterone log	Control	26	.17	.64	.13	Control	26	.17	.64
	CBSM	45	.15	.53	.08	CBSM	45	.15	.53

SD= Standard Deviation; SEM= Standard Error Mean, log= log transformed

Table 3. *Baseline levels of immune outcome variables.*

Variable	Condition	N	Mean	SD	SEM
CD4%	Control	26	21.03	10.65	2.09
	CBSM	45	22.67	10.77	1.60
CD4 Count cells/mm³,	Control	26	455.17	323.05	63.35
	CBSM	45	410.79	261.32	38.96
CD8%	Control	26	50.16	11.99	2.35
	CBSM	45	47.55	11.92	1.68
CD8 Count cells/mm³,	Control	26	1138.44	888.70	174.29
	CBSM	45	854.24	447.25	66.67
NK%	Control	26	5.12	4.23	.83
	CBSM	45	4.64	3.63	.54
NK Count cells/mm³,	Control	26	101.54	124.06	24.33
	CBSM	45	75.51	58.99	8.79
NKCC Day 1	Control	26	15.79	10.69	2.10
	CBSM	45	17.39	11.00	1.68
INKC Day 1	Control	26	16.80	11.67	2.29
	CBSM	45	18.21	11.04	1.68
NKCC Day 2	Control	26	4.80	4.24	.83
	CBSM	43	7.72	7.69	1.16
INKC Day 2	Control	26	6.64	6.24	1.22
	CBSM	45	8.03	9.18	1.40
Viral Load copies/mm³	Control	26	21,348.16	37,221.72	7,444.34
	CBSM	45	29,513.48	117,239.78	18,090.49
Viral Load log	Control	26	3.82	.99	.19
	CBSM	45	3.60	1.16	.17

NKCC=Natural Killer Cell Cytotoxicity; INKC= interferon stimulated NKCC; log=log transformed

Table 4. *Hierarchical multiple regression analyses using group assignment to predict psychological variables.*

Outcome	Step/ Model+	Total R^2	ß	SE	ΔR^2	ΔF	p
BDI Total	Step 1	.26			.26	(2,68) 11.92	.00
	BDI Total		.60	.14			
	PSQI Total		.05	.14			
	Step 2	.27			.01	(1,67) .99	.32
	BDI Total		.60	.14			
	PSQI Total		.06	.14			
	Condition		-.10	.11			
BDI Affective (BDI-A)	Step 1	.34			.34	(2,68) 17.38	.00
	BDI-A		.60	.14			
	PSQI Total		-.00	.14			
	Step 2	.34			.00	(1,67) .39	.54
	BDI-A		.58	.14			
	PSQI Total		.01	.14			
	Condition		-.06	.12			
BDI Somatic (BDI-S)	Step 1	.22			.22	(2,68) 9.73	.00
	BDI-S		.37	.12			
	PSQI Total		.17	.12			
	Step 2						
	BDI-S	.22			.05	(1,67) 4.42	.04*
	PSQI Total		.39	.12			
	Condition		.18	.12			
			-.22	.11			
IES Intrusive (IES-I)	Step 1	.26			.26	(2,68) 12.22	.00
	IES-I		.46	.11			
	PSQI Total		.12	.11			
	Step 2	.27			.01	(1,67) .53	.47
	BDI Total		.46	.11			
	PSQI Total		.13	.11			
	Condition		-.08	.11			
IES Avoidance (IES-A)	Step 1	.17			.17	(2,68) 17.38	.00
	IES Avoid		.41	.11			
	Step 2	.34			.00	(1,67) .39	.54
	IES-A		.41	.11			
	Condition		.02	.11			

BDI= Beck Depression Inventory; IES= Impact of Event Scale; + All baseline levels of outcome variables were controlled for in analyses; *p<.05; ß= standard regression coefficient; SE= standard error; ΔR^2= R square change; ΔF= F change; P= p value

Table 5. *Hierarchical multiple regression analyses using group assignment to predict endocrinological variables.*

