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Incident depression symptoms are associated with poorer HAART adherence: A longitudinal analysis from the Nutrition for Healthy Living (NFHL) study

D Kacanek, Sc.D[1,1], **DL Jacobson, Ph.D, M.P.H**[2], **D Spiegelman, Sc. D**[2,3], **C Wanke, M.D**[1], **R Isaac, M.B.B.S., M.D., M.P.H**[1,4], and **IB Wilson, M.D**[5]

[1] Department of Public Health and Family Medicine, Tufts University School of Medicine, Boston, MA

[2] Department of Biostatistics, Harvard School of Public Health, Boston, MA

[3] Department of Epidemiology, Harvard School of Public Health

[4] Christian Medical College, Vellore, India

[5] The Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA

Abstract

Objective—To determine the relationship between incident depression symptoms and sub-optimal adherence to HIV antiretroviral therapy (ART).

Methods—Participants in a cohort study of persons with HIV on HAART with at least 4 consecutive semi-annual study visits were included (n=225). Incident depression was defined as having two visits with a negative depression screening test followed by two visits with a positive test. Comparison group participants had four consecutive visits with a negative depression screening test. Sub-optimal adherence was defined as missing >5% of HAART doses in the past 7 days. We compared suboptimal adherence rates in those with and without incident depression symptoms and estimated the relative risk (RR) and 95% confidence intervals (CI) of suboptimal adherence at visit 4 in those adherent at baseline (n=177), controlling for sociodemographic, behavioral and clinical variables.

Results—Twenty-two percent developed depression symptoms. Those developing depression symptoms had higher rates of suboptimal adherence at follow-up (45.1% vs. 25.9%, p<0.01). Among those with optimal baseline adherence, those with incident depression were nearly 2-times more likely to develop suboptimal adherence (Adjusted RR=1.8, 95% CI=1.1, 3.0) at follow-up.

Conclusion—Incident depression symptoms were associated with subsequent suboptimal HAART adherence. Ongoing aggressive screening for, and treatment of, depression may improve HAART outcomes.

Keywords

Antiretroviral therapy; adherence; depression; longitudinal study; HIV; race

[1]Corresponding Author: 49 Burroughs St. #3, Jamaica Plain, MA 02138, Tel: 617-777-0115; Fax: 617-983-9325, Deborah.kacanek@tufts.edu.

[1]The first two items are from the DIS and are most strongly related to the criterion measure, the full DIS.

INTRODUCTION

Optimal adherence to highly active antiretroviral therapy (HAART) is crucial to maximize the clinical benefits of treatment, delay disease progression, and to prevent the emergence and transmission of drug-resistant viruses. Although recent data suggest that boosted protease inhibitors and non-nucleoside reverse-transcriptase inhibitors are more forgiving than nucleoside reverse transcriptase inhibitors and non-boosted protease inhibitors,[1,] 2 adherence at levels of 95% or greater has long been recommended.3 Maintaining long-term adherence to HAART is difficult due to complex regimens, unpleasant side effects and because patients with HIV infection must take HAART consistently for the duration of their lives. Thus it is critical to identify modifiable factors that impede long-term adherence to HAART.

Depression may be just such a factor. Depression is prevalent among persons with HIV infection and has been linked to suboptimal adherence to HAART. In a nationally representative sample of US women and men with HIV infection participating in the HIV Costs and Services Utilization Study (HCSUS), 36% screened positive for major depression, and 26.5% for dysthymia,[4] rates at least four times higher than in the general US population. Prevalence estimates of depression in persons with HIV infection vary depending on sample characteristics (e.g. demographic characteristics as well as the percentage with comorbid substance use), assessment technique and the definition of depression. Depression is also frequently under-diagnosed and untreated in persons with HIV infection,5 as well as in the general population in medical care.6 Some studies have also found that depression is also associated with more rapid disease progression in women and men with HIV infection.[7,] 8

While many cross-sectional studies have linked depression to suboptimal adherence to antiretroviral therapy,[9,10,11,12] others did not find an association.[13,14] Although several cross sectional studies and a few longitudinal studies[15,16,17,18] have found associations between depression and suboptimal adherence, the causal pathways relating depression to poor adherence remain unclear. In particular, few have examined whether *onset* of depression is associated with poorer adherence to HAART. One study found that an increase in average CESD depression symptom scores across a four-month follow-up period was associated with subsequent suboptimal adherence but baseline depression was not associated with later suboptimal adherence.[15] We therefore examined the relationship between the onset of depression symptoms and changes in adherence to HAART in a sociodemographically diverse cohort of persons with HIV in Eastern Massachusetts and Rhode Island.

