HHS Public Access

Author manuscript

Gen Hosp Psychiatry. Author manuscript; available in PMC 2016 July 01.

Published in final edited form as:

Gen Hosp Psychiatry. 2015 ; 37(4): 277–282. doi:10.1016/j.genhosppsych.2015.03.021.

Psychiatric Comorbidity in Depressed HIV-infected Individuals: Common and Clinically Consequential

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Abstract

Objective—To report on the prevalence of psychiatric comorbidity and its association with illness severity in depressed HIV patients.

Methods—As part of a multi-site randomized controlled trial of depression treatment for HIV patients, 304 participants meeting criteria for current Major Depressive Disorder (MDD) were assessed for other mood, anxiety and substance use disorders with the Mini-International Neuropsychiatric Interview, a structured psychiatric diagnostic interview. We also assessed baseline adherence, risk, and health measures.

Results—Complicated depressive illness was common. Only 18% of participants experienced MDD with no comorbid psychiatric diagnoses; 49% had comorbid dysthymia, 62% had ≥1 comorbid anxiety disorder, and 28% had a comorbid substance use disorder. Self-reported antiretroviral adherence did not differ by the presence of psychiatric comorbidity. However, psychiatric comorbidity was associated with worse physical health and functioning: compared to those with MDD alone, individuals with ≥1 comorbidity reported more HIV symptoms (5.1 vs. 4.1, p-value=0.01), and worse mental health-related quality of life on the SF-12 (29 vs. 35, p<0.01).

Conclusion—For HIV patients with MDD, chronic depression and psychiatric comorbidity are strikingly common, and this complexity is associated with greater HIV disease severity and worse quality of life. Appreciating this comorbidity can help clinicians better target those at risk of harder-to-treat HIV disease, and underscores the challenge of treating depression in this population.

Keywords

depression; psychiatric comorbidity; quality of life

1.1 INTRODUCTION

Twenty to thirty percent of HIV-infected patients have depression or depressive symptoms, and these states have been associated with decreased access to antiretroviral therapy (ART) [1-4], decreased likelihood of initiation of and retention in HIV care,[5, 6] poor antiretroviral adherence,[7] worse psychiatric outcomes,[8] and worse medical outcomes, including lower likelihood of virologic suppression, faster HIV disease progression, and higher mortality rates.[9, 10] HIV care providers and researchers have argued that increased access to effective depression treatment would lead to substantial improvements in HIV clinical outcomes for affected individuals,[8, 11] although current evidence is somewhat mixed on this point.[12-18]

A key consideration in determining whether improved depression care can lead to improved HIV outcomes in HIV-infected individuals with Major Depressive Disorder (MDD) is how

comorbid psychiatric illness might confound this relationship. Indeed, few studies have thoroughly considered the role of psychiatric comorbidity, i.e., the co-occurrence of other psychiatric disorders with depression, in explaining the observed association between depressive symptoms and adverse HIV outcomes. For psychiatric illness in general, and MDD in particular, having more than one concurrent psychiatric diagnosis is common.[19] This psychiatric comorbidity is strongly related to both greater psychiatric severity [20] and worse psychiatric outcomes (including greater fatigue and functional impairment[21] and higher rates of suicide attempts[22]). In addition, psychiatric comorbidity is associated with greater medical symptomatology[23] and worse medical outcomes.[24] Finally, MDD that is comorbid with dysthymic, anxiety, or substance use disorders is likely to be more difficult to treat, which might complicate efforts to reduce depressive severity and improve HIV outcomes through depression treatment interventions.

However, documentation of psychiatric comorbidity in HIV patients receiving treatment in limited. Indeed, while studies have reported on the heavy burden of psychiatric illness in HIV-infected populations,[25, 26] no prior study has specified psychiatric comorbidity in a sample of HIV-infected patients with a confirmed diagnosis of MDD, nor whether this comorbidity is associated with greater illness severity. In this paper, our team assesses the prevalence and correlates of psychiatric comorbidity among a population of HIV-infected patients with confirmed MDD who enrolled in a depression treatment study. We examine the extent to which depression treatment interventions for HIV-infected individuals needs to consider psychiatric comorbidity for maximal reach and effectiveness. Accordingly, our goals for this paper are 1) to describe the prevalence of comorbid psychiatric disorders in persons with MDD enrolling in a depression treatment study in a representative sample of HIV outpatients, and 2) to identify sociodemographic and clinical/behavioral features associated with the number and type of concurrent psychiatric conditions.

