2012

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AIDS PATIENT CARE and STDs
Volume 26, Number 12, 2012

DOI: 10.1089/apc.2012.0132

Sadness in the SUN: Using Computerized Screening to Analyze Correlates of Depression and Adherence in HIV-Infected Adults in the United States

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Abstract

We used a standardized screening tool to examine frequency of depression and its relation to antiretroviral medication adherence among HIV-infected persons on highly active antiretroviral therapy (HAART) in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN Study). This is a prospective observational cohort of 700 HIV-infected patients enrolled between March 2004 and June 2006 in four U.S. cities, who completed a confidential audio computer-assisted self-interview [ACASI] with behavioral risk and health-related questions at baseline and 6-month follow-up visits, including the nine-question PRIME-MD depression screener and a validated 3-day antiretroviral adherence question. Among 539 eligible participants receiving HAART, 14% had depression at baseline (22% women, 12% men). In multivariable analysis using generalized estimating equations (GEE) to account for repeated measurements through 24 months of follow-up, persons who reported depression on a given ACASI were twice as likely to report nonadherence to antiretrovirals on the same ACASI (Odds ratio [OR] 2.02, 95% CI: 1.15, 3.57] for mild/moderate depression versus none); such persons were also less likely to have HIV viral load < 400 copies/mL. Self-administered computerized standardized screening tools can identify at-risk individuals with depression who may benefit from interventions to improve antiretroviral adherence.

Introduction

Depression occurs frequently in HIV-infected persons. Reported rates of depression and depressive symptoms range from 22 to 54 percent in HIV-infected communities in the United States and typically exceed the prevalence found in the general population.[1–6]

The frequency of depression does not appear to vary according to the use of highly active antiretroviral therapy (HAART). In both the pre and post HAART era, depression as well as other disorders of anxiety and dysthymia are common.[6–8]

Despite the high prevalence of depression and depressive symptoms among HIV-infected persons, these conditions remain under-diagnosed.[9,10] For these individuals, the consequences of unrecognized and untreated depression can be significant and include increased mortality, diminished quality of life, and impaired adherence to antiretroviral therapy.[11–18] A recent meta-analysis documented an association between depression and nonadherence to antiretroviral therapy across different study populations, including some that represented diverse and contemporary HIV cohorts with a significant representation of women and persons of color.[19] As the current U.S. HIV epidemic disproportionately impacts communities of color, the relationship of gender and ethnicity to depression is important to document and understand.[20–26]

Depression and depressive symptoms do seem to occur more frequently in HIV-infected women compared to men.[3,15,16] Women living with HIV infection often have many

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sociodemographic and lifestyle characteristics associated with depression, such as poverty, isolation, higher rates of smoking, traumatic life events, and substance abuse.[2,27–30] Several reports indicate that cellular immune responses in women may be altered with depression.[29] Fortunately, treatment of depression pharmacologically or through other behavioral interventions can be beneficial with demonstrated improved clinical outcomes and HAART adherence;[12,31–36] however, differential use of antidepressants has been documented.[37–39]

The relationship of depression and its treatment and HAART adherence is a dynamic one and longitudinal evaluations of HIV-infected persons in the evolving chronic disease model of care are needed. Assessing depression in HIV-infected persons can be done through structured interviews or standardized screening instruments that may be self-administered or done electronically.[19,40–45] The PRIME-MD Patient Health Questionnaire-9 (PHQ-9) is a widely used instrument for depression screening that has been incorporated into primary care settings to identify the presence and severity of depression.[43,45,46] The ease of its administration enables the PHQ-9 to be used in long-term patient cohorts.

Using longitudinal data from the prospective SUN Study, a cohort of contemporary HIV-infected U.S. adults, we sought to examine the frequency and associated demographic, clinical, laboratory, and behavioral correlates of depression among participants prescribed HAART and followed for 24 months, and to evaluate the association between depression and adherence to HAART during the same period.

Methods

The SUN Study

The SUN Study is an ongoing, closed, prospective cohort study of 700 HIV-infected patients receiving care at HIV-specialty clinics in Denver, Colorado; Minneapolis, Minnesota; Providence, Rhode Island; and St. Louis, Missouri. Participants were enrolled between March 2004 and June 2006, and were followed for up to 24 months thereafter. Detailed methods and inclusion criteria have been described elsewhere.[47] The study protocol was approved and has been reviewed annually by the institutional review boards of the Centers for Disease Control (CDC) and all participating institutions. All participants provided written, informed consent.

Study population

We restricted all analyses to HAART-treated participants to examine risk factors for depression and the association between depression and antiretroviral medication (ARV) adherence within the same subset of participants followed from baseline up to 24-month study visit. Of 700 SUN Study participants, 539 were prescribed HAART and completed the baseline Audio Computer-Assisted Self Interview (ACASI) survey. The remaining patients were not included in this study because they did not complete a baseline ACASI survey data ($n = 23$) or were currently not prescribed HAART or were ARV-naïve ($n = 138$).

