DEPRESSIVE SYMPTOMS AND CERVICAL NEOPLASIA IN HIV+ WOMEN WITH HUMAN PAPILLOMAVIRUS INFECTION

By

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To Jeriann Dodd
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# TABLE OF CONTENTS

ACKNOWLEDGMENTS ............................................................................................................... 4

LIST OF TABLES .......................................................................................................................... 7

ABSTRACT ..................................................................................................................................... 8

CHAPTER

1 INTRODUCTION .................................................................................................................. 10

Epidemiology of HIV ............................................................................................................. 10
Pathophysiology of HIV/AIDS ............................................................................................... 10
HIV/AIDS Classification ........................................................................................................ 11
HIV and Human Papillomavirus ............................................................................................ 12
Psychoneuroimmunology and CIN ......................................................................................... 13
Depression and HIV ............................................................................................................... 14
Current Study .......................................................................................................................... 15

2 METHODS ............................................................................................................................. 17

Design ..................................................................................................................................... 17
Participants ............................................................................................................................. 17
Procedures ............................................................................................................................... 18
  Screening Visit ................................................................................................................ 18
  Psychosocial Interview .................................................................................................... 19
Statistical Procedures ........................................................................................................... 19

3 RESULTS ............................................................................................................................... 21

Demographics ......................................................................................................................... 21
Health Behaviors .................................................................................................................... 21
Health Status ........................................................................................................................... 22
Depressive Symptoms ........................................................................................................... 22
Relations between Depressive Symptoms and HIV-Related Immunity ................................. 22
Relations between Biobehavioral Variables and Cervical Neoplasia ..................................... 23
Relations between Depressive Symptomatology and Cervical Neoplasia ............................. 23

4 DISCUSSION ......................................................................................................................... 29

Study Limitations ................................................................................................................... 31
Future Directions .................................................................................................................... 32
LIST OF REFERENCES...............................................................................................................35

BIOGRAPHICAL SKETCH .........................................................................................................41
### LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>CDC classification of HIV/AIDS.</td>
<td>16</td>
</tr>
<tr>
<td>3-1</td>
<td>Comparison of continuous demographic and health variables in participants who provided full and partial data.</td>
<td>25</td>
</tr>
<tr>
<td>3-2</td>
<td>Comparison of categorical demographic and health variables in participants who provided full and partial data.</td>
<td>25</td>
</tr>
<tr>
<td>3-3</td>
<td>Predicting presence of cervical neoplasia from depressive symptoms.</td>
<td>26</td>
</tr>
<tr>
<td>3-4</td>
<td>Predicting presence of cervical neoplasia from cognitive/affective depressive symptoms.</td>
<td>27</td>
</tr>
<tr>
<td>3-5</td>
<td>Predicting presence of cervical neoplasia from somatic depressive symptoms.</td>
<td>28</td>
</tr>
</tbody>
</table>
Prior work has related elevated life stress to greater risk of cervical neoplasia in women co-infected with human immunodeficiency virus (HIV) and human papillomavirus (HPV). This study investigated associations between depressive symptoms (independent of life stress and other possible confounders) and cervical neoplasia in women with HIV and HPV infection. Participants for this study were 54 HIV+HPV+ women; most were African American. Participants underwent a colposcopy, HPV screening, Papanicolaou smear, and cervical biopsy to determine study eligibility. Eligible participants then completed the Beck Depression Inventory (BDI). Scores on the BDI were used as a whole and were also divided into cognitive/affective symptoms and somatic symptoms. Hierarchical logistic regression analysis revealed that women who reported more depressive symptoms had marginally greater odds of presenting with cervical neoplasia, $OR = 1.32, p = .062$. While cognitive and affective depressive symptoms were not significantly associated with greater odds of presenting with cervical neoplasia, women who reported more somatic depressive symptoms had greater odds of presenting with cervical neoplasia, $OR = 2.29, p = .022$, even after controlling for biobehavioral risk factors for cervical neoplasia (HIV viral load and high-risk HPV) and recent negative life events. Thus, women who reported more somatic depressive symptoms had greater odds of
presenting with cervical neoplasia. These findings may suggest that screening HIV+ women for somatic depression may help identify those at risk for cervical neoplasia. In addition, these findings suggest that future research on depression in medical populations should not ignore somatic depressive symptoms, as they may have important implications for health outcomes.
CHAPTER 1
INTRODUCTION

Epidemiology of HIV

Human immunodeficiency virus (HIV) is the virus that causes acquired immunodeficiency syndrome (AIDS). HIV and AIDS are serious global health threats. In 2003, an estimated 4.8 million people worldwide became newly infected with HIV. Approximately 37.8 million people are currently living with HIV. Over 20 million have died from the disease since the epidemic began in 1981; 2.9 million died in 2003 alone (Joint United Nations Programme on HIV/AIDS [UNAIDS], 2004). In the United States, 43,171 new AIDS cases were reported to the Center for Disease Control and Prevention (CDC) in 2003. Of these, 21,304 (49.3%) cases were diagnosed in African Americans compared to 12,222 (28.3%) cases diagnosed in Caucasians. AIDS-related mortality is also higher among African Americans than Caucasians. Death rates associated with AIDS are nearly 8 times higher in African American men than Caucasian men. For women the disparity was even larger: death rates for African American women due to AIDS are nearly 13 times higher than those for Caucasian women (National Center for Health Statistics, 2005). In 2002, HIV/AIDS was the leading cause of death in African American women between the ages of 25 and 34 (Anderson & Smith, 2005). These discrepancies are even more pronounced since African Americans constitute only 12.3% of the U.S. population (U.S. Census Bureau data for 2000, 2006). Although HIV and AIDS are serious health threats for all Americans, the virus and disease have a disproportionately large impact on the African American community.

