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Stress Buffering Effects of Oxytocin on HIV Status in Low-Income Ethnic Minority Women

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Abstract

Background—Elevated perceptions of psychosocial stress and stressful life events are linked to faster disease progression in individuals living with HIV and these associations may be stronger for women from ethnic minority populations. Levels of neurohormones such as oxytocin (OT), cortisol, and norepinephrine (NE) have been shown to influence the effects of psychosocial stress in different populations. Understanding how intrinsic neuroendocrine substances moderate the effects of stressors in minority women living with HIV (WLWH) may pave the way for interventions to improve disease management.

Methods—We examined circulating levels of plasma OT as a moderator of the effects of stress on disease status (viral load, CD4+ cell count) in 71 low-income ethnic minority WLWH.

Results—At low levels of OT, there was an inverse association between stress and CD4+ cell counts. Counter-intuitively, at high levels of OT there was a positive association between stress

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and CD4+ cell counts. This pattern was unrelated to women's viral load. Other neuroendocrine hormones known to down-regulate the immune system (cortisol, norepinephrine) did not mediate the effects of OT and stress on immune status.

Conclusions—OT may have stress buffering effects on some immune parameters and possibly health status in low income ethnic minority WLWH reporting elevated stress.

Keywords

Stress; Oxytocin; Neuroendocrine Hormones; HIV Disease Status; Low-Income Ethnic Minority Women

Women currently account for 32% of all cases of HIV in the United States and almost 75% of women living with HIV (WLWH) are from ethnic minority populations (Center for Disease Control and Prevention, 2007). For low-income ethnic minority women living with HIV, the experience of multiple life stressors including interpersonal violence, poverty, social isolation, and a greater likelihood of illness-related stigma, is linked with increased stress, distress, and illness related symptoms (Burns et al., 2008; Catz et al., 2002; Kimerling et al., 1999; Prado et al., 2004). Research on stress and disease status in individuals with HIV suggests that higher levels of both psychosocial and physiological stress indicators are associated with poorer immune status, increased viral load over time, faster disease progression, and higher rates of AIDS mortality (Ironson et al., 2005; Leserman et al., 2000; Leserman et al., 2007; Pettito et al., 2000).

Traditional theories of stress suggest that individuals' responses to stress are accompanied by activation of both the hypothalamic-pituitary-adrenal (HPA) axis, and sympathetic adrenal-medullary (SAM) systems (Romero and Butler, 2007; Selye, 1946). HPA axis stimulation is often associated with elevations in circulating levels of cortisol, an anti-inflammatory steroid, whereas SAM activation is associated with increases in circulating norepinephrine (NE) and epinephrine (E). Recent theory and research suggests that traditional neuroendocrine models of stress may be incomplete, and that it is important to acknowledge that oxytocin (OT) is also a part of the stress response process, particularly when social stressors are present. While some neuroendocrine changes known to accompany stress (e.g., cortisol and norepinephrine increases) may act to down-regulate immune cells (Antoni, 2003; Cole, 2008), other neuroendocrine molecules, including OT, may either offset these down-regulatory effects or may up-regulate immune cells (Detillion et al., 2004).

Some evidence suggests that OT is associated with immune status through modulating the production of both cortisol and NE. For example, exogenously administered OT was associated with a decreased cortisol response to a psychological stressor (Heinrichs et al., 2003). Similarly, women with higher levels of plasma OT evidenced lower levels of NE (Grewen et al., 2005). Therefore, OT may play an important role in the stress response process of individuals living with HIV as elevated levels of cortisol and NE have immunosuppressive effects and may contribute to long-term negative health outcomes including faster disease progression and slower immune system reconstitution on anti-retroviral treatment (Antoni et al., 2005; Cole, 2008; Clerici et al., 1997; Ironson et al., 1994; Leserman, 2003; Norbiato et al., 1997).