METHODS

Participants

We used data from the Nutrition for Healthy Living (NFHL) Cohort, a longitudinal observational study investigating the nutritional and clinical status of adult women and men (≥18 years of age) with HIV infection in Boston, Massachusetts and Providence, Rhode Island. Participants were invited to take part in the study through newspaper and radio advertisements, and through physician networks in Boston, MA and Providence, RI. The methods of this study are described in detail elsewhere.[19,]20,21 The study protocol received Institutional Review Board approval at Tufts University and the Miriam Hospital. NFHL enrolled 881 participants from February 1995 through December 2004, who took part in semi-annual study visits. Excluded from the study were those diagnosed with diabetes mellitus, those who were pregnant at time of recruitment, had severe diarrhea, thyroid disease, malignancies other than Kaposi's sarcoma, or were not fluent in English.

Sampling

Because the objective of the current analysis is to determine the relationship of change in depression symptom status to change in adherence to ART, this study included only participants on HAART who provided adherence information at four or more consecutive study visits and met the following additional criteria (n=225): Four consecutive study visits in a less than 2.5 year period, on HAART and providing adherence information at visits 1 or 2 and 3 or 4 in the four-visit interval, and no depression symptoms at either visit 1 or 2. Participants with missing values for both visit 1 and visit 4 adherence were removed from the subsample. In addition, participants with depression symptoms at any visit prior to the four selected consecutive visits were not included in this analysis..

Variables

Depression Symptoms—To assess depression symptoms we used Burnam's interviewer-administered 8-item screening tool[22] which includes six items from the 20-item Center for Epidemiological Studies in Depression scale (CES-D)[23,24,25,26] and two items from the Diagnostic Interview Schedule.[27,28] The Burnam screener is a widely-used measure[29,30,31,32,33,34,35] initially developed for inclusion in the Medical Outcomes Study. It uses weighted scoring to maximize the prediction of DSM-III-defined depressive disorder from the eight items, which are included in Appendix A.36 Although it is a screener which is not sufficient for a clinical diagnosis depression, it has high sensitivity and specificity for current depression (0.89 and 0.95, respectively).22 As recommended in the original paper,22 participants scoring greater than or equal to.06 were classified as testing positive for depression symptoms. We classified participants as "developed depression symptoms" or "no depression symptoms," based on their scores at four consecutive visits which were approximately 6 months apart. We defined participants who developed depression symptoms as having two visits with a negative screening test followed by two visits with a positive test. Participants in the comparison group ("No depression symptoms") were those with four consecutive negative depression screening tests.

Adherence—At each visit, we measured adherence to antiretroviral therapy by first asking participants to identify all of the antiretroviral medications that were currently prescribed to them. For each medication, participants reported the number of days over the last seven days that they had missed a dose of that antiretroviral medication. We then added up across all medications the number of days missed and divided it by the sum of the number of eligible days (7 days for each medication they were prescribed). We calculated suboptimal adherence as the proportion of the 7 days prior to the study visit that the participant missed a dose of any of his or her prescribed medications. Self-reported suboptimal adherence was defined as missing at least 5% of HAART doses in the seven days prior to the study visit. To be eligible for this analysis, participants had to report adherence information at visit 1 or 2 and visit 3 or 4 of the four selected consecutive visits. For participants with missing adherence data on the first of their four sequential visits, visit 2 adherence was substituted as their baseline adherence. When participants had missing adherence data on the fourth visit of their four sequential visits, visit 3 adherence was used.

Covariates—We examined other demographic (gender, age in years, education level, race/ethnicity, poverty), psychosocial (instrumental social support, current illicit drug use), and clinical (HIV transmission category, HIV viral suppression, CD4 cell count, duration of HAART use, and symptoms) covariates that have been associated with adherence in prior studies.7 Poverty was defined as having a household income less than $10,000/year. Instrumental social support was measured using indicators from the HCSUS study which assessed how often people were available to give the respondent money when he or she needed it, and to help with daily chores if he or she was sick.37 We used a 13-item symptom scale

similar to that used in the HCSUS study to measure the extent and severity of HIV-related symptoms.38 Participants were asked to endorse whether they experienced any of a list of HIV-related symptoms (e.g. severe or persistent headaches, white patches in mouth, painful rashes) and then evaluated on a 5 point scale (ranging from "not at all" to "extremely") how much each endorsed symptom interfered with their normal activities. We calculated an aggregate symptom score for each participant (ranging from 0 to 100) from the responses. Viral suppression was defined as an HIV1 RNA count of less than or equal to 400 copies/mL.

