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Resilience, Insight, and Causation as Moderators of the Relationships between Trauma, Perceived Stress, Distress, Depression, Salivary Cortisol, and DHEA through a Writing Intervention in a Diverse Sample of HIV-Positive Individuals

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DEPRESSION, SALIVARY CORTISOL, AND DHEA THROUGH A WRITING
INTERVENTION IN A DIVERSE SAMPLE OF HIV-POSITIVE INDIVIDUALS

By

Courtney Biondi Kelsch

A THESIS

Submitted to the Faculty
of the University of Miami
in partial fulfillment of the requirements for
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<u>Resilience, Insight, and Causation</u>
<u>as Moderators of the</u>
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<u>a Writing Intervention in a Diverse</u>
<u>Sample of HIV-Positive Individuals</u>

Abstract of a thesis at the University of Miami.

Thesis supervised by Professor Gail H. Ironson. (101)

Background: Adverse psychological factors such as depression and stressful life events have been found to accelerate HIV disease progression, while positive factors such as optimism and spirituality have been found to slow progression to AIDS. The potentially protective role of the positive psychological factor resilience in HIV/AIDS has not been studied extensively. The relationship of resilience to depression, trauma, stress, and stress-related biological markers in HIV remains to be elucidated. In addition, written emotional expression interventions have shown promise in positively influencing HIV disease course, although the mechanisms require further study. **Purpose:** The aims of this study were to explore the relationship of resilience to the stress-related biological markers salivary cortisol and the cortisol/DHEA ratio, as well as to perceived stress levels, and symptoms of depression and trauma-related distress. Another aim of this study was to examine the influence of insight- and causation-denoting words used in written emotional expression essays on perceived stress levels over the course of the study. **Method:** The study population comprised 246 HIV-positive men (57%) and women

(43%) who were randomized to either a control writing condition or an experimental writing condition which involved writing about personally traumatic events. Participants were seen for a baseline assessment, four writing intervention sessions, and three follow-up sessions over a one-year period, during which salivary samples and psychological data were collected. HLM was used to examine the relationship of resilience to stress-related biological markers, SEM was used to investigate the relationships between resilience, depression, and trauma-related distress, and linear regression was used to study the relationship of resilience to perceived stress, as well as the relationship of insight and causation words to perceived stress. **Results:** Trauma-related distress at baseline predicted depression at 6 month follow-up, and this relationship was moderated by high levels of resilience, which buffered against the development of depression following trauma in those with high distress at baseline. Resilience functioned as a mechanism which partially accounted for the relationship between perceived stress levels at baseline and perceived stress levels at 12 month follow-up, in that lower baseline perceived stress is associated with higher resilience, which is in turn associated with lower perceived stress at 12 month follow-up. Cortisol and the ratio of cort/DHEA did not change from baseline to 6 month follow-up. Resilience did not predict the slope of cortisol from baseline to 6 month follow-up, however, resilience was a positive predictor of the slope of cort/DHEA over this period of time. The percentage of insight and causation words used by participants in the traumatic writing condition did not influence the relationship of perceived stress at baseline to perceived stress at 6 month follow-up, either as a mediator or moderator. **Conclusions:** Resilience has the potential to play a positive role in HIV/AIDS, as high levels of resilience buffered against the development of depression

at 6 month follow-up in the presence of trauma-related distress symptoms at baseline. Resilience also influenced perceived stress levels in those with HIV, such that lower baseline perceived stress is associated with higher resilience, which is in turn associated with lower perceived stress at 12 month follow-up. These results indicate that further study of resilience and its relationship to both biological and psychological factors in HIV/AIDS is warranted.

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Chapter 1: Introduction

As of 2008, the World Health Organization estimates there were 33.4 million people worldwide living with HIV/AIDS (UNAIDS Report, 2009). In the United States, the Centers for Disease Control and Prevention estimates that over 1.1 million individuals were living with HIV/AIDS at the end of 2006, the most recent year in which data were available (HIV Surveillance Report, 2008). Prevention efforts have kept the rate of new infections in the United States stable since the early 1990's, but there is a continued need for further research on the psychological factors involved in both preventing and managing this disease, which represents a worldwide epidemic with troubling societal and personal costs.

Psychological factors have the potential to play a role throughout the course of HIV/AIDS, from the initial diagnosis with HIV, through the ongoing challenge of living with the disease, to the final stages of AIDS. Before the aims of this study are discussed in detail, a literature review discussing the physiology of the human stress response follows, with a focus on cortisol and dehydroepiandrosterone (DHEA), the role that these hormones play in physical and mental health, and how they relate to disease progression in HIV/AIDS. In addition, stress-management interventions in HIV/AIDS will be discussed, with a particular emphasis on written emotional expression interventions in HIV/AIDS, as well as psychological factors which may play a role in HIV/AIDS disease progression.

The Human Stress Response

According to a review by Gunnar and Quevedo (2007), the human response to stress is accompanied by neuroendocrine and cardiovascular changes which are mediated

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by the two divisions of the autonomic nervous system: the sympathetic-adrenal-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) axes. The activation of these two axes brings about various physiological responses involved in promoting the survival of the human organism when it is confronted by threatening and potentially dangerous stimuli. The authors discuss how the body's stress response system evolved to prompt a rapid, adaptive response to stressful stimuli, which prepares one to successfully handle the threatening situation. When the human organism is out of danger, the stress response begins to subside, until homeostasis is reached once again, and normal physiological functions resume.

States of chronic stress have been hypothesized to play a role in the onset and progression of various diseases, including depression, HIV/AIDS, and cardiovascular disease, although further study is needed before firm conclusions can be drawn (for a review, see Cohen *et al.*, 2007). In addition, it has been noted that more sophisticated theoretical frameworks are needed to account for the lack of uniform physiological and psychological responses to chronic stress amongst different individuals (Miller, Chen, and Zhou, 2007).

Both higher (e.g., the prefrontal cortex) and lower (e.g., the hippocampus) brain structures play a role in how stressors are appraised and reacted to by the individual. Several different pathways exist which regulate the timing and intensity of the stress response. For instance, both the HPA and SAM axes are regulated by the limbic system, including the hippocampus, amygdala, and the locus coeruleus (Gunnar and Quevedo, 2007). Stressful stimuli are processed by the limbic system before physiological stress responses are activated. Both the HPA and SAM axes must work in concert in order for

the body to respond appropriately to stress without sustaining damage from prolonged reactions to it. The SAM axis releases catecholamines into peripheral circulation: epinephrine (from the adrenal medulla) and norepinephrine (from the locus coeruleus, adrenal medulla and sympathetic nerves). This promotes the "fight or flight" response which mobilizes metabolic resources by binding to receptors located in many tissues of the body. Of these two axes, the HPA appears to be the main focus of research efforts: a Medline search for "HPA axis" produced 5,264 results, while a search for "SAM axis" produced 8 results.

Cortisol

As described in detail by Sanchez (2006), the HPA axis releases corticosteroids, steroid hormones which are found in human beings as cortisol, and corticosterone in other animals. The activation of the HPA axis is initiated by the paraventricular nucleus of the hypothalamus, in parvocellular neurons which release corticotrophin releasing factor (CRF). This stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland into the bloodstream, which stimulates the release of cortisol from the adrenal cortex. Unlike epinephrine and norepinephrine, cortisol is able to cross the blood-brain barrier (McEwen *et al*., 1986). Being a steroid hormone, cortisol acts on the cells of the body and brain by altering their gene expression (Charmandari *et al*., 2005; McEwen *et al*., 1986), which is why its effects are more long-lasting than those of epinephrine and norepinephrine (Gunnar and Quevedo, 2007). Nearly any type of stress, whether physical or psychological, is followed within minutes by increased cortisol secretion (Adinoff *et al*., 1998), peaking at approximately 30 minutes after exposure to a stressor (Kirschbaum and Hellhammer, 1994). The HPA axis is regulated by a negative

feedback mechanism in which the increased levels of cortisol, produced through the stress response, inhibit the hypothalamus and pituitary from further production of CRF and ACTH, respectively (Adinoff *et al*., 1998).

As described by Sanchez (2006), cortisol binds to two types of intracellular receptors in the brain which alter HPA axis activity: mineralocorticoid recptors (MR) and glucocorticoid receptors (GR). MR maintain the basal activity level of the HPA axis, maintain blood pressure, are located in the hippocampus and are abundant in the prefrontal cortex, which may relate to the presumed effects of cortisol on behavior, cognition, and mood. GR are also abundant in prefrontal cortex, they have lower affinity for cortisol than MR, and they respond via negative feedback during the daily cortisol cycle as well as following an acute stressor. Interestingly, the number of cortisol receptors in the brain can change across the lifespan in response to environmental, endocrine, and neurochemical factors (McEwen *et al*., 1986).

According to Kirschbaum and Hellhammer (1989), cortisol has been reported to affect blood pressure, metabolism, immune function, reproduction, cognition, learning, memory, neural plasticity, and mood, and is considered to be a primary biomarker for the physiological response to stress. The secretion of cortisol in healthy human adults follows a circadian rhythm, with peak secretion occurring one to two hours before awakening, with gradually declining levels throughout the day, and with the lowest secretion occurring around midnight. Average morning values (7-9 a.m.) were found to be 14.32±9.1 nmol/l, afternoon values (3-5 p.m.) were 4.50±3.5 nmol/l, and evening values (8-10 p.m.) were 1.96±1.7 nmol/l.

Normally, cortisol secretion is not continuous, but released in bursts throughout

the daily cycle. These bursts are enhanced by experiencing stressful or threatening

situations, especially those that are experienced as novel, unpredictable, or uncontrollable

(Kirschbaum and Hellhammer, 1994). Across a 24-hour period, healthy adults have been

found to undergo an average of 9 secretory episodes and to secrete a total of 16 mg of

cortisol on average, with a mean half-life of 66 minutes of cortisol decay (Weitzman *et

al.*, 1971). The spontaneous release of cortisol has been found to occur in response to

physiological and psychosocial stimuli, including heavy exercise, exposure to extreme

temperatures, nicotine use, illness, fever, hypoglycemia, and physical pain, as well as

fear, anxiety, and other negative mood states (van Eck *et al.*, 1996; Kirschbaum and

Hellhammer, 1994). These stimuli can cause cortisol to be released both more frequently

and in greater quantities than is needed to maintain the daily baseline cortisol rhythm.

There is a large degree of variation in baseline cortisol levels between individuals, and

also in the degree of cortisol secretion that is evoked in response to stress. This variation

is thought to be genetically influenced (Bartels *et al.*, 2003). As discussed by Kirschbaum

and Hellhammer (1994), there is evidence that men secrete up to twice as much cortisol

as women in anticipation of a stressor. However, the literature on sex differences in

cortisol secretion is mixed and sex differences appear to be related to the nature of the

stressor as well as to mental and physical health status (Paris *et al.*, 2010). Kirschbaum

and Hellhammer note that habitual nicotine exposure was found to lead to continually

elevated cortisol levels, which may explain some of the variability observed in baseline

cortisol levels (1994). Additionally, a perception by the individual that a situation

threatens to be personally detrimental also plays a role in the degree of cortisol response

to stress (Kirschbaum and Hellhammer, 1994). More recent research continues to

examine the roles of cognitive appraisal and emotion regulation in influencing the degree of cortisol response to stress, with evidence that increased perception of threat to one's social status may promote excess cortisol reactivity (Denson, Spanovic, and Miller, 2009).

DHEA and DHEA-S

According to Regelson *et al*., DHEA-S, a steroid hormone, is the most abundant product of the adrenal cortex (1994). As described by the authors, about 1% of circulating DHEA-S exists in the unsulfated form, DHEA. DHEA has a half-life of about 30 minutes and follows a circadian rhythm. DHEA-S has a half-life of 7-10 hours and has a weak circadian rhythm. As described by Kalimi *et al*., most DHEA-S is made by the adrenal cortex, while smaller amounts are made by the gonads, central nervous system, and the skin (1994). After being produced, DHEA-S is converted to DHEA by enzymes within the bloodstream, liver and kidneys. This results in the maintenance of an equilibrium between its two forms. In healthy adults, plasma levels of DHEA are 0.01-0.02 µM, while DHEA-S levels are 5-7 µM. DHEA can be converted into estrogen and testosterone, and is considered a precursor hormone for these sex steroids. Both cortisol and DHEA are derived from the same precursor, pregnenolone, which itself is derived from cholesterol. During periods of stress or severe illness, there is a shift away from the conversion of pregnenolone to DHEA, toward the conversion of pregnenolone to cortisol (Kalimi *et al*., 1994; Regelson *et al*., 1994).

Kalimi *et al*. (1994) note that, like cortisol, DHEA is capable of crossing the blood-brain barrier, and that DHEA and its metabolites have been found throughout the human brain, with no apparent areas of high concentration. According to a review by

Maninger *et al.* (2009), there are large differences in DHEA concentration found within various regions of the human brain between individuals. Overall, brain DHEA levels are higher than plasma DHEA levels, which are higher than DHEA levels in the cerebrospinal fluid. Within the brain, DHEA can be synthesized locally, or derived from peripheral synthesis. Within the brain, DHEA can be used to synthesize DHEA-S. The authors note that it is unlikely that brain DHEA-S comes from the periphery, as it is hydrophilic and will not readily cross the blood-brain barrier. DHEA-S is primarily transported out of the brain rather than into it.

As noted by Wolf and Kirschbaum (1999), in contrast to cortisol, which binds to intracellular receptors and thus acts on DNA, DHEA exerts its effects by binding exclusively to cell surface receptors. The production of DHEA is stimulated by ACTH, yet, in contrast with cortisol, there is no negative feedback of DHEA on the pituitary gland or hypothalamus. In the year before puberty a sharp rise in DHEA production occurs, with levels peaking in the 30's and declining throughout adulthood, until old age, at which time DHEA is produced at only 20% of its former levels. This is in contrast to basal cortisol levels, which remain steady or increase throughout older adulthood. Both DHEA and DHEA-S decline at a rate of 2% per year after peak levels are reached in the 30's (Vermeulen, 1995). Interestingly, DHEA levels rise during physical exercise, and are lowered by following a vegetarian diet (Regelson *et al.*, 1994).

To date, DHEA has been studied most thoroughly in rodents and non-human primates, hence, much remains to be discovered about its role in the human stress response. As discussed by Wolf and Kirschbaum (1999), in animal models, DHEA was found to act on receptors within the central nervous system that are involved in learning

and memory. For example, it was found that DHEA administration caused increased acetylcholine release from the hippocampus. DHEA administration also caused increased serotonin secretion by the hypothalamus and was accompanied by a decrease in food intake and body weight. In rats specifically, it was found that DHEA uptake was most pronounced in the amygdala, hippocampus, thalamus, midbrain, and frontal cortex (Kalimi *et al*., 1994).

In rodents, an anti-glucocorticoid effect of DHEA has been observed in many experiments, which has immunological implications, as glucocorticoids have been associated with a weakened immune response in both rodents and humans (Oberbeck *et al.*, 2001, Kalimi *et al.,* 1994; Regelson *et al*., 1994). Interestingly, in both species, DHEA receptors have been found on lymphocytes and monocytes, and DHEA has been found to directly influence immune cell cytotoxicity (Oberbeck *et al.* 2001). It appears that an intact immune system is required in order for DHEA administration to produce an immunostimulatory effect (Regelson *et al*., 1994). In a study in which sepsis was experimentally induced in mice, DHEA administration improved survival by nearly 35%, by preventing the immunosuppression that often accompanies sepsis, by enhancing T-lymphocyte function, and by preventing the release of cytokines which promote septic shock (Oberbeck *et al*., 2001). There are no parallel studies in humans, so the potential effects of DHEA on immunity remain largely unknown at this time.

As discussed by Wolf and Kirschbaum (1999), it is thought that the presence of high glucocorticoid levels over a prolonged period can impair memory, but conflicting results on DHEA's effects on memory in rodents have been reported, and all studies to date have been of a short duration. Most studies showed a memory-enhancing effect of

DHEA, but optimal DHEA levels for enhancing memory in rodents have yet to be determined. Also found in rodents was DHEA's ability to decrease aggressiveness and anxiety, perhaps by increasing GABAergic tone, by reducing pregnenolone sulfate (an excitatory neurosteroid) or by acting on serotonin. The specific mechanisms of action of DHEA on the rodent brain are not currently known. The results of rodent studies cannot be directly applied to human beings, but they have been used to guide human studies of DHEA.