Animal models suggest that OT is released centrally and peripherally in response to stress, and may inhibit the effects of biological stress responses on disease processes (Neumann, Kromer, et al., 2000; Neumann, Torner, et al., 2000). For example, Watanabe Heritable Hyperlipidemic (WHHL) rabbits who experienced stable social environments had higher concentrations of OT and also had less evidence of aortic atherosclerosis compared to

WHL rabbits exposed to unstable social environments (Paredes et al., 2006). The majority of research on peripheral OT in human populations uses laboratory paradigms with acute stressors and finds that OT levels rise during and after stressors occur. These increases in OT are also associated with increased affiliative behaviors (i.e., tend and befriend), including social contact, engaging in nurturing and caregiving behaviors, and seeking out social support (Taylor et al., 2000; Taylor, 2006). Seeking out support and engaging in affiliative behaviors during times of stress has both mental and physical health benefits, including changes in immune parameters (Taylor, 2006).

OT levels increase as a result of interpersonal contact and support from partners, but decrease as a result of negative emotions (Grewen et al., 2005; Holt-Lunstad et al., 2008; Turner et al., 1999; Light et al., 2005). Higher levels of plasma OT are also associated with lower blood pressure and heart rate (Grewen et al., 2005; Light et al., 2005). This suggests that women who have higher levels of plasma OT may experience a more 'efficient' psychological (and possibly) physiological response to stress (Light et al., 2005). However, some research suggests that higher levels of OT may be associated with social stress, rather than increases in social affiliation or social contact (Taylor et al., 2006; Turner et al., 1999). The complicated relationship between stress, OT, and social relationships and factors that modulate these relationships still remains unclear.

Given that WLWH from low-income ethnic minority populations often have multiple stressors and a lack of social resources (Hader et al., 2001; Moore et al., 1999), it is possible that OT plays an important role in women's stress appraisals, stress responses, and HIV disease status. Preliminary evidence suggests that African American women may generally have lower levels of OT than Non-Hispanic White counterparts (Grewen et al., 2008). In addition, OT is posited to have protective effects against the development and progression of breast and ovarian carcinoma cells (Cassoni et al., 2004; Morita et al., 2004), suggesting that OT may enhance immune status. However, the role of circulating levels of OT in human HIV disease progression in low income chronically stressed populations is unknown at present. Our study addresses this question by examining how naturally circulating levels of OT are associated with stress and immune/disease status in a sample of low-income minority WLWH.

Specifically, the present study examined whether OT moderates the effects of stress on HIV disease status in minority WLWH, and whether this stress moderating effect is explained by HPA and SAM activity. We examined both general perceptions of women's stress as well as stressful life events known to be prevalent among women from low-income ethnic minority populations. First we hypothesized that higher levels of OT would buffer the negative effects of stress on disease status (viral load, CD4+ cell count), whereas lower levels of OT would exacerbate the negative effects of stress on disease status. Second, we hypothesized that levels of women's HPA axis and SAM system neuroendocrine hormones (cortisol and NE) would explain the interactive effects of stress and OT on disease status.

Methods

Participants and Procedure

Our study utilized baseline data from a larger study of WLWH conducted from 1998 to 2004, which examined psychosocial, behavioral and physiological factors in WLWH on highly active antiretroviral therapy (HAART). Inclusion and exclusion criteria for the study are described in detail elsewhere (see Weaver et al., 2005). Women who were interested and eligible for the study signed informed consent, completed psychosocial measures, provided morning peripheral venous blood samples between 8:00 a.m. and 12:00 p.m., and a 24-hour urine sample.

Eighty-five women from the larger study who identified that they were from an ethnic minority population and who provided adequate blood and urine samples were initially included in the current study. Twelve of these women were not included with the sample for the main analyses because they did not have detectable levels of plasma OT (i.e., less than 0.5 pg/ml). An additional two cases were also excluded from the current analyses because they had extreme OT levels and were determined to be outliers that were potentially skewing the data. These 14 women who were not included in the study did not differ from the 71 women included in the study on any key study variables or sociodemographic characteristics.

Measures

Perceived stress—The 14-item Perceived Stress Scale (PSS; Cohen et al., 1983) measured how often women appraised situations in their lives as being stressful on a scale of 0 (never) to 4 (very often). Positive items were reverse scored and items were summed to create a total PSS score. Women's mean perceived stress score was 24.76 ($SD = 7.2$; $\alpha = .71$; range = 9 – 43).