Outcome	Step/ Model+	Total R^2	ß	SE	ΔR^2	ΔF	P
Cortisol 15 hour (Cort-15h)	Step 1	.01			.01	(1,66) .72	.40
	Cort-15h		.10	.12			
	Step 2	.01			.00	(1,65) .03	.86
	Cort-15h		.10	.12			
	Condition		-.02	.12			
Cortisol (Cort)	Step 1	.07			.07	(1,69) 5.34	.02
	Cort		.27	.12			
	Step 2	.07			.00	(1,68) .06	.80
	Cort		.27	.12			
	Condition		-.03	.12			
Norepinephrine 15 hour (NE-15h)	Step 1	.00			.00	(1,69) .16	.69
	NE-15h		-.05	.12			
	Step 2	.01			.00	(1,68) .57	.45
	NE-15h		-.06	.12			
	Condition		.09	.12			
Norepinephrine (NE)	Step 1	.05			.05	(1,69) 3.37	.07
	NE		.22	.12			
	Step 2	.08			.03	(1,68) 2.08	.15
	NE		.22	.12			
	Condition		-.17	.12			
Dehydroepiandrosterone Sulfate (DHEA-S)	Step 1	.22			.22	(1,69) 19.93	.00
	DHEA-S		.47	.11			
	Step 2	.23			.00	(1,68) .03	.86
	DHEA-S		.47	.11			
	Condition		.02	.11			
Cortisol/ Dehydroepiandrosterone Sulfate Ratio (Ratio)	Step 1	.00			.00	(1,66) .06	.81
	Ratio		.03	.12			
	Step 2	.01			.00	(1,65) .26	.61
	Ratio		.02	.12			
	Condition		-.06	.12			
Progesterone (PR)	Step 1	.15			.15	(2,54) 4.60	.01
	PR		.22	.12			
	Step 2	.10				(1,53) .24	.63
	PR		.22	.12	.00		
	Condition		-.17	.12			
Estradiol (ER)	Step 1	.08			.08	(2,68) 2.75	.07
	ER		.12	.12			
	PSQI		.25	.12			
	Step 2	.09			.01	(1,67) .74	.15
	ER		.12	.12			
	PSQI		.26	.12			
	Condition		-.10	.12			

+ All baseline levels of outcome variables were controlled for in analyses; *p<.05; ß= standard regression coefficient; SE= standard error; ΔR^2= R square change; ΔF= F change; P= p value

Table 6. *Hierarchical multiple regression analyses using group assignment to predict changes in immunological variables. Part 1.*

Outcome	Step/ Model+	Total R^2	ß	SE	ΔR^2	ΔF	P
CD4 Percent (CD4-P)	Step 1	.37			.37	(1,69)	.00
	CD4-P		.60	.10		39.60	
	Step 2	.36			.02		.20
	CD4-P		.60	.10		(1,68) 1.65	
	Condition		.12	.10			
CD4 cell counts (CD4-C)	Step 1	.28			.28	(1,69)	.00
	CD4-C		.53	.10		27.07	
	Step 2	.29			.03		.09
	CD4-C		.54	.10		(1,68) 2.85	
	Condition		.17	.10			
CD8 Percent (CD8-P)	Step 1	.49			.49	(1,69)	.00
	CD8-P		-.05	.12		65.35	
	Step 2	.51			.02		.45
	CD8-P		-.06	.12		(1,68) .67	
	Condition		.09	.12			
CD8 cell counts (CD8-C)	Step 1	.25			.25	(1,69)	.00
	CD8-C		.50	.10		22.79	
	Step 2	.25			.00		.91
	CD8-C		.50	.11		(1,68) .01	
	Condition		.01	.11			
NK Percent (CD56-P)	Step 1	.35			.35	(1,69)	.00
	CD56-P		.47	.11		36.30	
	Step 2	.35			.00		.67
	CD56-P		.47	.11		(1,68) .20	
	Condition		.02	.11			
NK cell counts (CD56-C)	Step 1	.02			.02	(1,69) 1.53	.22
	CD56-C		.03	.12			
	Step 2	.08			.06	(1,68) 4.47	.04*
	CD56-C		.02	.12			
	Condition		-.06	.12			

+ All baseline levels of outcome variables were controlled for in analyses; *p<.05; ß= standard regression coefficient; SE= standard error; ΔR^2= R square change; ΔF= F change; P= p value