1.2 MATERIALS AND METHODS

1.2.1 Study Design/setting

SLAM DUNC was a randomized controlled effectiveness trial implemented at the infectious diseases clinics at 3 academic medical centers: Duke University (lead site; Clinic 2J), the University of North Carolina at Chapel Hill (UNC Infectious Diseases Clinic), and the University of Alabama at Birmingham (1917 Clinic).[27] It was designed to test whether evidence-based decision support for antidepressant management, when integrated into HIV care, would improve HIV medication adherence and clinical outcomes (ClinicalTrials.gov registry # NCT01372605). Eligible and consenting participants were randomized to one of two conditions: Measurement-Based Care (MBC, hereafter referred to as “intervention”) or enhanced treatment as usual (hereafter referred to as “usual care”). No advertisements for clinical trial participants were conducted; all potential participants were already patients in the respective clinics.

1.2.2 Study population

Patients seeking care at participating sites were eligible if they were HIV-infected, ages 18-65 years old, English-speaking, prescribed or about to start any FDA-approved

antiretroviral medication, scored 10 or higher on the Patient Health Questionnaire-9 depression screener [28], and subsequently had a current major depressive disorder diagnosis confirmed by the Mini International Neuropsychiatric Interview (MINI), a commonly used short structured diagnostic interview with excellent reliability and good-to-very good convergent validity relative to other gold standards for a variety diagnoses.[29-31] Patients were excluded if they had a history or a current diagnosis of either a bipolar spectrum disorder (n=34) or a psychotic disorder or psychotic symptoms (n=19) as diagnosed by the MINI; were currently suicidal or had a substance use disorder requiring immediate inpatient treatment (n=1); or failed to respond to adequate trials of ≥2 different antidepressants during the current depressive episode (n=2). Written informed consent was obtained from each participant and all study activities were approved by the Institutional Review Boards at Duke University, the University of North Carolina at Chapel Hill, and the University of Alabama at Birmingham.

1.2.3 Assessment of Psychiatric Comorbidity

All diagnoses were based on DSM-IV-TR criteria.[32] At the time of enrollment, patients were evaluated for dysthymia (a chronic, low grade depressive illness now referred to as persistent depressive disorder in the DSM-V[33]), panic disorder, generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), alcohol dependence/abuse, and substance dependence/abuse, using the relevant subsections of the MINI.

1.2.4 Associated baseline variables of interest

We collected standard sociodemographic measures as well as clinical and behavioral measures thought to be relevant to psychiatric comorbidities. Specifically, we assessed adherence, using a baseline self-report along a visual analog scale from 0-100% of how much of the time the participant took all of the prescribed HIV/AIDS medicines over the prior month;[34] a self-report of 12 potential HIV-related symptoms over the prior 6 months (headaches; fever, sweats or chills; pain in the mouth; white patches in the mouth; painful rashes or sores; nausea or loss of appetite; eye trouble; sinus infection; numbness in hands or feet; persistent cough; diarrhea);[35] a self-report measure of sexual behaviors, including unprotected sex, over the prior 3 months; a measure of health-related quality of life using the Short Form 12 (SF-12),[36] which has a general population mean of 50 for physical and mental health subscores and for which higher scores indicate better quality of life; suicidality over the past week, as indicated on the Hamilton Rating Scale for Depression-17 item version (HRSD)[37]; detectable viral load (HIV RNA VL >48 copies/mL); and self-report of hospitalization and emergency department use over the prior 3 months.