Stressful life events—The Difficult Life Circumstances Questionnaire (DLC; Barnard, 1989) assessed whether or not women were currently experiencing 34 different stressors that are relevant to poor, inner city women (e.g., neighborhood crime, concerns over safety, conflicts with partners or family members, financial problems, drug or alcohol problems). Prior research confirms this measure is both an indicator of stressors as well as a predictor of distress in minority women (Oakley et al., 2005; Prado et al., 2004). The number of stressful life events was summed to create a total Difficult Life Circumstances score ranging from 0 – 34. Women's mean number of stressful life events was 7.33 ($SD = 4.1$; $\alpha = .79$; range = 0 – 17), which is similar to the mean number of stressors in other studies of low-income minority women (Oakley et al., 2005; Prado et al., 2004).

Oxytocin—OT was assayed using plasma collected through morning peripheral venous blood samples collected from participants in ethylenediaminetetraacetic acid (EDTA) tubes (Vacutainer-EDTA, Becton-Dickinson, Rutherford, NJ). Plasma was separated by centrifugation at 4° C, 2000 rpm, for 30 minutes and stored at –80° C. Prior to being assayed, OT was extracted from all plasma samples using solid phase chromatography using Sep-Pak columns (Peninsula Laboratories, San Carlos, CA) (Paredes et al., 2006). A commercially available enzyme immunoassay (Assay Design, Ann Arbor, MI) was then used to assay extracted samples for OT. This test uses 100 mL of sample and has a lower limit of sensitivity of .5 pg/mL and an upper limit of sensitivity of 1000 pg/mL. The limit of detection was 1.2 pg/well and intra- and inter-assay variability were 9% and 15% as reported by the manufacturers. The women in our study had a mean OT level of 21.02 pg/mL ($SD = 22.4$; range = 1.33 – 115.14).

Disease status—Disease status was assessed via women's viral load and CD4+ cell counts using morning peripheral venous blood samples collected from participants in EDTA tubes (Vacutainer-EDTA, Becton-Dickinson, Rutherford, NJ). *HIV-1 viral load* was determined on EDTA plasma using an in-vitro reverse transcriptase polymerase chain reaction (RT-PCR) assay (AMPLICOR, Roche Laboratories, US #83088). This is an ultrasensitive assay that has a lower limit of 50 copies/mL. Because viral load was not normally distributed, we used a base-10 logarithmic transformation in all analyses. *CD4+ Cell Count* was determined using whole blood four-color direct immunofluorescence with a Coulter XL and flow cytometer (Fletcher et al., 2000). Women had a mean viral load of 14,556.66 copies/mm³ ($SD = 83,416.01$; range = 0 – 700,986.00), and a mean CD4+ cell count of 475.87 cells/mm³ ($SD = 285.34$; range = 43.0 – 1256.0).

Urinary neuroendocrines—Cortisol and NE were measured via 24-hour urine collection. Substance use and urine volume were monitored to assess compliance with urine collection. Urinary free cortisol was determined by radioimmunoassay from Diagnostic Products (Los Angeles, CA) kits with 50 ml of a 500-ml sample extracted with 10 ml of dichloromethane. Fifty μ l of urine extract were evaporated to dryness under nitrogen. One ml of 125 I-labeled cortisol was added to tubes coated with antibodies, incubated for 45-min, decanted, and quantified for 1 minute with a gamma counter. Cortisol levels were calculated with a standard calibration curve and cortisol values are expressed as μ g per 24 hours (Antoni et al., 2005). NE was determined using a high-pressure liquid chromatography with an electrochemical detection method to quantify the level of NE, which was expressed as μ g per 24 hours (Kumar et al., 1991; Kumar et al., 1993). Because cortisol and NE were not normally distributed, we used a base-10 logarithmic transformation in all analyses.