Table 7. *Hierarchical multiple regression analyses using group assignment to predict immunological variables. Part 2.*

Outcome	Step/ Model+	Total R^2	ß	SE	ΔR^2	ΔF	P
Natural Killer Cell Cytotoxicity Day 1 (NKCC D1)	Step 1 NKCC D1	.25	.50	.11	.25	(1,65) 21.79	.00
	Step 2 NKCC D1 Condition	.26	.51 -.08	.11 .11	.01	(1,64) .48	.49
Natural Killer Cell Cytotoxicity Day 2 (NKCC D2)	Step 1 NKCC D2	.36	.60	.10	.36	(1,68) 38.16	.00
	Step 2 NKCC D2 Condition	.36	.61 -.05	.10 .10	.00	(1,67) .28	.60
Interferon stimulated NKCC Day 1 (INKC D1)	Step 1 INKC D1	.06	.24	.12	.06	(1,65) 3.90	.05
	Step 2 INKC D1 Condition	.03	.24 .00	.12 .12	.00	(1,64) .00	.99
Interferon stimulated NKCC Day 2 (INKC D2)	Step 1 INKC D2	.22	.46	.11	.22	(1,65) 17.76	.00
	Step 2 INKC D2 Condition	.23	.45 .13	.11 .11	.02	(1,64) 1.30	.26
Viral Load (VL)	Step 1 VL	.09	.31	.12	.09	(1,69) 36.30	.01
	Step 2 VL Condition	.11	.29 -.13	.12 .12	.02	(1,68) .20	.25

+ All baseline levels of outcome variables were controlled for in analyses; *p<.05; ß= standard regression coefficient; SE= standard error; ΔR^2= R square change; ΔF= F change; P= p value

Table 8. *Bootstrapping results for the influence of BDI somatic (BDI-S) and 15-hour urinary norepinephrine (NE) on the relationship between group assignment and NK and CD4+ cells.*

OUTCOME	DIRECT EFFECTS	INDIRECT EFFECTS	
Predictor/ Mediator	b (SE)[1]	Estimate[2]	$CI_{bootstrap}$[3]
NK			
CBSM	25.61 (11.67)		
BDI-S	.44 (2.21)	-.94	(-8.28, 4.28)
NK			
CBSM	25.61 (11.67)		
NE	-12.34(15.14)	1.62	(-1.47, 8.59)
CD4+			
CBSM	106.27(56.89)		
BDI-S	-21.39 (10.12)	25.93	(3.77, 74.35)
CD4+			
CBSM	97.92 (56.48)		
NE	-92.71(76.83)	11.52	(-.94, 82.41)

[1] Predictor to outcome with mediators.
[2] Bootstrapped estimates of indirect effects.
[3] Bias-corrected confidence intervals.

Figure 1. Model illustrating pathways by which a CBSM intervention may exert changes in disease.

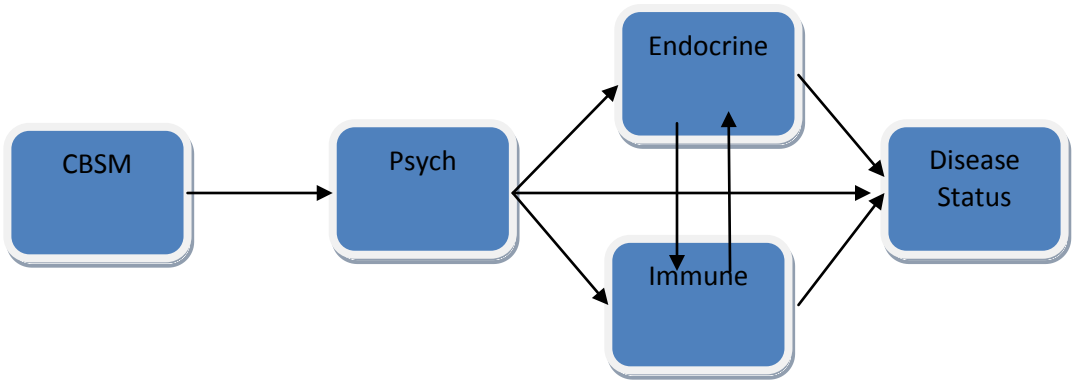


Figure 2. CBSM effects on BDI Somatic scores from baseline (T1) to post-intervention (T2) versus the control condition.