1.2.5 Data Analysis

Data are presented as means (standard deviations) or percentages. Chi-square tests, t-tests, and ANOVA were used to compare categorical and continuous characteristics and outcomes (a) between those with no vs. one or more comorbidities, and (b) between those with depressive disorders only (depression with or without dysthymia) vs. those with comorbid anxiety disorders (but no substance use) or vs. those with comorbid substance use disorders (with or without anxiety disorders). We used multiple linear and logistic regression to estimate the independent associations of dysthymic, anxiety, and substance use disorders

with a range of behavioral and health outcomes, with all models adjusted for covariates determined to be important *a priori* (age, gender, and employment status). A p-value of <0.05 was considered statistically significant; a p-value between 0.05 and 0.10 was considered a trend. No adjustments of P-values for multiple comparisons were performed given the exploratory nature of this report.

1.3 RESULTS

1.3.1 Sample description

The SLAM-DUNC study enrolled 304 participants (Table 1). The mean age of those participating was 44 years, and 71% were male. The sample averaged 13 years of completed education. Sixty-two percent of those enrolled were black, 51% were single or never married, and 73% were unemployed. On average, participants had been diagnosed with HIV for 11 years.

Self-reported adherence to ART was high, with a mean self-reported adherence of 87%. The mean number of reported HIV symptoms was 5.1. Both mental functioning (mean SF-12 Mental Health Composite Score = 30) and physical functioning (mean SF-12 Physical Composite Score = 44) suggested below average health-related quality of life. Thirty-three percent of participants had a detectable viral load (>48 copies/mL), and 18% reported having had unprotected sex in the past 3 months.

1.3.2 Prevalence of comorbid disorders

All participants had complete comorbidity information. Complicated depressive illness was common. Most MDD (59%) was recurrent (Table 1). Only 18% (4% single episode, 14% recurrent) were experiencing MDD with no comorbid psychiatric diagnoses (Figure 1). Chronic depression was common, with 49% of MDD patients having a concurrent dysthymic disorder (Table 2). Comorbid anxiety disorder was present in 62%, most commonly GAD (48%), followed by PTSD (22%) and Panic Disorder (14%). A comorbid substance use disorder existed in 28%, with the prevalence of dependence on alcohol or drugs (15-16%) being more common than abuse (3-5%). Of all participants, 30% had one comorbid diagnosis besides MDD, 28% had 2 concurrent diagnoses, and 25% had 3 or more comorbidities.

1.3.4 Clinical and sociodemographic features associated with various degrees of comorbidity

There was little difference in baseline sociodemographic variables between those with no comorbidities and those with 1 or more (Table 3). The comorbid group did not differ from the MDD alone group by age, sex, race, income level, time since diagnosis, or education. However those with any comorbidity were significantly more likely to be unemployed (76% vs. 59%, p=0.01). Compared to those with only depression and/or dysthymia, the likelihood of unemployment was higher among those with anxiety disorders (79% vs. 62%, p=0.01) and showed a trend toward being higher among those with substance use disorders (75% vs. 62%, p=0.08).

Comorbidity, in general, was associated with greater disease severity. Of note, this association was not observed in self-reported adherence or HIV viral load suppression at baseline, which did not vary between groups (Table 3). However, psychiatric comorbidity was associated with greater HIV symptom severity. Compared to those with MDD alone, the comorbid group reported more mean HIV symptoms (5.1 vs. 4.1, p=0.01) and tended to report worse physical functioning on the SF-12 (43 vs. 47, p=0.08). Also, the comorbid group reported lower overall mental health functioning (p<0.01). Compared to those with depressive or dysthymic disorders alone, mental health functioning was lower among those with anxiety disorders (mean=28 vs. 33, p<0.01) but was not statistically significantly different among those with substance use disorders (31 vs. 33, p=0.14).

Finally, we used multivariable regression models to assess whether there were independent associations between the specific types of psychiatric comorbidity and HIV behavioral and health outcomes (Table 4). Having a comorbid dysthymic disorder was significantly associated with worse mental functioning and nearly twice the likelihood of suicidality within the past week. Further, there was a trend towards a greater likelihood of an emergency department visit for this population (p<0.10). Having a comorbid anxiety disorder was significantly associated with a greater number of reported HIV symptoms and worse mental health functioning, but no clear association with increased suicidality or increased emergency department use. There was a trend towards worse physical functioning (p<0.10) for those with a comorbid anxiety disorder.

