

Life Stress and Adherence to Antiretroviral Therapy among HIV-Positive Individuals: A Preliminary Investigation

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ABSTRACT

The present study sought to investigate the impact of life stress on treatment adherence and viral load of HIV-positive individuals. Three different aspects of life stress were examined in this investigation (perceived stress, acute life events unrelated to the HIV illness, and HIV-related acute life events). Furthermore, we examined whether these relationships were moderated by depressive severity, self-esteem, and neuroticism. Participants ($n = 24$) were treatment-seeking HIV-positive individuals who completed a series of questionnaires for this investigation. The majority of the participants in this sample were middle-aged, Caucasian males who identified themselves as either homosexual or bisexual, had contracted HIV via sexual contact, and met criteria for AIDS (mean CD4 count = 324). This sample was highly self-selected and varied from the county HIV-positive population in terms of gender, ethnicity, and HIV risk factor. Information on their adherence and viral load was collected from their medical records 6 to 9 months after completion of the psychological measurements. Results indicated that perceived stress, but not acute events, prospectively predicted adherence. Moreover, marginal trends suggested that depressive symptoms and neuroticism moderated the effect of perceived stress on adherence. Neither perceived stress nor acute life events were associated with viral load.

INTRODUCTION

THE LIVES OF INDIVIDUALS diagnosed with HIV and the subsequent illness, AIDS, are often chaotic because these individuals deal with the physical, emotional, and interpersonal sequelae of this illness. Previous research has illustrated that people living under stressful conditions frequently engage in poor health practices, which ultimately increase their risk for disease and disease progression.^{1,2} Moreover, Leserman and colleagues³ have demon-

strated that life stress hastens AIDS diagnosis among HIV-positive individuals. However, contrary to the original study hypotheses, physiologic measures, including cortisol levels and lymphocyte subsets (CD8 and natural killer [NK] cells), did not mediate or moderate the relationship between life stress and AIDS diagnosis. Therefore, it is imperative to investigate other potential factors that may account for this relationship. One compelling possibility is that experience of life stressors leads to disease progression via

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poor treatment adherence among HIV-positive individuals.

The mortality rate of people living with HIV or AIDS has been decreasing with the advent of new antiretroviral medications: the highly active antiretroviral therapies (HAART). While many HIV-positive individuals are experiencing better physical health and greater longevity of life after the introduction of HAART, it is of note that similar improvements have not been found with regard to psychological health.^{4,5} Although it was widely believed that this new combination of medications would lead to increased hope and optimism among HIV-positive individuals, it appears that HAART's primary function is to impact physical, rather than psychological, health. Specifically, these medication combinations have been shown to be effective at suppressing plasma HIV ribonucleic acid (RNA) levels to almost undetectable levels and to sustain viral suppression over long periods of time.^{6,7} However, these medications are only effective at decreasing viral load with near-perfect adherence to one's regimen.⁷⁻⁹ Recent research investigating the association between treatment adherence and virologic failure has found that nonadherence was the strongest predictor of failure when using HAART to achieve viral suppression.^{10,11} Regrettably, poor treatment adherence with HAART is common. For example, a recent investigation by Hewitt and colleagues¹² found that 63% of the HIV-positive participants had missed at least one dose of their prescribed regimens in the 48 hours prior to their study visit. Given that nonadherence has life-threatening consequences to the individual and major public health consequences in terms of the spread of resistant strains, it is imperative that barriers to adherence be identified in order to aid caretakers in encouraging adherence.

Experience of stressful life events may deter HIV-positive individuals from adhering to their treatment regimens. People living with HIV often experience stress related to the symptoms and stigma associated with their illness including interpersonal violence, housing eviction, loss of insurance, denial of health care, loss of supportive services, and loss of employment.¹³⁻¹⁵ Moreover, recent research has found high levels of self-reported posttrau-

matic stress disorder (PTSD) symptomatology among HIV-positive individuals after their initial diagnosis.^{16,17} Given that HIV-positive individuals may be experiencing a wide variety of stressors, it is of interest to examine the impact of various aspects of stress on treatment adherence. Whereas some researchers have focused on the cumulative impact of self-reported acute stressful life events on outcomes such as depressive symptomatology, others have focused on the role of one's perception of stress.¹⁸⁻²⁰ Our investigation seeks to explore potential differences in the role of both aspects of stress. For example, it may be that the perception of stress, irrespective of actual acute life events, is associated with poor adherence. One previous investigation of HIV-positive women with young children found that women who reported higher levels of perceived stress were more likely to be nonadherent in the past week than those with lower levels of perceived stress.²¹ Alternatively, adherence may be more strongly related to the number of stressors that one endures, with adherence decreasing further after each subsequent stressor. A recent study with HIV-positive mothers found that experience of acute stressful life events was associated with missed pills and appointments at follow-up.²² The present study investigated the role of both aspects of stress on treatment adherence among HIV-positive adults.