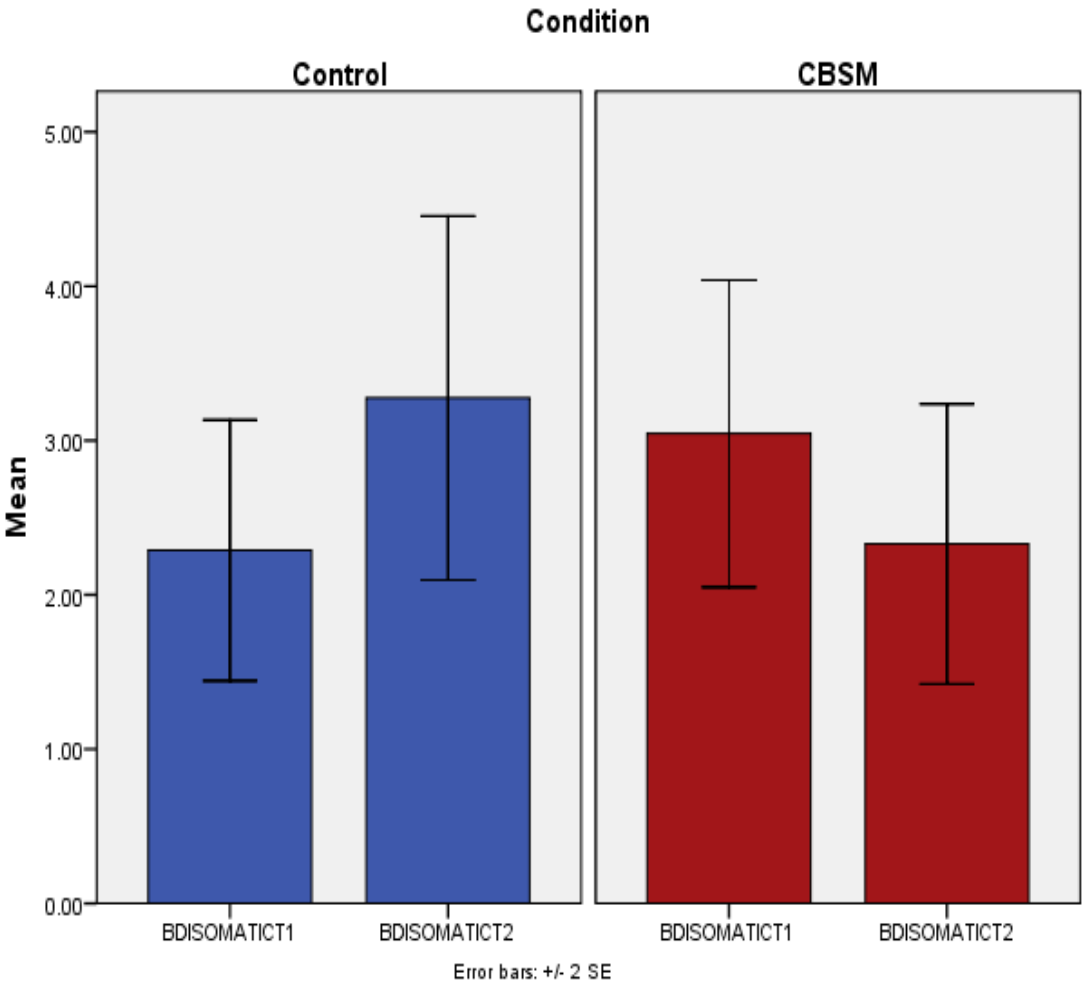


Figure 3. CBSM effects on Norepinephrine (NE) from baseline (T1) to post-intervention (T2) versus the control condition.