Pathophysiology of HIV/AIDS

Infection with HIV occurs through mucosal contact with bodily fluids infected with the virus. This occurs through sexual intercourse or the sharing of contaminated needles. In the past,
HIV infection occurred following medical transfusion of infected blood products; this has become rare subsequent to blood screening procedures to identify infected blood. Approximately 2-6 weeks following initial infection, most (but not all) individuals experience an influenza-like illness corresponding with the initiation of HIV-specific cellular immune responses (Nadler, 2006). During this time, cytotoxic T-cells (CD8 T-cells) are activated and work to kill HIV infected cells and HIV antibody production occurs (Janeway, Travers, Walport & Shlomchik, 2001).

After the primary infection stage, HIV enters the second stage of infection, often referred to as the asymptomatic stage. Though individuals in this stage generally do not express any clinical symptoms, the virus continues to replicate and CD4 T-cell counts continue to decline (Nadler, 2006). One of the primary factors influencing the amount of time an individual remains in the asymptomatic stage is the initial effectiveness of the immune response to contain the infection. The HIV viral load that is established subsequent to initial infection remains fairly stable over several years, and those with the highest viral loads generally have faster progressing HIV infection (Nadler, 2006). For most individuals, this second stage of HIV infection eventually progresses to clinical AIDS, which is characterized by low CD4 cell counts and/or the development of an AIDS-defining illness, as described below.

**HIV/AIDS Classification**

In 1993, the CDC revised the classification system for HIV/AIDS. According to the revisions, HIV/AIDS is classified using three ranges of CD4 cell counts and three clinical categories.

The three ranges of CD4 cell counts used to classify HIV infection are 500 cells/µL or greater (Category 1), 200-499 cells/µL (Category 2), and less than 200 cells/µL (Category 3). Individuals in Category 3 are classified as having developed AIDS, regardless of whether they
have developed an AIDS defining condition. Category determinations are made based upon the lowest accurate CD4 cell count for that individual, which is not necessarily the most recent cell count obtained (CDC, 1992).

The three clinical categories of HIV/AIDS are Category A, B, and C. An individual is categorized as being in Category A, or asymptomatic HIV, if they have never experienced a symptomatic AIDS condition or an AIDS-defining illness (described below). Category B, or symptomatic HIV, is assigned to individuals who have experienced a symptomatic condition occurring in an HIV infected individual that is either attributed to the HIV infection or indicates a deficit in cell-mediated immunity, or conditions that have a clinical course that is complicated by the HIV infection. These do not include conditions designated as AIDS-defining illnesses. Category C, or clinical AIDS, is reached when an individual experiences an AIDS-defining illness as defined by the CDC. Classification of the clinical categories are based upon the history of HIV progression, thus once an individual meets criteria for a category they cannot move back into a previous category, even if the symptoms or illness placing them in the category is resolved (CDC, 1992).

Based upon the three CD4 cell count categories and the three clinical categories, there are nine mutually exclusive categories for the staging of HIV/AIDS, ranging from A1-C3 (Table 1-2). Categories A3, B3, C3, C1, and C2 confer a diagnosis of AIDS.

**HIV and Human Papillomavirus**

HIV infection may have a different course in women compared to men. Specifically, several opportunistic illnesses are more common, harder to treat, or occur exclusively in women with HIV as compared to their male counterparts. Examples include disorders of the upper genital tract, such as pelvic inflammatory disease, as well as disorders of the lower genital tract, such as cervical intraepithelial neoplasia (CIN) (CDC, 1992). CIN is the pre-malignant phase of
cervical cancer that is initiated and promoted to cervical cancer by oncogenic Human Papillomavirus (HPV) infection, including HPV 16 and 18 infections. HPV is one of the most common sexually transmitted infections in the United States. Among immunocompetent women with HPV infection, adequate cellular immune responses, most notably T helper type 1 (Th1) cell immune responses (Scott, Stites, & Moscicki, 1999), will survey the virus before it promotes the pre-malignant or malignant transformation of cells (Munoz et al., 2003). However, HPV infected women with suppressed cellular immune responses, such as women with immunodeficiency due to HIV infection, are not able to mount an adequate immune defense against HPV, resulting in persistent and severe HPV infection and risk for malignant transformation of cells. Additional risk factors for CIN and cervical cancer among women with HIV include degree of immunosuppression (low T helper/inducer lymphocyte [CD4+CD3+] cell counts) (Phelps et al., 2001; Davis et al., 2001), tobacco smoking (Hocke et al., 1998), and uncontrolled HIV viral load (Davis et al., 2001).