Covariates—Potential covariates included sociodemographic (i.e., age, ethnicity, education, employment, income), social (i.e., marital status, living arrangements), and health (i.e., medication adherence, menstrual cycle) characteristics. Social support is strongly linked to both perceptions of stress and OT, but the direction of these associations is not consistent (Taylor et al., 2000). Therefore, our study focused on associations between perceived stress, OT, and disease status, while controlling for women's perceived social support in all analyses. Perceived social support was measured using the *Social Provisions Scale* (SPS; Cutrona and Russell, 1987), which measures women's general perceptions of perceived social support across multiple domains. Women's mean perceived support was 71.07 (SD = 9.87; actual range = 51 – 89; potential range = 24 – 96; α = .87). Similarly, because negative mood is associated with higher OT levels (Cyranowski et al., 2008; Parker et al., 2010; Scantamburlo et al., 2007), we controlled for women's depressive symptoms in all analyses. Depressive symptoms were measured using the *Center for Epidemiologic Studies-Depression Scale* (CES-D; Radloff, 1977). Women's mean depressive symptomatology was 18.04 (SD = 10.14; actual range = 0 – 39; potential range = 0 – 60; α = .87). Bivariate correlations revealed that neither social support nor depressive symptoms were associated with women's OT levels (Table 1).

Analysis Plan

We conducted moderated regression analyses to test our first hypothesis. Covariates were entered into the first step followed by the predictor variable (perceived stress or stressful life events). The moderator variable (OT) was entered into the third step, and an interaction term between the predictor (stress) variable and OT was entered into the final step of the model. The predictor and moderator variables were centered to protect against multicollinearity and significant interaction terms were decomposed and graphed with one standard deviation above and below the centered mean representing high and low levels of the moderator variable (Holmbeck, 2002).

To examine our second hypothesis, we conducted mediated moderation analyses. To establish mediated moderation, there must first be a significant interaction between the predictor (perceived stress or stressful life events) and moderator variable (OT) in explaining the outcome variable (CD4+ cell count or viral load). Next, the interaction term between the predictor variable and the moderator variable (perceived stress $\times$ OT or stressful life events $\times$ OT) must be significantly associated with the mediator variable (cortisol or NE). Finally, either the mediator, or an interaction between the mediator and the moderator (cortisol $\times$ OT or NE $\times$ OT), must be significantly associated with the dependent variable and simultaneously reduce the magnitude of the interaction effect of the independent variable and the moderator on the dependent variable (Muller et al., 2005).

Bivariate correlations were conducted to identify covariates. Any potential covariates that were significantly associated with a predictor, moderator or outcome variable were controlled for in all analyses. Therefore, in addition to perceived support and depressive symptoms, all analyses included months since HIV-diagnosis and medication adherence as covariates.

Results

Descriptive Statistics

Sociodemographic characteristics—Women in our study had a mean age of 38.4 ($SD = 7.2$; range = 20 – 49) years and had been living with HIV for approximately 7.8 years ($SD = 4.2$; range = .92 – 22.1). The majority of the women were Black non-Hispanic (85.9%) and the rest were Hispanic (11.3%), American Indian/Alaskan Native (1.4%), or Asian/Pacific Islander (1.4%). About half of the women had a high school education or greater (56.3%) and most of the women were unemployed or receiving disability (74.7%). The average yearly income for the women was between \$5,000 and \$10,000.

Stress measures—The most common stressful life events reported by women were not having enough money for necessities (71.8%), not having a car (60.6%), not having enough education (56.3%), and problems with credit/bill collectors (38.0%). Bivariate correlations (Table 1) reveal that women's perceptions of stress and the number of stressful life events they were currently experiencing were moderately correlated ($r = .36$, $p < .01$).

Associations Among Stress, Oxytocin, Neuroendocrines and Disease Status

Neither perceived stress nor the number of stressful life events women were experiencing was associated with OT levels, disease status, or neuroendocrine hormones. OT was positively correlated with CD4+ cell count ($r = .25$, $p < .05$), but OT was not associated with viral load or neuroendocrine hormones. The two measures of disease status (CD4+ cell counts, viral load) were not associated with the neuroendocrine hormones cortisol or NE. Women's cortisol levels, however, were positively associated with their NE levels ($r = .27$, $p < .05$), and women's viral load and CD4+ cell count were negatively correlated ($r = -.36$, $p < .01$).