Measures

SUN Study participants completed an ACASI at enrollment (baseline) and every 6 months thereafter; not all participants completed ACASI at all timepoints. Information collected by ACASI included sociodemographic factors, education, employment status, tobacco, alcohol and drug use, sexual risk behaviors, depressive symptoms, suicidal ideation, quality of life, and adherence to antiretroviral medications. The ACASI questionnaire could be taken in English or Spanish. To ensure participant confidentiality and encourage self-disclosure of accurate information, participants listened to questions alone while logged onto a dedicated computer terminal in a private area. All data collected from the ACASI were held confidentially and not shared with the participants' healthcare providers. For this analysis, we examined ACASI data from baseline through the 24-month study visit, as available. In addition, we abstracted CD4 T-lymphocyte cell counts (CD4), plasma HIV-1 RNA viral loads (HIV VL), diagnoses of depression and hepatitis C infection, and prescriptions given for antiretroviral and antidepressant medication from participants' medical records.

Definitions of the outcome variables

Depression by PRIME-MD. Depression was assessed using the Patient Health Questionnaire (PHQ-9), also known as PRIME-MD, which is a series of nine questions regarding the frequency of depressive symptoms over the last 2 weeks that has been validated for diagnosis of depression (Table 1).[43,45,46] Each question has four possible responses: "not at all," "several days," "more than half the days," and "nearly every day." Each response was scored from 0 to 3,

Table 1. PRIME-MD Instrument for Depression Screening

Depression Screening Questions

Over the past 2 weeks, how often have you been bothered by any of the following problems....?

1. Little interest or pleasure in doing things
2. Feeling down, depressed or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. *Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people could have noticed? Or the opposite-being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead or hurting yourself in some way.

*This question was omitted from the ACASI, in error, through the end of 2006. For analyses at these time points, we instead used a question in the ACASI asked in the following way: "How often in the last 4 weeks have you had a lot of energy?" and coded that variable in reverse fashion in the following manner:

0 All the time (tired = 0)
1 Most of the time (tired = 0)
2 A good bit of the time (tired = 0)
3 Some of the time (tired = 1)
4 A little of the time (tired = 2)
5 None of the time (tired = 3)

Sensitivity analyses at 24 months for participants who had both original question #4 and substitute question, revealed that the distribution of total depression scores was similar, and 96.5% (274/284) of participants had concordant level of depression severity (none, mild, moderately severe, severe).

respectively. The total score could range from 0 to 27. Depression severity was defined as none/minimal (total score 0–4), mild (total score 5–9), moderate (total score 10–14), moderately severe (total score 15–19), and severe (total score 20–27), as previously reported.[43,45,46] We defined major depression as (1) a score of 2 or 3 on four of the nine items, including on each of the screener's first two items; or (2) a score of 2 or 3 on five of the nine items, including on at least one of the screener's first two items. Based on each patient's score at baseline or at any one of the subsequent 6-monthly ACASI evaluations, the patient was assigned a binary depression outcome (yes or no) for his or her depression status at that point in time; thus depression status could vary over time (e.g., new onset, resolution, or intermittent depression).

Adherence to antiretroviral medication. Adherence to antiretroviral medication was assessed from self-report on the ACASI. Nonadherence was defined as having missed one or more doses of prescribed antiretroviral medications in the past 3 days.

Definitions of predictor variables and other covariates

Participants' age, hepatitis C co-infection status (defined by either serostatus or presence of the clinical diagnosis in the medical records if serostatus was absent), marital status, and type of health insurance were determined at the baseline SUN Study visit. Employment status, drinking 3 or more alcoholic drinks per day in the past 30 days, current tobacco use ('Do you currently smoke cigarettes?'), nonprescription drug use in the past 6 months (an aggregate variable for use of cocaine, heroin, injected drugs, methamphetamines, poppers, marijuana, erectile dysfunction agents, or a club or party drugs [e.g., gamma hydroxybutarate, ketamine]), family history of depression were updated every 6 months based on interval ACASI responses. Receipt of antidepressants, CD4 count, and HIV VL were updated every 6 months based on data abstracted from the medical records. Two clinicians reviewed the medical records to confirm that antidepressant medications were prescribed for depression and not other uses (e.g., neuropathy, smoking cessation). HAART was defined as a regimen comprised of ≥ 3 nucleoside reverse transcriptase inhibitors or ≥ 3 antiretroviral drugs from at least 2 different classes, as per SUN Study inclusion criteria.[47]

For repeated measures analyses (see *Statistical Analyses* section, below), the closest value for each 6-month predictor variable was taken from the same 6-month ACASI evaluation as the binary outcome variable for depression status (yes/no) at that point in time. For the plasma HIV VL and CD4 count, the closest values from medical chart abstraction (within 12 months before up to 3 months after) to the 6-month ACASI were used.

Statistical analyses

First, we described sociodemographic and clinical factors associated with depression at baseline according to baseline PRIME-MD score, overall and stratified by sex. Univariate differences were assessed using the chi-square test (discrete variables) or the Wilcoxon rank sum test (continuous variables). The chi-square test was used to test for trend. Second, we performed two sets of longitudinal regression analyses: (i) to identify patient-level factors associated with depression at a given ACASI evaluation, and (ii) to assess the association of depression with nonadherence each defined at a given ACASI evaluation, and adjusted for other patient-level covariables. For both of these regression analyses we used data from the baseline, 6-, 12-, 18- and 24-month ACASI, as available.