As reviewed by Maninger *et al.* (2009) both *in vivo* and *in vitro* animal studies have demonstrated neuroprotective effects of moderate concentrations of DHEA and DHEA-S, while low and high concentrations were ineffective or neurotoxic, respectively. Both forms of the steroid may function through different mechanisms, few of which are currently known. In cultures of human neural stem cells DHEA increased neurogenesis, and in adult cortical tissue cultures DHEA-S increased cell survival. The authors note that these different effects suggest that a balance between the two forms plays a role in nervous system development and maintenance. In addition, they note that DHEA's effects may depend on the concentrations of other hormones (such as glucocorticoids) affecting the tissue as well as the organism's physiological state. Additionally, in rats, DHEA has been found to stimulate dopamine release, and may play a role in stimulating catecholamine release. In other rat studies, DHEA and DHEA-S were found to have antioxidant effects both *in vivo* and *in vitro.*

Cortisol, DHEA, Disease and Aging

Wolf and Kirschbaum note that higher functioning elderly individuals were found to have higher DHEA levels than those lower in functioning (1999). They also note that,

in elderly women, low DHEA levels were associated with a variety of problems, including limited mobility, difficulty in breathing, depression, frailty, and lower subjective health and life satisfaction. Studies have reported different relationships between DHEA levels and cognitive performance for men versus women. For example, although 2 weeks of DHEA administration buffered men and women against a decrease in attention following a laboratory stressor, it led to poorer recall performance following a stressor in both men and women, with women performing worse on a memory task (Wolf *et al*., 1998). Wolf and Kirschbaum conclude that DHEA may be a general indicator of health status in the elderly, but has not been found to be strongly related to cognitive abilities or their decline with age (1999). This is consistent with a more recent, double-blind, placebo-controlled study of elderly men and women, which concluded that DHEA supplementation over a 1 year period had no effect on cognitive performance (Kritz-Silverstein, *et al*., 2008).

As discussed by Maninger *et al*. (2009), DHEA and DHEA-S concentrations decline with age and with chronic and sub-chronic stress, and may predict mortality. In one study of men and women, low baseline DHEA-S levels were found to predict mortality over a 27-year follow-up period, independent of other risk factors.

In humans, several disease states involve reduced DHEA levels, including rheumatoid arthritis, burn trauma, anorexia, liver disease, HIV/AIDS, cancer, polycystic ovary syndrome, chronic fatigue syndrome, Alzheimer's disease, and Cushing's disease (Kalimi *et al*., 1994). Low DHEA levels have also been found in patients in the ICU, including those with severe illness. It has been hypothesized that an imbalance between DHEA and cortisol is related to physical disease and mental illness (Kalimi *et al*., 1994),

as well to as the aging of the immune system (Buford and Willoughby, 2008). Depression is thought to involve HPA axis abnormalities, including elevated basal cortisol levels, increased CRF secretion by the hypothalamus, and abnormal responses to endocrine challenge tests, in which administration of the powerful glucocorticoid dexamethasone does not lead to the usual negative feedback mechanisms which decrease cortisol production (Goodyer *et al.,* 1998; Plotsky, Owens, and Nemeroff, 1998). Elevated cortisol may account for the cognitive impairment seen in depressed patients (Wolf and Kirschbaum, 1999). In teenagers, lower DHEA and higher cortisol levels were independently associated with the development of major depression and with subsequent negative life events (Goodyer *et al.,* 1998), whereas in depressed adults, both higher DHEA and cortisol levels were found (Elzinga *et al.*, 2007).

As noted by Wolf and Kirschbaum, a few short-term studies in elderly patients found that treatment with DHEA reduced depressive symptoms but had no effect on cognition (1999). DHEA was also found to increase feelings of well-being, sleep quality, and relaxation in middle-aged patients (Wolf and Kirschbaum, 1999). Currently, studies on the effects of DHEA administration in human beings have produced mixed results overall, due to a lack of standardization in dosage, duration of treatment, use of a placebo control, as well as the presence of various confounding factors, so further study is needed before firm conclusions can be drawn.

Although research on DHEA in humans has produced more questions than answers thus far, there are some clear themes which have developed. According to a 1994 review by Kalimi *et al.*, DHEA has been shown to have effects in obesity, diabetes, cancer, aging, stress, immunity, pregnancy, as well as cardiovascular and nervous system

pathophysiology. There is still much that remains to be elucidated about the specific role of DHEA in the above conditions, but it is thought that DHEA's anti-glucocorticoid effect may point toward a common link between them. In several studies in human beings, administration of DHEA led to reduced cortisol levels (Wolf and Kirschbaum, 1999). Cortisol itself has both immunosuppressive and anti-inflammatory properties (Bauer, 2005). In general, cortisol suppresses immune function, while DHEA enhances it (Buford and Willoughby, 2008).

As discussed by Bauer (2005), another aspect of the study of DHEA and cortisol concerns the aging of the immune system, immunosenescence, which involves changes to the immune system, including lower lymphocyte counts, impaired responses to newly-encountered antigens, and blunted T-lymphocyte proliferation. Several of these changes in immune function are also found in those under chronic stress. Chronic stress is associated with dysfunction of the HPA axis, which is associated with increased susceptibility to both infectious and autoimmune diseases. Chronic stress is thought to increase pro-inflammatory cytokine production, which is associated with a host of diseases including certain cancers, cardiovascular disease, HIV/AIDS, diabetes, osteoporosis, type II diabetes, wasting syndrome, gastrointestinal disorders, autoimmunity, and depression (Gunnar and Quevedo, 2007; Bauer, 2005; Cruess *et al.*, 1999; Kirschbaum and Hellhammer, 1994). Similar patterns of alteration in immune function have been observed during the aging process, the reaction to stress, and the experimental administration of cortisol.

Excessive stress over the lifespan is thought to tax both the immune system and the stress response system, and may increase the risk of physical and mental illness

(Gunnar and Quevedo, 2007). Excessive cortisol exposure has been shown to promote muscle atrophy, osteoporosis, hyperlipidemia, atherosclerosis, type II diabetes, and depression, which may help to explain how the risk of developing some of these conditions increases with age (Bauer, 2005; Kalimi *et al.*, 1994). Individual differences in sensitivity to cortisol release are also likely to explain why some individuals are at greater risk of developing diseases in which stress plays a role, as well as whether the aging process will proceed normally, or will result in early disability, disease, and death (van Eck *et al.*, 1996; Bohnen *et al.*, 1991).

As discussed by Bauer (2005), cortisol and DHEA appear to work in opposition to each other, in both human and animal models. Bauer also notes that, if cortisol production is blocked using metyrapone, DHEA production and secretion increases. Additionally, in comparison with younger individuals, the ratio of cortisol to DHEA (cort/DHEA) rises notably in those over 60 years of age, which is caused by a decrease in DHEA levels with age, and the simultaneous maintenance of or an increase in cortisol levels. Those who experience heightened stress in old age tend to produce the greatest amount of cortisol, beyond the generally elevated cortisol levels seen in the elderly.

Cortisol, DHEA, and Mental Health

One area in which a fair amount of research on cortisol and DHEA in human beings has been carried out is in the realm of mental health. In particular, several studies have been conducted on the relationship of cortisol and DHEA levels to anxiety and depression. Currently, it is widely hypothesized that the dysregulation and dysfunction of the HPA axis play a role in several psychiatric disorders, including depression and anxiety (Elzinga *et al.*, 2008; Jezova and Hlavacova, 2008). In general, higher

cort/DHEA ratios are associated with higher anxiety. In a study of healthy human subjects, those with higher cortisol and lower DHEA levels were found to experience a stronger fear-potentiated startle reaction (Grillon *et al.* 2006).

It is thought that prolonged elevated cortisol levels can lead to the dysregulation of the HPA axis, which may in turn lead to increased risk for the development of psychiatric disorders (Goodyer *et al.*, 1998). It is also hypothesized that cortisol is associated with fear, stress, and anxiety, while DHEA may counteract these emotional and physiological states. As mentioned previously, DHEA administration in rodents led to fewer anxiety behaviors and reduced fear conditioning, as well as lower levels of aggression (Wolf and Kirschbaum, 1999).

A small number of studies in human beings have shown initially promising results on the ability of DHEA administration to reduce depression, anxiety, psychological withdrawl, apathy, to improve mood and insight, to instill a sense of well-being, vitality and relaxation, and to improve energy levels, sexual function, sleep quality, and school and work performance (Labrie et al., 2009; Wolkowitz *et al.*, 2000; Wolf and Kirschbaum, 1999; Kalimi *et al.*, 1994). Due to methodological differences, these results should be interpreted cautiously, but they do point to potentially fruitful areas for follow-up. It is worth noting that currently the appropriate pharmacologic doses and treatment durations for DHEA administration are unknown, and that its long term (greater than 6 months) effects have not been extensively studied (Gunnar and Quevedo, 2007).

Although results are inconsistent, many studies have found lower levels of DHEA or higher cort/DHEA ratios in patients experiencing depression, anxiety, low life satisfaction, and psychosocial stress (Huckelbridge *et al.*, 2005; Young *et al.*, 2002;

Wolkowitz *et al.*, 2000). It remains to be seen whether prolonged high cortisol alone is

sufficient to lead to the development of physical or mental illness, or whether a

simultaneous decrease in DHEA is also a prerequisite condition. In schizophrenic

patients, low DHEA but high DHEA(S) were reported in addition to elevated basal

cortisol levels, and in panic disorder patients, a lower cort/DHEA-S ratio was found

(Gallagher *et al.,* 2006; Wolkowitz *et al.*, 2000). In PTSD patients, elevated cortisol was

demonstrated in response to the anticipation of stressful events, yet these patients also

tend to show lower baseline cortisol levels (Jezova *et al.*, 2008). Similarly, patients high

in anxiety were found to have a diminished cortisol response to laboratory stressors,

which is presumed to be due to the inability to mount an adequate cortisol response to an

acute stressor (Takai *et al.*, 2007). Conversely, individuals at high genetic risk for

developing depression demonstrated an increased, prolonged cortisol response to

laboratory stressors (Gotlib *et al.*, 2008). These complex relationships between cortisol,

DHEA, and mental illness may be due to HPA axis dysfunction, an adaptive down-

regulation of the HPA axis, genetics, cognitive appraisal, or to other factors, but further

research is needed to uncover the underlying processes that are at work.

Posttraumatic Stress Disorder, Cortisol, and DHEA

      PTSD has been associated with alterations in HPA axis function, presumably

because it is a chronic stressor which can tax and may eventually dysregulate the HPA

axis, thus leading to abnormal cortisol and DHEA levels.

      A study of 26 women with PTSD found that morning cortisol levels were

abnormally low, while morning DHEA levels were abnormally high, when compared

with both traumatized controls and nontraumatized controls (Gill, Vythilingham and

Page, 2008). Interestingly, low cortisol levels (hypocortisolism) have been found not only in those suffering from PTSD, but also in those with fibromyalgia, chronic fatigue syndrome, and asthma, as well as in those who are undergoing chronic stress but are otherwise healthy (for a review, see Heim, Ehlert and Hellhammer, 2000). The authors suggest that hypocortisolism is not a specific correlate of PTSD itself, but may be associated with multiple forms of chronic stress.

In a study of civilian men and women with PTSD, it was found that PTSD patients had significantly lower cortisol levels than controls, with cortisol levels decreasing as PTSD severity increased (Olff *et al*. 2006). This study also found increased DHEA-S levels in men, but not in women, with PTSD. A study of male veterans found significantly elevated DHEA levels in those with PTSD versus controls, non-significant elevation of DHEA-S, and a significantly lower cort/DHEA levels in men with PTSD (Yehuda *et al*., 2006). Yehuda's study also found that DHEA levels were predicted by subjective improvement of PTSD symptoms and coping skills.

A recent study of 33 adult PTSD patients, aged 21-57 years, found significantly elevated plasma levels of both DHEA and DHEA-S, as well as significantly lower cort/DHEA ratios, in participants who had been exposed to childhood abuse (Kellner *et al.*, 2010). The authors note that in research involving PTSD, the role of childhood trauma must be considered, as it may lead to HPA axis dysregulation at a sensitive period during development. The HPA axis alterations found in this study may reflect stress and trauma resilience processes, HPA axis dysregulation, or some other phenomenon, which must be clarified by future studies.

A meta-analysis of 37 studies measuring cortisol levels in adults with PTSD attempted to clarify the conditions under which lowered cortisol levels occur in those with PTSD (Meewisse *et al.*, 2007). Studies included in the meta-analysis measured basal cortisol levels (reflecting normal levels of psychological stress) and used a variety of collection methods (plasma, saliva, etc.). The meta-analysis compared mean pooled cortisol values for those with PTSD versus those without PTSD. The analyses found no significant effect of collection method or of co-morbid depression on cortisol levels in those with PTSD versus controls, but did find significantly lower afternoon cortisol levels in those with PTSD. There was no difference in cortisol levels between men with PTSD versus men without, but significantly lower cortisol levels were found in women with PTSD versus women without PTSD. The study also examined cortisol levels according to whether the trauma experienced was due to physical or sexual abuse, war, refugee status, or a variety of causes. In those with PTSD due to physical or sexual abuse, cortisol levels were lower than in controls. This study also found significantly lower cortisol levels in those with PTSD in comparison with non-traumatized controls, but that there was no difference in cortisol levels between those with PTSD and those exposed to trauma who had not developed PTSD. The authors note that this suggests that it is not PTSD per se that is associated with low basal cortisol levels, but trauma exposure in general, which may explain some discrepancies in the literature.

Cortisol, DHEA, and Resilience

Resilience has been defined as the ability to maintain self esteem, self efficacy, positive affect, and a sense of mastery and perspective on one's situation in the face of stress or adversity (Bonanno, 2004; Simoni *et al.*, 2006). It has been hypothesized that

resilience may play a role in how stress is experienced by different individuals and whether prolonged stress will lead to physical or mental illness. Individual differences in perception, appraisal, prior life experiences, and genetics may determine who is most affected by stress, and to what extent (Bohnen *et al.*, 1991). This is a relatively new area of focus in cortisol and DHEA research, and may provide insight into some of the conflicting reports in studies on human health, which are much harder to conduct and interpret than studies using animal models. For example, Gunnar and Quevedo (1999) note that much research has been conducted in rodents and non-human primates on the effects of adverse early experiences and their ability to alter HPA axis function and behavioral reactivity to stress later in life. Specifically, they discuss how maternal separation or neglect was found to produce permanent changes in HPA functioning in rodents and non-human primates. These early adverse experiences led to disrupted HPA regulation, which was characterized by prolonged stress reactions, greater vulnerability to stress, and behavioral disturbances. Gunnar and Quevedo point out that there is some evidence that exposure to enriched environments and social stimulation can offset these negative consequences.

In those with a history of adverse childhood events, alterations of neural activity patterns, vagal tone, and the cortisol response to stress have been observed, suggesting that early adverse experiences may also lead to disrupted HPA regulation in human beings. HPA dysregulation has been linked with increased risk for behavioral and emotional problems in childhood, and there is abundant evidence that early adverse events increase the risk of developing psychiatric disorders later in life (Sanchez, 2006; Gunnar and Quevedo, 1999).

It has been postulated that the reduced baseline cortisol seen in many survivors of abuse and neglect, as well as in many psychiatric patients, may not signal a risk factor for the development of stress-related illness, but may instead be a biomarker for resilience, a sign that the human organism has successfully adapted to and coped with the environment (Grillon *et al.*, 2006; Gunnar and Quevedo, 1999). This down-regulation of the stress response system may indeed be a protective mechanism which prevents further damage to the system in the face of prolonged stress.

The notion of resilience against stress, as it relates to the cort/DHEA ratio, has not been examined in detail, but future research will hopefully lead to an illumination of the physiological correlates of this interesting psychological construct. One related study involving a stressful military diving navigation test found that soldiers with higher baseline DHEA (S) levels demonstrated superior performance (Morgan *et al.*, 2009). In addition, soldiers exhibiting elevated DHEA levels induced by the diving test exhibited fewer stress-related symptoms of dissociation during the dive. The authors note that baseline DHEA levels might be used to predict performance under stress, and that the study provides evidence in support of the hypothesis that DHEA buffers against the effects of stress.