Psychoneuroimmunology and CIN

Psychoneuroimmunology (PNI) is the investigation of the relations among psychosocial variables, neuroendocrine and immunologic functioning, and health outcomes. Research investigating psychosocial variables and the presence and/or persistence of CIN has yielded inconsistent results. Previous research has shown that poorer psychological well-being (greater pessimistic attitude, greater negative life event stress) is associated with lower cell-mediated and natural immunity (Byrnes et al., 1998), greater number of genital herpes recurrences (Pereira et al., 2003b), and greater odds of progression and/or persistence of cervical neoplasia (Pereira et al., 2003a) in women with HIV and HPV infections. In contrast, other researchers have reported no associations between CIN progression or regression with negative life events, lack of social support, or coping style (Tiersma et al., 2005; Tiersma et al., 2004). However, no research to
date has explored whether other common and treatable psychological conditions, such as depression, are associated with cervical neoplasia in women with HIV and HPV infections.

**Depression and HIV**

The relationship between depression and health status in HIV+ women is particularly important to examine for several reasons. Depressive symptoms and disorders are common among individuals with HIV infection. Studies have shown that nearly half of individuals with HIV infection meet diagnostic criteria for depression (Chandra et al., 1998). HIV+ women may be at particularly high risk of experiencing depressive symptoms. Studies have shown that women in the general population experience major depression twice as often as men (Weissman & Olfson, 1995), and women infected with HIV experience major depression significantly more often than healthy women (Morrison et al., 2002). In addition, HIV+ women experience depression at rates twice that of HIV+ men (Evans et al., 2002). Notably, depressive symptoms in HIV+ individuals are associated with more rapid decline of CD4+CD3+ cell counts (Rabkin et al., 1991; Lyketsos et al., 1993; Sahs et al., 1994; Vedhara, Schifitoo, & McDermott, 1999; Burack et al., 1993; Ickovic et al., 2001), decreased natural killer (NK) cell activity, increased HIV viral load, and greater risk of HIV related mortality (Burack et al., 1993; Ickovics et al., 2001; Mayne et al., 1996; Leserman et al., 1999). Depressive symptoms are also associated with faster development of any AIDS defining condition (Leserman et al., 2002).

In spite of this research, no research to our knowledge has investigated the possible relationship between depressive symptoms and cervical neoplasia, a female-specific HIV associated opportunistic illness. This relationship is of particular interest, because susceptibility to depression is elevated among women experiencing high life stress (Kendler, Karkowski, & Prescott, 1999) and individuals who are dispositionally pessimistic (Beck, 1967; Pyszczynski, Holt, & Greenberg, 1987), two psychosocial factors previously associated with lowered
immunity and progression and/or persistence of cervical neoplasia in HIV+ HPV+ women (Byrnes et al., 1998; Pereira et al., 2003).

**Current Study**

The purpose of the current study was to determine whether recent depressive symptoms were associated with the presence of cervical neoplasia in a sample of primarily Black/African American women with HIV and HPV infections recruited for a trial examining the effect of a cognitive behavioral stress management (CBSM) intervention on health (e.g., cervical neoplasia) and quality of life outcomes. It was specifically hypothesized that women with greater recent depressive symptomatology would have greater odds of cervical neoplasia at study entry. Given that HIV-related symptoms and medication side effects may be confounded with somatic symptoms of depression (Blaney et al., 2004; Jones, Beach, & Forehand, 2001), we also examined whether greater cognitive/affective symptoms of depression, specifically, were associated with greater odds of cervical neoplasia.
Table 1-1 CDC classification of HIV/AIDS.

<table>
<thead>
<tr>
<th>CD4 Cell Categories</th>
<th>A (Asymptomatic HIV)</th>
<th>B (Symptomatic HIV)</th>
<th>C (AIDS defining illness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 500 or greater cells/µL</td>
<td>A1</td>
<td>B1</td>
<td>C1</td>
</tr>
<tr>
<td>2 200-499 cells/µL</td>
<td>A2</td>
<td>B2</td>
<td>C2</td>
</tr>
<tr>
<td>3 less than 200 cells/µL</td>
<td>A3</td>
<td>B3</td>
<td>C3</td>
</tr>
</tbody>
</table>

Note: Categories A3, B3, C3, C1 and C2 receive a diagnosis of AIDS.
CHAPTER 2
METHODS

Design

The current study utilized a cross-sectional design. Fifty-four women co-infected with HIV and HPV underwent a colposcopy, HPV testing and subtyping, a peripheral venous blood draw, urine collection, and a 60-90 minute psychosocial interview assessing mood and health behaviors. Statistical analyses examined the relationships between depressive symptomatology and the presence or absence of cervical neoplasia at study entry, while controlling for known biobehavioral risk factors for cervical neoplasia.

Participants

Participants for this study were recruited as part of a longitudinal National Cancer Institute (NCI) funded study investigating the effects of a cognitive-behavioral stress management (CBSM) intervention on the health and quality of life of women with HIV at risk for cervical cancer (PI: Michael H. Antoni, Ph.D., 5 P50 CA 084944-05). Inclusion criteria were: (a) HIV+ women ages 18 to 60 years old, (b) history of at least 2 Papanicolaou smears indicating low grade squamous intraepithelial lesions (LSIL) or 2 cervical biopsies indicating CIN I in the 2 years prior to study entry, and (c) fluency in spoken English. Exclusion criteria were: (a) 2 or more negative Papanicolaou smears in the 2 years prior to study entry, (b) any history of high grade SIL (HSIL) or any history of CIN II, CIN III, or invasive cervical cancer, (c) any diagnostic or treatment procedures for CIN in the 6 months prior to study entry, (d) life expectancy < 12 months as determined by the study’s research nurse, and (e) current major, severe psychiatric illnesses that would interfere with the ability to provide valid psychosocial assessment data (e.g., suicidality, psychoticism, HIV dementia).
Procedures

Participants for this study were recruited through Special Immunology Clinics at the University of Miami/Jackson Memorial Hospitals. Patients at the Special Immunology Clinics were initially screened based on medical record data to determine whether they met basic eligibility requirements. If a patient passed the preliminary eligibility screening, a researcher approached her during her visit to the clinic and explained the study. Patients that were interested in participating in the study were scheduled to come in for a formal screening appointment.