Life stress can interfere dramatically with people's ability to function. Numerous studies have shown that the onset of depressive episodes is etiologically linked to stressful life events.²³⁻²⁵ Likewise, it has been suggested that stress may lead to an induction of depressive symptoms in HIV-positive individuals.²⁶ A recent cross-sectional investigation by Roberts and colleagues²⁷ explored the impact of stressful life events on emotional distress of HIV-positive individuals. This study suggested that both general and HIV-specific life events predicted depressive symptoms and perceived stress amongst these individuals. Moreover, the relationship between acute life events and perceived stress was moderated by the psychological variables of dysfunctional attitudes, self-esteem, and neuroticism. Delahanty and colleagues²⁸ have also reported poorer adherence among HIV-positive individuals who were experiencing higher levels of

PTSD in response to stress. Finally, Weaver and colleagues²⁹ examined the role of perceived stress and coping on quality of life and found that perceived stress mediated the relationship between coping style and quality of life. As such, it appears plausible that perception of stress and experience of stressors may impact adherence in different ways. It is likely that these effects may vary as a function of the psychological functioning of particular individuals.

In sum, treatment adherence represents an important self-care behavior for HIV-positive individuals. This investigation investigated the impact of perceived stress and acute negative events on treatment compliance. We hypothesized that greater numbers of acute negative life events and higher levels of perceived stress would be related to poorer adherence. Moreover, given that factors such as depression, neuroticism, and self-esteem have been shown to moderate the relationship between stress and distress, we hypothesized that these psychological variables would also moderate these relationships. Specifically, we predicted that stress would have a greater impact on individuals with high levels of depressive symptoms and neuroticism or lower levels of self-esteem. This investigation aimed to advance our knowledge of psychosocial processes that may affect HIV patients' ability to comply. Clear understanding of these mechanisms will aid caregivers in developing interventions to increase adherence.

MATERIALS AND METHODS

Participants and procedure

Eligible participants were HIV-positive patients being treated at the Erie County Medical Center's Immunodeficiency Clinic in Buffalo, New York. Five hundred patients were approached when they came in for their regular checkups between April 1997 and February 1998. Seventy-eight individuals consented to complete a questionnaire packet of psychological measures and to allow disease progression markers to be gathered from their medical files. The most frequent reason stated for not consenting was lack of time. The final study sample is composed of 24 patients (23 males, 1 fe-

male) for whom psychological questionnaire and adherence data existed.^a The majority of the sample (79.2%) was Caucasian with the remaining 5 individuals reporting that they were African American, Hispanic, or mixed race origin. The mean age of participants was 36.17 years (standard deviation [SD] = 7.15). Approximately three fourths of the sample (77.3%) identified themselves as homosexual or bisexual. More than half of the participants (54.2%) were diagnosed with AIDS at the time of participation. On average, the sample was of low income with a median income bracket of \$10,000 to \$20,000. The final study sample varied significantly from the original consented participants with incomplete data ($n = 54$) in terms of gender ($\chi^2(2) = 5.14, p = 0.08$) and ethnicity ($\chi^2(3) = 8.16, p = 0.04$), with Caucasian males being overrepresented, but did not differ in terms of age ($t(73) = 1.18, p = 0.24$) or HIV risk factor ($\chi^2(1) = 0.95, p = 0.33$). It also differed from the HIV-positive population in Buffalo, New York, as of 1998 ($n = 2288$)³⁰ in terms of gender ($\chi^2(1) = 4.21, p = 0.04$), ethnicity ($\chi^2(4) = 26.46, p < 0.01$), and HIV risk factor ($\chi^2(1) = 20.63, p < 0.01$), but not age ($\chi^2(4) = 2.22, p = 0.70$). Our sample had significantly more Caucasian males who contracted HIV via sexual contact. This investigation was approved by the University's Institutional Review Board.

Psychosocial measures

Depressive symptoms. The Inventory to Diagnose Depression (IDD) was used to measure overall depressive severity by summing its 22 items.³¹ This index has been found to correlate highly with total scores on the Beck Depression Inventory ($r = 0.87$). In the present sample, the mean score was 20.87 (SD = 12.94) and the coefficient α was 0.90.