To account for the correlation between repeated ACASI interview results for each participant, we used generalized estimating equations (GEE) models, assuming a binomial distribution for each of two outcome variables (depression, adherence) in separate models; for each model, results are reported as an odds ratio (OR) with associated 95% confidence interval (CI). Variables possibly associated ($p < 0.10$) with the outcome of interest in the univariate analyses were included in multivariable models; separate models were constructed for the outcomes of depression and non-adherence.

We constructed separate models for predictors of depression in women and men, because in exploratory analyses the associations between risk factors and depression varied by sex, as did the prevalence of depression. By contrast, we combined data from men and women when modeling the association between depression and adherence, because we did not observe marked differences in associations by sex.

We did not include HIV RNA (viral load, VL) as a predictor variable in the models for depression and nonadherence as we hypothesized it to be an outcome of depression and nonadherence rather than a predictor (i.e., reverse causal relationship). Final models were obtained by backward selection and retained only predictor variables with a p value < 0.05. Finally, we also described the association between prevalent depression severity and the likelihood of having a suppressed HIV VL (i.e., < 400 copies/mL) at that point in time. Analyses were repeated using a viral suppression threshold of < 50 copies/mL after excluding the minority of patients who had their viral load measured with assays with a lower limit of detection of < 400 copies/mL and who had undetectable results (i.e., censored, non-evaluable data). All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, North Carolina).

Results

Baseline

Of 539 participants, 21.2% were women, 60.9% white, 26.7% non-Hispanic black and 8.2% Hispanic (Table 2). Overall, 75 (13.9%) participants had symptoms of depression at baseline. Depression was more prevalent among women (21.9%) compared with men (11.8%, $p = 0.005$) and among non-Hispanic blacks (17.4%) and Hispanics (29.6%) compared with non-Hispanic whites (10.7%) (race/ethnicity overall comparison, $p = 0.003$). The prevalence of depression at baseline by sex and race/ethnicity is displayed in Fig. 1.

Other baseline characteristics associated with depression (Table 2) included having no marital/sexual partner, heterosexual, or intravenous-drug-use (IDU) risk for HIV transmission versus men who have sex with men (MSM) risk, hepatitis C co-infection, use of public insurance, and current tobacco use. There was a decreasing frequency of depression with increasing extent of employment; retired or other status (27.3%), unemployed (21.9%), part-time employed (8.1%), and full-time employed (6.1%) ($p < 0.001$). Depression was more frequent among participants with a family history of

Table 2. Baseline Characteristics of the Study Population and Prevalence of Depression for HAART-Treated Participants, the SUN Study, 2004–2006