Substance use comorbid with depression was associated with a trend towards greater odds of having a detectable viral load and greater odds of unprotected sex in the previous 3 months (p<0.10)

1.4 DISCUSSION

In the only study to date that provides a diagnostic assessment of psychiatric comorbidity in a sample of HIV patients with MDD receiving ART, we found that having a comorbid psychiatric illness is the norm. Nearly half of study participants had a comorbid dysthymic disorder, a chronic depressive illness distinct from MDD that is an independent risk factor for treatment-resistant depression.[38] Even when one excludes dysthymia, three quarters of depressed patients had a comorbid anxiety and/or substance use disorder. Thus, in this patient population of HIV-infected individuals selected as reasonable candidates for a depression treatment study, the prevalence of comorbid psychiatric disorders likely to complicate the depression treatment course was high.

Prior assessments of psychiatric comorbidity have been limited and primarily based on either retrospective chart reviews of diagnoses.[39] or by positive psychiatric screens (rather than diagnostic assessments),[40] which can overstate prevalence rates by as much as 16% in this population. [41, 42] One exception carefully assessed multiple psychiatric diagnoses using the Structured Clinical Interview for DSM-IV on a convenience sample of 66 patients who had screened positive for depression, but this study did not characterize psychiatric comorbidity in those specifically with MDD.[43] Further, their sample differed by including depressed patients with psychotic symptoms or bipolar spectrum illness, which our selection

criteria excluded, and by assessing for dysthymia. Their findings showed MDD-only diagnosis in 4% of the screen positive sample, and they reported the same proportion (62%) had anxiety comorbid with MDD. However, twice as many in their sample were diagnosed with comorbid anxiety, depressive, and substance use disorders (30% vs. 14% prevalence). Further, specific types of comorbidity differed. We identified 22% with comorbid PTSD, compared to 10% in their population of those with screen-positive depression. These differences are likely related to the dissimilar populations sampled, but underscore the complexity of comorbid psychiatric presentations in HIV clinical settings.

In our study, psychiatric comorbidity was associated with greater HIV disease severity and worse quality of life, reflected in greater HIV symptomatology and worse physical and mental health functioning. For example, those with comorbid dysthymia were nearly twice as likely to have suicidal thoughts in the past week, suggesting a greater need for more frequent and closer monitoring of psychological status. Having a comorbid substance use disorder was associated with nearly twice the likelihood of having a detectable viral load while on ART, suggesting a greater need for more frequent and closer monitoring of a patient's HIV treatment response. Having both comorbidities (12% of our sample) might suggest the need to monitor both psychiatric and HIV clinical status more closely. In any case, the frequency and associated effects of these comorbidities suggest the need for more comprehensive treatment plans for patients presenting to the HIV clinic with MDD.

Our study has limitations. It is cross-sectional and so can only assess associations, not causal relationships. However, these results underscore the complexity of HIV-infected patients presenting with depression and identify psychiatric comorbidity as a potential key confounder of the association between depression and adverse HIV outcomes. Also, our findings apply only to those with MDD, and are not applicable to patients with psychotic or bipolar disorders. Such a focus, however, is likely more representative of patients whose mental health might be managed in an outpatient HIV clinic, as those with psychotic or bipolar spectrum presentations more often would be referred to a mental health professional. Finally, our study is exploratory in nature and a first step towards better understanding this comorbidity; larger studies are necessary to confirm these findings.

For HIV patients with major depression, psychiatric comorbidity and chronic depression are strikingly common rather than the exception, and this complexity is associated with greater HIV disease severity and worse prevention and treatment indicators. An appreciation of this comorbidity can help clinicians better target those at risk of harder-to-treat HIV disease, and it underscores the challenge of treating depression in this population.

Acknowledgements

This study was supported by grant R01MH086362 of the National Institute of Mental Health and the National Institute for Nursing Research, National Institutes of Health, Bethesda, MD, USA. Support was also provided by the Centers for AIDS Research at the University of North Carolina at Chapel Hill, Duke University, and the University of Alabama at Birmingham NIH-funded programs (P30- AI50410; P30-AI064518; and P30-AI027767). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIMH or the NIH.