Interactions Between Oxytocin and Stress Related to Disease Status

Our first hypothesis examined OT as a moderator of the relationship between women's stress and their disease status. As shown in our model examining OT as a moderator of women's perceived stress and disease status (Table 2), women's perceived stress was not associated with viral load or CD4+ cell count. OT was positively associated with women's viral load ($\beta = .27$, $SE = .12$, $p < .05$; $\Delta R^2 = .07$, $p < .05$). Finally, OT interacted with women's perceived stress in explaining their CD4+ cell count ($\beta = .33$, $SE = .11$, $p < .01$; $\Delta R^2 = .10$, $p < .01$) but not viral load ($\beta = -.17$, $SE = .12$, ns ; $\Delta R^2 = .03$, ns). Similarly, in our model examining life stress (Table 2), women's life stress was not associated with viral load or CD4+ cell count. OT interacted with women's stressful life events in explaining women's CD4+ cell count ($\beta = .36$, $SE = .11$, $p < .01$; $\Delta R^2 = .11$, $p < .01$) but not viral load ($\beta = -.18$, $SE = .12$, ns ; $\Delta R^2 = .03$, ns).

Decomposing the significant interaction effects for both measures of stress (Figure 1) revealed that the slope of the association between stress and CD4+ cell count was significant at both high and low levels of the moderator (for perceived stress: $\beta = .39$, $SD = .19$, $t_{67} = 1.99$, $p < .05$ for high OT and $\beta = -.40$, $SD = .19$, $t_{67} = -2.15$, $p < .05$ for low OT; for stressful life events: $\beta = .42$, $SD = .17$, $t_{67} = 2.47$, $p < .05$ for high OT and $\beta = -.42$, $SD = .18$, $t_{67} = -2.34$, $p < .05$ for low OT). Specifically, for women who have low levels of

circulating OT, higher levels of perceived stress or stressful life events were associated with a lower CD4+ cell count. In contrast to this, for women who have high levels of circulating OT, higher levels of perceived stress or stressful life events were associated with a higher CD4+ cell count. This suggests that the presence of high levels of circulating OT may act as a buffer against the negative effects of stress on immune status in low income minority women with HIV.

Neuroendocrine Hormones as Mediators of the Interactive Effects of Oxytocin and Stress

Our second hypothesis examined cortisol and NE as possible mediators of the interaction effect of OT and perceived stress and between OT and stressful life events on women's CD4+ cell count. For both measures of stress, the interaction between OT and stress was not associated with cortisol ($\beta = .06$, $SE = .13$, *ns* for perceived stress; $\beta = -.11$, $SE = .13$, *ns* for stressful life events) or NE ($\beta = -.10$, $SE = .12$, *ns* for perceived stress; $\beta = .16$, $SE = .13$, *ns* for stressful life events). Secondly, our proposed mediators, cortisol and NE, were not associated with CD4+ cell count (for perceived stress: $\beta = .06$, $SE = .11$, *ns* for cortisol and $\beta = .03$, $SE = .12$, *ns* for NE; for stressful life events: $\beta = .15$, $SE = .11$, *ns* for cortisol and $\beta = .03$, $SE = .11$, *ns* for NE) and interactions between OT and cortisol and OT and NE were also not associated with women's CD4+ cell count (for perceived stress: $\beta = .12$, $SE = .16$, *ns* for OT $\times$ cortisol and $\beta = .03$, $SE = .14$, *ns* for OT $\times$ NE; for stressful life events: $\beta = .24$, $SE = .15$, *ns* for OT $\times$ cortisol and $\beta = -.16$, $SE = .13$, *ns* for OT $\times$ NE). These associations remained non-significant even after controlling for health behaviors such as cocaine, nicotine, and alcohol use. Thus, the interactive effects of perceived stress/stressful life events and OT on CD4+ cell count in the current sample of low income minority women with HIV were not mediated through women's HPA and SAM urinary hormone levels.

Post-hoc analyses

The positive associations between stress and CD4+ cell count at high levels of OT and between OT and viral load were unexpected. As such, we conducted several post-hoc analyses to try and explain these unexpected findings. We divided women into high, low, and average OT tercile groups. Next, we conducted a series of independent *t*-tests and chi-square analyses to examine whether women in the high versus low tercile differed on any study variables (stress measures, CD4+ cells, viral load, cortisol, NE), psychosocial characteristics (social support, depression), and sociodemographic and health characteristics (age, months since HIV diagnosis, medication adherence, marital status, employment, and income). Women in the high OT tercile had significantly higher CD4+ cell counts compared to women in the low OT tercile $t_{45} = -1.99$, $p = .05$; $M = 570.04$ for high OT and $M = 401.70$ for low OT. No additional significant differences emerged among women based on their OT tercile.