	Total N = *539* n *(%)*	*No depression* N = *464* n *(%)*	*Depression*[a] N = *75* n *(%)*	*% with depression*	p *Value*
Age (baseline), years					0.136
<35	113 (21.0)	101 (21.8)	12 (16.0)	10.6	
35–44	231 (42.9)	191 (41.2)	40 (53.3)	17.3	
≥45	195 (36.2)	172 (37.1)	23 (30.7)	11.8	
Sex					0.005
Male	425 (78.9)	375 (80.8)	50 (66.7)	11.8	
Female	114 (21.2)	89 (19.2)	25 (33.3)	21.9	
Race/ethnicity					0.003
Non-Hispanic black	144 (26.7)	119 (25.7)	25 (33.3)	17.4	
Hispanic	44 (8.2)	31 (6.7)	13 (17.3)	29.6	
Other, or unknown	23 (4.3)	21 (4.5)	2 (2.7)	8.7	
Non-Hispanic white	328 (60.9)	293 (63.2)	35 (46.7)	10.7	
Marital status					0.152
Married	71 (13.2)	63 (13.6)	8 (10.7)	11.3	
Single without a partner	260 (48.2)	217 (46.8)	43 (57.3)	16.5	
Single with partner	92 (17.1)	82 (17.7)	10 (13.3)	10.9	
Divorced, widowed or separated	63 (11.7)	43 (9.3)	10 (13.3)	18.9	
Unknown	63 (11.7)	59 (12.7)	4 (5.3)	6.4	
Partner status					0.017
Alone	313 (58.1)	260 (56.0)	53 (70.7)	16.9	
Partner, or unknown	226 (41.9)	204 (44.0)	22 (29.3)	9.7	
Employment status					<0.001
Full time	262 (48.6)	246 (53.0)	16 (21.3)	6.1	
Part time	62 (11.5)	57 (12.3)	5 (6.7)	8.1	
Unemployed	96 (17.8)	75 (16.2)	21 (28.0)	21.9	
Retired or other	119 (22.1)	86 (18.5)	33 (44.0)	27.3	
HIV risk group					0.016
Heterosexual	132 (24.5)	107 (23.1)	25 (33.3)	18.9	
IDU	36 (6.7)	27 (5.8)	9 (12.0)	25.0	
MSM	322 (59.8)	289 (62.3)	33 (44.0)	10.3	
Other	49 (9.1)	41 (8.8)	8 (10.7)	16.3	
Insurance status					0.043
Private	219 (40.6)	196 (42.2)	23 (30.7)	10.5	
Public	178 (33.0)	144 (31.0)	34 (45.3)	19.1	
Other, or unknown	142 (26.4)	124 (26.7)	18 (24.0)	12.7	
Tobacco use (current)					<0.001
Yes	233 (43.2)	182 (39.2)	51 (68.0)	21.9	
No	306 (56.8)	282 (60.8)	24 (32.0)	7.8	
Drug use past 6 months					0.108
Yes	277 (51.4)	232 (50.0)	45 (60.0)	16.3	
No	262 (48.6)	232 (50.0)	30 (40.0)	11.5	
Alcohol use past 30 days					0.879
<3 drinks per day	392 (72.7)	338 (72.8)	54 (72.0)	13.8	
3 or more drinks per day	147 (27.3)	126 (27.2)	21 (28.0)	14.3	
BMI (median), kg/m^2	25.6 (22.8,29.0)	25.6 (22.8, 29.0)	25.8 (22.5, 30.0)		0.713
<25	240 (44.5)	210 (45.3)	30 (40.0)	12.5	0.350
25–29.9	195 (36.2)	169 (36.4)	26 (34.7)	13.3	
≥30	104 (19.3)	85 (18.3)	19 (25.3)	18.3	
CD4 (median), cells/mm^3	455 (296,675)	465 (299, 680)	403 (239, 596)		0.058
<200	60 (11.2)	51 (11.0)	9 (12.2)	15.0	0.440
200–349	129 (24.0)	108 (23.3)	21 (28.4)	16.3	
350–500	120 (22.4)	101 (21.8)	19 (25.7)	15.8	
>500	228 (42.5)	203 (43.8)	25 (33.8)	11.0	
HIV viral load <400 cp/mL					
Yes	476 (88.6)	414 (89.4)	62 (83.8)	13.0	0.156
No	61 (11.4)	49 (10.6)	12 (16.2)	19.7	
Median VL ($\log_{10}$ cp/mL) if viremic	3.2 (2.9,4.3)	3.3 (2.9,4.1)	3.2 (3.1,4.7)		0.814
Hepatitis C co-infection					0.001
Yes	72 (13.4)	53 (11.4)	19 (25.3)	26.4	
No	467 (86.6)	411 (88.6)	56 (74.7)	12.0	

(*continued*)

Table 2. (Continued)

	Total N = *539* n *(%)*	*No depression* N = *464* n *(%)*	*Depression*[a] N = *75* n *(%)*	*% with depression*	p *Value*
Family history of depression					< 0.001
Yes	180 (33.4)	140 (30.2)	40 (53.3)	22.2	
No	351 (65.1)	317 (68.3)	34 (45.3)	9.7	
Missing	8 (1.5)	7 (1.5)	1 (1.3)	12.5	
Prescribed antidepressant in the past 6 months					
No	397 (73.7)	361 (77.8)	36 (48.0)	9.1	< 0.001
Yes	142 (26.3)	103 (22.2)	39 (52.0)	27.5	
Missed dose of ARVs in the past 3 days					0.041
Yes	78 (14.5)	60 (12.9)	18 (24.0)	23.1	
No	454 (84.2)	398 (85.8)	56 (74.7)	12.3	
Missing	7 (1.3)	6 (1.3)	1 (1.3)	14.3	
Time since HIV diagnosis (baseline)					0.801
< 5 years	266 (49.4)	230 (49.6)	36 (48.0)	13.5	
≥ 5 years	273 (50.6)	234 (50.4)	39 (52.0)	14.3	

[a]Depression was defined based on the results from PRIME-MD screen, as described in the methods. ARV, antiretroviral therapy; BMI, body mass index; HCV, hepatitis C virus; IDVU, injection drug users; MSM, men who have sex with men.

depression, and among participants prescribed antidepressants within 6 months prior to baseline. Participants who reported nonadherence to ARVs were more likely to have depression than participants who did not or who were missing adherence data (23.1% vs. 12.3% vs. 14.3%, $p = 0.04$). There were no significant differences in the frequency of depression at baseline according to age, marital status, illicit or nonprescribed recreational drug use, body mass index (BMI), CD4 count, or HIV VL.

Longitudinal correlates of depression

Of 539 patients who had baseline ACASI data available, 383 (71.1%) completed an ACASI at the 24-month study visit; the remaining 156 (28.9%) participants were not surveyed because they were lost to care (e.g., transferred to another HIV clinic), died, or missed the 24-month study visit and did not complete the ACASI. Among patients who completed the 24-month study visit, 54 (14.1%) reported depression at baseline, compared with 21 (13.5%) among patients who did not complete the 24-month visit ($p = 0.84$). Overall, 75 (13.9%) and 41 (10.7%) participants, at the baseline and 24-month visit, respectively, reported depression by ACASI.