ABBREVIATIONS

MDD	Major Depressive Disorder
SLAM DUNC Study	Strategies to Link Antidepressant and Antiretroviral Management at Duke University, University of Alabama-Birmingham, Northern Outreach Clinic, and University of North Carolina-Chapel Hill Study
MINI	Mini International Neuropsychiatric Interview
GAD	Generalized Anxiety Disorder
HRSD	Hamilton Rating Scale for Depression
ANOVA	Analysis of Variance
SF-12	Short Form 12
PTSD	Post-Traumatic Stress Disorder

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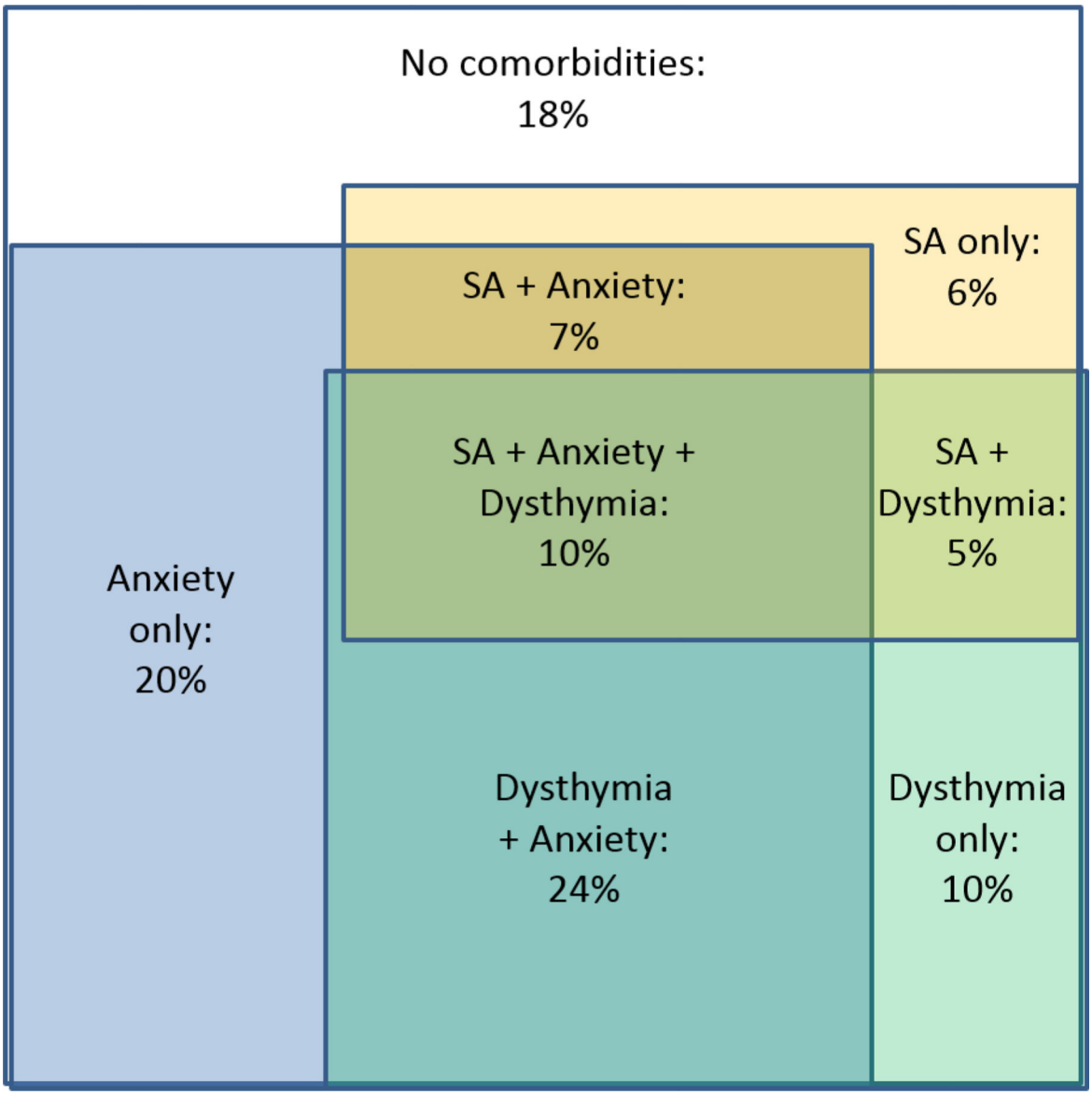

Figure 1.
Psychiatric comorbidities among HIV-infected people with major depression.