The Measurement of Cortisol and DHEA

Finally, how are cortisol and DHEA typically measured in behavioral medicine research studies? As discussed in a 1989 review by Kirschbaum and Hellhammer, both can be measured by drawing blood samples from study participants, but this is not generally viewed as the preferred collection method when studying stress, as blood draws can be aversive to many individuals, and can serve as a confounding variable which may

lead to alterations in cortisol and DHEA levels. The measurement of cortisol in urine over a 24-hour period has also been used in research, but compliance with the collection protocols is a disadvantage of this method (Hellhammer, Wüst, and Kudielka, 2009). The measurement of salivary cortisol has been widely used, and is considered a reliable, inexpensive, and accurate way to assess free cortisol levels, and can be used to make repeated measurements in a variety of settings in which drawing blood would not be practical (Hellhammer, Wüst, and Kudielka, 2009; Kirschbaum and Hellhammer, 1989). In addition, salivary cortisol levels have been found to be comparable to the active, free hormone fraction in the bloodstream. Salivary cortisol measurements have been used in several hundred studies (Kirschbaum and Hellhammer, 1989) and several dozen studies have reported high levels of agreement between salivary and serum cortisol measurements, with correlations ranging from 0.71 to 0.96 (Kirschbaum and Hellhammer, 1994). Furthermore, salivary cortisol levels are not affected by salivary flow rate (Kirschbaum and Hellhammer, 1994).

The measurement of salivary DHEA has not been performed as extensively as the measurement of salivary cortisol, but it appears that salivary DHEA levels correlate fairly well with plasma DHEA levels (Gallagher e*t al*., 2006; Granger *et al*., 1999). Further validation of these results will be needed before the measurement of salivary DHEA becomes a standard research method in behavioral medicine.

There have been a wide range of studies performed over the past several decades on the relationship between stress and health, both in human beings and in animal models. As knowledge continues to expand, it has become clear that measuring salivary cortisol as a biomarker for stress has significant utility to the field of behavioral

medicine. Over the past few decades DHEA has come to the foreground as another potential source of valuable information on the human stress response, and how stress can play a role in both medical and psychiatric illness and health. For all of the research that has been conducted on DHEA in human beings thus far, more questions than answers remain, which leaves many avenues of inquiry open in this interesting area of behavioral medicine research. With all of the diseases that have been linked to stress, it is of great importance to be able to track the influence of stress on physiology, as well as its psychological correlates, and salivary cortisol and DHEA have shown great potential in this regard.

The Role of Cortisol and DHEA in HIV/AIDS

Both cortisol and DHEA have been studied as stress-related biomarkers associated with disease progression in HIV/AIDS. Elevated cortisol and decreased DHEA levels are among the endocrine changes that have been observed in HIV/AIDS (Chittiprol *et al*., 2009; Christeff *et al*., 1997; Enwonwu *et al.,* 1996; Lo and Grinspoon, 2010). It has been proposed that elevated cortisol levels may promote HIV replication (Corley, 1996) and T-lymphocyte apoptosis (Clerici *et al*., 1997), yet there are also reports to the contrary (Gorman *et al*, 1991), as discussed in a recent review by Cole (2008).

Leserman and colleagues found that, over the 7.5 year duration of their study, elevated serum cortisol was significantly associated with the progression to AIDS in a sample of 82 men aged 30.3±5.9 years old, 21% of whom were minorities (2000). The average time in the study for those without AIDS was 4.46 years. Elevated cortisol levels predicted disease progression independent of stressful life events, denial, social support satisfaction, baseline CD4+ count and VL. Specifically, for each 1 μg/dl increase in

average serum cortisol levels, the risk of developing AIDS was increased by 14%, and for each 5 µg/dl increase the risk nearly doubled.

In a study of 37 individuals, Enwonwu and colleagues (1996) found that mean salivary cortisol levels in unmedicated HIV patients (27.4 ±9.3 nmol/L) were significantly higher than in HIV-sereonegative control participants (10.1±3.5 nmol/L) matched for age, gender, and ethnicity. The authors noted that the individual variability in salivary cortisol levels was higher in HIV patients than controls. Additionally, the highest salivary cortisol values were found in HIV patients who had oral candidiasis, peridontitis, or oral Kaposi's sarcoma lesions, suggesting impaired oral immunity due to increased cortisol levels.

A 5-year, prospective study was performed by Mulder and colleagues (1992) which measured serum DHEA levels in 123 homosexual men in whom clinical and laboratory tests were performed every three months. After data were collected, each of the 41 unmedicated HIV+ patients who had progressed to AIDS was age-matched to two control participants: one, an unmedicated HIV+ nonprogressor, and the other, a HIV-seronegative control participant. At study entry a significant difference in DHEA levels was found between HIV-seronegative controls (13.3 nmol/L) and both the HIV+ progressors (7.2 nmol/L) and HIV+ non-progressors (9.2 nmol/L). At an average of five months before participants with HIV had progressed to AIDS, significant differences were found between the DHEA levels of HIV+ progressor group (median 5.6 nmol/L) and the combined matched control group (median 8.8 nmol/L). DHEA levels less than 7 nmol/L predicted progression to AIDS independent of CD4+ lymphocyte counts and HIV-1 p24 antigen status. The authors note that measuring DHEA in HIV+ patients could

have clinical value, but that the results could be due to impaired adrenocortical function that develops as the disease progresses, so further study is needed.

Psychological Factors and Disease Progression in HIV/AIDS

A variety of psychological factors have been associated with accelerated HIV disease progression, including hopelessness (Ironson *et al*., 2005), depression (Ironson *et al*., 2005; Patterson *et al*., 1996) and avoidant coping (Ironson *et al.,* 2005; Vassend and Eskild, 1998). Depression and stressful life events were shown to predict disease progression while controlling for initial disease status, both before and since the availability of highly active antiretreoviral therapy (HAART) (for a review see Leserman, 2008). Conversely, psychological factors such as optimism (Ironson 2005b; Milam, 2004), spirituality (Ironson *et al*., 2006) and social support (Leserman *et al*., 1999) were found to predict slower progression to AIDS in the era of HAART.

A recent meta-analysis of 36 articles representing prospective studies in HIV, published between 1991 and 2008, was conducted which analyzed 100 psychosocial and disease-based relationships (Chida and Vedhara, 2009). The authors note that, even with the advent of HAART, there is still considerable variability in the course of disease, some of which has been attributed to psychosocial factors. A small overall *r*-effect size (0.059) of adverse psychosocial factors on HIV disease progression was found, with coping styles and distress being more strongly associated with disease progression than the presence of stress *per se*.

Simoni and colleagues discuss the role of "psychological resourcefulness" in how individuals with HIV cope with the disease (2006). Psychological resourcefulness includes efforts to make meaning out of challenging circumstances, to enhance one's self-

esteem, and to attain mastery over one's life, despite having a stigmatizing, life-threatening disease. Mastery, self-esteem, and self-efficacy are closely related, and involve the sense that one is an agent in control of one's own life, rather than fate or other external forces, and that one can meet the challenges imposed by life circumstances and events. In a diverse sample of 373 women living with HIV/AIDS, Simoni *et al.* found that psychological resourcefulness mediated the inverse relationship between social support and symptoms of depression, presumably through the enhancement of self-esteem, the increased sense of mastery, and improved self-efficacy (2006).

Moskowitz studied positive affect as a predictor of AIDS mortality by analyzing data from the San Francisco Men's Health Study which followed 1043 men over a nine year period from 1984 to 1993 (2003). Of the total cohort, 407 men were HIV+ at baseline, and data from these participants were analyzed by Moskowitz. Positive affect was found to predict longer time until death, while controlling for CD4+ lymphocyte counts and antiretroviral use. For every 1-point increase in positive affect on the Center for Epidemiologic Studies Depression Scale (CES-D), there was a 10% decrease in risk of death from AIDS. Moskowitz notes that scores on the other subscales of the CES-D (negative affect, somatic, and interpersonal) were not significantly associated with mortality when statistically controlling for disease progression, which suggests that positive affect was the key component of the CES-D that predicted decreased mortality. Moskowitz suggests that increasing positive affect, rather than just decreasing negative affect, should be a component of psychological interventions for those living with HIV/AIDS, and warrants further study.

The Psychological Construct of Resilience

Resilience is considered to be a dynamic and multifaceted process characterized by positive adaptation in the face of threat, adversity, or severe stress (Luthar, Ciccetti and Becker, 2007). Although resilience-related constructs such as psychological resourcefulness and hardiness have been studied in the context of HIV/AIDS (Blaney *et al*., 1991), resilience itself has not been studied extensively in this population. This is unfortunate, given the large literature on resilience, which has its origins in developmental psychology and began in the 1950's with the investigation of factors which promote resilience in the face of childhood adversity (for a summary and discussion, see Werner, 1993). Connor and Davidson (2003) state that, following stress and disruption, individuals may experience increased resilience; a return to baseline functioning; recovery with loss leading to lowered baseline level of functioning; or a dysfunctional state of maladaptive coping behaviors leading to functioning that is well below baseline levels. In a similar vein, Bonanno (2005) describes a resilient trajectory of healthy functioning post-trauma, which is characterized by brief, mild disruptions in functioning, followed by a stable period of resilient functioning that goes beyond mere recovery alone. The presence of resilience following stress or trauma has been found to be much more typical than previously assumed in the literature (Bonanno, 2005), although it remains to be seen whether resilience functions in a similar fashion in those with HIV/AIDS.

Psychological Interventions in HIV/AIDS

Carrico and Antoni reviewed 14 randomized controlled trials measuring the effects of psychological interventions on HIV disease markers, including hormonal and

immune markers, and found that 7 trials demonstrated effects on disease markers (2008). The authors note that the effects of psychological interventions were more apparent in studies of patients at earlier stages of HIV, and that interventions which reduce depression appear to be most likely to improve immunity. The authors conclude that psychological interventions are a feasible method of improving psychological adjustment to the disease and potentially improving immunity, in conjunction with HAART.

However, in a meta-analysis of 35 randomized controlled trials of stress-management interventions for those with HIV, it was determined that stress-management interventions did not improve immune or endocrine function, and did not alter stress levels, but did improve mental health and quality of life, as well as fatigue (Scott-Sheldon *et al.*, 2008). As noted by the authors, this may be due to the relatively short follow-up period for post-intervention assessment (typically one week), the lack of participant diversity, advanced disease status (average of five years living with HIV), and different inclusion and adherence criteria for ART. Clearly, there is a need for a greater number of studies which use sufficient follow-up periods, and samples which are diverse with respect to culture and disease status, as stress management interventions may have different effects on disease progression at different stages of the disease. It is also possible that not all of the relevant psychological factors influencing disease progression were successfully targeted by the interventions in the meta-analysis.

A study of a ten-week, group cognitive behavioral stress management (CBSM) intervention in 67 HIV-seropositive men (aged 29-44 years old) was performed that involved 2.5 hours per week of combined stress management and relaxation training (Cruess *et al.,* 1999). The plasma cort/DHEA-S ratio was measured before and after the

intervention, and it was found that there was no significant change in the cort/DHEA-S ratio among those in the CBSM group (*n*=43), while there was a significant increase in the cort/DHEA-S ratio in the control group (*n*=24), from 0.092 ± 0.090 nmol/L pre-intervention, to 0.115 ± 0.099 nmol/L post-intervention. This was due to the significant decrease in DHEA-S in the control group, from 223.18 ± 123.15 nmol/L pre-intervention, to 181.88 ± 126.92 nmol/L post-intervention. The authors note that CBSM prevented the decline of DHEA-S levels, and hence, the increase in the cort/DHEA-S ratio, and that this may be due to the significantly reduced mood disturbance and perceived distress found in the CBSM participants. This study suggests that interventions which affect psychological factors such as stress can alter endocrine function in those with HIV, which may have implications for slowing disease progression.

A related study was conducted to measure the effects of a ten-week CBSM intervention in 30 symptomatic HIV+ men (aged 18-49 years old) matched to waitlist controls (Cruess et al., 2000). Salivary cortisol levels were measured before and after 45-minute relaxation sessions conducted three times over the 10-week CBSM intervention. There was a significant decrease in pre-session cortisol levels across the three relaxation sessions, with pretreatment levels going from 366 ± 58 ng/dL before the first session, to 225 ± 21 ng/dL before the third session. There were significant within-session decreases during the first two relaxation sessions, and a trend toward a significant decrease during the third session. These decreases were associated with the at-home practice of relaxation exercises. The authors note that the study provides evidence for the effectiveness of stress-management interventions in altering HPA axis activity in HIV-infected men, and supports the use of salivary cortisol measurement to track HPA changes both in short- and

long-term interventions. The authors note that several factors could be responsible for the results, including enhanced self-efficacy due to at-home relaxation practice, group social support, decreased distress, or coping strategies, and that further study is needed to determine which factors are at work.

An intervention-based study by Ironson *et al*. was conducted of 56 culturally-diverse women living with AIDS, 50% of whom were on HAART, and 19% were unmedicated (2005). Participants, aged 36.9±7.2 years, were recruited from three large urban centers within the United States, and randomized to either a group therapy intervention or a low-intensity control condition. The intervention group met weekly for ten weeks in 120 minute sessions, consisting of 90 minutes of CBSM plus 30 minutes of relaxation. The control condition involved ten weekly individual 120 minute sessions, consisting of 45 minutes of watching an informational videotape on stress management and coping with AIDS, plus 75 minutes of watching an entertaining videotape. Interestingly, over the course of the intervention there was a significant association between increased self-efficacy for AIDS, increased CD4 cell count, and decreased VL (independent of medication status), and a significant association between increased cognitive-behavioral self-efficacy and decreased VL, suggesting that increasing self-efficacy may be a fruitful target for future intervention studies.

Written Emotional Expression and Health

The relationship between written emotional expression and health was first studied by Pennebaker, who found that healthy undergraduate students who wrote for fifteen minutes over four consecutive days about personally traumatic, rather than trivial, life events, made fewer visits to the health center over the following six months

(Pennebaker and Beall, 1986). Heart rate, blood pressure, mood, and physical symptoms were measured daily, before and after each writing session. Those who wrote about both the facts and the emotions associated with a traumatic event had temporary elevations of blood pressure and negative mood, yet made fewer visits to the health center over the next six months. Pennebaker and Beall assert that psychological work is required to inhibit the expression of personally traumatic events, which adds to the cumulative burden of stress on the body, and thus written emotional expression of personal traumas may play a role in preventing physical illness (1986).

As noted in a meta-analysis by Frisina and colleagues (2004), follow up studies using Pennebaker's writing paradigm showed robust evidence for its effectiveness in promoting clinically significant changes such as fewer health center visits, fewer absentee days, and higher liver enzyme and immune system function, yet most of these studies were carried out using psychologically and physically healthy college students and employees. In their 2004 meta-analysis, Frisina and colleagues included only studies of clinical populations, and found that emotionally expressive writing was moderately effective (d=0.19) at reducing physical symptoms, and less effective at reducing psychological symptoms (d=0.07). Physical improvements such as improved breathing, decreased pain, and increased immunity occurred in those with asthma, arthritis, and several types of cancer, respectively. Frisina and colleagues note that, while emotionally expressive writing interventions were less effective overall for psychological disorders, structured writing interventions appear effective for depressed and anxious patients, and were found to be quite effective (d=0.49) in those with PTSD.

As discussed by Frattaroli, experimental disclosure, which involves disclosing personally meaningful information, thoughts, and emotions, has been shown to have effects on health, yet the exact mechanisms through which disclosure works remain unknown (2006). Frattaroli notes that although the cathartic expression of unresolved emotion was proposed as the means through which emotional expression could benefit health, it became clear as the field progressed that catharsis does not fully account for the effects of emotional expression interventions. Subsequent work in the field suggested that the process of gaining insight into and making sense of traumatic events could account for the effects of emotional expression on health. Other theories developed based on the notion that expressive writing enables one to develop emotion-regulation abilities, and that writing about trauma assists one in relating to one's social world more effectively, both of which may lead to a state of physical health.