Among 539 patients included, 403 (74.8%) reported no depression at baseline or during available follow-up visits through 24 months ('no evidence of depression'); 61 (11.3%) reported no depression at baseline but depression on at least one follow-up visit ('potential depression onset'); 44 (8.2%) reported depression at baseline and no depression on one or more follow-up visits ('intermittent or resolved depression');

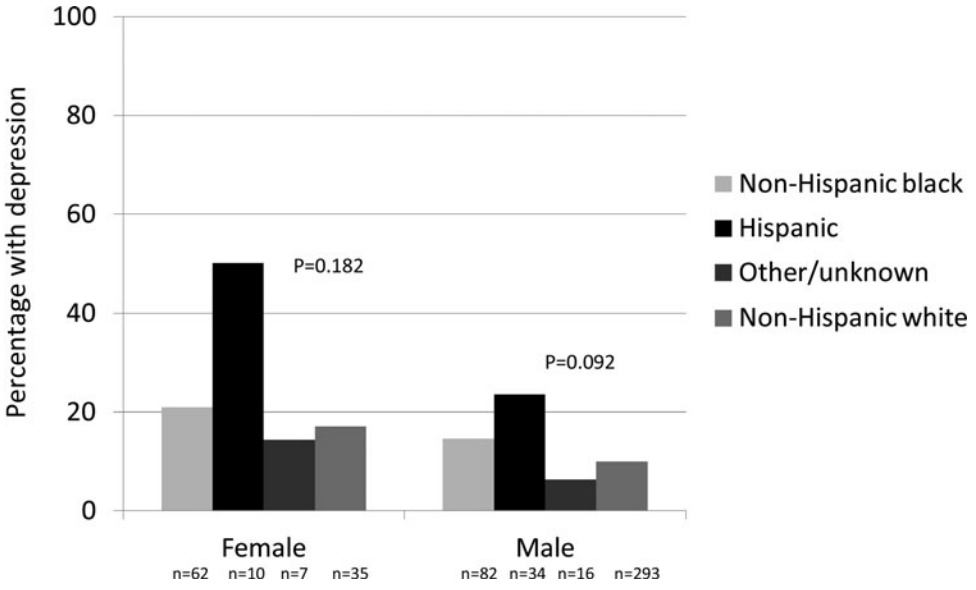

FIG. 1. Frequency of depression at baseline among HAART-experienced participants in the SUN Study, by sex and race/ethnicity, 2002–2006 ($n = 539$).

Table 3. Longitudinal Correlates of Depression by PRIME-MD, Baseline to 24 Months of Observation in the SUN Study, 2004–2008

	Women (N = 114)		*Men (N = 425)*	
	Univariate OR (95% CI)	*Multivariable OR (95% CI)*	*Univariate OR (95% CI)*	*Multivariable OR (95% CI)*
Age (baseline), years				
< 35	Referent	Referent	Referent	
35–44	3.89 (2.01, 7.50)	2.19 (1.08, 4.46)[c]	1.45 (0.91, 2.34)	
≥ 45	2.91 (1.45, 5.84)	1.46 (0.68, 3.17)	1.54 (0.95, 2.47)	
Race/ethnicity				
White	Referent	Referent	Referent	Referent
Black	1.29 (0.74, 2.22)	1.61 (0.88, 2.92)	1.86 (1.30, 2.66)	2.03 (1.40, 2.94)[c]
Hispanic, other, or unknown	2.29 (1.18, 4.46)	3.43 (1.60, 7.37)[c]	1.56 (0.99, 2.44)	1.75 (1.10, 2.78)[c]
Partner status[a] (baseline)				
Partner or unknown	Referent		Referent	Referent
No partner	1.62 (0.94, 2.78)		1.71 (1.25, 2.34)	1.47 (1.06, 2.03)[c]
Employment status (closest[b])				
Full, part time	Referent		Referent	
No job, retired, or other	18.20 (7.22, 45.87)		6.14 (4.41, 8.55)	
Insurance status (baseline)				
Private, other, or unknown	Referent		Referent	
Public	1.60 (1.01, 2.54)		1.77 (1.29, 2.42)	
Current tobacco use (current)				
No	Referent	Referent	Referent	Referent
Yes	5.85 (3.93, 10.09)	5.38 (3.01, 9.64)[c]	2.43 (1.79, 3.30)	2.24 (1.64, 3.07)[c]
Drug use in last 6 months				
No	Referent		Referent	
Yes	2.05 (1.27, 3.29)		1.23 (0.91, 1.66)	
Alcohol use past 30 days				
< 3 drinks per day	Referent		Referent	
3 or more drinks per day	1.58 (0.91, 2.75)		1.20 (0.88, 1.68)	
BMI, kg/m^3				
< 25	Referent		Referent	
25–29.9	0.78 (0.44, 1.37)		1.06 (0.77, 1.47)	
≥ 30	0.60 (0.35, 1.03)		0.86 (0.53, 1.40)	
CD4 count (closest[b])cells/mm^3				
< 200	3.50 (1.66, 7.37)	3.84 (1.67, 8.81)[c]	1.67 (0.95, 2.92)	
200–349	1.49 (0.81, 2.74)	1.36 (0.70, 2.62)	1.36 (0.91, 2.04)	
350–500	1.48 (0.83, 2.64)	1.32 (0.70, 2.49)	1.37 (0.95, 1.99)	
> 500	Referent	Referent	Referent	
HCV (baseline)				
No	Referent		Referent	
Yes	3.51 (2.14, 5.74)		2.62 (1.79, 3.83)	
Family history of depression (closest)				
No/unknown	Referent		Referent	Referent
Yes	1.89 (1.19, 2.97)		1.91 (1.41, 2.60)	1.96 (1.42, 2.69)[c]
Prescribed antidepressant in the past 6 months				
No	Referent		Referent	
Yes	3.17 (1.53, 6.58)		2.64 (1.67, 4.17)	
Duration since HIV diagnosis (baseline)				
< 5 years	Referent		Referent	
≥ 5 years	1.57 (0.99, 2.48)		0.75 (0.56, 1.02)	