Table 1

Description of sample (n=304).

Characteristic	Mean (SD) or n (%)
Sociodemoaraphic Measures	-
Age, years	44(10)
Sex	
Male	215 (71%)
Female	89 (29%)
Race	
White non-Hispanic	93 (31%)
Black non-Hispanic	188 (62%)
Hispanic	9 (3%)
Other	14 (5%)
Income (monthly), $	$1,534 (2,887)
Marital Status	
Married/co-habitating	68 (23%)
Separated, divorced, widowed	78 (26%)
Single/never married	155 (51%)
Employment Status	
Employed	81 (27%)
Unemployed	219 (73%)
Time since diagnosis (years)	11 (8)
Education (years completed)	13 (3)
Past depressive episodes	
None	124 (41%)
≥1	180 (59%)
Behavioral and Health Measures	-
Self-reported adherence, past month	87 (23)
Number HIV symptoms, past 6 months	5.1 (3.0)
SF-12 mental functioning	30 (10)
SF-12 physical functioning	44 (12)
HIV RNA VL >48 copies/mL	101 (33%)
Any unprotected sex, past 3 months	56 (18%)
Any unprotected sex with HIV- or status-unknown partner	25 (8%)
Any suicidality, past week	91 (30%)
Any hospitalization, past 3 months	20 (7%)
Any emergency department visit, past 3 months	74 (25%)

Table 2

Prevalence of psychiatric comorbidities at baseline among SLAM DUNC study participants.

Diagnosis	n	%
Dysthymia	148	49%
Any anxiety disorder	187	62%
Panic disorder, current	43	14%
PTSD, current	65	22%
GAD	144	48%
Any substance use disorder	85	28%
Alcohol abuse (no dependence)	14	5%
Alcohol dependence	44	15%
Drug abuse (no dependence)	8	3%
Drug dependence	47	16%
Number of comorbid diagnoses*		
0	54	18%
1	90	30%
2	85	28%
3 or more	75	25%