Self-esteem. The Rosenberg Self-Esteem Questionnaire (RSE) was used to measure self-esteem.³² This instrument is a 10-item measure

^aTwo individuals were missing self-esteem and neuroticism data, and one individual was missing acute life event data. As such, analyses utilizing these variables were conducted with 22 or 23 participants.

that assesses global self regard. Participants were asked on a 5-point Likert scale to indicate their agreement with the statements (1 = "strongly disagree" to 5 = "strongly agree"). In the present sample, the mean score was 37.45 (SD = 6.56) and the coefficient α was 0.81.

Neuroticism. The Neuroticism Scale of the Eysenck Personality Questionnaire-Revised Short Scale is a 12-item subscale that was used to measure a personality style indicative of affective instability.³³ Published data from a community sample of individuals aged 16–70 reported a mean score of 4.95 (SD 3.44). In the present sample, the mean score was 5.81 (SD = 3.05) and the coefficient α was 0.81.

Experience of general-life events. The Life Experiences Survey (LES) is a list of 59 life events covering a wide range of experiences.³⁴ Participants were asked to indicate if they had experienced each event within the past 3 months and to report how negative or positive they were on a 7-point scale (−3 = "extremely negative"; 0 = neutral; +3 = "extremely positive"). Those rated as "−3," "−2," or "−1" were considered to be "negative" events. Nine items were removed from the original measure because of their specificity to college life (e.g., academic probation, changing a major), resulting in an inventory of 50 items. In the present sample, the mean number of negative events experienced was 5.57 (SD 7.95) and the range spanned from 0 to 36.

HIV-specific life events. The Buffalo HIV Life Events Survey (BHLES) is an inventory of 64 life events specifically related to being HIV-positive.²⁷ Participants were asked to indicate if they had experienced each event within the past 3 months. A total of 20 positive events were included in order to reduce emotional reactions to completing the inventory. Items covered a wide range of life arenas, including relationship (e.g., death of a friend because of AIDS), financial (e.g., experienced difficulty affording treatment), health (e.g., experienced significant medication side effects), employment (e.g., was terminated from job), and spiritual/religious (e.g., asked to leave or made to feel unwelcome in church/congregation) events.

The inventory also provided the opportunity to write in up to three additional events. Participants were reminded throughout the inventory to only report events that were specifically tied to being HIV-positive. Again, participants were asked to indicate if they had experienced each event within the past three months and to report how negative or positive they were on a 7-point scale (−3 = "extremely negative"; 0 = neutral; 3 = "extremely positive"). Those rated as "−3," "−2," or "−1" were considered to be "negative" events. Scores were based on raw counts of events reported as "negative." The mean number of HIV-related events experienced was 3.65 (SD = 7.27) and the range was 0 to 35.

Perceived stress. The Perceived Stress Scale (PSS) was used to measure psychological stress.²⁰ This instrument is a 14-item questionnaire that assesses thoughts and feelings associated with subjective levels of distress (e.g., "felt nervous or stressed," "felt that things were going your way"). Participants were asked on a 5-point scale to indicate how often they had similar thoughts or feelings (0 = never, 4 = very often). For this study, participants were asked to base their ratings on the last 3 months. Two college student samples had mean scores of 23.2 (SD = 7.3) and 23.7 (SD = 7.8) on this instrument, whereas a community sample of individuals in a smoking cessation program had a mean score of 25.0 (SD = 8.0). In the present sample, the mean score was 33.08 (SD = 9.32) and the coefficient α was 0.82.

Adherence measurements

Self-reported adherence. The routine inquiry of patient adherence was implemented through the use of a customized patient progress note that included a line item about patient adherence with antiretroviral therapy (ART) during the 48-hour period prior to each clinic visit. The adherence inquiry asked about the number of doses of an antiretroviral that had been missed in the 48 hours prior to the clinic visit. Patients were categorized based on their responses to inquiries at two separate medical appointments between 6–9 months after the completion of the psychological questionnaires. Initial category

rization was as follows: category A (excellent adherence): 0 and 0 missed doses; category B (good adherence): 0–1 and 0–1 missed doses; category C (fair adherence): 0 and > 1 missed doses; and category D (poor adherence): > 1 and > 1 missed doses. Our sample included 9 individuals with excellent adherence, 3 with good adherence, 4 with fair adherence, and 8 with poor adherence. As optimal viral suppression requires 95% or greater adherence, participants were categorized as having either excellent adherence or suboptimal adherence (categories B, C, and D combined).³⁵ The final sample therefore included 9 individuals in the “excellent” category and the remaining 15 in the “suboptimal” category.