[a]Includes marital status. Persons married or with a partner are categorized as having a partner; [b]"Closest": means that data for this variable were taken from the same (6-monthly) ACASI evaluation as the data for the depression outcome; for VL and CD4, take closest values from the medical record (-1 year to + 3 month window). [c]Statistically significant association at $p < 0.05$.

BMI, body mass index; OR, odds ratio.

and 31 (5.8%) reported depression at baseline and on all their follow-up visits through 24 months ('persistent depression').

In sex-specific univariate analyses for the 114 women and 425 men included in our analysis, the following factors were significantly associated with depression for both sexes during the 24 months of observation on HAART: unemployed or retired employment status versus employed part or full time, use of public insurance versus other forms of insurance or no insurance, current tobacco use, hepatitis C co-infection, a family history of depression, and receipt of antidepressant medication in the past 6 months (Table 3). Furthermore, among women, age 35 years and older, Hispanic race/ethnicity compared with non-Hispanic white, illicit or non-prescribed recreational drug use, as well as CD4 count < 200

versus ≥500 cells/mm^3, were associated with depression. In men, non-Hispanic black race/ethnicity and no marital/sexual partner were also associated with depression. In the multivariable sex-specific analysis, a number of factors remained independently associated with risk of depression in both groups, but certain further distinctions emerged. Among women, depression was significantly associated with age 35–44 years compared with age <35 years, Hispanic ethnicity or other/unknown race compared with non-Hispanic white race/ethnicity, current tobacco use, and CD4 count <200 cells/mm^3 compared with ≥500 cells/mm^3. Among men, factors associated significantly with depression included black race and Hispanic ethnicity, having no marital/sexual partner, current tobacco use, and family history of depression.

Association between depression and nonadherence to ARVs

Nonadherence to ARVs was reported by 78 (14.5%) of the 539 participants at baseline and 60 (15.7%) of the 383 participants at the 24-month visit. Among participants with a 24-month visit, 52 (13.6%) reported nonadherence to ARVs at baseline compared with 26 (16.7%) among patients who did not go on to complete a 24-month visit ($p = 0.38$). In univariate longitudinal analysis, depression of any severity on an ACASI assessment was associated with approximately twofold higher odds of nonadherence on the same ACASI assessment (Table 4). Other factors associated with nonadherence in univariate analyses were female sex, non-white race or Hispanic ethnicity, heterosexual and IDU risk group compared with MSM, unemployment, public insurance, tobacco use, illicit drug use, consumption of 3 or more alcoholic drinks daily, HIV diagnosis ≥5 years, and CD4 count <200 cells/mm^3 compared with ≥500 cells/mm^3.

In the multivariable longitudinal analysis, participants who reported mild or moderate levels of depression and persons who reported moderately severe or severe depression had higher odds of nonadherence (OR 2.02, 95% CI 1.15–3.57 and OR 1.74, 95% CI 1.19–2.56, respectively) than participants who were not depressed (Table 4). Other factors that remained independently associated with nonadherence were female sex, non-Hispanic black and Hispanic or other race/ethnicity, tobacco use, consuming ≥3 alcoholic drinks daily, longer duration since HIV diagnosis, and CD4 count <200 cells/mm^3.

Association between depression and virologic suppression

At baseline, the prevalence of viral suppression (HIV VL <400 copies/mL) among the 537 participants was 88.6%: viral suppression was 89.4% among the 464 persons who were not depressed, 84.2% among the 19 persons who were mildly or moderately depressed, and 83.6% among the 56 moderately severely or severely depressed (test for trend $p = 0.17$). In all time points after baseline, patients who reported any level of depression had lower rates of virologic suppression (Fig. 2)

Discussion

This analysis based on data from a confidential self-administered computerized standard screening instrument administered to a contemporary and sociodemographically diverse cohort of HIV-infected patients in care extends previous findings that depression is prevalent, but not uniformly distributed, among HIV-infected US patients in the HAART era. We also found, as have others, a concerning association of depression with nonadherence to antiretroviral therapy and with lower levels of virologic suppression over 24 months of follow-up.