In order to address some of the mixed results that have arisen as more experimental disclosure studies have accumulated, Frattaroli performed a meta-analysis of 146 randomized studies (2006). Frattaroli notes that written emotional disclosure may not benefit all individuals in all situations, and that subject differences must be accounted for. Additionally, Frattaroli states that the variety of methods used to forewarn participants that they may write about trauma, to elicit written emotional expression, and to time the follow-up writing periods have added to the lack of clarity in the literature on the effectiveness of this intervention. Frattaroli's meta-analysis determined the mean r-effect size of written emotional disclosure on a variety of outcomes (0.075) to be significant. Specifically, written emotional disclosure significantly affected psychological health (r=0.056), physiological functioning (0.059), general functioning (0.046), reported

health (0.072), and the subjective experience of participating (0.159), but not on health behaviors. Interestingly, it was found that written emotional disclosure had a significant, positive *r*-effect of 0.331 on HIV viral load.

Potential Mechanisms Underlying Written Emotional Expression

Written emotional expression may help individuals make sense of stressful life events through facilitating balanced emotional reactions and processing of such events (Lepore *et al.*, 2002, Smyth *et al*., 2008). There is evidence that written emotional expression interventions may also facilitate habituation to the trauma, and promote the restructuring of cognitions surrounding it (Smyth *et al*., 2008). The authors argue that a writing task centered on the expression of negative emotion may not be necessary to produce beneficial health and psychological outcomes, as the expression of positive emotion may promote personal and social resource-building and enhance positive affect, both of which can influence health. However, at present there are not enough studies on positive written emotional expression to test this hypothesis.

There is evidence that writing about a traumatic event that has not previously been disclosed to others promotes a greater sense of perceived control over the event, an increased ability to account for the event, and increased positive affect (Paez, Velasco and Gonzalez, 1999). This is especially true for intensive writing which involves directly confronting emotional memories and cognitively reframing the traumatic event (Paez, Velasco and Gonzalez, 1999). This may be because the process of writing about a traumatic event provides an opportunity to confront trauma memories, while managing one's negative emotions, and gaining emotional and mental clarity about the trauma.

In a discussion of the literature on written emotional expression, Pennebaker notes that it is not the expression of emotion alone that leads to improved mental and physical health, but the translation of personal experiences into language (1997). Pennebaker also discusses how, in six separate writing interventions, participants who experienced the greatest health benefits tended to use the greatest number of positive emotion words, accompanied by a moderate number of negative emotion words, and also tended to use the greatest number of words demonstrating insight and causation, suggesting that these participants had come to an understanding of life events and developed coherent, meaningful narratives of them.

In another paper, Pennebaker, Mayne and Francis discuss their working model of how expressive writing affects health (1997). The authors hypothesize that writing about a traumatic experience requires the individual to put the emotions and memories associated with the trauma into words, and through writing expressively, often on multiple occasions, the experience becomes coherently organized, better understood, and less emotionally arousing. Gaining insight, coming to terms with emotions surrounding the traumatic experience, coping, being self-reflective, and thinking actively are often part of this process. In several studies involving such diverse groups as college students, maximum security prisoners, out-of-work engineers, and both HIV-negative and HIV-positive male partners of men with AIDS, Pennebaker and colleagues found that both health and adaptive behaviors increased along with increased use of insight (*realize, understand, consider*) and causation (*cause, effect, because, infer*) words throughout the course of the writing intervention studies (1997).

It is possible that, over time, writing interventions decrease the physiological

arousal associated with traumatic experiences, which may have implications for preventing the deleterious psychobiological effects of prolonged exposure to stress. A study examining expressive writing on immunity and distress was performed, using 50 healthy college students randomly assigned to write about a trauma or a mundane topic for 20 minutes over 4 consecutive days (Pennebaker, Kiecolt-Glaser and Glaser, 1988). It was found that, through the 6-week follow-up period, those writing about a trauma had significantly enhanced lymphocyte response to *in vivo* antigen exposure and paid fewer visits to the health center. In addition, at the 3-month follow-up, the trauma writing group reported significantly greater levels of happiness. However, there were no significant effects at the 3-month follow-up of the writing intervention on health-related behaviors. Future writing intervention studies using multiple biomarkers and longer intervention and follow-up periods are needed, in a variety of populations, so that this promising intervention can be fully explored.

Written Emotional Expression and HIV/AIDS

The investigation of written emotional expression in HIV/AIDS represents a relatively new area of inquiry. In a study of the relationship between written emotional disclosure, depth processing, and long-term AIDS survivorship, O'Cleirigh, Ironson *et al*. compared long-term AIDS survivors (at 4 years past the onset of Category C symptoms) to an HIV+ comparison group (with CD4+ counts between 150-500 cells/mm^3) that was equivalent in terms of gender, viral load and CD4+ counts at entry into the study (2003). Both groups were asked to write about their feelings related to the most traumatic event since (and including) being diagnosed with HIV. Depth processing in the writing samples was considered to include positive cognitive appraisal change, experiential involvement,

improved self-esteem, and adaptive coping strategies. Depth processing indicates the extent to which an individual is resolving, integrating, and making sense of a stressful experience. The long-term survivors demonstrated significantly more depth processing and emotional expression in their writing. The authors note that depth processing mediated the relationship between emotional expression and survival over the long-term, which suggests that emotional expression may enhance AIDS survivorship through cognitive appraisal changes, self-esteem enhancement, and enhanced coping. Additionally, in both women and men, depth processing was found to be positively related to adherence to antiretroviral medication regimens. Interestingly, follow-up analyses uncovered significant relationships by gender: for women in the study, depth processing was inversely associated with viral load, and positive emotional expression was inversely associated with viral load. Both exploratory findings point toward important avenues for further study.

Petrie *et al*. (2004) conducted an emotional disclosure writing intervention in which 37 HIV+ adults were randomly assigned to write about their deepest thoughts and feelings pertaining to their most traumatic life experiences (*n*=20) or about trivial events (*n*=17). There was a significant increase in CD4+ cell counts in the emotional disclosure group, through the six-month follow-up period. This suggests that written emotional disclosure interventions may benefit the health of HIV patients through increasing immune activity. However, it must be noted that psychological outcomes were not included in this study.

A study of 40 HIV+ men who had recently lost a partner to AIDS was conducted on the role of cognitive processing and finding meaning in response to the loss, and its

relationship to disease progression and mortality (Bower *et al*., 1998). The authors

defined cognitive processing as actively contemplating a stressor and the feelings and

thoughts accompanying it, while also considering its present and future implications for

the self. One outcome of this contemplation may be finding meaning, which involves

integrating traumatic, stressful events into one's sense of self and within the context of

one's life story. The authors examined participant interviews, and developed a coding

system in which all statements demonstrating "deliberate, effortful, or long-lasting

thinking about the death" were considered to reflect cognitive processing, and those

demonstrating "a major shift in values, priorities, or perspectives in response to the loss"

were considered to reflect finding meaning. Finding meaning predicted a significant

decrease in the rate of CD4-lymphocyte decline across a 2- to 3-year follow-up period,

whereas cognitive processing alone did not predict such a decrease. The discovery of

meaning was associated with decreased mortality from AIDS across a 4- to 9-year

follow-up period, while controlling for initial health status, AZT usage, and health

behaviors. The authors note that despair need not be the inevitable outcome of stressful

events such as the loss of a loved one. Instead, growth, reevaluating one's life goals and

values, and the enhancement of the immune system may also result from such events.

Westling, Garcia and Mann conducted a one-month writing intervention with 41

HIV+ women to study how discovering meaning in having HIV is related to antiretroviral

medication adherence (2007). As defined by the authors, the discovery of meaning in a

challenging event involves thoughtful reflection on the event while being optimistic,

versus reflection that leads to pessimistic rumination. A shift in perspective and

clarification of one's values is characteristic of finding meaning. As noted by the authors,

the discovery of meaning has also been referred to in the literature as benefit-finding, posttraumatic growth, and stress-related growth. Using the coding methods of Bower *et al.* (1998) with two raters, the study found that those who discovered meaning over time also significantly increased their self-reported medication adherence over time; conversely, those who did not find meaning decreased their adherence. Those who came to discover meaning engaged in cognitive processing in their writing samples, and were significantly more optimistic, both dispositionally and situationally, at baseline.

Wagner *et al*. studied expressive writing in a diverse sample of 44 individuals with HIV/AIDS who were randomized to write about a current or past trauma (*n*=20) or a trivial topic (*n*=24) for twenty minutes weekly over four weeks (2010). Cognitive adaptability was measured at baseline, as an individual difference variable that serves as a potential moderator of expressive writing on psychological and physical outcomes. Cognitive adaptability is a coping resource that can be called upon during stressful times, which involves optimism about the future and a sense of self-worth, personal control, and competence. This study found no effect of the writing intervention at the one month follow-up point on psychological outcomes (including sense of coherence, perceived stress, positive and negative affect, and HIV-specific optimism), or on pain and physical functioning, which the authors note may be due to the small sample size, short follow-up period and exclusive use of self-report measures, versus objective measures such as CD4+ count. However, the study also found that higher baseline cognitive adaptability predicted better outcomes for physical and psychological functioning as well as pain in the expressive writing group. The authors note that those higher in cognitive adaptability appear to benefit more from expressive writing, and to have more negative outcomes

when asked to write about trivial topics. These findings point toward the need for further

research which can be used to discover which individuals with HIV/AIDS may be best

served by expressive writing interventions, which aspects of writing interventions are

effective, and through which mechanisms expressive writing may operate.

Chapter 2: Objectives

In an effort to contribute to the literature on emotional expression and HIV/AIDS, this study will examine PTSD symptoms, perceived stress, distress, depression, salivary cortisol and the cort/DHEA ratio through an expressive writing intervention in HIV-positive individuals. Additionally, consistent with previous studies (Simoni *et al*., 2006; Yi *et al.*, 2008) resilience will be examined using a variable comprised of measures of self esteem, self efficacy, and positive affect. Written essays will be analyzed to determine the percentage of total words demonstrating insight and the assignment of causation. Resilience, insight, and causation will each be examined separately as potential moderators and/or mediators of the relationships between PTSD symptoms, perceived stress, distress, depression, cortisol, and cort/DHEA.

Aims, Hypotheses and Proposed Analyses

In this study four main hypotheses will be tested: 1) Resilience at baseline will predict the slope of salivary cortisol levels at all pre-intervention time points from baseline to 6-month follow up, and resilience will predict the slope of salivary cort/DHEA levels from baseline to 6-month follow up; 2) resilience will moderate the relationship between trauma-related distress at baseline and depression at 6-month follow up; 3) resilience will moderate or mediate the relationship between perceived stress at baseline and 12-month follow up periods, and 4) the percentage of insight and causation words used during expressive writing will serve as mediators of the relationship between perceived stress at baseline and perceived stress at 6-month follow up periods. The maximum treatment effect is expected at the 6-month follow up period, thus all analyses

will be run through this time point, with the exception of the third analysis, which will be run through 12-month follow up, in order to maximize the number of resilience data points available for analysis across the course of the study.

   Aim 1: To determine whether baseline resilience predicts changes in salivary cortisol and cort/DHEA through the 6-month follow up period of the study.

   Hypothesis 1: Resilience at baseline will predict the slope of salivary cortisol levels at all pre-intervention time points from baseline to 6-month follow up, and baseline resilience will predict the slope of salivary cort/DHEA levels from baseline to 6-month follow up, while controlling for writing group membership (a dichotomous variable representing Trauma versus Daily writing conditions).

   Analysis 1: Hierarchical linear modeling (HLM) will be used to model change in salivary cortisol and cort/DHEA over the course of the study, as HLM allows for slope to be predicted using multiple time points. Variance in the levels of these biomarkers is separated into two levels, with Level 1 representing a growth model for each participant which accounts for within-subject changes in biomarker levels. Level 2 models differences between individuals in parameters of individual change and will use the between-subject difference of resilience at baseline to predict change in biomarkers. In this way, systematic variability in Level 1 slopes and intercepts are modeled by resilience as a Level 2 predictor.

The following equation illustrates the analysis to be conducted at Level 1 for change in salivary cortisol; a similar analysis will be conducted separately for cort/DHEA:

$Y_{ti} = \beta_{0i} + \beta_{1i}$ (months since baseline)$_{ti} + e_{ti}$

Using this equation, the following parameters will be estimated:

Y_{ti} = Cortisol value for participant i at time point t

β_{0i} = Cortisol value for participant i at time point 0 (Baseline)

β_{1i} = Slope representing linear change in cortisol for participant i

e_{ti} = Residual term for participant i at time point t

The following equation illustrates the analysis to be conducted at Level 2 for resilience as a proposed predictor of change in salivary cortisol; a similar analysis will be conducted separately for cort/DHEA:

β_{01} (intercept) = $\gamma_{00+} + u_0$

β_{1i} (slope) = $\gamma_{10} + \gamma_{11}$ (baseline cortisol)$_i$ + γ_{12} (writing group) + γ_{13} (resilience) + u_1

Using this equation, the following parameters will be estimated:

γ_{00} = Group average of baseline cortisol

γ_{10} = Average linear change in cortisol per month

γ_{12} = Effect of writing group membership (T vs. D) on change in cortisol

γ_{13} = Effect of individual differences on cortisol slope (γ_{10}) attributable to resilience

$u_{0,\ 1}$ = Unexplained individual variance related to the estimation of the γ coefficients

Aim 2: To develop a structural model for the relationship between the latent variables Trauma-related Distress and Depression, to determine whether baseline Trauma-related Distress predicts Depression at 6-month follow up periods for all study participants, and to determine whether resilience moderates this relationship.

Hypothesis 2: The theoretical construct of Trauma-related Distress will be represented as a latent variable which is best measured by the observed variables PTSD Symptoms (Davidson PTSD Scale), Distress (Subjective Units of Distress), Perceived Stress (Perceived Stress Scale), and Impact of Events (Impact of Events Scale). The theoretical construct of Depression will be represented as a latent variable, best accounted for by three measures of depressive symptoms (Beck Depression Inventory, Hamilton Rating Scale for Depression, Profile of Mood States depression subscale) and one measure of negative affect (the negative subscale of the Positive and Negative Affect Schedule).   Trauma-related Distress will predict Depression longitudinally, from baseline to 6-month follow up. Resilience will serve as a moderator of this relationship. Higher resilience scores will weaken the relationship between Trauma-related Distress at baseline and Depression at 6-month follow up.

Analysis 2: Structural Equation Modeling (SEM) will be used to develop a model characterizing the relationship between the latent variables Depression and Trauma-related Distress longitudinally from baseline to 6-month follow up. In the first step, confirmatory factor analysis (CFA) will be conducted to develop separate measurement models for each of the latent variables, Depression and Trauma-related Distress. Overall model fit will be assessed separately for each of the two models according to the criteria of Hu and Bentler (1999). Specifically, overall model fit will be tested using the following fit indices: Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI), and Standardized Root Mean Squared Residual (SRMR). Good model fit is indicated by RMSEA values less than 0.06, CFI values greater than 0.95 and SRMR values less than 0.08. Observed variables with at least

minimally adequate standardized factor loadings ($\lambda \geq 0.3$) onto the corresponding latent

variable will be retained in the model (Floyd and Widiman, 1995). In the second step, a

structural model will be developed, and if adequate model fit is obtained using the

previously-mentioned fit indices, linear regression will be used to determine whether

Trauma-related Distress at baseline predicts Depression at 6-month follow up. In the third

step, linear regression will be used to determine whether resilience moderates this

relationship. The proposed predictive model is depicted in Figure 1.

The proposed measurement models for CFA are represented by the following

equations, in which λ represents individual factor loadings, X represents observed

variables, and ε represents error values, with intercepts omitted for simplicity:

$$X1: \text{PTSD} = \lambda_1 \text{ (Trauma-related Distress)} + \varepsilon_1$$
$$X2: \text{SUDS} = \lambda_2 \text{ (Trauma-related Distress)} + \varepsilon_2$$
$$X3: \text{PSS} = \lambda_3 \text{ (Trauma-related Distress)} + \varepsilon_3$$
$$X4: \text{IES} = \lambda_4 \text{ (Trauma-related Distress)} + \varepsilon_4$$

$$X1: \text{BDI} = \lambda_1 \text{ (Depression)} + \varepsilon_1$$
$$X2: \text{Hamilton} = \lambda_2 \text{ (Depression)} + \varepsilon_2$$
$$X3: \text{PANAS} = \lambda_3 \text{ (Depression)} + \varepsilon_3$$
$$X4: \text{POMS} = \lambda_4 \text{ (Depression)} + \varepsilon_4$$

Aim 3: To determine whether baseline perceived stress levels predict

perceived stress levels at 12-month follow-up, and to test whether resilience serves as a

moderator or mediator of this relationship in all study participants.