Screening Visit

At the formal screening appointment, the study was explained in more detail and informed consent was completed. In addition, the participant provided information on her gynecologic history, underwent a psychological screening, was provided an educational module regarding colposcopies, and a colposcopy was performed. The colposcopy was comprised of a Papanicolaou smear, colposcopic-guided cervical biopsy, and cervical swab for the detection and subtyping of HPV infection. Based on the results of the colposcopy, participants were classified as being positive or negative for cervical neoplasia at study entry. Hybrid Capture (HC) II assay (Digene Corporation, Gaithersburg, MD) was used to classify HPV subtypes as intermediate to high risk HPV (oncogenic subtypes) or low risk HPV subtypes. Immediately following the colposcopy, participants were administered the Psychosocial Effects of Abnormal Pap Smears Questionnaire (PEAPS-Q – Bennetts et al., 1995) to measure distress related to the colposcopy. Participants also underwent a peripheral venous blood draw in order to measure CD4+CD3+ cell counts and plasma HIV viral load. At the end of this visit, participants were given urine collection materials and instructions on collecting urine before their next visit. They were then
contacted approximately one week later with the results of the screening and to inform them of whether or not they were ultimately eligible to participate in the study.

**Psychosocial Interview**

If the participant was eligible for study participation after the formal screening, she was scheduled for another visit. At this visit, participants completed a psychosocial assessment interview. This interview included the Beck Depression Inventory (BDI – Beck, Ward, Mendelson, Mock & Erbaugh, 1961) and a general demographic questionnaire, among other psychosocial measures. The BDI is a 21-item self-report questionnaire that measures symptoms of depression. The BDI has been used extensively in previous research investigating depressive symptoms in HIV+ populations (Castellon, Hinkin, Wood & Yarema, 1998; Ferrando, Rabkin, de Moore & Rabkin, 1999; Judd et al., 2005; Laperriere et al., 2005; Weiser et al., 2006).

Questions on the BDI assess both cognitive and affective (e.g., sadness, hopelessness) as well as somatic (e.g. fatigue, weight change) depressive symptoms. Thus it is possible to create scale scores from the BDI, which measure an individual’s levels of cognitive/affective and somatic depressive symptoms independently.

**Statistical Procedures**

Results presented in this paper are based upon cross-sectional psychosocial (i.e., BDI scores) and biological (i.e., cervical neoplasia) data. We started by examining relations between potential demographic and biobehavioral control variables and cervical neoplasia in this sample. We then examined the relationship between recent depressive symptoms and the presence of cervical neoplasia in women with HIV and HPV infection using hierarchical logistic regression. Regression equations contained two blocks of predictor variables: the first block consisted of traditional, well-established risk factors for cervical neoplasia in HIV+ women (CD4+CD3+ cell count, HIV viral load, HR-HPV infection, and tobacco smoking) (Davis et al., 2001; Hocke et
al., 1998; Phelps et al., 2001), and the second block consisted of our psychosocial predictor of interest – scores on the BDI. Two hierarchical logistic regression equations were analyzed. The first equation contained scores from all 21 items of the BDI. The second equation contained scores from only the cognitive/affective items of the BDI (i.e., BDI items 1 – 15). The criterion in both equations was presence (“1”) or absence (“0”) of cervical neoplasia by histology (cervical biopsy) at study entry. If a cervical biopsy was clinically contraindicated for a particular participant, the presence or absence of squamous intraepithelial lesions (SIL) by cervical cytology (Papanicolaou smear) at study entry was used.
CHAPTER 3
RESULTS

Demographics

Sixty-six women met study criteria and were enrolled in this study. The results reported here are based on 54 participants who provided full psychosocial, colposcopic, and immune data. Results of t-tests and chi-square analyses revealed that participants who provided complete data did not differ significantly ($p > .05$) from those who had incomplete data in age, yearly income, years of education, ethnicity, marital status, presence of neoplasia, presence of high-risk HPV, HIV stage, or CD4+CD3+ cells/mm$^3$. (Tables 3-1 & 3-2).

The 54 participants who provided full data ranged in age from 18-45 years ($M = 30$ years, $SD = 8.5$ years). The majority of the women were non-Hispanic Black/African American (85.2%), with the remainder of the sample being comprised of Hispanic Caucasian (9.3%), non-Hispanic Caucasian (3.7%), and other (1.9%). The women had an average yearly income of $11,601 (SD = $8,089), and averaged 11.6 years of education (SD = 1.23 years). The majority of women in the study (55.6%) were single/never married. Of the remaining 44.4%, 20.4% were married or in an equivalent relationship and 24% were separated, divorced, or widowed.