Next, due to the fact that bivariate correlations between OT and viral load were not significant, we examined whether any of the covariates in our models were acting as suppressor variables. We reanalyzed the regression model and added each covariate separately. Although months since diagnosis was not significantly associated with viral load ($\beta = .21$, $SD = .12$, *ns*), including this covariate in the model caused the association between OT and viral load to become significant (from $\beta = .20$, $SD = .12$, *ns* to $\beta = .24$, $SD = .12$, $p < .05$). No other covariates (i.e., adherence, social support, or depressive symptoms) had this effect on the association between OT and viral load.

Finally, we reanalyzed our data twice, first including the 12 women who were excluded from the currently study due to undetectable OT levels (i.e., less than 0.5 pg/ml) and then again with total 14 women who were excluded due to undetectable OT levels ($n = 12$) or

outlier values on their OT levels ($n = 2$). Neither of these analyses revealed an appreciably different pattern of results than our main analyses excluding these women.

Discussion

Our study found that low-income minority WLWH who had low levels of circulating oxytocin (OT) (i.e., 1 SD below the centered mean) showed the hypothesized association between elevated stress and lower CD4 cell counts. However, those women who had high levels of OT (i.e., 1 SD above the centered mean) showed a counter-intuitive association between greater stress and higher levels of CD4+ cells. These relationships were evident after controlling for sociodemographic factors such as months since HIV diagnosis, HAART medication adherence, perceived social support and negative mood. Neither variations in women's HPA or SAM hormones, or health behaviors such as drug, alcohol, or nicotine use, explained the interactive effects of OT and stress on women's CD4+ cell counts.

These results suggest that for low-income minority WLWH, OT levels are particularly important when situations are perceived as stressful and during the occurrence of stressful life events. It is possible that OT has stress buffering effects, in that higher levels of OT prevent stress from having a negative effect on immune status. Although one would hypothesize stress to be unrelated to CD4+ count if high OT levels had classic stress-buffering effects, our study actually found that high OT women reveal a positive association between stress and CD4+ cell counts. Our bivariate correlations, however, did not show a positive association between stress and CD4+ cell counts overall. It is possible that the positive association between stress and CD4+ cell count in high OT women was not because OT buffered the negative effects of stress, but rather was due to OT's ability to enhance immune status directly (Cassoni et al., 2004; Morita et al., 2004). Our post-hoc analyses provide some support for this explanation, as compared to women in the lowest tercile of OT, women in the highest tercile of OT had significantly higher CD4+ cell counts.

Moreover, as OT has anxiolytic effects and promotes support seeking behaviors, women with higher levels of OT may be more likely to have intrinsic resources to better manage stress or may seek out the resources they need to cope with their stress. As increased social support and reductions in distress are associated with better immune and disease status (Antoni, Carrico et al., 2006; Antoni et al., 2005), high OT women who may be driven to seek out coping resources, including social resources (Taylor et al., 2000), may ultimately enhance their immune status as a result of experiencing stress or stressful life events. Other research on positive growth during times of stress, such as the stress of illness, agrees that stressful life events may actually lead to positive health benefits, such as enhanced immune function and slower disease progression (Milam, 2006). In contrast, our results also suggest that lower levels of OT permit or *exacerbate* the negative effects of perceived stress and stressful life events on immune status. Thus, for WLWH who are socially marginalized, impoverished, and often lack adequate social resources to cope with their illness, the stress-regulatory effects of OT may play a critical role in enhancing immune function and possibly slowing disease progression.