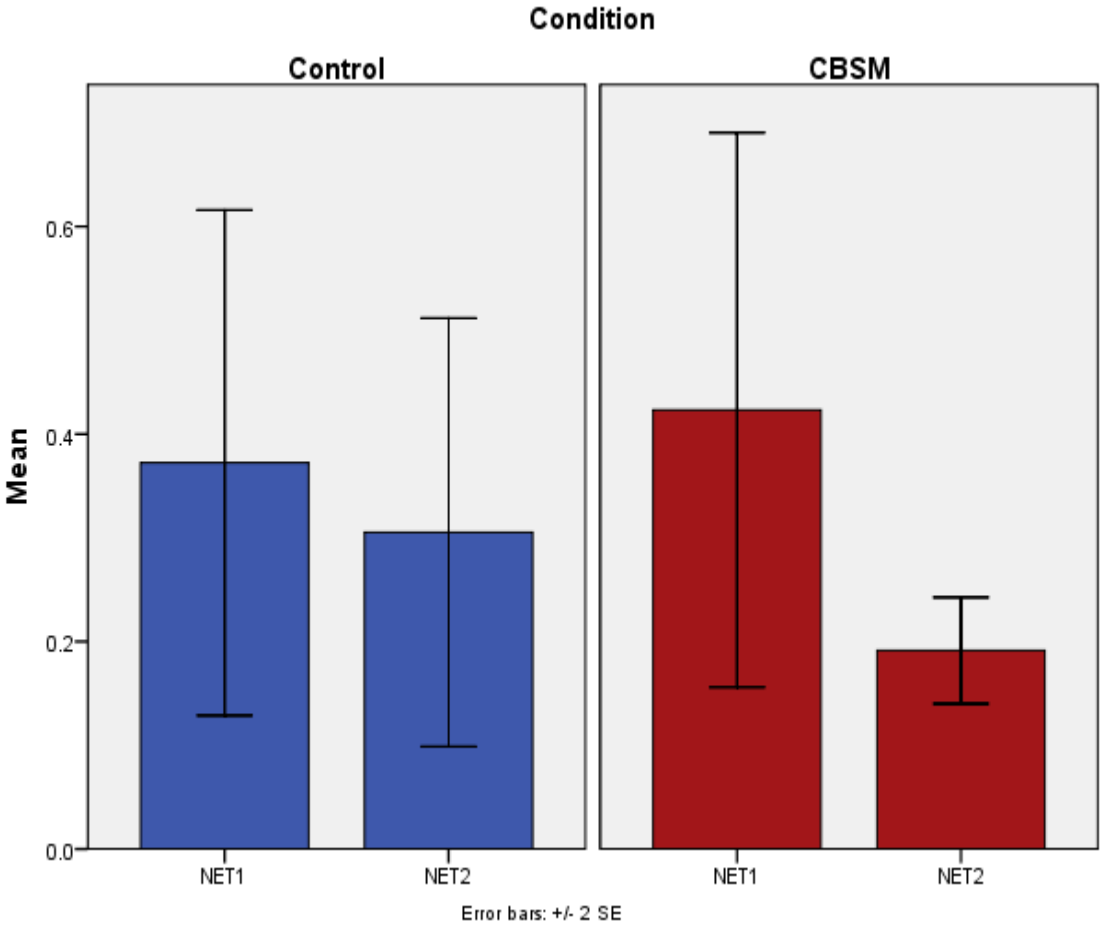


Figure 4. CBSM effects on CD56+ cell counts from baseline (T1) to post-intervention (T2) versus the control condition.