Similar to the general population, HIV-infected SUN Study participants who were most likely to be diagnosed as depressed were women and persons of color (Hispanics and African-Americans).[4] For ethnic minorities in the US, the complex interaction of poverty, lifetime trauma, chronic illness, and illicit drug use result in a syndemic of HIV infection and mental illness.[48,49] We found that current tobacco smoking was associated with depression, potentially because tobacco use has been associated with poor socioeconomic and psychosocial status. Factors such as unemployment and having public health insurance, both of which are also generally associated with lower socioeconomic status, were associated with depression in the crude longitudinal analyses, although they were not independently associated after adjustment for sex and race.

Among the most prevalent co-morbid chronic illnesses in HIV-infected adults that can increase the risk for depression and poor clinical outcomes is hepatitis C infection. Hepatitis C infection itself leads to recognized neurologic sequelae including depression.[50] In our baseline analysis, the frequency of depression was high among HIV-infected participants co-infected with hepatitis C (26.4%). Hepatitis C co-infection was not associated with depression in multivariable analyses in our study, but has been independently prognostic of depression in other HIV cohorts.[51,52]

We performed separate analyses by sex to elucidate factors associated with the high rates of depression in women. While Hispanics and non-Hispanic blacks were more likely to be depressed overall, Hispanic women had the highest rates of depression (as shown in Fig. 1). What accounts for the higher rate in Hispanics may not be discernible in the study, although the possibility that the computerized PHQ screening instrument in Spanish actually identified more depressed women is an intriguing possibility. Women with CD4 counts below 200 cells/mm^3, those using tobacco, and the "middle-aged" group of 35- to 44-year-olds were among those most likely to be depressed. Among the already vulnerable, these depressed women may be at particular risk to be nonadherent to medication. The interplay with depression and adherence at lower CD4 strata can result in a cycle of more symptomatic HIV disease or disease progression.[53,54] In the Women's Interagency HIV Study, depression, early discontinuation of HAART, low income, illicit drug use and smoking were associated with worse clinical outcomes.[55]

In the present analysis, we found that nonadherence to HAART over 24-months of follow-up was also associated with depression, after controlling for other independent risk factors that included female sex, being a person of color, retired or 'other' (not full- or part-time) employment status, tobacco use, drinking 3 or more alcoholic beverages per day, having been diagnosed with HIV infection ≥5 years ago, and a CD4 cell count <200 versus >500 cells/mm^3. Sociodemographic correlates of nonadherence have been studied extensively in HIV-infected patients, and others have linked nonadherence to non-white race, alcohol and illicit drug use,

Table 4. Longitudinal GEE Analyses of Depression and Other Factors Associated with Nonadherence to Antiretroviral Therapy, SUN Study, 2004–2008

	Univariate		*Multivariable*	
	OR	*95% CI*	*OR*	*95% CI*
Age (baseline), years				
<35	Referent	Referent		
35–44	1.12	0.82, 1.52		
≥45	0.82	0.60, 1.14		
Sex				
Male	Referent	Referent	Referent	Referent
Female	2.09	1.62, 2.69[a]	1.71	1.28, 2.28[a]
Race/ethnicity				
Non-Hispanic black	2.12	1.64, 2.73[a]	1.59	1.18, 2.14[a]
Hispanic/other	1.68	1.19, 2.36[a]	1.49	1.04, 2.14[a]
Non-Hispanic white	Referent	Referent	Referent	Referent
Partner status[b]				
Alone	1.15	0.91, 1.45		
Partner or unknown	Referent	Referent		
Employment status (closest)[c]				
Full time	Referent	Referent	Referent	Referent
Part time	1.33	0.93, 1.91	1.06	0.73, 1.54
Unemployed	2.48	1.84, 3.36[a]	1.36	0.96, 1.93
Retired or other	1.21	0.90, 1.64	0.60	0.42, 0.87[a]
HIV risk group				
Heterosexual	1.82	1.40, 2.36[a]		
IVDU	2.43	1.60, 3.70[a]		
MSM	Referent	Referent		
Other or unknown	1.45	0.95, 2.21		
Insurance status (baseline)				
Private or other	Referent	Referent		
Public	1.73	1.37, 2.19[a]		
Current tobacco use				
No	Referent	Referent	Referent	Referent
Yes	1.92	1.52, 2.41[a]	1.66	1.28, 2.15[a]
Drug use past 6 months				
Yes	1.29	1.03, 1.62[a]		
No	Referent	Referent		
Alcohol use past 30 days				
<3 drinks/day	Referent	Referent	Referent	Referent
3 or more drinks/day	1.69	1.33, 2.16[a]	1.66	1.28, 2.15[a]
BMI, kg/m^3				
<25	Referent	Referent		
25–29.9	0.80	0.62, 1.03		
≥30	0.83	0.61, 1.14		
CD4 count, cells/mm^3				
<200	3.16	2.14, 4.64[a]	3.13	2.07, 4.73[a]
200–349	1.26	0.93, 1.72	1.25	0.90, 1.74
350–500	1.22	0.91, 1.63	1.23	0.90, 1.66
>500	Referent	Referent	Referent	Referent
HCV (baseline)				
No	Referent	Referent		
Yes	1.81	1.35, 2.43[a]		
Prescribed antidepressant in the past 6 months				
Yes	1.13	0.80, 1.59		
No	Referent	Referent		
Duration since HIV diagnosis (baseline)				
<5 years	Referent	Referent	Referent	Referent
≥5 years	1.33	1.06, 1.67[a]	1.45	1.13, 1.86[a]
Depression by PRIME-MD (closest)[c]				
None	Referent	Referent	Referent	Referent
Mild or moderate	2.52	1.42, 4.28[a]	2.02	1.15, 3.57[a]
Moderately severe or severe	2.14	1.52, 3.00[a]	1.74	1.19, 2.56[a]