Hypothesis 3: Baseline perceived stress levels will predict perceived stress

levels at 12-month follow up. Resilience will moderate or mediate this relationship. If

resilience functions as a moderator, it will buffer against increases in perceived stress. If

resilience serves as a mediator, it will suggest a mechanism accounting for the relationship between perceived stress at baseline and 12-month follow up.

Analysis 3: In the first part of the analysis, linear regression will be used to test the relationship between baseline perceived stress levels and those at 12-month follow up, and to determine whether resilience serves as a moderator of this relationship, using the methods of Baron and Kenny (1986). The following regression equation illustrates the moderation analysis to be conducted:

$$Y = a + bX + cM + dXM + e$$

Using this equation, the following parameters will be estimated:

a = the constant representing the intercept

b = the simple effect of baseline perceived stress levels (X) on perceived stress levels at 12-month follow up (Y), when no moderation effect is present (M = 0)

c= the effect of resilience (M) on 12-month perceived stress values (Y) when X equals 0

d = the effect of the interaction between resilience (M) and baseline perceived stress (X) on 12-month perceived stress values (Y)

e = the error of estimation

A statistically significant effect of the interaction term on perceived stress at 12 months (d) while controlling for baseline perceived stress and resilience suggests a moderation effect of resilience.

In the second part of the analysis, multiple linear regression will be performed to determine whether resilience mediates the relationship between perceived stress levels (PSS) at baseline and 12-month follow up periods, using the methods of Baron and Kenny (1986) and Preacher and Hayes (2004). The following regression

equations will be estimated:

$$Y \text{ (PSS at 12 months)} = i_1 + cX \text{ (PSS at Baseline)} + e_1$$

$$Y \text{ (PSS at 12 months)} = i_2 + c\text{'}X \text{ (PSS at Baseline)} + bM \text{ (Resilience)} + e_2$$

$$M \text{ (Resilience)} = i_3 + aX \text{ (PSS at Baseline)} + e_3$$

$$Y \text{ (PSS at 12 months)} = i_4 + aX \text{ (PSS at Baseline)} + bM \text{ (Resilience)} + e_4$$

Using the above equations, the following parameters will be estimated:

i = y-intercepts when X equals 0

c = the direct effect of baseline perceived stress levels (X) on perceived stress levels at 12-month follow up (Y)

$c\text{'}$ = the effect of baseline perceived stress (X) on perceived stress at 12-month follow up (Y), adjusted for the effect of resilience (M)

b = the effect of resilience (M) on perceived stress at 12-month follow up (Y), adjusted for the effect of baseline perceived stress (X)

a = the effect of baseline perceived stress (X) on resilience (M)

e = residual error values

The mediation analysis involves the four following steps and is depicted below:
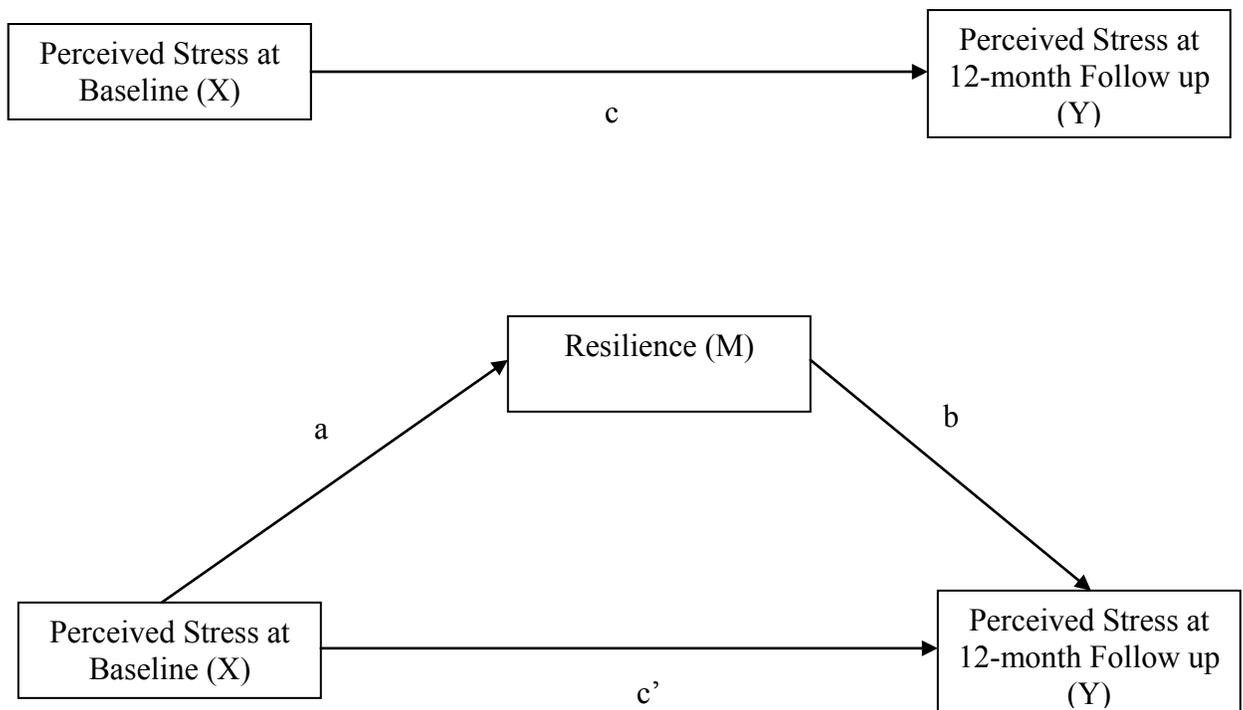
Step 1 of the mediation analysis involves estimating path c by determining the direct relationship between baseline perceived stress (X) and perceived stress at 12-month follow up (Y). Step 2 involves estimating path a, the relationship between X and the potential mediator, resilience (M). Step 3 estimates path b by testing the relationship between M and Y, while controlling for X, by entering X in the first step of the analysis. Step 4 involves estimating path c', which is the direct effect of X on Y while controlling for M. If the effect of X on Y becomes zero when the effects of M are accounted for, complete mediation is suggested; a weakening of the relationship between X and Y while accounting for M indicates partial mediation. The mediation effect (ab) will be calculated, and the significance of the mediation effect will be determined using the Sobel test (Sobel, 1982), which is represented by the following equation:

$$z\text{-value} = ab \div \sqrt{(b^2 s_a{}^2 + a^2 s_b{}^2 + s_a{}^2 s_b{}^2)}$$

$$s_a = \text{standard error of path a}$$

$$s_b = \text{standard error of path b}$$

The resulting z-value will be compared with the critical z-value (± 1.96) from a normal distribution at $\alpha = 0.05$. Values greater than 1.96 or less than -1.96 indicate a significant mediation effect.

Aim 4: To determine whether the relationship between baseline perceived stress levels and perceived stress levels at 6-month follow up (if significant) is mediated by the mean percentage of total written words denoting the use of insight in the Trauma writing group in the first two writing sessions. To determine whether the above

relationship is also mediated by causation words, as well as by a combination of insight and causation words.

Hypothesis 4: Baseline perceived stress levels will predict perceived stress levels at 6-month follow up. The mean percentage of insight words used during the first two writing sessions will mediate the relationship between perceived stress at baseline and 6-month follow up periods. Similarly, the mean percentage of causation words will also serve as a mediator. It is hypothesized that greater use of insight and causation words will account for a weaker relationship between perceived stress at baseline and 6-month follow up, indicating a partial mediation effect.

Analysis 4: After performing linear regression to analyze the direct effect of baseline perceived stress on perceived stress at 6-month follow up, separate multiple linear regression analyses will be used to test the potential mediating effects of insight words, causation words, and the combination of insight and causation words, using methods similar to Analysis 3.

Chapter 3: Methods

Participants:

A group (N=246) of HIV-positive men (57%) and women (43%) was recruited and enrolled between 2004 and 2009 in the Miami metropolitan area. Participants were eligible for inclusion if they had CD4+ cell counts between 100 and 600 cells/mm³ upon entering the study, indicating the mid-range of the disease. Participants were excluded from the study if they had a history of having a CD4+ cell count below 75cells/ mm³ or had ever been diagnosed with more than one Category C (AIDS-defining) illness. In addition, participants were excluded if they had used intravenous drugs within the last month, were currently dependent on alcohol or drugs, were actively suicidal or psychotic, or had less than an eighth grade education. Participants were also excluded if they were under age 18, had undergone recent surgery, medication regimen changes, bereavement, or were suffering from a non-HIV related life threatening illness or were taking medication known to interfere with stress hormones.

Design:

Data for this project come from an intervention in which participants were seen at four assessment time points and four intervention time points during a one-year period. For the purposes of the present study, participants were included if they had completed the baseline assessment session and at least two writing sessions. Participants who met the inclusion criteria underwent an initial baseline assessment and were equally randomized into one of two groups: the control "daily" (D) writing group or the experimental "trauma" (T) writing group. Assessments were conducted at the baseline

visit (Baseline), at each of the four writing sessions (W1, W2, W3, W4) and follow-up visits at 1, 6, and 12-months post-intervention (F1, F6, F12).

Procedures:

During the initial visit, informed consent and demographic information were obtained from study participants. During the initial and follow-up periods, saliva samples were collected for the analysis of cortisol and DHEA. Participants were instructed to refrain from eating, drinking, or smoking for 30 minutes before saliva samples were collected. Upon arrival at the laboratory, all participants were asked to sit in the waiting room for 15 minutes to promote a resting, baseline state of arousal before providing saliva samples or completing psychological measures. All pre-intervention saliva samples were collected between 10 o'clock a.m. and 1 o'clock p.m. Each participant was instructed on how to use a Salivette® saliva collection tube, and while saliva was being absorbed by the cotton roll, the participant was given the pre-intervention SUDS (Subjective Units of Distress) and POMS (Profile of Mood States) questionnaires to complete. Immediately following this, the saliva sample was refrigerated, and the participant was given a picture of a neutral scene and asked to write for 30 minutes about the scene, which served as a measure of writing ability. Immediately after the writing session was finished, the participant was given a fresh Salivette® collection tube and used it to collect saliva while completing the post-intervention SUDS and POMS questionnaires. Saliva samples were refrigerated immediately following collection, and were then centrifuged, frozen, and stored at negative 20ºC within 24 hours of collection. Next, a battery of self-report questionnaires was completed, followed by an interview, and finally a blood sample was drawn. Blood samples were drawn on a total of four

occasions: at the end of the initial visit and at the conclusion of the three follow-up visits at one, six and twelve months post-intervention.

On the four subsequent visits to the laboratory which comprised the writing intervention phase of the study (W1-W4), participants followed similar procedures for saliva collection and questionnaire administration. In addition, while in the laboratory, participants wrote for 20 minutes on either a daily topic (D) or traumatic experience (T), followed immediately by 10 additional minutes of writing on a daily topic (D), or by 10 minutes of writing using directed questions (T) described in the following paragraph. During two ensuing follow-up visits at F1 and F12, participants spent 30 minutes reading what they had written during the writing intervention phase. At the F6 visit, saliva samples were collected and questionnaires were administered, but participants did not read their previously written essays.

The T writing group was given the following prompt: "During the four writing days, please write about your most traumatic or upsetting experiences of your entire life" and participants were asked to write about the same experience on all four days if possible. T group participants were instructed to write about a major trauma that has not been discussed in detail with others, while letting go and exploring one's deepest emotions and thoughts, and to write for 20 minutes. Immediately following this, the T writing group was asked to write using the following prompt to enhance depth of processing: "Please write for 10 minutes about how you've tried to understand the experience(s) that you have just written about and how you make sense of it." T group participants were also write about how they were trying to understand the experience if it does not make sense to them currently.

The D writing group was given the following written prompt: "In today's writing, I want you to describe what you did yesterday from the time you got up until the time you went to bed" and was asked not to describe emotions or opinions, but to be as objective as possible, and to write for 20 minutes. Immediately following this, a similar prompt was given pertaining to the current day's activities and 10 minutes were allowed for writing.

Throughout the duration of the study, every effort was made to ensure that each participant came into our laboratory at the same time of day: if a participant arrived at 10 o'clock A.M. for the initial visit, all subsequent visits were scheduled for 10 o'clock A.M. Immediately following saliva collection, the Salivette® tubes were refrigerated for an average of 4 hours (but occasionally up to a maximum of 24 hours) before being transported in a cooler to an off-site laboratory where they were frozen at -20 ºC until being assayed.

Biological Assays:

Salivary cortisol levels were determined through enzyme-linked immunosorbent assay (ELISA) using commercially available kits from Immuno-Biological Laboratories (Minneapolis, MN). 100 µl of each saliva sample was added to the wells of a microtiter plate which was coated with an antibody specific to the cortisol molecule. Next, 200 µl of enzyme conjugate containing a competitively binding molecule was added to each well. The plate was incubated for 60 minutes at room temperature, decanted, and washed. Following the wash, 200 µl of substrate was added to each well, which turned purple in an inverse proportion to the amount of cortisol in each sample, during 30 minutes of incubation at room temperature. The absorbance of cortisol to the antibody was measured

on a microtiter plate reader and a standard calibration curve was used to calculate cortisol

levels for each sample.

Salivary DHEA levels were determined through ELISA using commercially

available kits from Immuno-Biological Laboratories (Minneapolis, MN), following an

assay procedure similar to that of salivary cortisol. 50 µl of each saliva sample was added

to the wells of a microtiter plate which was coated with an antibody specific to the DHEA

molecule. Next, 100 µl of enzyme conjugate containing a competitively binding molecule

was added to each well. The plate was incubated for 60 minutes at room temperature,

decanted, washed, and 100 µl of substrate was added to each well. The absorbance was

measured and a standard calibration curve was used to calculate DHEA levels for each

sample.

*Linguistic Inquiry and Word Count (*LIWC; Pennebaker *et al.,* 2001):

The Linguistic Inquiry and Word Count (LIWC) computer software program was

developed as a means of efficiently assessing the psychological and linguistic

characteristics of written essays that have been transcribed into an electronic text format

(Pennebaker *et al.*, 2001). The 2007 version of the LIWC software contains a dictionary

of words based on Standard English which are grouped according to linguistic,

grammatical, and psychological categories. LIWC measures: parts of speech (verbs,

pronouns, word tenses), words denoting relationships (social, family, friend), affective

and emotion words (anxiety, anger, sadness, positive, negative), cognitive words (insight,

causation, discrepancy, certainty), perceptual words (see, hear, feel), physical words

(body, health, ingestion), words denoting relativity (motion, space, and time), and words

denoting work, leisure, religion, and death, as well as swear words and "filler" words

such as "um". For each essay or group of essays analyzed, the LIWC program produces an output of 63 variables, each of which reflects a different linguistic or psychological category. Each variable calculated by LIWC, such as Insight, represents the number of insight-denoting words as a percentage of the total number of words in each individual essay.

For this project, participants' first two essays were transcribed into electronic text format and analyzed by LIWC (2007 version). Two variables from the LIWC output were used in this project: one denoting insight ("Insight") and one denoting the assignment of causation ("Cause"), with the goal of expanding upon prior research on insight and causation words (Pennebaker, 1997).

Psychological Measures:

A variety of psychological measures were used in this study, for which the means, standard deviations and ranges can be found in Table 1.

For Analyses 2 and 3, resilience was measured using a variable composed of standardized scores on measures of self esteem, self efficacy, and positive affect, averaged across all time points from B through F6. For Analysis 1, the resilience variable represents an average of these three measures from the Baseline time points, prior to W1. The three measures comprising the resilience variable are described below.

Self esteem was measured using the Rosenberg Self Esteem Scale, a 10-item self-report measure of global self-esteem which has been found to be reliable and is widely used (Silber and Tippet, 1965). Scores can range from 10 to 40, with higher scores indicating higher self esteem. It assesses items such as self worth, positivity toward the self, and satisfaction with the self.

Self efficacy was measured using the Pearlin Mastery Scale, a 7-item self-report measure of the extent to which individuals feel that they are in control of the circumstances affecting their lives. This measure was found to correlate positively with self esteem and negatively with depression (Pearlin *et al.*, 1981). Scores range from 7 to 28, with higher scores indicating higher self efficacy. It assesses such constructs as one's sense of competence, control, and empowerment.