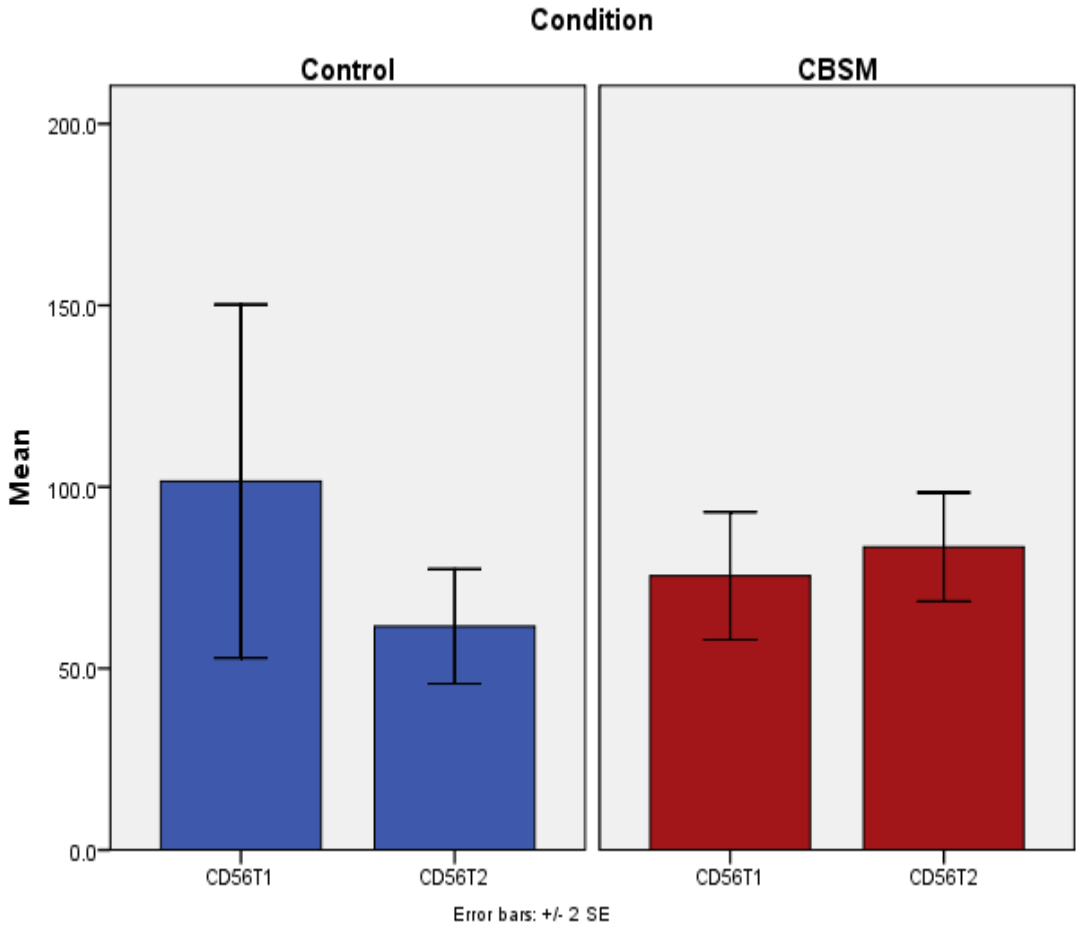


Figure 5. CBSM effects on CD4+ cell counts from baseline (T1) to post-intervention (T2) versus the control condition.