Health Behaviors

Seventy-two percent of the women who participated in this study were taking highly active anti-retroviral therapy (HAART) at the time of study entry. Self-reported adherence to HAART was significantly negatively correlated with HIV viral load, $r = -.413$, $p = .011$. Nearly 60% of the participants reported never having smoked. Of the remaining women who did report a history of smoking ($N = 22$), pack-years of smoking ranged from 6 - 5,110 ($M = 1,904$, $SD = 1,880$).
Health Status

Colposcopic-guided cervical biopsy revealed that 44 women (81.5%) presented with cervical neoplasia at study entry, while 10 women (18.5%) did not show evidence of cervical neoplasia. HPV screening and typing revealed that 42 women (77.7%) tested positive for intermediate or HR-HPV types.

Twenty-three women (42.6%) had Category A (asymptomatic) disease at study entry. Thirteen women (24.1%) had Category B (symptomatic) disease, and 17 women (31.5%) had Category C (clinical AIDS) disease. The mean CD4+CD3+ cells/mm³ was 455.43 (SD = 285.47). Eight women (14.8%) had CD4+CD3+ cell counts below 200 cells/mm³, 27 women (50%) had cell counts between 200 and 500 cells/mm³, and 19 women (35.2%) had cell counts above 500 cells/mm³.

Depressive Symptoms

Possible scores on the BDI range from 0-63, with higher scores indicating more depressive symptoms reported. The women in this study scored between 0-44 on the full BDI, with a mean of 8.6 (SD = 9.81). Previous research with HIV populations has utilized a BDI cutoff score of 10 to indicate depression (Laperriere et al., 2005), thus the average score for women in this study was below depression cutoffs on the BDI. Twenty-one women (39%) in the study obtained BDI scores of 10 or greater.

Relations between Depressive Symptoms and HIV-Related Immunity

The results of correlational analyses demonstrated that neither total BDI scores nor cognitive/affective BDI scores were correlated with CD4+CD3+ cell counts; however, women with greater somatic BDI scores had significantly lower CD4+CD3+ cell counts, r = -.286, p = .036. BDI scores (total, cognitive/affective, and somatic) and HIV viral load were not correlated (p’s > .05).
Relations between Biobehavioral Variables and Cervical Neoplasia

Correlational and chi-squared analyses were conducted to determine whether variables that have been shown to be risk factors of cervical neoplasia in HIV+ women (HIV viral load, presence of HR-HPV subtypes, CD4+CD3+ cell counts, and tobacco smoking) were related to cervical neoplasia in this sample. HIV viral load ($r = .30, p = .027$) and presence of HR-HPV subtypes ($x^2 [1] = 5.48, p = .019$) were significantly related to the presence of neoplasia. Despite the fact that CD4+CD3+ cell counts and tobacco smoking were not significantly related to neoplasia, all four potential risk factors were entered as control variables into Block 1 of the regression equations as a conservative measure based on their strong associations with incidence of neoplasia in previous research.

Relations between Depressive Symptomatology and Cervical Neoplasia

Using scores from the entire BDI as the predictor of interest, a marginally significant relationship emerged between greater depressive symptomatology and greater odds of cervical neoplasia, $OR = 1.19, 95\% CI = .98 – 1.45, p = .084$. The overall model was significant, $x^2 (5) = 16.72, p = 0.005$ (Table 3-3). Subsequently, the relationship between only the cognitive/affective items of the BDI, specifically, and cervical neoplasia was examined. Contrary to our hypothesis, there was no significant relationship between cognitive/affective symptoms of depression and the odds of cervical neoplasia, $OR = 1.18, 95\% CI = 0.95 – 1.48, p = 0.181$ (Table 3-4).

Given that there was (a) a marginally significant relationship between scores on the entire BDI and cervical neoplasia and (b) no significant relationship between the cognitive/affective scores and neoplasia, we explored the possibility that scores on the somatic items of the BDI (BDI items 16-21) were related to greater odds of cervical neoplasia. Hierarchical logistic regression analysis revealed that women who reported higher levels of recent somatic depressive
symptomatology had over two-fold greater odds of cervical neoplasia, \( \text{OR} = 2.21, 95\% \text{ CI} = 1.03 - 4.73, p = 0.042 \). The overall model was significant, \( \chi^2 (5) = 19.77, p = 0.001 \) (Table 3-5). In order to ensure that the relationship between recent somatic depressive symptoms and cervical neoplasia was independent of life stress, a factor previously demonstrated to be associated with the progression and/or persistence of cervical neoplasia in HIV+ women over time (Pereira et al., 2003), we also controlled for the impact of recent negative life event stress using an abbreviated 10-item version of the Life Experiences Survey (LES) (Sarason, Johnson, & Seigel, 1978) described in detail elsewhere (Pereira et al., 2003). A significant relationship remained between greater somatic depressive symptoms and greater odds of cervical neoplasia after controlling for risk factors for neoplasia and life stress, \( \text{OR} = 2.19, 95\% \text{ CI} = 1.01 - 4.74, p = 0.046 \) (not shown).

Finally, to investigate whether an individual somatic depressive symptom was driving the association between somatic depressive symptomatology and cervical neoplasia, correlational analyses were conducted on each of the somatic BDI items and neoplasia. Results of these analyses showed that only the BDI question regarding difficulty sleeping was significantly correlated with cervical neoplasia (\( r = .313, p = .021 \)). However, when the BDI question regarding sleep was removed from the hierarchical logistic regression, the remaining somatic depressive symptoms continued to be significantly associated with greater odds of presenting with cervical neoplasia (\( \text{OR} = 2.27, p = .049, 95\% \text{ CI} = 1.01-5.12 \)). Thus, it appears that the constellation of somatic depressive symptoms and not necessarily difficulty sleeping is associated with greater odds of presenting with cervical neoplasia.
### Table 3-1 Comparison of continuous demographic and health variables in participants who provided full and partial data.