Analysis

We conducted all analyses using SAS 9.1 (SAS Institute, Inc., Cary, NC).[39] We compared the characteristics at visit 1 of those who subsequently developed depression versus those who did not develop depression using χ^2 tests for categorical variables, t-tests for normally distributed continuous variables, and the Kruskal-Wallis test for non-normally distributed variables. At visits 1 and 4 separately, we compared the proportion non-adherent in those who developed depression versus the comparison group using the χ^2 test. Among those who were adherent at baseline (n-177), we estimated the relative risk (RR) and 95% confidence intervals (CI) of non-adherence at follow-up of those who developed depression relative to those who did not using generalized estimating equations with a log link and the binomial distribution.[40] Sociodemographic, behavioral, and clinical variables were tested as possible confounders of the relationship between depression and non-adherence. Variables that were associated with suboptimal adherence at $p \leq 0.2$ in univariate models were included in multiple regression analyses.

RESULTS

Participant Characteristics

Of the 225 participants eligible for this analysis, 23% were female, 40% were non-white, and 89% were high school graduates (Table 1). Sixty-three percent had an undetectable viral load (<400) at the end of the four visit interval, and participants had been on HAART for an average of 3.2 years.

Correlates of developing depression symptoms

Among the 225 without depressive symptoms at the first two selected visits, fifty-one (22%) developed depression symptoms at visits three and four (Table 1). Those who developed depressive symptoms, compared to those without depressive symptoms, were more likely to be women (37% vs. 18%, p=0.005), have an annual household income of less than $10,000 (58% vs. 36%, p=0.005), have a baseline CD4 count greater than 500 (46% vs 29% p=0.05), have higher median symptom scores (18.3 vs. 8.8, p=0.0001), and lower median levels of instrumental social support (53.1 vs. 80, p=0.0001).

Rates and correlates of suboptimal adherence

The proportion of participants with suboptimal adherence at baseline (visit 1 or 2) was similar among those that developed depression symptoms and those that did not develop depression symptoms (25.5% and 20.1%, respectively, p=0.41). In contrast, those who developed depression symptoms were more likely than the comparison group to report suboptimal adherence at follow-up (45.1% vs. 25.9%, p=0.01) (Figure 1).

Across the four-visit period, 137 (61%) were adherent at baseline and follow-up (maintained adherence), 20 (9%) had suboptimal adherence at baseline and became adherent at follow-up, 40(18%) were adherent at baseline and had suboptimal adherence at follow-up, and 28 (12%) had suboptimal adherence at both baseline and follow-up. Among the 177 adherent at baseline,

34% of those developing depression symptoms had suboptimal adherence at follow-up, compared to 19% of those without depression symptoms (p=.05).

The correlates of suboptimal adherence at visit four among those who were adherent at visit 1 (n=177) are shown in Table 2. In univariate analysis developing depression symptoms was significantly associated with suboptimal adherence at follow-up (RR=1.7, 95% CI=1.0, 3.1). Other variables that were significantly associated with suboptimal adherence included female sex (RR=2.2, 95% CI=1.3 to 3.7) and African American race (RR=2.0, 95% CI=1.2, 3.5). Poverty was marginally associated with suboptimal adherence. Age, education, viral load, CD4 count, duration of HAART use, symptom score, instrumental social support and current drug use were not associated with suboptimal adherence.

In the multivariate model (Table 2), those developing symptoms of depression at follow-up had a nearly two fold greater risk of suboptimal adherence at follow up (RR=1.8, 95% CI=1.1, 3.0), adjusted for gender, race, and income. African American race was a significant independent determinant of developing suboptimal adherence (RR=1.9, 95% CI=1.2, 3.3).

DISCUSSION

In this longitudinal study of women and men with HIV infection, we found that incident depression symptoms were associated with subsequent suboptimal adherence. We also found a relatively high incidence of depression symptoms. Our finding that 22% of women and men with HIV infection and no previous depression symptoms developed depression symptoms at follow-up is high. It underscores the importance of ongoing screening for and attention to depression among women and men with HIV infection.