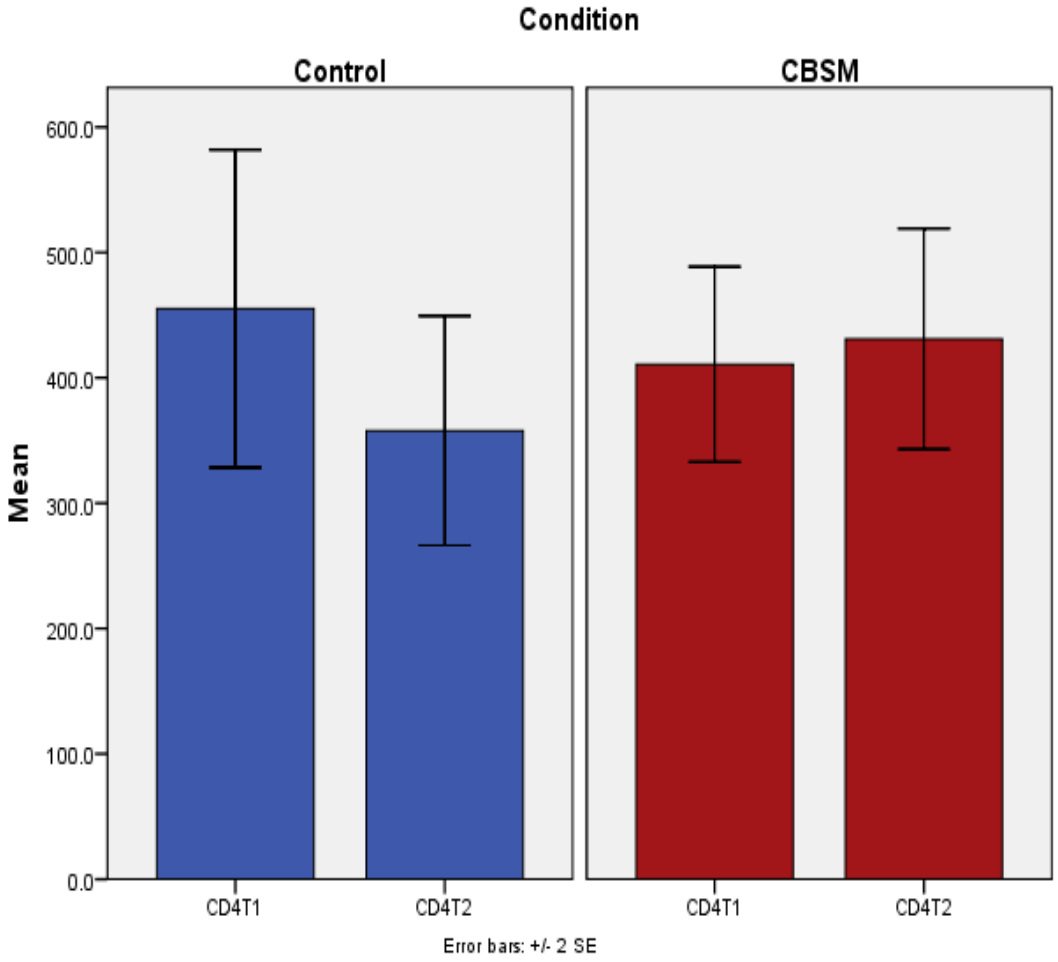
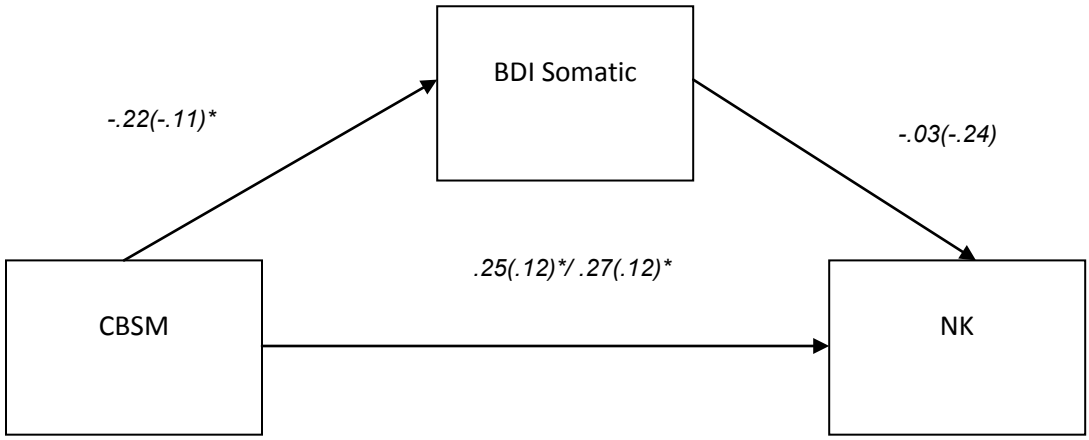
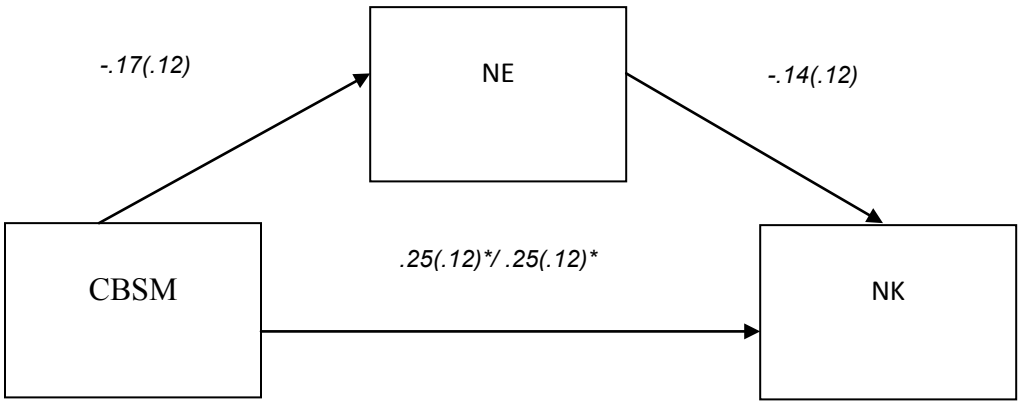