Positive and negative affect were measured using the Positive and Negative Affect Schedule (PANAS) which is a 20-item self-report measure of the general dimensions of positive and negative mood via two subscales, each of which represents a distinct construct. Scores can range from 0 to 50 on each of the two subscales, with higher scores representing greater levels of positive or negative affect. The PANAS has been shown to have good reliability and validity, and the negative affect scale was found to correlate well with measures of depression (Watson *et al.*, 1988).

Depressive symptoms were measured using the Beck Depression Inventory (BDI), a 21-item self report measure which is widely used (Beck *et al.*, 1961). The BDI consists of an 8-item subscale measuring affective symptoms of depression, and a 13-item subscale measuring somatic symptoms of depression. Total scores range from 0 to 63, with higher scores representing more severe levels of depression.

Depressive symptoms were also measured using the Hamilton Depression Rating Scale (HDRS), a 17-item clinician-administered measure of depressive symptoms (Hamilton, 1960). Scores of 10-13 are considered mild, 14-17 are considered moderate, and scores greater than 17 are considered moderate to severe.

Depressive symptoms were further measured using the depression subscale of the Profile of Mood States (POMS), a 65-item measure of mood fluctuation in six affective mood states (McNair, Lorr, and Droppelman, 1971).

Subjective distress was measured using a Subjective Units of Distress (SUDS) scale, a self report measure using a rating scale to indicate the intensity of subjective feelings of distress. Scores range from of 0 to 100 (in increments of 10 units) with higher scores reflecting greater subjective distress levels.

Subjective stress levels were measured using the Perceived Stress Scale (PSS), a 10-item self-report measure which demonstrates good reliability and is designed to measure the degree to which life events are perceived as being stressful by the individual. Scores range from 0 to 56, with mean scores of 25±8 in a community sample (Cohen, Kamarck, and Mermelstein, 1983).

PTSD symptoms were measured using the Davidson Trauma Scale, a 17-item self-report measure which assesses PTSD symptoms using the DSM-IV criteria (Davidson *et al,* 1997). Scores range from 0 to 136, with scores greater than 30 reflecting subthreshold PTSD symptoms with impairment, and scores greater than 60 reflecting clinically significant PTSD symptoms (Davidson, Tharwani and Connor, 2002).

The impact of traumatic and stressful life events was measured using the Impact of Events Scale (IES), a 15-item self-report measure that assesses current levels of both thought intrusion and avoidance responses (Horowitz, Wilner and Alvarez, 1979). In this study, participants used the IES to rate the current impact of learning of one's HIV-positive status.

Analyses

All statistical analyses were performed using SPSS (version 18) and Mplus (version 6) software programs. Preliminary analyses were performed in which all variables were checked for outliers, normality, skew, kurtosis, and multicollinearity. The values of cortisol, DHEA, and the cort/DHEA ratio were windsorized to trim outliers: values beyond 2.5 standard deviations from the mean were removed, the mean and standard deviation of the new distribution were calculated, and the outlying values were replaced with scores at 2.5 standard deviations from the mean. The windsorized cortisol values were then $\log_{10}$ transformed to normalize their distribution. Before testing the overall structural model, a separate measurement model was tested for the latent variables Trauma-related Distress and Depression. The latent variable Depression is measured by the indicator variables BDI, Hamilton, PANAS (negative subscale only), and POMS, and is composed of measures taken at multiple time points. The latent variable Trauma-related Distress is measured by PTSD, SUDS, PSS, and IES. Moderation analyses were conducted without centering predictor or outcome variables, consistent with recent recommendations (Dalal and Zickar, 2011; Kromrey and Foster-Johnson, 1998).

Structural Model

The proposed structural model depicted in Figure 1 was tested using SEM, and the final model is shown in Figure 3, with ovals representing latent variables and rectangles representing indicator variables. The main parameters estimated were path coefficients measuring direct effects, which were estimated using maximum likelihood which assumes data are missing at random, and tested using a *z*-distribution at the 0.05 significance level.

Chapter 4: Results

The purpose of this study was to investigate the potential relationships of resilience to salivary cortisol and to cort/DHEA through the F6 period of the study, as well as the relationship of resilience to perceived stress across the study. Additionally, this study aimed to develop a structural equation model relating trauma, depression, and resilience. A final purpose of this study was to investigate the role of insight- and causation-denoting words as potential mediators of the relationship between perceived stress at Baseline and F6 periods. All reported coefficients are standardized unless otherwise noted.

Analysis of the Role of Resilience in Predicting Salivary Cortisol and Cort/DHEA

It was hypothesized that resilience at Baseline will predict the slope of salivary cortisol levels at all pre-intervention time points from Baseline to F6, and similarly, that resilience will predict the slope of salivary cort/DHEA levels from Baseline to F6, while controlling for writing group assignment (Trauma vs. Daily) and baseline biomarker values in both analyses. For these analyses, the resilience variable included only the Baseline time points, measured before the writing intervention. HLM was used to model change in salivary cortisol and cort/DHEA from Baseline through the F6 time point of the study.

In the first step of the analysis, the slope of cortisol values was estimated with months since baseline as a Level 1 predictor, to determine whether cortisol values changed significantly over time. As shown in Table 6, there was no change in cortisol values from Baseline to F6, for all participants, as indicated by a non-significant p-value (0.175) for months since baseline as a predictor of cortisol slope.

In the second step of the analysis, resilience was tested as a Level 2 predictor of the slope of cortisol values from Baseline through F6. As shown in Table 6, resilience did not predict the slope of cortisol values while controlling for writing group assignment and cortisol values at Baseline, as indicated by a non-significant p-value (0.999) for this model.

Following a similar procedure, Level 1 and 2 models were tested to determine whether the ratio of cort/DHEA changes from Baseline to F6, and whether resilience predicts the slope of cort/DHEA. In the Level 1 model, as shown in Table 6, there was no change in cort/DHEA values from Baseline to F6, as indicated by a non-significant p-value (0.385) for months since baseline as a predictor of cort/DHEA slope. In the Level 2 model, as shown in Table 6, resilience was found to predict the slope of cort/DHEA values while controlling for writing group membership and baseline cort/DHEA values, as indicated by a significant p-value (0.049) for this model.

Analysis of Trauma, Depression, and Resilience through SEM Model Development

The study's second hypothesis was that the latent variable Trauma-related Distress at Baseline will predict Depression at F6, and that resilience will serve as a moderator of this relationship for all study participants. It was hypothesized that higher resilience scores would weaken the relationship between trauma-related distress at Baseline and depression at F6. For this analysis, the resilience variable comprised all time points from Baseline through F6.

Prior to developing the SEM model, Pearson zero-order correlations were conducted to examine the interrelationships between resilience and all indicator variables in the SEM model, as shown in Table 2. The correlation (r) between resilience and each

indicator is as follows: Beck Depression Inventory (-0.475), Hamilton Rating Scale for Depression (-0.378), Profile of Mood States, depression subscale (-0.267), Positive and Negative Affect Schedule, negative subscale (-0.152), PTSD Symptoms (-0.307), Distress (-0.245), Perceived Stress (-0.458), and Impact of Events (-0.177). All correlations were significant at $p < 0.05$.

In the first step of the analysis, a measurement model was tested via confirmatory factor analysis, using the following variables measured at the Baseline time point: PTSD Symptoms, Distress, Perceived Stress, and Impact of Events, which were hypothesized to be indicators of the latent factor Trauma-related Distress. The model had good fit to the data ($X^2 (2) = 1.99$, $p = 0.370$; RMSEA $= 0.00$; SRMR $= 0.015$; CFI $= 1.00$). All standardized loadings were 0.50 or greater.

In the second step, a similar procedure was followed to test the following variables measured at F6: Beck Depression Inventory, Hamilton Rating Scale for Depression, Profile of Mood States (depression subscale) and the Positive and Negative Affect Schedule (negative subscale) as potential indicators of the latent factor Depression. With one minor modification, this model also had good fit to the data ($X^2 (1) = 0.904$, $p = 0.342$; RMSEA $= 0.00$; SRMR $= 0.009$; CFI $= 1.00$). All standardized loadings were 0.50 or greater for all indicators except for the Hamilton Rating Scale for Depression, which had a standardized loading of 0.473. The unique variance of this indicator correlated with that of the Beck Depression Inventory, which represented the only modification made to the hypothesized model.

In the third step, the hypothesis that Trauma-related Distress at Baseline will predict Depression at F6 was tested using a structural model with the latent variable

Depression regressed on Trauma-related Distress; the final model is depicted in Figure 3. This model fit the data well (X^2 (18) = 26.61, p = 0.053; RMSEA = 0.47; SRMR = 0.037; CFI = 0.979). All standardized loadings were 0.50 or greater for all indicators, except for the Hamilton Rating Scale for Depression, which had a value of 0.499. All loadings were significant at p < 0.0001. Standardized path coefficients, standard errors, and z-values are shown in Table 3. The results indicate that Trauma-related Distress at Baseline significantly predicts Depression at F6 (β = 0.653, z(264) = 9.54 , p = 0.000).

In the final step, the hypothesis that resilience would moderate the relationship between Trauma-related Distress at Baseline and Depression at F6 was tested. Parameter estimates in the third, fourth, and fifth steps of the analysis are reported below as unstandardized values, due to constraints imposed by testing interactions among latent variables using the Mplus program. For the first step of the moderation analysis, Depression at F6 was regressed on Trauma-related Distress at Baseline and this relationship was found to be significant (β = 0.653, z(264) = 9.54, p = 0.000). In the second step, Depression at F6 was significantly regressed on resilience (β = -0.482, z(264) = -6.44, p = 0.000). In the third step, Depression at F6 was regressed on the interaction between resilience and Trauma-related Distress at the Baseline time point (B = -0.049, z(264) = -1.14, p = 0.256). Although this regression equation was not significant, this does not rule out an overall moderation effect according to the criteria of Baron and Kenny (1986). In the fourth step, Depression at F6 was significantly regressed on the interaction term (Resilience x Trauma-related Distress) while controlling for Trauma-related Distress at Baseline and resilience, (B = -0.113, z(264) = -2.54 , p = 0.011), indicating a moderation effect of resilience on the relationship between Trauma-related

Distress at Baseline and Depression at F6. In the fifth and final step of this analysis, the moderation effect of resilience was probed by repeating the analysis using resilience as a dichotomized variable, split at the median into "high" and "low" values of resilience. The interaction effect of low resilience and Trauma-related Distress at Baseline on Depression F6 was significant ($B = -0.246$, $z(133) = -2.47$, $p = 0.006$), whereas the effect of high resilience was not ($B = 0.68$, $z(131) = 1.17$, $p = 0.241$). This indicates that Trauma-related Distress at Baseline predicts Depression at F6 for individuals with lower levels of resilience, but not for those higher in resilience.

Analysis of the Relationship of Resilience to Perceived Stress

The third hypothesis of this study was that perceived stress at baseline would predict perceived stress at F12 for all study participants. Additionally, this study aimed to determine resilience would either moderate or mediate this relationship. For this analysis, the resilience variable comprised all time points from Baseline through F6.

First, resilience was tested as a moderator; results are reported in Table 4. For the first step of the moderation analysis, perceived stress levels at F12 were regressed on those at Baseline and this relationship was found to be significant ($\beta = 0.566$, $z(171) = 10.907$, $p = 0.000$). In the second step, perceived stress levels at F12 were significantly regressed on resilience ($\beta = -0.555$, $z(192) = -11.11$, $p = 0.000$). In the third step, perceived stress at F12 was significantly regressed on the interaction between resilience and perceived stress at the Baseline time point ($\beta = -0.475$, $z(192) = -8.51$, $p = 0.000$). In the final step, stress at F12 was regressed on resilience and the interaction term while controlling for perceived stress at Baseline. This final regression equation was not significant ($\beta = -0.059$, $z(192) = -0.431$, $p = 0.666$), indicating that there was no

moderation effect of resilience on the relationship between stress levels at Baseline and F12.

Next, resilience was tested as a mediator; results are reported in Table 5. In the first step of the mediation analysis, perceived stress levels at F12 were significantly regressed on perceived stress levels at the Baseline time point ($\beta = 0.566$, $z(171) = 10.907$, $p = 0.000$). In the second step, resilience was significantly regressed on perceived stress at Baseline ($\beta = -0.458$, $z(263) = -9.402$, $p = 0.000$). In the third step, perceived stress at F12 was significantly regressed on resilience while controlling for perceived stress at Baseline ($\beta = -0.314$, $z(171) = -4.713$, $p = 0.000$). In the final step, perceived stress at F12 was significantly regressed on perceived stress at Baseline while controlling for resilience ($\beta = 0.410$, $z(171) = 5.932$, $p = 0.000$), indicating a significant mediation effect of resilience on the relationship between perceived stress levels at Baseline and at F12 periods. This mediation effect was tested for significance using the Sobel test, using procedures described previously in this paper. The resulting z-value (3.95) was significantly ($p < 0.0001$) larger than the critical z-value of 1.96, which indicates that the indirect effect of perceived stress at Baseline on perceived stress at F12 via resilience is significantly different from zero, thus confirming that a mediation effect of resilience is present. As depicted in Figure 2, these results indicate that resilience partially accounts for the relationship between perceived stress at Baseline and F12 time points, such that lower initial perceived stress is associated with higher resilience, which is in turn associated with lower perceived stress at follow-up. These results suggest that resilience serves as a mechanism which influences how stress is perceived by the individual. In

those who are resilient, the influence of perceived stress at Baseline on perceived stress at F12 is reduced.

Analysis of the Relationship of Insight and Causation Words to Perceived Stress

The final hypothesis of this study is that the mean percentage of insight and causation words used by those in the Trauma writing condition during the first two writing sessions (W1 and W2) will mediate the relationship between perceived stress at Baseline and F6 periods. Specifically, it was hypothesized that the influence of initial perceived stress on perceived stress at F6 will be reduced in those participants who use more words denoting insight and causation in their written essays.

In the first step of the mediation analysis, perceived stress levels at F6 were significantly regressed on perceived stress levels at Baseline ($\beta = 0.557$, $z(95) = 7.864$, $p = 0.000$). In the second step of the mediation analysis, insight was regressed on perceived stress at Baseline, although this relationship was not significant ($\beta = 0.04$, $z(115) = 0.429$, $p = 0.668$). This indicates that insight cannot function as a mediator of perceived stress, as this non-significant regression equation violates the requirement that X significantly predicts M (Baron and Kenny, 1986).

Next, causation was tested as a potential mediator of perceived stress. Similarly to the previous analysis, in the second step, causation was not significantly regressed on perceived stress at the Baseline time point ($\beta = 0.036$, $z(115) = 0.384$, $p = 0.701$). This indicates that causation cannot function as a mediator of perceived stress, as this non-significant regression equation violates the requirements of mediation models.

Finally, the combined mean percentage of insight and causation words was tested as a potential mediator of perceived stress. In the second step of the analysis, a variable

representing the combined mean percentage of insight and causation words was regressed on perceived stress at Baseline, although this relationship was not significant ($\beta = 0.049$, $z(115) = 0.525$, $p = 0.600$). This non-significant second step indicates that the combined mean percentage of insight and causation words does not function as a mediator of perceived stress.

Additional analyses were conducted to determine whether insight and/or causation words function as moderators of the relationship between perceived stress at Baseline and F6, using procedures similar to those described in Analysis 3. In each case, the final regression equations were not significant for either insight ($\beta = 0.619$, $z(93) = 1.547$, $p = 0.122$), or causation ($\beta = 0.104$, $z(93) = 0.789$, $p = 0.430$), indicating that neither factor moderates the relationship between stress levels at Baseline and F6.

Chapter 5: Discussion

A main goal of this study was to examine potential relationships between resilience and both salivary cortisol and cort/DHEA through F6. In addition, this study intended to determine the influence of resilience on perceived stress, trauma, and depression, by testing resilience as a potential mediator and/or moderator of these factors over the course of the study. A final purpose of this study was to investigate the role of insight- and causation-denoting words in written expression essays as potential mediators of the relationship between perceived stress over the 6-month course of the study. To date, very few studies have examined the role of resilience in HIV/AIDS, change in cort/DHEA, or the role of insight and causation words in written emotional expression interventions in those with HIV/AIDS.