Surrogate markers. HIV infection was documented for all participants with enzyme-linked immunoabsorbent assay (ELISA) confirmed by Western blot. CD4 cell percentages were determined by three-color panel flow cytometry. Absolute CD4 cell counts were calculated using the total white blood cell count and total lymphocyte percentage by traditional hemocytometry. HIV-RNA levels (viral load) were measured by Roche Amplicor assay (Roche Diagnostics, Indianapolis, IN) where the level of undetectability was less than 400 copies per milliliter. Continuous measures of viral load were not utilized in analyses because the distribution of this variable was positively skewed and was not amendable to standard transformation. As such, a dichotomous variable of “undetectable” or “detectable” was created with participants being classified as undetectable if their viral load was below 400 copies per milliliter and detectable if it was at least 400 copies per milliliter. The most recent CD4 cell count and viral load were recorded after being gathered from the participants’ medical records.

Data analytic strategy

Because of the small sample size and the non-normal distribution of our data, nonparametric techniques were used for these analyses. Simple descriptive statistics and Spearman correlation were used to assess the relationship between adherence and viral load with demo-

graphic factors. Fisher’s exact test was used to assess the relationship between excellent versus suboptimal adherence with detectable versus undetectable viral load. Finally, logistic regression was used to examine the impact of the three forms of stress on adherence and viral load and to test whether psychological factors (self-esteem, depression, and neuroticism) moderated these effects. These analyses were conducted using the statistical package R 2.0.1.³⁶ Although p values less than 0.05 were considered statistically significant, given the small sample size we also examined marginal trends of $p \leq 0.10$.

RESULTS

Adherence category and viral load

All participants received antiretroviral therapy during the study. A total of 19 (79.2%) were receiving 3 or more antiretrovirals. The remaining 5 participants (20.8%) were receiving 2 antiretrovirals. Seven participants (29.2%) had viral loads that were undetectable. Our sample included 9 individuals (37.5%) with excellent adherence and 15 individuals (62.5%) with suboptimal adherence. Excellent adherence was associated with having an undetectable viral load, $p = 0.042$, one-tailed Fisher’s exact test. There was a trend between absolute CD4 count and adherence ($r = -0.35$, $p = 0.09$), with those individuals with excellent adherence having lower CD4 count. However, there was no relationship between absolute CD4 count and viral load ($r = 0.24$, $p = 0.26$). Finally, there was no relationship between adherence and age and ethnicity (all $ps > 0.38$).

Prospective prediction of adherence

Logistic regression analyses indicated a statistically significant association between perceived stress and future self-reported HIV treatment adherence ($\beta = 0.12$, $p = 0.04$, odds ratio [OR] = 0.88, confidence interval [CI] = 0.77–0.98). Individuals with excellent adherence had lower scores on the PSS than those with suboptimal adherence. In contrast, the associations between acute general, $p = 0.60$, and acute HIV-related life events, $p = 0.32$, were not statistically signif-

icant. Likewise, the bivariate associations between adherence and self-esteem, $p = 0.91$, depression, $p = 0.38$, and neuroticism, $p = 0.45$, were not statistically significant. In terms of the potential role of psychological factors as moderators of the effects of life stress, there was a marginal perceived stress \times depression interaction ($\beta = 0.03$, $p < 0.07$, OR = 0.97, CI = 0.94–1.00) and a marginal perceived stress \times neuroticism interaction ($\beta = 0.20$, $p < 0.06$, OR = 0.82, CI = 0.66–1.02). However, the perceived stress \times self-esteem interaction ($\beta = 0.03$, $p = 0.26$, OR = 1.03, CI = 0.97–1.10) was not statistically significant and neither were any of the interactions involving acute general events (all $ps > 0.14$) or acute HIV-related events (all $ps > 0.61$).