This is the first report that we are aware of that examines the effect of incident depression symptoms on adherence in persons with HIV. Spire et al. (2002) found that a change in median CESD scores over a four month period was associated with non-adherence over the same time period, but because they measured changes in CESD scores, it is not possible to know how many people at each time point had major depression. In a study of men in the Multicenter AIDS Cohort Study (MACS) depression at the start of a six month interval was associated with a decline in adherence over the subsequent six months, but it was not true that the absence of depression was associated with improved adherence (Kleeberger, 2004). Carrieri et al. (2003) found that baseline depression was associated with an inability to maintain adherence at 18 months follow-up in a cohort of injection drug users initially adherent to ARV treatment in France. Our study extends the findings of these previous longitudinal studies, by demonstrating that onset of depression symptoms is associated with increasing rates of suboptimal adherence.

A meta-analysis of depression and adherence to medical care regimens in general (not only HIV ARVs) found that patients with depression had a three-fold higher odds of poor adherence and suggested possible mechanisms linking depression to poor adherence to medical treatments.[41] Included in these possible mechanisms were: the feeling of hopelessness which often accompanies depression, social isolation and an absence of social support.15 Any or all of these mechanisms may be operative in individuals with HIV infection. It has been shown that the presence of social support and other psychosocial resources have been associated with increased survival in women with HIV infection42; improved survival may be a result of improved adherence.

African Americans in our study had a higher risk of decline in adherence over time compared with whites. In contrast, Kleeberger et al. (2004) found that African American race was not associated with a decline in adherence among those with perfect adherence, but did predict continued suboptimal adherence among patients who already had poor adherence, while white race predicted later improvements in adherence in those with poor adherence. Some cross-

sectional studies have identified an association between African American race and suboptimal adherence to HAART and others have not.9 Although several studies have highlighted this association, further research is needed to identify the mechanisms by which race and adherence may be related. Studies investigating racial disparities in health care have identified patient-level factors including lack of trust in health care providers and the health care system, and provider-level factors, including unfair treatment, discrimination43 or other aspects of the quality of the doctor-patient relationship, as well as structural factors (e.g., inadequate access to or lower quality of care) which could contribute to racial disparities in adherence. It could also be that unmeasured variables such as skepticism about the efficacy of antiretrovirals, or distrust in the provider or health care system contribute to the findings we observed.

A strength of this study is our stringent criteria for classification of depression based on two visits without depression symptoms followed by two visits with depression symptoms, which makes it more possible to establish a clear temporal relationship between depression symptoms and changes in adherence. There are some study limitations. First, we assessed adherence to HAART through participant self-report, so rates of adherence may be overestimates.[44,45] Second, the conservative cutoff we used for depression symptoms, which required screening positive for depression symptoms at two consecutive visits may have missed some people who may have had diagnosable depression at just one visit. Third, this study did not include all possible profiles of depression symptom transitions over the four study visits. For example, participants who reported depression symptoms at all four visits were not included in this analysis. The effects of chronic depression are likely different from those of incident depression. Fourth, although it is possible that prior poor adherence contributed to onset of depression symptoms which in turn contributed to worse adherence, this is clinically unlikely. Furthermore, visit 1 non-adherence was not associated with subsequent development of depression symptoms. Finally, it was not possible to analyze the contribution of treatment for depressive symptoms to adherence outcomes.

The results from this study highlight that in persons with HIV infection, the relationship of depressive symptoms to HAART adherence is dynamic rather than static. Our finding that depression symptom onset is associated with a change to suboptimal adherence supports the need for further research to evaluate the impact of treatment for depression on adherence to HAART. Depression can be effectively treated with medications in patients with HIV infection.[46] Some studies have found that mental health therapy with and without anti-depressant medication leads to an increase in HAART utilization in women with HIV infection.[47] In addition, some studies have demonstrated the effectiveness of cognitive behavioral therapy in improving adherence.[46, 48, 49] Further research is needed to evaluate the impact of psychosocial and pharmacological treatment interventions for depression on clinical outcomes in patients with HIV and to identify interventions that prevent worsening adherence or improve adherence over time.

The results from this study also underscore the importance of ongoing aggressive screening for depression in order to intervene to improve mental health and HAART adherence in patients with HIV infection. For screening to be cost effective and have an impact, it is critical to strengthen referral systems to ensure appropriate treatment of and follow up for depression for patients with HIV and depression, not only because it may improve adherence as well as HAART outcomes, but because of its potential impact on quality of life overall.