<table>
<thead>
<tr>
<th>Potential control variable</th>
<th>Respondents mean (SD)</th>
<th>Non-respondents mean (SD)</th>
<th>t</th>
<th>Df</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.04 (8.45)</td>
<td>35.0 (7.55)</td>
<td>1.938</td>
<td>65</td>
<td>0.057</td>
</tr>
<tr>
<td>Yearly income ($)</td>
<td>11,601 (8,089)</td>
<td>11,575 (9,877)</td>
<td>-0.010</td>
<td>64</td>
<td>0.992</td>
</tr>
<tr>
<td>Years of education</td>
<td>11.55 (1.23)</td>
<td>11.38 (2.47)</td>
<td>-0.231</td>
<td>64</td>
<td>0.821</td>
</tr>
<tr>
<td>HIV viral load (cells/mm(^3) [log(_{10}) transformed])</td>
<td>2.55 (1.93)</td>
<td>1.75 (2.18)</td>
<td>-1.138</td>
<td>61</td>
<td>0.26</td>
</tr>
<tr>
<td>CD4+CD3+ (cells/mm(^3))</td>
<td>455.43 (285.47)</td>
<td>384.33 (318.05)</td>
<td>-.681</td>
<td>61</td>
<td>0.498</td>
</tr>
</tbody>
</table>

### Table 3-2 Comparison of categorical demographic and health variables in participants who provided full and partial data.

<table>
<thead>
<tr>
<th>Potential control variable</th>
<th>(\chi^2)</th>
<th>df</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>4.298</td>
<td>7</td>
<td>0.745</td>
</tr>
<tr>
<td>Marital status</td>
<td>2.75</td>
<td>4</td>
<td>0.601</td>
</tr>
<tr>
<td>Presence of dysplasia</td>
<td>0.578</td>
<td>1</td>
<td>0.447</td>
</tr>
<tr>
<td>HIV clinical axis</td>
<td>0.535</td>
<td>2</td>
<td>0.765</td>
</tr>
<tr>
<td>HPV status</td>
<td>1.667</td>
<td>1</td>
<td>0.197</td>
</tr>
</tbody>
</table>
Table 3-3  Predicting presence of cervical neoplasia from depressive symptoms.

<table>
<thead>
<tr>
<th>(Step number) predictor</th>
<th>β</th>
<th>Wald statistic</th>
<th>Odds ratio</th>
<th>p Value</th>
<th>95% confidence interval Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Biological variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV viral load (cells/mm$^3$ [log$_{10}$ transformed])</td>
<td>.476</td>
<td>3.151</td>
<td>1.609</td>
<td>0.076</td>
<td>0.952</td>
<td>2.722</td>
</tr>
<tr>
<td>High-risk HPV</td>
<td>1.634</td>
<td>3.007</td>
<td>5.126</td>
<td>.083</td>
<td>.808</td>
<td>32.514</td>
</tr>
<tr>
<td>CD4+CD3+ (cells/mm$^3$)</td>
<td>0.000</td>
<td>0.057</td>
<td>1.000</td>
<td>0.812</td>
<td>0.997</td>
<td>1.004</td>
</tr>
<tr>
<td>Smoking</td>
<td>.001</td>
<td>2.103</td>
<td>1.001</td>
<td>0.147</td>
<td>1.000</td>
<td>1.002</td>
</tr>
<tr>
<td>(2) Psychological variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full BDI score</td>
<td>0.175</td>
<td>2.977</td>
<td>1.191</td>
<td>.084</td>
<td>0.997</td>
<td>1.453</td>
</tr>
</tbody>
</table>

$N = 54$. Significance of the model, $\chi^2 (5) = 16.724, p = .005$. Nagelkerke $R^2 = .432$
Table 3-4 Predicting presence of cervical neoplasia from cognitive/affective depressive symptoms.

<table>
<thead>
<tr>
<th>(Step number)</th>
<th>Predictor</th>
<th>$\beta$</th>
<th>Wald statistic</th>
<th>Odds ratio</th>
<th>$p$ value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Biological variables</td>
<td>HIV viral load (cells/mm$^3$ [log$_{10}$ transformed])</td>
<td>0.487</td>
<td>3.462</td>
<td>1.627</td>
<td>0.063</td>
<td>0.974 - 2.716</td>
</tr>
<tr>
<td></td>
<td>High-risk HPV</td>
<td>1.585</td>
<td>3.036</td>
<td>4.88</td>
<td>0.081</td>
<td>0.821 - 29.026</td>
</tr>
<tr>
<td></td>
<td>CD4+CD3+ (cells/mm$^3$)</td>
<td>0.000</td>
<td>0.040</td>
<td>1.000</td>
<td>0.841</td>
<td>0.997 - 1.004</td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td>.001</td>
<td>2.486</td>
<td>0.1001</td>
<td>.115</td>
<td>1.000 - 1.002</td>
</tr>
<tr>
<td>(2) Psychological variable</td>
<td>Cognitive/affective BDI score</td>
<td>.169</td>
<td>2.266</td>
<td>1.184</td>
<td>0.132</td>
<td>0.950 - 1.476</td>
</tr>
</tbody>
</table>