The form of the perceived stress \times depression interaction is displayed in Figure 1 using the Effects package in R to examine the effects of perceived stress at two levels of depression: 1 SD above the mean and 1 SD below the mean.³⁷ The significance of these effects was tested using simple slopes analyses.³⁸ As can be seen, the relationship between perceived stress and likelihood of excellent adherence was negative at high levels of depression ($\beta = -0.82$, $p < 0.05$, OR = 0.44, 95% CI = 0.19–1.02), suggesting that, for individuals with

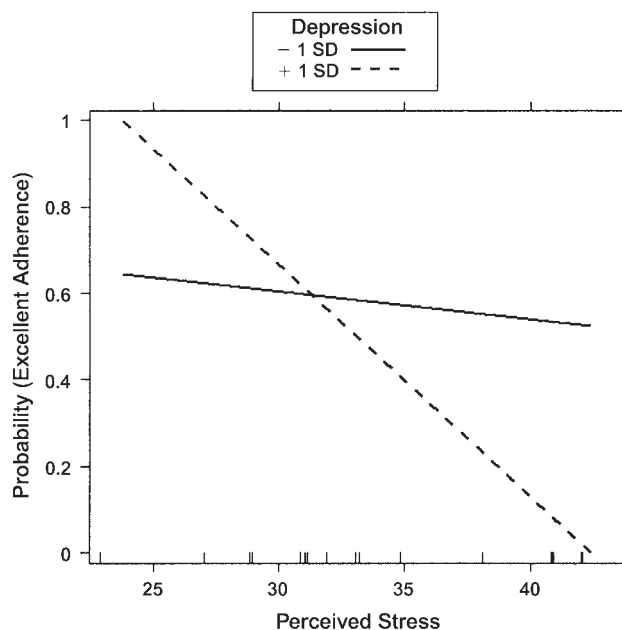


FIG. 1. Perceived stress \times depression severity interaction effect on probability of excellent adherence.

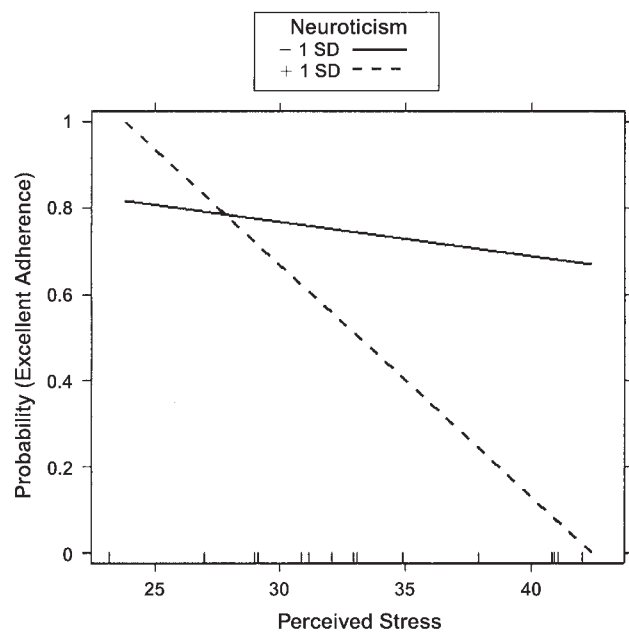


FIG. 2. Perceived stress \times neuroticism interaction effect on probability of excellent adherence.

higher levels of depressive severity, higher levels of perceived stress led to decreased probability of having excellent adherence. The simple slope for lower depression severity was not significant ($\beta = -0.03$, $p = 0.75$, OR = 0.97, CI = 0.81–1.16), suggesting that for those who were less depressed, varying levels of perceived stress were not associated with adherence.

The form of the perceived stress \times neuroticism interaction is displayed in Figure 2. Perceived stress was negatively related with likelihood of excellent adherence at higher levels of neuroticism ($\beta = -1.24$, $p < 0.05$, OR = 0.29, 95% CI = 0.08–1.06). For individuals with higher levels of neuroticism, higher levels of perceived stress led to decreased probability “of having excellent adherence. The simple slope for lower neuroticism was not significant ($\beta = -0.04$, $p = 0.78$, OR = 0.96, CI = 0.72–1.29). For those with lower levels of neuroticism, varying levels of perceived stress did not impact adherence.

Prospective prediction of viral load

Due to the non-normal distribution of viral load scores, these data were analyzed with a dichotomous variable of detectable versus

undetectable. The same analytic strategy was used as described above. There was a marginal trend between depressive symptoms and viral load ($r = -0.36, p = 0.10$), suggesting that those with detectable viral load were experiencing greater severity of depressive symptoms. None of the bivariate associations between viral load and any form of life stress (all $ps > 0.30$) or any of the psychological factors (all $ps > 0.23$) were statistically significant. Further, none of the interactions between any of the forms of life stress, depressive symptoms, and personality were statistically significant (all $ps > 0.30$).