The first set of findings in the current study is that levels of salivary cortisol and cort/DHEA did not change significantly from the Baseline through F6 periods of the study. The techniques of HLM were used to model change in salivary cortisol and cort/DHEA from Baseline through F6, and to test resilience at Baseline as a predictor of the slopes of these biomarkers. In an HIV-positive sample, cortisol and cort/DHEA levels would be expected to change over time due to increasing dysregulation of the HPA axis (Kumar *et al.,* 2002), however, the mechanisms of this dysregulation and patterns of change are still under investigation. A 10-week CBSM intervention study which measured serum cortisol in HIV-positive men found no significant changes in cortisol over time in treatment or control groups, even though men in the treatment group experienced significant reductions in distress (Cruess *et al*., 2000b). Although the maximum effect of our writing intervention was expected to be attained at F6, with a

potential decrease in the effect of the intervention expected at F12, it is possible that this relatively short time frame from Baseline to F6 was not sufficient to capture change in cortisol and cort/DHEA, as such changes potentially reflect gradual changes in health. It is possible that extending the analyses to F12 would indicate a change in these biomarkers.

A longitudinal study of 120 asymptomatic HIV patients and 29 seronegative controls over 2 years found that cortisol levels significantly increased over the first year of the study, with values reaching a plateau after one year, then remaining high at the 2-year point (Chittiprol *et al*., 2008). It is possible that our study measured participants with cortisol values that had already reached a plateau, and thus cortisol change did not occur during the period of our study. In contrast, other studies have reported that serum cortisol levels have been found to be elevated throughout all stages of HIV infection relative to seronegative controls (Christeff *et al.,* 2000), whereas serum DHEA levels are higher in the asymptomatic stage relative to later stages, and levels in those who have progressed to AIDS are reduced from baseline, to levels lower than seronegative controls (Christeff *et al.,* 2000). These studies suggest that cortisol change could occur in a shorter span of time than change in DHEA. Other studies have reported elevated cortisol levels during the acute phase of the HIV infection, but blunted cortisol responses to acute stressors have also been found (Kumar *et al*., 2002). Cortisol levels may fluctuate over the course of HIV, depending on disease stage and current stress level, which may also account for the lack of change seen in our study.

Very few studies have examined change in cort/DHEA over time. One small longitudinal study of 16 HIV-positive men with hemophilia in the pre-HAART era found

that the cort/DHEA ratio increased over time, due to changes in DHEA-S (Chatterton *et al.*, 1996). The study found that 30% of participants had no change in plasma DHEA-S over 11 years, 44% had progressive declines in DHEA-S, and 22% had steep declines in DHEA-S. None of these changes were correlated with cortisol levels, which did not change over time. Over the 11-year study period, mean DHEA-S levels decreased by 30%.

A CBSM intervention study of 64 HIV-positive men found that, in the control group, plasma DHEA-S decreased over the 10-week study period and cortisol did not change, leading to an increase in the cort/DHEA ratio, while CBSM buffered against these changes in the treatment group (Cruess *et al.*, 1999). As the few studies to examine changes in cort/DHEA have involved only male participants, it is possible that changes in cortisol and cort/DHEA may be influenced by gender, which was not examined in this project, but would represent a worthwhile aim of future analyses.

This study also found that resilience at Baseline did not predict the slope of cortisol from Baseline to F6, however, resilience directly predicted the slope of cort/DHEA during this same period. Although no significant change occurred in either of these biomarkers, the finding that resilience predicts the slope of cort/DHEA indicates that resilience is positively correlated with cort/DHEA in our sample. Pearson bivariate correlation analyses indicate that resilience is positively correlated with cort/DHEA at F6 ($r = 0.211$, $p = 0.026$). Bivariate correlation analyses indicate that resilience is negatively correlated with salivary cortisol at Baseline (Spearman's *rho* $= -0.149$, $p = 0.031$) and at F12 (Pearson's $r = -0.175$, $p = 0.032$). Resilience was not found to be correlated with DHEA in this study.

Although resilience does not appear to have previously been studied in relationship to cort/DHEA in HIV, or in any other medical populations, a study of 677 children (347 of whom had been maltreated) found that lower morning salivary cortisol was related to higher resilience, but only for non-maltreated children (Cicchetti and Rogosch, 2007. These findings are consistent with the inverse relationships found between resilience and morning salivary cortisol in our study. Due to a baseline incidence of PTSD of 30.1% in our participants, as measured by the Davidson PTSD Scale (using a cut-off score of 40 or greater), it is possible that relationships between cortisol and resilience at other time points were obscured in our study. Future analyses should examine whether cortisol or cort/DHEA change as a function of PTSD symptoms in our sample, as hypocortisolism has been found in those with PTSD (Heim, Ehlert and Hellhammer, 2000; Olff *et al*. 2006). Similarly, it has been found that, even in psychologically and physically healthy adults, greater exposure to adverse experiences in childhood and adolescence is associated with a lower salivary cortisol response to acute laboratory stressors (Lovallo *et al*., 2011). Therefore, future studies should also take previous adverse experiences into account, even in the absence of PTSD or other psychological disorders. These factors may also account for an overall lack of change seen in cortisol, as well as in cort/DHEA, through the F6 period.

Cicchetti and Rogosch (2007) also found that a higher cort/DHEA ratio was associated with higher resilience for all children, regardless of maltreatment status. This relates to our findings that resilience is positively associated with cort/DHEA at F6, and appears to be driven by the relationship between resilience and cortisol, rather than DHEA, as DHEA was not found to be significantly correlated with resilience in our

study. Similarly to the extremely sparse literature relating resilience to cort/DHEA, few studies have examined resilience and cortisol. However, one such study of 28 healthy young men measured salivary cortisol changes over 120 minutes at 8 time points, before, during, and after a stressful speech task (Mikolajczak *et al*., 2008) and found a trend toward lower total cortisol secretion among those higher in resilience. Interestingly, this study found that resilience moderated cortisol secretion during the anticipation of the stressor, rather than at other time points. Those higher in resilience secreted less cortisol while anticipating the stressor, which suggests that resilience may buffer against elevations in cortisol during the period of anticipating stress, which, as the authors note, often lasts longer than the stressor itself. It is possible that, over the lifespan, those who can better manage these periods of anticipation are at decreased risk for the deleterious effects of stress on physical and mental health, and that this may point toward one potential protective role for resilience.

The second set of findings in the present study involves the development of a structural model relating distress, depression, and resilience. It was found that each of the hypothesized indicator variables (PTSD Symptoms, Distress, Perceived Stress, and Impact of Events) significantly loaded onto the latent factor Trauma-related Distress and that the resulting model fit the data from this study's particular sample. These findings suggest that this combination of measures of stress, trauma and distress would be appropriate for capturing the shared variance associated with the latent variable Trauma-related Distress. Similarly, it was found that the indicator variables Beck Depression Inventory, Hamilton Rating Scale for Depression, Profile of Mood States (depression subscale) and the Positive and Negative Affect Schedule (negative subscale) significantly

loaded onto the latent factor Depression at F6, and that the resulting model fit the data well. These findings suggest that this combination of measures of depression and negative affect reflected the latent variable Depression. As hypothesized, the latent variable Trauma-related Distress at Baseline was found to significantly predict the latent variable Depression at F6, and resilience moderated this relationship. These findings suggest that the presence of Trauma-related Distress upon entry into the study influenced depressive symptoms at the F6 period, and that one's degree of resilience altered the extent to which initial Trauma-related Distress predicted Depression several months later. Specifically, high levels of Trauma-related Distress at Baseline were associated with high levels of Depression at F6 in those participants who are low in resilience, but not in those high in resilience. This study found significant inverse relationships between resilience and all indicators of Depression and Trauma-related Distress. Overall, these results suggest that greater resilience buffers individuals against depressive symptoms in the presence of initial Trauma-related Distress symptoms.

In a recent article by Kleim, Ehlers, and Glucksman (2012), the authors discuss various models which have been used to account for the development of depression following traumatic events, and note that, although depression and PTSD are both common outcomes after a traumatic event, cognitive factors have been found to play a role in the development of depression in the face of trauma. These cognitive factors may interact with pre-existing individual vulnerabilities, including heightened stress, distress, and trauma, to either buffer an individual against developing depression, or promote it. The authors note that cognitive models point toward individual differences in the interpretations of distressing or traumatic events, and the meaning assigned to these

events, as being key cognitive factors in the development of depression. In their study of 222 assault survivors, the authors found that several post-traumatic cognitions at 2 weeks after the assault predicted a diagnosis of depression at 6 months (Kleim, Ehlers, and Glucksman, 2012). Specifically, these cognitions involved self-devaluation, hopelessness, and attributions for negative events which are global, internal, and stable. Resilience, which involves self-esteem, self-mastery, and positive affect, may influence the manner in which distressing or traumatic events are interpreted. High resilience may promote more adaptive cognitions which preserve self-esteem, positive affect, and a sense of self-mastery, by enabling the individual to account for and cope with negative events in ways which do not decrease self-worth, induce helplessness, or promote depression. The specific cognitive mechanisms of resilience may be an interesting area of future study.

In light of these findings, an important area of study involves identifying which psychosocial factors may be protective against these cognitions in the wake of trauma, adversity, and stressful events, or may assist in coping with distressing trauma-related cognitions and other trauma symptoms so that depression does not develop. Many such factors have been identified, including social support (Meyer *et al.*, 2012; Quale and Schanke, 2010), coping (deRoon-Cassini , 2010; Meyer *et al.*, 2012), resilience (Quale and Schanke, 2010; Tugade & Fredrickson, 2004; White, Driver and Warren, 2010), positive affect (Quale and Schanke, 2010; Tugade & Fredrickson, 2004), optimism (Quale and Schanke, 2010), low levels of self-blame (Meyer *et al.*, 2012) and low levels of stress (Meyer *et al.*, 2012).

Our finding that the latent variable Trauma-related Distress at Baseline was found to significantly predict the latent variable Depression at 6-month follow up is consistent

with the work of Kleim, Ehlers, and Glucksman (2012). Our study also found that resilience moderates the relationship between Trauma-related Distress at Baseline and Depression at F6, which suggests that those higher in resilience are buffered against depression in the wake of trauma and stress. These findings are consistent with the literature on resilience as a protective factor against deleterious, lasting psychological consequences in the face of stress (Morgan *et al.*, 2009) and trauma (Anderson and Bang, 2011; Bonanno *et al*., 2007), which may also promote psychological growth (Bensimon, 2012).

Depression has been found to predict accelerated HIV disease progression in the HAART era, (Ironson *et al*., 2005; Leserman, 2008). PTSD and depression independently predict reduced HAART adherence, and when these disorders are comorbid, detectable viral load is more likely to occur as well (Boarts *et al.*, 2006). Although estimates vary, the prevalence of PTSD (Martin and Kagee, 2011) and depression (Ickovics *et al*., 2001) in those with HIV is high relative to those without HIV/AIDS. Given the impact of these symptoms on disease progression in HIV, psychosocial factors which may positively impact such symptoms are an important focus. Results of this study indicate that resilience is a worthwhile psychological construct for further investigation. As resilience was measured in our study using a composite of self-esteem, self-mastery, and positive affect, it is possible that those who were low in resilience were unable to manage feelings of trauma-related distress, which promoted the development of depressive symptoms. These individuals who are low in resilience may have a variety of unhelpful cognitions and emotions pertaining to their self-worth and self-efficacy, and may be unable to experience significant positive affect. These circumstances are unlikely to be conducive

to healthy psychological functioning, and may decrease motivation for medication adherence and other health-promoting behaviors which may affect HIV disease course in this vulnerable population. Future studies will hopefully play a role in identifying the specific aspects of resilience serve as a buffer in HIV, and targeting these aspects through intervention.

The third main finding of this study is that perceived stress at Baseline predicted perceived stress at F12 for all participants, and that resilience mediates this relationship, indicating that resilience serves as a mechanism which influences how stress is experienced. In those who are resilient, the influence of perceived stress at Baseline on perceived stress at F12 is reduced. Resilience partially accounts for the relationship between perceived stress at the Baseline and F12 time points, in that lower Baseline perceived stress is associated with greater resilience, which is in turn associated with lower perceived stress at F12. Conversely, high perceived stress at Baseline may promote lower resilience, which may promote greater perceived stress at F12.

As noted by Baron and Kenny (1986), mediator variables represent a property of the individual which transforms the independent variable in some fashion. In our study, resilience appears to change the perception of stress in a way that weakens the relationship between initial perceived stress levels and those at follow-up, suggesting that resilience protects against increases in stress over time.

However, results should be interpreted with caution, as they involve potential descriptive mechanisms based on correlations. As noted by Holmbeck (2002), meditational mechanisms may not be causal in nature, particularly if the predictor and mediator variables were not randomly assigned, as is the case in our study.

As reviewed by Leserman (2008), stressful life events have been shown to predict HIV disease progression while controlling for initial disease status and HAART usage. Many intervention studies have targeted stress in HIV/AIDS (Cruess *et al*., 2002; Ironson *et al.,* 2005; Scott-Sheldon *et al*., 2008), and our study presents preliminary evidence that resilience may positively influence the experience of stress in those with HIV/AIDS. Regarding the relationship of stress to resilience, several studies point to a protective effect of resilience in the face of stress (Almieda, 2005; Catalano *et al*., 2011; Diehl and Hay, 2010). One such study followed 239 adults from a random community sample spanning a broad age range (18-89 years) over a 30-day period and assessed a variety of psychological factors using both measures and daily diary entries (Diehl and Hay, 2010). The study found that those who were higher in the resilience factor perceived control reported lower negative affect and stress over the 30-day study period, as well as lower mood reactivity to stressors on a daily basis.

As the self-efficacy aspect of our resilience variable relates to greater perceived control, this sense of personal control and effectiveness may have played a role in mediating the perception of stress over time, in combination with the positive affect and self-esteem components, which would presumably enable individuals to "bounce back" from stress and negative mood states, or perhaps be less susceptible to being overwhelmed by perceived stress and experiencing reduced self-esteem as a result. This is consistent with findings from a longitudinal daily diary study of older adults, whose levels of daily perceived stress and negative affect were measured over a 56-day period (Montpetit *el al*, 2010). In this study of 42 adults, aged 65-92 years, those who were more resilient experienced less negative affect in the midst of daily stress, and returned to

baseline mood levels more quickly after experiencing stress. Resilience was conceptualized as being a dynamic process involving protective individual traits and external social support resources, and measured using the Dispositional Resilience Scale (Bartone *et al.*, 1989) which assesses feelings of control and self-efficacy, commitment to pursuing meaningful activities, and perceiving challenges as being opportunities for growth, rather than disruptive and threatening. Our method of measuring resilience also measured self-efficacy, and presumably, those who are high in self-esteem would experience challenges as opportunities rather than insurmountable obstacles, and the pursuit of meaningful activities would be associated with both self-esteem and positive affect. Therefore, our resilience variable appears to be similar to the way in which it was measured in the Montpetit *el al.*, (2010) study.

These results indicate that the construct of resilience warrants further study within the context of HIV/AIDS. These findings indicate that resilience may serve as an appropriate target for intervention in those living with the disease. Future studies should examine whether resilience can be increased in HIV/AIDS patients, and whether this leads to reductions in perceived stress levels over time. More generally, investigating the relationships between resilience and a variety of additional biopsychosocial factors may prove fruitful. In a review of the literature on positive psychological factors in HIV/AIDS, two components of our composite resilience variable, self-efficacy and positive affect, are associated with decreased distress and lowered mortality, respectively (Ironson and Hayward, 2008). In light of these findings, future studies should determine whether there are different effects of resilience as a whole in HIV/AIDS, or whether only certain components of resilience are most relevant to the biopsychosocial factors in this

disease. Additionally, it would be interesting to examine the effects of incorporating an intervention to increase resilience within the context of a CBSM intervention, to determine if this would enhance the intervention, or whether resilience should be targeted independently. Conducting intervention studies to increase resilience in those with HIV/AIDS and to examine the effects on relevant biobehavioral outcomes would be especially timely, as recent pilot studies have demonstrated the ability to increase resilience in other medical populations, including diabetics (Steinhardt *et al.*, 2009) and breast cancer patients (Loprinzi *et al.*, 2011).