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Appendix A: Burnam Depression Screener Items

1. In the past year, have you had 2 weeks or more during which you felt sad, blue, or depressed; or when you lost all interest or pleasure in things that you usually cared about or enjoyed? (1=Yes/0=No)

2. Have you had 2 years or more in your life when you felt depressed or sad most days, even if you felt okay sometimes? (1=Yes/0=No) If not go to question 3.

2a. Have you felt depressed or sad much of the time in the past year? (1=Yes/0=No)

3. For each statement below, mark one circle that best describes how much of the time you felt or behaved this way during the past week. Response options are:

0: Rarely or None of the time (less than one day)

1:Some or a little of the time (1–2 days)

2:Occasionally or moderate amount of the time (3–4 days)

3: Most or all of the time (5–7 days)

During the past week:

- **a.** I felt depressed
- **b.** I had crying spells
- **c.** I felt sad
- **d.** I enjoyed life [reverse scoring]
- **e.** My sleep was restless
- **f.** I felt that people disliked me

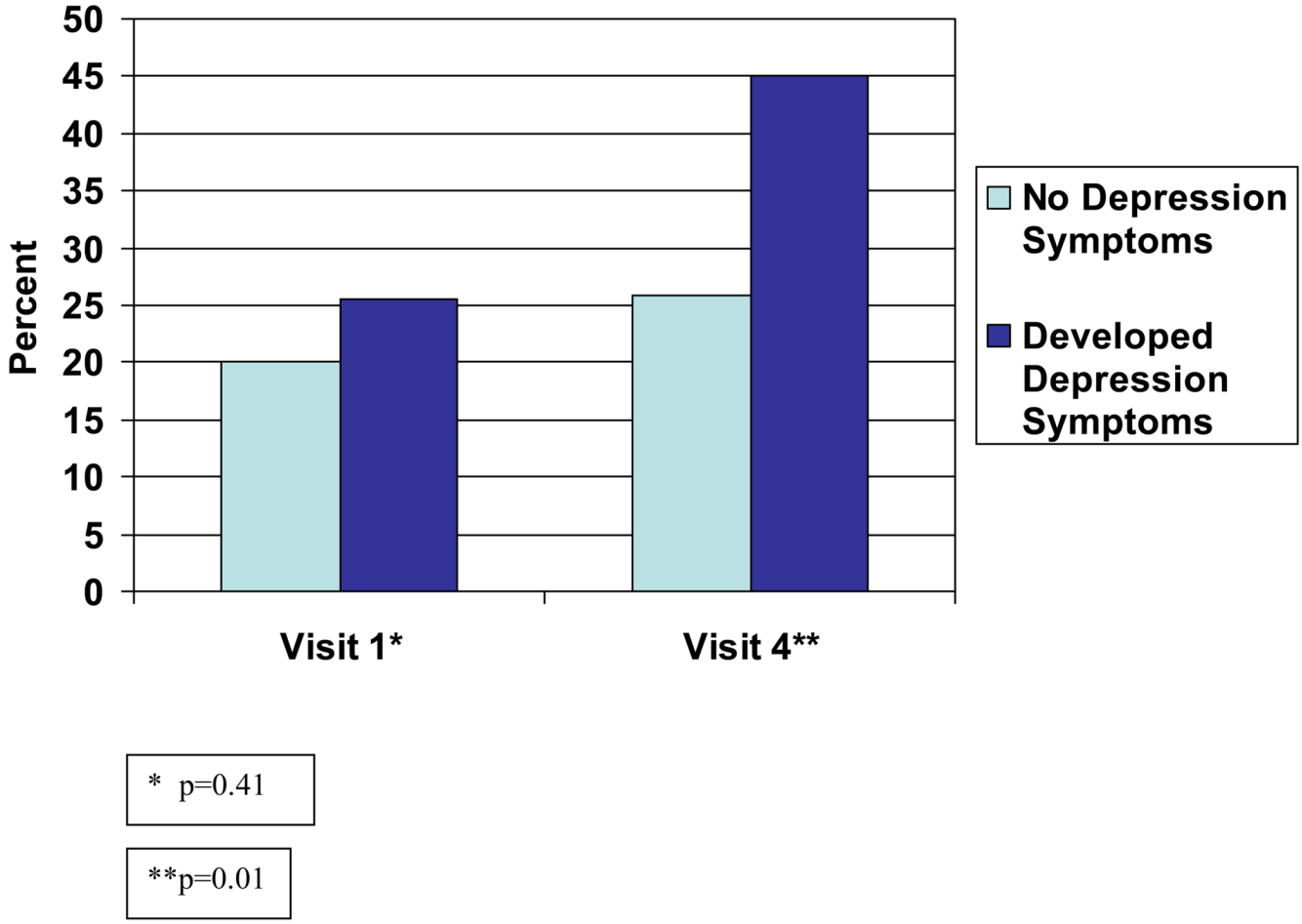

Figure 1.
Proportion with suboptimal adherence at visit 1 and visit 4 by depression symptom status