* In addition to MDD

Table 3

Demographic, behavioral, and health correlates of comorbidity

	Number of comorbidities			Type of comorbidity*				
	None	1 or more	P Value	None or dysthymia	Anxiety but no SA	P value*	Substance use	P Value***
n	54 (18%)	250 (82%)		83 (27%)	136 (45%)		85 (28%)	
Age, years	44 (11)	44 (10)	0.84	44 (11)	45 (9)	0.44	43 (11)	0.55
Sex								
Male	35 (65%)	180 (72%)	0.29	59 (71%)	87 (64%)	0.28	69 (81%)	0.13
Female	19 (35%)	70 (28%)		24 (29%)	49 (36%)		16 (19%)	
Race								
White non-Hispanic	12 (22%)	80 (32%)	0.24	21 (25%)	48 (35%)	0.05	24 (28%)	0.65
Black non-Hispanic	38 (70%)	150 (60%)		55 (66%)	81 (60%)		52 (61%)	
Hispanic	1 (2%)	12 (5%)		2 (2%)	6 (4%)		5 (6%)	
Other	3 (6%)	7 (3%)		5 (6%)	1 (1%)		4 (5%)	
Income, log (10)	2.7 (1.1)	2.7 (1.0)	0.98	2.7 (1.1)	2.7 (1.0)	0.97	2.7 (1.0)	0.89
Marital Status								
Married/co-habitating	10 (19%)	58 (23%)	0.73	16 (19%)	37 (27%)	0.28	15 (18%)	0.95
Separated, divorced, widowed	15 (28%)	63 (26%)		21 (25%)	37 (27%)		20 (24%)	
Single/never married	29 (54%)	126 (51%)		46 (55%)	61 (45%)		48 (58%)	
Employment Status								
Employed	21 (41%)	59 (24%)	0.01	31 (38%)	29 (21%)	0.01	21 (25%)	0.08
Unemployed	32 (59%)	187 (76%)		51 (62%)	106 (79%)		62 (75%)	
Time since diagnosis (years)	12 (10)	11 (8)	0.50	11 (9)	12 (8)	0.78	10 (8)	0.56
Education (years completed)	14 (4)	13 (2)	0.48	13 (4)	13 (2)	0.83	13 (3)	0.42
Self-reported adherence, past month	86% (24%)	87% (22%)	0.83	84% (27%)	88% (21%)	0.24	86% (19%)	0.76
Number of HIV symptoms, past 6 months	4.1 (3.0)	5.1 (2.9)	0.01	4.2 (3.0)	5.4 (2.9)	0.01	5.6 (2.8)	0.00
SF-12 MCS Score	35 (13)	29 (9)	0.00	33 (12)	28 (8)	0.00	31 (9)	0.14
SF-12 PCS Score	47 (13)	43 (12)	0.08	46 (13)	42 (11)	0.01	46 (12)	0.97
Self-reported adherence >=80%, past month	41 (84%)	185 (81%)	0.68	64 (82%)	104 (85%)	0.64	48 (76%)	0.38
HIV RNA VL >48 copies/mL	16 (31%)	74 (33%)	0.85	23 (31%)	35 (28%)	0.69	32 (42%)	0.16
Any unprotected sex, past 3 months	10 (20%)	46 (21%)	0.94	15 (19%)	21 (17%)	0.65	20 (29%)	0.16
Any unprotected sex with HIV-or status-unknown partner	5 (10%)	20 (9%)	0.81	7 (9%)	11 (9%)	0.96	7 (10%)	0.81
Any suicidality, past week	12 (24%)	79 (36%)	0.10	22 (28%)	46 (38%)	0.17	23 (34%)	0.46
Any hospitalization, past 3 months	3 (6%)	17 (7%)	0.72	3 (4%)	10 (7%)	0.25	7 (9%)	0.19
Any emergency department visit, past 3 months	13 (24%)	61 (25%)	0.91	23 (28%)	35 (26%)	0.77	16 (20%)	0.22

All statistics presented as mean (SD) or n (%).

Substance use: Alcohol or substance abuse or dependence, with/without anxiety disorders.

*P value comparing None or dysthymia to Anxiety but no SA

***P value comparing None or dysthymia to Substance use

Table 4

Independent associations of dysthymia, anxiety, and substance use comorbidity with HIV behavioral and health outcomes

	Dysthymia	Anxiety	Substance use
Mean difference (95% CI)			
Number of HIV symptoms, past 6 months	0.54 (−0.14, 1.23)	0.73 (0.02, 1.44)^	0.61 (−0.15, 1.38)
SF-12 mental functioning	−2.77 (−5.01, −0.52)^	−3.89 (−6.18, −1.59)^	0.51 (−1.97, 2.99)
SF-12 physical functioning	−2.57 (−5.31, 0.17)	−1.78 (−4.59, 1.03)	2.45 (−0.57, 5.48)
Self-reported adherence, past month	0.81 (−4.69, 6.31)	4.49 (−1.12, 10.09)	−1.28 (−7.37, 4.82)
Odds ratio (95% CI)			
HIV RNA VL >48 copies/mL	1.16 (0.69, 1.95)	0.90 (0.52, 1.53)	1.65 (0.95, 2.86)
Any unprotected sex, past 3 months	1.39 (0.76, 2.54)	0.79 (0.43, 1.54)	1.87 (0.98, 3.54)
Any unprotected sex with HIV- or status-unknown partner	0.68 (0.29, 1.58)	1.00 (0.43, 2.33)	1.23 (0.49, 3.12)
Any suicidality, past week	1.98 (1.17, 3.35)^	1.22 (0.71, 2.09)	0.89 (0.49, 1.62)
Any hospitalization, past 3 months	1.39 (0.54, 3.57)	2.56 (0.82, 7.97)	1.48 (0.56, 3.90)
Any emergency department visit, past 3 months	1.63 (0.95, 2.80)	0.82 (0.47, 1.42)	0.64 (0.34, 1.20)

* From ordinary least squares or logistic regression models, adjusted for age, gender, and employment status.

^ $p < 0.05$