Table 3-5 Predicting presence of cervical neoplasia from somatic depressive symptoms.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>β</th>
<th>Wald statistic</th>
<th>Odds ratio</th>
<th>p value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Biological variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV viral load (cells/mm(^3) [log(_{10}) transformed])</td>
<td>0.472</td>
<td>2.786</td>
<td>1.603</td>
<td>0.095</td>
<td>0.921 2.789</td>
</tr>
<tr>
<td>High-risk HPV</td>
<td>1.307</td>
<td>1.764</td>
<td>3.695</td>
<td>0.184</td>
<td>.537 25.423</td>
</tr>
<tr>
<td>CD4+CD3+ (cells/mm(^3))</td>
<td>0.001</td>
<td>0.002</td>
<td>1.001</td>
<td>0.567</td>
<td>0.998 1.005</td>
</tr>
<tr>
<td>Smoking</td>
<td>.001</td>
<td>1.537</td>
<td>1.001</td>
<td>0.215</td>
<td>1.000 1.002</td>
</tr>
<tr>
<td>(2) Psychological variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic BDI score</td>
<td>0.791</td>
<td>4.126</td>
<td>2.206</td>
<td>0.042</td>
<td>1.028 4.733</td>
</tr>
</tbody>
</table>

N = 54. Significance of model, \(\chi^2(5) = 19.77\) p = .001. Nagelkerke’s \(R^2 = .497\)
Previous research has shown that depression and depressive symptoms are associated with negative health outcomes for individuals with HIV infection (Burack et al., 1993; Ickovics et al., 2001; Mayne et al., 1996; Leserman et al., 1999; Leserman et al., 2002). However, very little research has investigated the possible relationship between depressive symptoms and HIV-specific pathophysiologic disease processes in women. This is a significant gap in the current literature, because the relationship between depression and specific HIV disease outcomes may help to explain the associations that have already been demonstrated between depression and more global yet highly significant outcomes, such as HIV progression and mortality. By identifying the specific disease processes that may underlie the previously demonstrated link between depression and HIV progression and mortality, specific screening and interventions can be tailored to provide the most effective and comprehensive treatments for HIV+ women.

The current study is the first, to our knowledge, to examine the relationship between depressive symptoms and HPV-initiated cervical neoplasia, the pre-malignant stage of cervical cancer. Cervical cancer is the most common AIDS defining malignancy in women with HIV infection (Maiman et al., 1997). The progression of cervical neoplasia in HIV+ women has significant clinical implications, as CIN II advances HIV+ women to symptomatic disease status and CIN III advances HIV+ women to a clinical AIDS diagnosis. Fortunately, cervical neoplasia is easily detectable via cervical cytology and histology, thus allowing for the initiation of treatment prior to the development of invasive cervical cancer. In addition, cervical neoplasia is initiated by HPV infection, a common, sexually-transmitted virus that is controlled by the immune system and, by implication, potentially influenced by psychosocial factors that are known to influence the immunosurveillance of latent viruses.
As expected, HR-HPV and cervical neoplasia were highly prevalent in our sample. HR-HPV infection was detected in 78.2% of the study participants, and cervical neoplasia was present in 81.8% of the participants. Participants in our sample included women who were asymptomatic, as well as those with advanced HIV disease. Therefore, it is likely that these results can be generalized to women at any stage of the HIV disease continuum.

Women in this study presented with wide variability in degree of depressive symptomatology, ranging from endorsing no current depressive symptoms to endorsing clinically-significant depressive symptomatology. It is possible that women with the most severe depressive symptomatology were not adequately sampled, because they did not present for routine obstetric and gynecologic care, refused research participation, or did not complete full study procedures. However, in spite of the challenges of recruiting and retaining participants with severe depressive symptomatology, 11% of our sample endorsed symptoms suggestive of clinically significant depression.

Total depressive symptomatology was only marginally associated with cervical neoplasia in this sample of HIV+ women with HPV infection and there was no relationship between the cognitive/affective symptoms of depression and cervical neoplasia. Only greater levels of somatic depressive symptoms were significantly associated with greater odds of cervical neoplasia, specifically increasing the odds of cervical neoplasia by approximately two-fold. This finding persisted after controlling for recent negative life event stress, a factor associated with the progression and/or persistence of cervical neoplasia in our prior research.

This finding is consistent with research suggesting that African Americans, who comprised the majority of our sample, may tend to manifest depression through primarily somatic symptoms (Das et al., 2006). In addition, it is consistent with the wealth of research
demonstrating that women tend to present frequently with “atypical depression,” which includes somatic symptoms such as weight gain and problems with sleep (Bhatia & Bhatia, 1999). The results of the current study also appear to be consistent with some published research on somatic depression and HIV outcomes. Perkins et al. (1995) found that fatigue and insomnia were associated with dysphoric mood and major depressive disorder in HIV+ individuals. Furthermore, one large-scale, longitudinal study demonstrated that somatic depressive symptoms were associated with progression to AIDS, progression to HIV-dementia, and shortened survival, even after controlling for HIV medication use (Farinpour et al., 2003). Taken together, these findings suggest that somatic depression may be a particularly important marker of depressive disorders and a correlate of important disease outcomes in HIV.