We did not find that OT moderated associations between stress and fluctuations in women's viral load, despite the fact that women's CD4+ cell count and viral load were moderately and negatively correlated. However, we did find a positive association between OT and viral load in our regression models ($\beta = .27$, $SE = .12$, $p < .05$) even though bivariate correlations between OT and viral load were not significant. It appears as though the number of months since women's HIV diagnosis acted as a suppressor variable in our regression models, causing the association between OT and viral load to become significant. It is possible that the associations among OT, viral load, and disease progression are more complex than we

were able to test in our study and warrant future research attention. We suggest that future work carefully control for time since diagnosis as this measure of “chronicity” may play a key role in elucidating psychoendocrine associations.

It is important to keep in mind that the women in our study were chronically stressed. They had comparable levels of chronic life stressors to other studies of chronically stressed women from ethnic minority populations (Oakley et al., 2005; Prado et al., 2004) and they also had higher levels of perceived stress compared to the population norm (Cohen & Williamson, 1983). Higher stress is associated with greater HPA-axis and SAM-system activity, which over time can lead to chronically elevated levels of stress hormones and faster disease progression (Leserman, 2003). However, since our study was limited to measuring levels of stress hormones and immune and disease status at one time point, we were not able to examine how OT, cortisol, and NE reacted in response to acute stress nor how they may have been chronically dysregulated.

Our inability to test stress reactivity or chronic neuroendocrine dysregulation may also explain why our study did not find the interactive effects of perceived stress and OT on CD4+ cell counts to be mediated through HPA or SAM-related neuroendocrine measures. It is arguable that documenting an accumulation of stress in conjunction with alterations in OT and HPA and SAM hormones is needed to explain the interactions among these variables that are most relevant in predicting immune components and HIV disease course. Given that chronically elevated levels of NE and cortisol have immunosuppressive effects in HIV-infected persons (Leserman, 2003), future research should examine if over time, cumulative changes in circulating plasma OT are associated with fluctuations in neuroendocrine hormones that precede changes in immune parameters and disease progression in this population. It is also possible, however, that the interactive effects of OT and stress on immune status may be explained through other pathways, including modulating or suppressing the production of proinflammatory cytokines (Clodi et al., 2008; DeVries et al., 2007; Szeto et al., 2008). Future research should explore the associations between OT, inflammatory responses, and immune status in low-income ethnic minority WLWH.

Additionally, although research consistently links OT to social support, in our study OT was not associated with the perceived support measure we used as a covariate. The measure of social support we used in our study was the *Social Provisions Scale* (Cutrona and Russell, 1987), which is a general measure of perceptions of social support and social integration. It is possible that this measure fails to capture the nature and sources of social support resources prevalent in the target population (e.g., spiritual or religious sources). Other measures of interpersonal phenomena that are more specific to negative social interactions, including social conflict and isolation, may show more consistent and reliable associations between support and OT in this population and others (Zuckerman and Antoni, 1995). Future research should examine longitudinal studies to determine the temporal associations among psychosocial stress, stigmatization, social resources and conflicts, OT, and physiological functioning in low-income minority women living with HIV.

Our findings are among the first to show associations between circulating levels of OT and immune status in human populations and the first in minority WLWH. Moreover, our results are consistent with research in animal stress models suggesting that higher levels of OT relate to better health outcomes such as wound healing and inhibited growth of cancer cells (Cassoni et al., 2004; Detillion et al., 2004; Morita et al., 2004). Finally, our study strengthens existing literature on OT by showing associations between perceptions of stress, naturally existing levels of plasma OT, and immune status in low-income ethnic minority population of women who are living with HIV. The fact that these associations were present using both a global measure of perceived stress as well as a measure of stress that was

designed to be highly relevant to the target population of minority WLWH suggests that the present findings are reliable.

Regardless of its strengths, our study is limited in several ways. Our measure of OT was sampled through plasma rather than cerebrospinal fluid. Despite the growing body of research on plasma OT in human populations, it is still not clear what plasma OT levels reflect about central oxytocinergic activity. Some research suggests that plasma OT levels remain fairly constant over the course of several hours in individuals despite changes observed in central OT levels and that OT does not have a diurnal rhythm like other neuroendocrine hormones tend to have (Amico et al., 1983). However, other research shows that OT levels may vary greatly over the course of an hour, particularly in depressed women (Cyranowski et al., 2008). Given that our study was a naturalistic study drawn from the baseline data of a larger study, we did not assess multiple diurnal blood samples from our participants. Future researchers interested in naturalistic studies of OT may elect to measure multiple blood samples over several time points from participants so as to control for diurnal fluctuations in OT. Our study is cross-sectional, so we cannot establish causal relationships or make inferences about OT reactivity or regulation of the stress response process due to chronic life adversity. Future research should attempt to replicate and extend the current research findings using longitudinal research designs and larger samples. Because our sample involved only women from low-income ethnic minority backgrounds, it is also unclear how our results would generalize to other ethnic and sociodemographic groups, or individuals from other illness populations.