DISCUSSION

Previous investigations have found that HIV-positive individuals have difficulty adhering to their treatment regimens. The present study was designed to investigate the impact of perceived stress and stressful life events. Moreover, we sought to investigate the potential moderating role of depressive symptomatology, neuroticism, and self-esteem on the adherence of HIV-positive individuals. Our results suggest that perception of stress, rather than acute stressful life events, prospectively predicts poor adherence among HIV-positive individuals. Those individuals classified as excellent adherers reported lower perceived stress than those with suboptimal adherence. Moreover, we found trends suggesting that depressive symptomatology and neuroticism moderate the relationship between perceived stress and future adherence. More specifically, it appears that for those individuals with higher levels of depressive symptoms or neuroticism, higher levels of stress are associated with a decreased probability of excellent adherence. However, in the absence of elevated depressive symptoms or high levels of neuroticism, level of perceived stress is not associated with adherence. Thus, it appears that these dysphoric individuals have a more difficult time remaining adherent as their level of perceived stress increases. These findings are alarming given that HIV is associated with a twofold increase in risk for depressive disorders and that both depression and neuroticism themselves increase the risk of experiencing

further stressors.³⁹⁻⁴¹ It appears that stress-prone individuals with high levels of depressive symptomatology and neuroticism are at particularly high risk for failing to comply with treatment and consequent declines in health.

In contrast to perceived stress, the acute stressful life events were not significantly related to adherence. However, as this was a prospective investigation over several months, we were unable to accurately assess the direct impact of stress on adherence. For example, it may be that adherence drops significantly for several weeks after a major life stressor but that returns to previous levels once the individual's distress has subsided.

Finally, we did not find evidence of a relationship between perceived stress or life stressors and viral load. Although we hypothesized that those individuals with increased stress, either perceived or acute, would have higher viral loads, our data did not support these hypotheses. Given that previous investigations have found stress to be related to HIV disease progression, we had expected to find a relationship between stress and viral load.^{3,42} Although perceived stress was associated with suboptimal treatment adherence, the magnitude of this relationship may not have been strong enough to impact viral load. Alternatively, because our participants were at various stages of the disease, it is possible that the relationship between stress and viral load is better examined using a measure of change in viral load rather than a discrete measurement of viral load. Finally, it is also possible that the time lag between perceived stress and viral load is greater than the lag between stress and treatment adherence. In other words, stress might have a relatively immediate impact on decreasing treatment adherence, but suboptimal adherence would only translate into higher viral load over the course of time.

There are several strengths to this investigation. First, this is a prospective investigation of the impact of stress on adherence of our participants. This allows us to examine the temporal relationship between life stress and subsequent adherence. Second, our self-reported measure of adherence included two separate measurements, thereby providing a broader picture of each participant's adherence level.

Finally, researchers have long disputed the best way to measure stress.⁴³ We attempted to investigate several aspects of stress by measuring both perception of stress and the number of events experienced. Furthermore, we were able to gather information on general life stressors and HIV-related stressors in order to examine whether general or illness-related events have differential impacts on treatment adherence.

As with any investigation, there are limitations to our study. First, we have a relatively small sample size and therefore, limited power to test our hypotheses. As previously noted, the lives of HIV-positive individuals are chaotic and a large percentage of the individuals approached for this study were unable to participate because of time constraints. Moreover, many of the individuals with incomplete data left the testing session early due to time pressures and did not return to complete their packets. Future investigations will need to improve recruitment strategies in order to obtain a larger sample size that is more representative of the diversity of HIV-positive individuals. Second, there are presently more sophisticated methods of measuring treatment adherence. Moreover, it is now understood that percentage of adherence is highly correlated with viral load. As such, different types of adherence measures may have provided us with more fine-grained information about our participants' adherence styles. These data were gathered before much of this information was known and therefore, our methodology was unable to incorporate these techniques. Finally, self-report measures of life events have been criticized as being vulnerable to reporting biases.⁴³ Use of interview-based life event assessment measures, such as Brown and Harris' Life Events and Difficulties Schedule, may provide for more accurate measurements of stress among HIV-positive individuals.²³

CONCLUSION

In conclusion, higher levels of perceived stress prospectively predicted poor adherence by HIV-positive individuals to their medication regimens, particularly among patients who

have higher levels of depressive symptomatology or neuroticism. This information may be clinically relevant and suggests that treatment providers could pay particular attention to the adherence of those patients who report particularly stressful lives. It may be that these individuals will require additional counseling to improve adherence or, alternatively, adjunctive counseling to manage their distress and depression.

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