The fourth and final finding was that the percentage of insight and causation-denoting words (as a proportion of total words) used in written emotional expression essays did not mediate or moderate the relationship between perceived stress at Baseline and F6 periods. This indicates that insight and causation words used during the W1 and W2 sessions by participants assigned to the Trauma writing condition did not play a mechanistic role in accounting for the relationship between perceived stress at Baseline and F6, as implied by a meditational model. Contrary to our mediation hypothesis that variations in Baseline perceived stress would influence the use of written insight and causation words, by either increasing or decreasing the use of such words, there was not a significant relationship between insight or causation words and perceived stress at Baseline. Our moderation hypothesis was not supported either, indicating that regardless of the degree to which insight or causation-denoting words were used by the Trauma-writing group, this did not influence the relationship between perceived stress at the Baseline and F6 periods. This implies that one's level of insight into traumatic events, or

one's ability to assign causation to these events, does not determine whether perceived stress levels change over time.

A study of 79 men and women with HIV was conducted in which participants were randomized into a written emotional expression intervention or control condition (Rivkin *et al*., 2006). Four writing sessions were conducted, and participants were followed through 6 months. It was found that those in the written emotional expression condition who increased their use of insight and causation-denoting words over the course of the study had better immune function (as measured by beta2-microglobulin, a measure of systemic immune function) and reported more positive changes (as measured qualitatively by interviews) in perceived social support, finding benefit in being HIV-positive, and health behavior changes. Although this sub-group of participants in the Rivkin *et al*. (2006) study reported some positive changes, perceived stress was not measured. Our study indicated that perceived stress may not be among the psychosocial factors which are related to insight and causation. However, future analyses of our data should also include insight and causation measured at W3 and W4 time points, to assess potential change over time, and to determine whether such a change may be related to perceived stress.

Although increasing use of insight and causation words over the course of written emotional expression interventions has been associated with fewer sick days, doctor visits, and better immune function in healthy adult populations, (Pennebaker, 1993), to our knowledge the Rivkin *et al*. (2006) study is the first to examine insight and causation in relationship to HIV/AIDS. Although our study did not find a relationship between

insight, causation, and perceived stress, in light of previous studies, further investigation of insight and causation in HIV/AIDS appears warranted.

Conclusions

This study has demonstrated that the psychological construct of resilience plays a role in HIV/AIDS, particularly as it relates to perceived stress, depression, trauma-related distress, and the cort/DHEA ratio, and warrants further investigation, as resilience has not yet been well-studied in relationship to this disease. A structural equation model was developed which indicates that trauma-related distress at Baseline predicts symptoms of depression at the F6 period, for all study participants. In this study our resilience variable comprises measures of self-esteem, self-mastery, and positive affect. Resilience was found to moderate the relationship between trauma-related distress at baseline and symptoms of depression at the F6 period, such that, even in the presence of trauma-related distress at Baseline, those high in resilience are less likely to experience depressive symptoms at F6 than those low in resilience.

In addition, this study found that resilience partially mediates the relationship between levels of perceived stress over time for all participants, in that lower perceived stress at Baseline is associated with greater resilience, which is in turn associated with lower perceived stress at F12. Conversely, high perceived stress at Baseline may promote lower resilience, which may, in turn, promote greater perceived stress at F12. Results indicate that resilience may change the perception of stress in a way that serves a protective function against increased stress over time.

This study also found that Baseline resilience predicts the slope of cort/DHEA values for all participants, through F6, while controlling for writing group membership

and cort/DHEA values at Baseline. Although values of these biomarkers did not significantly change over time, our findings suggest that resilience is positively correlated with cort/DHEA in our sample. These results suggest that resilience influences stress-related biological markers in those with HIV/AIDS. As such, these relationships warrant further investigation.

Finally, this study found that, in participants randomly assigned to write about traumatic events, the use of insight- and causation-denoting words (as a proportion of total words) used in written essays at the W1 and W2 periods did not mediate the relationship between perceived stress levels at the Baseline and F6 periods. This indicates that the use of insight and causation words did not play a mechanistic role in accounting for the relationship between perceived stress at Baseline and F6. Neither did the use of such words moderate perceived stress at the Baseline and F6 periods. These findings indicate that one's level of insight into traumatic events, or one's ability to assign causation to these events, does not influence perceived stress levels over time.

Overall, results of this study indicate that resilience relates to a variety of psychological factors in HIV/AIDS, including depression, trauma-related distress, and perceived stress, as well as to biological factors, as measured by the cort/DHEA ratio. In those assigned to write about traumatic events in our study, insight and causation did not play a role in influencing the experience of perceived stress between Baseline and F6 periods. Taken as a whole, our results suggest that the construct of resilience deserves further study within the context of HIV/AIDS, and may serve as an appropriate target for intervention in those living with the disease. Future studies should examine whether

resilience can be increased in HIV/AIDS patients, and whether an increase in resilience

may positively affect relevant biobehavioral factors in this disease.

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Figures

Figure1. Hypothesized structural equation model representing the latent variable Trauma-related Distress at baseline as a predictor of the latent variable Depression at the 6-month follow up period, with resilience moderating this relationship
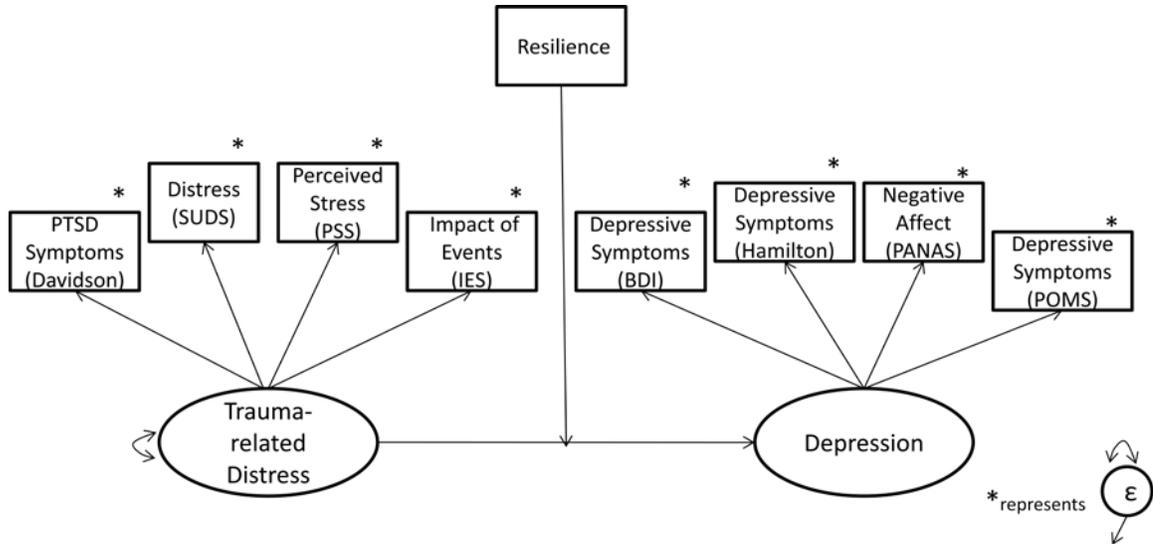
Figure 2. Path diagram model for testing Resilience as a mediator of the relationship between Perceived

Stress at baseline (B) and 12-month follow up (F12)

*$p \leq .001$; ns = not significant
Numbers in parentheses are correlations; numbers outside parentheses are standardized beta coefficients in models with Perceived Stress at F12 as the dependent variable and PSS at B and Resilience as predictors.

Figure 3. Final model representing the latent variable Trauma-related Distress at baseline as a predictor of the latent variable Depression at the 6-month follow up period, with resilience moderating this relationship
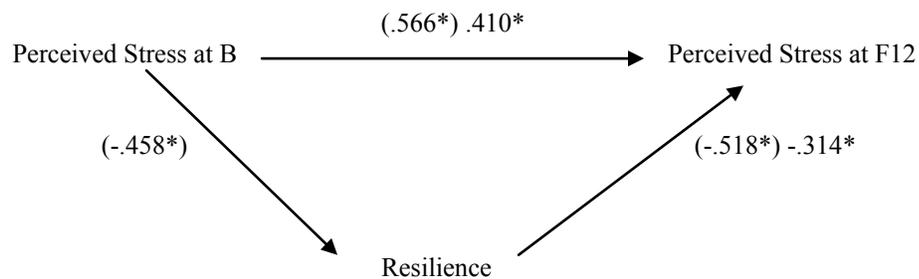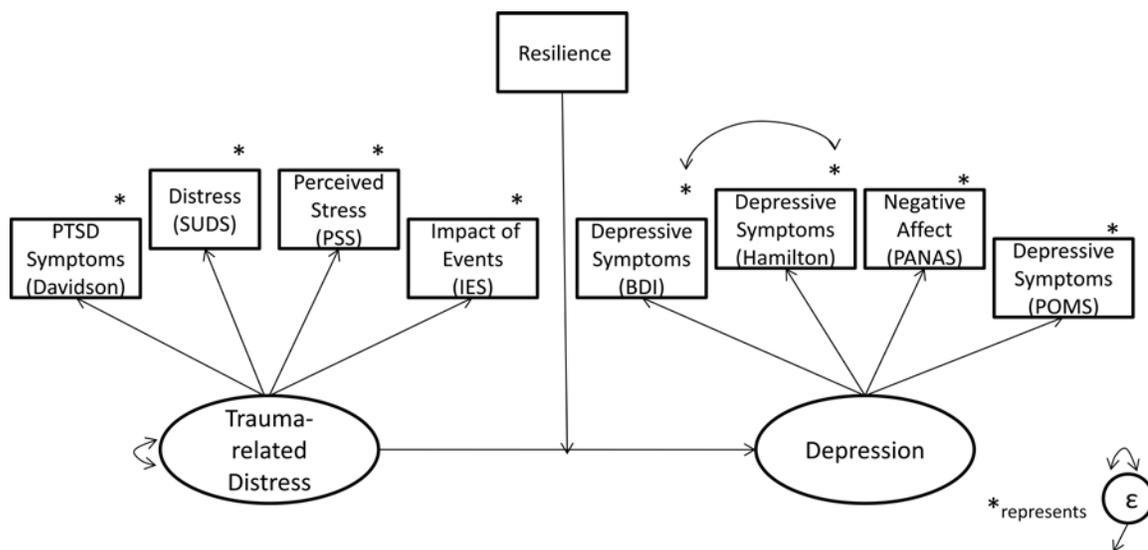
Tables

Table 1.　　　　Means (M) and Standard Deviations (SD) for Biological and Psychological Measures

	M	SD	Range
Cortisol (ng/ml)*	0.475	0.480	0.03-4.77
DHEA (ng/ml)*	1.31	1.15	0.01-5.44
Cortisol/DHEA*	7.31	9.35	0.03-47.46
Perceived Stress (PSS)	16.2	5.96	2.00-31.00
Depression (BDI)	9.54	7.30	0.00-42.00
Depression (POMS)	0.371	0.503	0.00-2.80
Depression (Hamilton)	9.15	5.37	0.00-25.5
Negative Affect (PANAS)	15.0	4.61	10.00-30.5
Subjective Distress (SUDS)	18.5	18.1	0.00-90.00
PTSD (Davidson)	24.2	20.9	0.00-123.3
Impact of Events (IES)	20.5	14.9	0.00-73.0
Self Esteem (Rosenberg)	3.11	0.461	2.10-4.00
Self Mastery (Pearlin)	59.2	12.9	9.33-80.00
Positive Affect (PANAS)	29.9	8.73	10.00-50.00
Insight (LIWC)	3.48	1.23	0.91-8.83
Causation (LIWC)	1.99	0.836	0.42-5.42

* Windsorized values are reported.

Table 2.   Pearson correlations (*r*) between resilience and indicator variables used in SEM model

	*r**	*N*
Perceived Stress (PSS) at Baseline	-0.458	263
Subjective Distress (SUDS) at Baseline	-0.245	263
Impact of Events (IES) at Baseline	-0.177	236
PTSD (Davidson) at Baseline	-0.307	260
Depression (BDI) at F6	-0.475	192
Depression (POMS) at F6	-0.267	192
Depression (Hamilton) at F6	-0.378	192
Negative Affect (PANAS) at F6	-0.152	192

* All correlations are significant at $p < 0.01$ except Negative Affect, which is significant at $p < 0.05$

Resilience is comprised of measures from the Baseline through F6 time points.

Table 3.   SEM Model: Standardized Path Coefficients (β), Standard Errors, and z-Values for Direct Effects

	β	SE	z*
Overall Structural Model			
Baseline:			
Trauma to Davidson PTSD	0.713	0.048	14.88
Trauma to SUDS	0.517	0.058	8.971
Trauma to PSS	0.709	0.048	14.69
Trauma to IES	0.511	0.057	8.952
6-month Follow Up:			
Depression to BDI	0.770	0.047	16.55
Depression to Hamilton	0.499	0.068	7.313
Depression to PANAS	0.746	0.074	15.85
Depression to POMS	0.710	0.049	14.45
Depression at F6 on Trauma at Baseline	0.653	0.068	9.541

"Trauma" denotes the latent variable Trauma-related Distress, which was measured at Baseline; the latent variable Depression was measured at F6.

*All z-values are significant at $p < 0.001$

Table 4.   Analysis 3: Baseline PSS Predicting PSS at F12 with Resilience as a Moderator

Variable	Parameter Estimate[†]	Standard Error	z	Significance
Intercept	1.223	0.208	5.87	0.000*
PSS at Baseline	0.566	0.052	10.91	0.000*
Resilience	-0.555	0.056	-11.11	0.000*
Interaction	-0.059	0.137	-0.431	0.666

*$p < .001$, † = standardized coefficients are reported

Moderation Equation: $Y = a + bX + cM + dXM + e$

PSS_F12 = 1.223+ 0.566 *PSS B* + -0.555 *Resilience* +
-0.059 *PSS B* x *Resilience* + *error*

Table 5. Analysis 3: Baseline PSS Predicting PSS at F12 with Resilience as a Mediator

Variable	Parameter Estimate[†]	Standard Error	z	Significance
Intercept	1.119	0.200	5.591	0.000*
PSS at Baseline	0.566	0.052	10.91	0.000*

PSS at 12 months = 1.119 + 0.566 *PSS at Baseline* + error

Variable	Parameter Estimate[†]	Standard Error	z	Significance
Intercept	1.484	0.212	7.013	0.000*
PSS at Baseline	0.410	0.065	6.348	0.000*
Resilience	-0.314	0.067	-4.713	0.000*

PSS at 12 months = 1.484 + 0.410 *PSS at Baseline* + -0.314 *Resilience* + error

p < .001, † = standardized coefficients are reported

Table 6. Basic Hierarchical Linear Model Including Coefficients and Significance Tests for Level 1 and Level 2 Covariates in Prediction of Cortisol and Cortisol/DHEA slope from Baseline to 6-months (F6)

	Coefficient	Std. Err.	t Ratio	df	p
Cortisol					
Level 1 Fixed Effects					
Cortisol Intercept, β_0	0.3815	0.0281	13.631	209	0.000
Cortisol Slope, β_1	0.0115	0.0085	1.362	209	0.175
Level 2 Fixed Effects					
Cortisol Intercept, β_0	0.3833	0.0288	13.312	198	0.000
Cortisol Slope, β_1	-0.0091	0.0236	-0.387	195	0.699
Baseline Cortisol, γ_{11}	0.0614	0.0278	2.207	195	0.028
Writing Group, γ_{12}	0.0134	0.0158	0.847	195	0.398
Resilience, γ_{13}	-0.0001	0.0093	-0.001	195	0.999
Cortisol/DHEA					
Level 1 Fixed Effects					
Cort/DHEA Intercept, β_0	10.52	1.719	6.121	61	0.000
Cort/DHEA Slope, β_1	0.3013	0.3442	0.875	61	0.385
Level 2 Fixed Effects					
Cort/DHEA Intercept, β_0	9.009	1.168	7.717	113	0.000
Cort/DHEA Slope, β_1	0.4656	0.9046	0.515	110	0.607
Baseline Cort/DHEA, γ_{11}	0.0084	0.0267	0.313	110	0.754
Writing Group, γ_{12}	-0.0062	0.5764	-0.011	110	0.992
Resilience, γ_{13}	0.8427	0.4234	1.990	110	0.049