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Table 1

Baseline Sample Characteristics (n=225)

Characteristic	All (n=225)	Developed Depression Symptoms (n=51)	Did not Develop Depression Symptoms (n=174)	P
Socio-Demographic Characteristics				
Age, in years, mean (SD)	45 (7.4)	42 (7.4)	43 (7.5)	0.33
Female, n(%)	51 (23)	19 (37)	32 (18)	0.005
Race/Ethnicity, n(%)				
African American	64 (28)	15 (29)	49 (28)	
Latino/Hispanic	10 (4)	5 (10)	5 (3)	
White	136 (60)	28 (55)	108 (62)	
Other	15 (7)	3 (6)	12 (7)	0.19
High School Graduate, n(%)	200 (89)	43 (84)	157 (90)	0.08
Annual Income<$10,000, n(%)	89 (41)	29 (58)	60 (36)	0.005
HIV Clinical Characteristics				
HIV Transmission Category, n(%)				
MSM only	121 (55)	18 (37)	103 (60)	
Any IDU	47 (21)	14 (29)	33 (19)	
Heterosexual	47 (21)	15 (31)	32 (19)	
Other	5 (3)	2 (4)	3 (2)	0.06
HIV Viral Load <400 (undetectable) at visit 1(copies/mL) (n=218), n(%)	125 (57)	25 (53)	100 (58)	0.33
HIV Viral Load <400 (undetectable) at visit 4(copies/mL) (n=212), n(%)	133 (63)	29 (60)	104 (63)	0.84
CD4 Cell Count at visit 1, %				
<200	48(21)	11(22)	37 (21)	
200–500	102(46)	16(32)	86 (50)	
>500	73(33)	23(46)	50 (29)	0.05
CD4 Cell Count at visit 4,%				
<200	41(19)	9(18)	32 (19)	
200–500	94(43)	21(43)	73 (43)	
>500	83(48)	19(39)	64(38)	0.99
Duration of HAART use (in months) at visit 4, mean(SD)	38.4 (17.5)	44.1 (21.6)	37 (15.7)	0.06
13 item symptom score first visit, median (IQR)	12.5 (5, 21.3)	15 (10, 29)	11.2 (5.0, 20.0)	0.01
13 item symptom score fourth visit median (IQR)	11.7 (5, 20)	18.3 (12.3, 30.8)	8.8 (3.8,16.9)	0.0001

Characteristic	All (n=225)	Developed Depression Symptoms (n=51)	Did not Develop Depression Symptoms (n=174)	P
Substance Use				
Current drug use (excluding marijuana only users), n(%)	28 (12)	8 (16)	20 (12)	0.73
Psychosocial Characteristics				
Instrumental Social Support, median (IQR)	73.3 (50, 100)	53.3 (26.7, 80)	80 (60, 100)	0.0001
Affective Social Support, median (IQR)	67.5 (55, 80)	67.5 (47.5, 77.5)	67.6 (57.5, 80)	0.2

Table 2

Factors Associated with Non-Adherence to HAART at Visit 4 among participants adherent at Visit 1 (n=177)

Characteristic	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Developed depression symptoms	1.7 (1.0, 3.1)	1.8 (1.1, 3.0)
Age (in years)	0.9 (0.9, 1.0)	--
Gender (Female vs. Male)	2.2 (1.3, 3.7)	1.6 (0.9, 2.9)
Race/ethnicity (Black vs. White, Hispanic, Other)	2.0 (1.2, 3.5)	1.9 (1.2, 3.3)
Education level (High School Graduate vs. no)	2.2 (0.6, 8.2)	--
Income<$10,000 (below poverty line vs. no) at visit 4	1.5 (0.9, 2.6)	1.2 (0.7, 2.0)
Duration of HAART use (in months) at visit 4, mean, (SD)	0.9 (0.9, 1.0)	--
13 item symptom score first visit	1.0 (0.9, 1.0)	--
13 item symptom score fourth visit	0.9 (0.9, 1.0)	--
Current Drug use (excluding marijuana only users)	1.3 (0.6, 2.7)	--
Instrumental Social Support	0.9 (0.9,1.0)	--