Figure 6. Proposed Mediation Model of the BDI somatic subscale explaining the relationship between CBSM and NK cell counts, with standardized coefficients paths and standard errors.



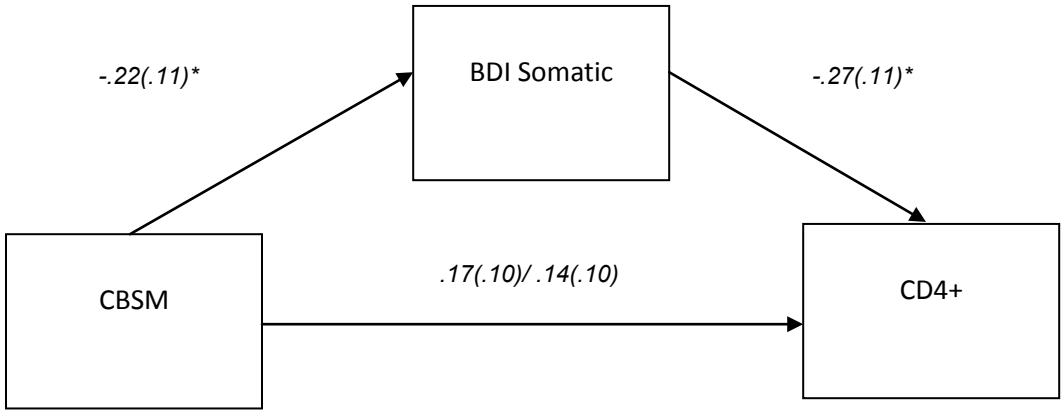
*p<.05, **p<.01

Figure 7. Proposed Mediation Model of Norepinephrine (NE) explaining the relationship between CBSM and NK cell counts, with standardized coefficients paths and standard errors.



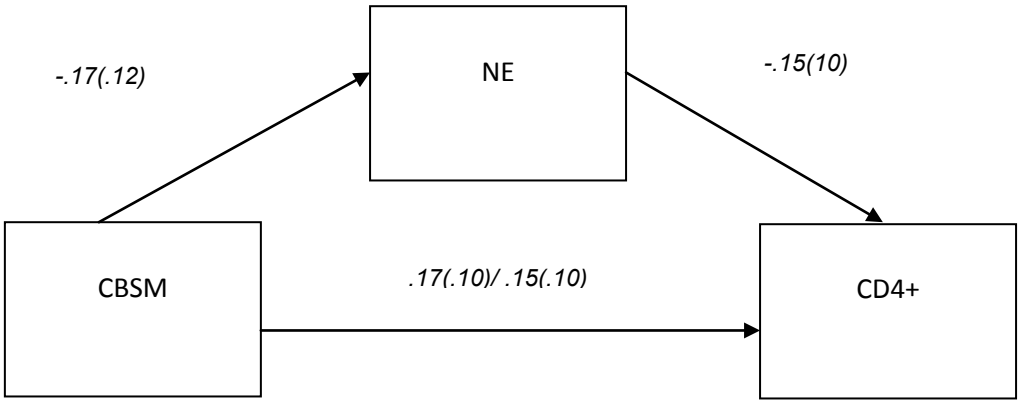
*p<.05, **p<.01

Figure 8. Proposed Mediation Model of the BDI somatic subscale explaining the relationship between CBSM and CD4+ cell counts, with standardized coefficients paths and standard errors.



*p<.05, **p<.01

Figure 9. Proposed Mediation Model of Norepinephrine (NE) explaining the relationship between CBSM and CD4+ cell counts, with standardized coefficients paths and standard errors.



*p<.05, **p<.01

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