Implications

Because social contact and support from significant network members (e.g., spouses, partners) in the form of hugs, hand holding, or massage is effective in increasing OT levels (Grewen et al., 2005; Holt-Lundstad et al., 2008; Light et al., 2005), these results may have implications for intervention approaches. Some psychosocial interventions developed for HIV-infected persons may lower stress and depression, increase perceived support, and increase quality of life in persons living with HIV by teaching individuals how to cognitively reappraise potentially stressful events and assertively communicate their needs to social network members (Antoni et al., 2008; Carrico et al., 2005; Lechner et al., 2003). It remains to be seen whether these forms of intervention could provide salutary effects on health outcomes by way of OT-associated processes. WLWH who are at risk for faster disease progression due to stigmatization, stress, and social isolation may benefit from culturally sensitive group-based psychosocial interventions designed to include significant social network members, increase intimacy in social relationships, and teach interpersonal skills. One might speculate that gaining interpersonal skills may help these women modulate OT levels, which in turn may relate to a more efficient stress response process and better immune status.

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Figure 1.

OT as a moderator of stress and immune status (CD4+ cell count) in low income minority WLWH ($n = 71$).

Note. Graphs were constructed using unstandardized regression coefficients and centered values of the predictor and moderator variable.

Figure 2. Scatterplots of decomposed interaction effects for OT as a moderator of stress and immune status (CD4+ cell count) in low income minority WLWH ($n = 71$).

Table 1

Correlations among study variables (n = 71).

	1	2	3	4	5	6	7	8	9	10	11
1. Perceived Stress (PSS)	---										
2. Stressful Life Events (DLC)	.36**	---									
3. OT	.04	.07	---								
4. CD4+ Cell Count	.00	.01	.25*	---							
5. Viral Load	.02	-.10	.20	-.36**	---						
6. Cortisol	.09	.07	.11	.17	-.22	---					
7. Norepinephrine	-.01	-.06	.16	.12	-.09	.27*	---				
8. Perceived Social Support	-.26*	-.07	.03	.10	-.17	.00	-.02	---			
9. Medication Adherence	-.18	-.21	.05	.23*	-.17	-.01	.11	.28*	---		
10. Months Since Diagnosis	-.24*	-.11	-.16	-.27*	.21	-.03	.04	-.01	.06	---	
11. Depressive Symptoms	.56***	.25*	.14	-.01	.04	-.10	-.05	-.46***	-.08	-.04	

*
p < .05;**
p < .01;***
p < .001

Table 2

OT as Moderator of Perceived Stress and Disease Status Indicators in Low-Income Ethnic Minority Women Living with HIV (n = 71).

	Viral Load β (SE)	ΔR^2	CD4+ Cell Count β (SE)	ΔR^2
<u>Perceived Stress (PSS)</u>				
Covariates ^I	-----	.09	-----	.13*
Perceived Stress	.04 (.15)	.00	-.05 (.15)	.00
OT	.27 (.12)*	.07*	.19 (.12)	.03
OT*Perceived Stress	-.17 (.12)	.03	.33 (.11)**	.10**
<u>Stressful Life Events (DLC)</u>				
Covariates ^I	-----	.09	-----	.14*
Stressful Life Events	-.13 (.12)	.01	.03 (.12)	.00
OT	.27 (.12)*	.07*	.19 (.12)	.04
OT*Stressful Life Events	-.18 (.12)	.03	.36 (.11)**	.11**

* p < .05;

** p < .01

^I Models control for medication adherence, months since HIV diagnosis, perceived social support, and depressive symptoms.