**Study Limitations**

Caution must be used when interpreting our findings given our modest sample size, undersampling of severely depressed women, and cross-sectional design, the latter of which precludes the ability to establish whether somatic depression causes cervical neoplasia or vice-versa. Of note, the BDI was administered to participants after they had been notified of their Papanicolaou smear and cervical biopsy results. This was unavoidable given that (a) study eligibility was based upon these results, and (b) colposcopic examinations were clinically indicated, and thus it would have been unethical to withhold cytology/histology results from participants for research purposes. Although this raises some concern that BDI results may be confounded with CIN-related distress, it should be noted that only participants with no or grade I (mild) cervical neoplasia were eligible for the study. In addition, approximately four to six weeks typically elapsed between notification of cytology/histology results and administration of the BDI, which assessed depressive symptomatology over the prior week only. Finally, an examination of the BDI and PEAPS-Q scores demonstrated that there was no association
between distress related to the colposcopy and depressive symptoms \( (p > .05) \). In concert, these factors may have restricted the degree of CIN-related distress that could be confounded with depressive symptomatology. An additional limitation of this study is that several participants did not have a cervical biopsy performed due the presence of clinical contraindications for biopsy. A cervical biopsy is necessary to establish a diagnosis of cervical neoplasia, and it is possible that cervical cytology may have underestimated the degree of cervical neoplasia present among these participants.

**Future Directions**

Future research should utilize prospective, longitudinal, and/or experimental designs to facilitate the examination of possible causal mechanisms between depressive symptoms and cervical neoplasia. For instance, somatic depression may increase odds of cervical neoplasia through impaired immune functioning. Somatic depression may be associated with a shift in the production of cytokines from a pattern that promotes cellular immunity (Th1 cytokine production: e.g., interferon-gamma, interleukin-2, tumor necrosis factor-alpha) to one that promotes primarily humoral immunity (Th2 cytokines production: e.g., interleukin-4, interleukin-10). This shift has been implicated in the progression of both HPV and HIV (Bais et al., 2006; Kedzierska & Crowe, 2001). Suppression of cellular immunity through a decreased Th1 cytokine response may allow for tumor growth and metastasis to occur (Rankin et al., 2003), while enhancement of a Th2 cytokine response may promote the survival of cancer cells through the prevention of programmed cell death (“apoptosis”) (Conticello et al., 2004).

Depression has also been strongly implicated in alterations (increases) in pro-inflammatory cytokines, including IL-1\(\beta\), IL-6, and IFN-\(\gamma\), which are capable of inducing sickness behaviors, including fatigue, lethargy, muscle and joint pain, and anorexia (Dantzer,
2006), symptoms that overlap greatly with somatic depressive symptoms. In addition, recent evidence has indicated that chronic inflammation, and thus an increase in the associated cytokines, may be involved in carcinogenic processes (Antoni et al., 2006; Balkwill, Charles, & Mantovani, 2005). Chronic inflammation has also been implicated specifically as a risk factor for HPV persistence and progression to cervical cancer (Castle, 2004). Thus, bidirectional relationships between somatic depression and cytokine production, on the one hand, and cytokine production and cervical neoplasia on the other hand, may account for the present findings. In the sample used for the current study, greater somatic depressive symptoms were associated with lower CD4+CD3+ cell counts at study entry ($r = -.286, p = .036$). Cognitive/affective depressive symptoms were not associated with CD4+CD3+ cell counts. In addition, neither somatic nor cognitive/affective depressive symptoms were significantly associated with HIV viral load, though there was a positive relationship between somatic depressive symptoms and HIV viral load that approached significance ($r = .243, p = .077$).

While it is intriguing to consider that cytokine production may mediate the relationship between somatic depressive symptoms and cervical neoplasia, it is equally possible that this relationship may be accounted for by the effects of depression on health care behaviors, such as Papanicolaou smear screening and medication adherence. Therefore, future research should be guided by a comprehensive model that would allow the testing of (a) multiple mediators of the relationship between somatic depression and cervical neoplasia, including both cytokine production and health behaviors, and (b) bidirectional relationships among these variables.

In summary, the findings of the present study suggest that it may be important to assess the presence and severity of depressive symptoms, most notably somatic depressive symptoms, among HIV+ women attending gynecologic and obstetric clinics. Ultimately, the identification
and treatment of somatic depression among HIV+ HPV+ women may enhance health-related quality of life in part via reduction in risk of cervical cancer.
LIST OF REFERENCES


U.S. Census Bureau; Census 2000, Profile of General Demographic Characteristics (DP-1); generated by Stacy Dodd; using American Factfinder; http://factfinder.census.gov/; (26 April 2006).

BIOGRAPHICAL SKETCH

Stacy Dodd graduated with honors from the University of Michigan in 2005, receiving a Bachelor of Arts degree in Psychology. During her time at the University of Michigan, she worked as a research assistant for the Families and Communities Together Coalition on a study investigating the effects of a group intervention for women and children who had experienced domestic violence. She also completed an undergraduate honors thesis on the worries of childhood cancer patients and their mothers and the abilities of each to predict the worries of the other.

Stacy began attending graduate school at the University of Florida in the department of Clinical and Health Psychology in August 2005. She is focusing her research on psychoncology, psychneuroimmunology, and women’s health. She is currently pursuing her Ph.D. in Clinical Psychology.