[a]Statistically significant association at $p<0.05$; [b]Includes marital status. Persons married or with a partner are categorized as having a partner; [c]"Closest": means that data for this variable were taken from the same (6-monthly) ACASI evaluation as the data for the depression outcome; for VL and CD4, closest values were taken from the medical record (-1 year to+3 month window).

ARV, antiretroviral therapy; BMI, body mass index; HCV, hepatitis C virus; IDVU, injection drug users; MSM, men who have sex with men.

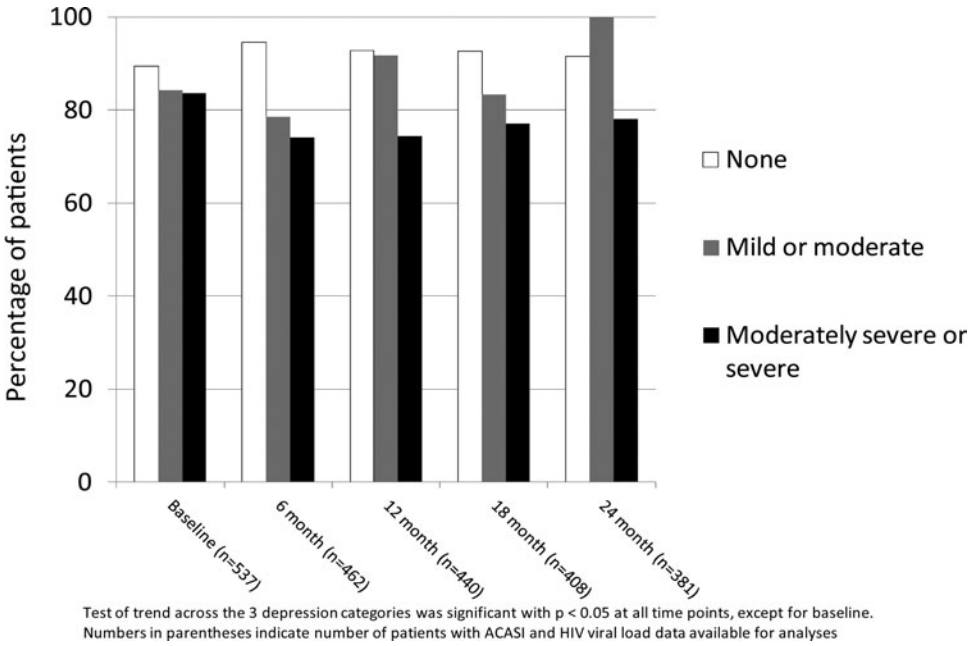

FIG. 2. Percentage of patients with suppressed viral load (< 400 copies/mL) by depression level and follow-up time, SUN Study, 2004–2006.

and longer duration of HIV infection. In a previously reported baseline cross-sectional analysis in the SUN Study cohort, nonadherence has been associated with black race, unemployment, HIV diagnosis ≥ 5 years , drinking 3 or more alcoholic beverages per day, and having not engaged in aerobic exercise in the last 30 days.[56]

The association of depression with nonadherence to ARVs in our study is also consistent with findings from prior studies, which used a variety of methods for ascertaining depression.[22,57–59] Indeed, depression of any severity observed among SUN Study participants was associated with nonadherence; even mild and moderate levels of depression doubled the odds of reporting nonadherence. Given the increased risk for HIV disease progression and mortality (due to AIDS-related and non-AIDS-related causes) associated with suboptimal adherence and lack of virologic suppression, these findings are concerning.

In this study, we administered the PRIME-MD standard depression screening instrument as part of an ACASI performed in the primary HIV care setting. The self-administration aspect of the technology enabled the collection of data in busy clinical settings as well as the ability to interview Spanish speaking patients. Such longitudinal data in a diverse population have not been described extensively. The data collected by ACASI are valuable in the management of HIV-infected patients, providing the ability to screen and identify depressed patients, elicit correlates of depression, and assess the potential impact of depression on adherence to prescribed care.

Our findings are subject to several limitations. Even in these integrated care settings, 28.9% of participants did not complete all the required visits and scheduled ACASIs. Loss to follow-up and resultant missing data could introduce a bias, particularly in the observed association of depression and nonadherence. In the SUN Study, the documentation of diagnoses of depression in medical charts was not standardized across participating sites. Participants could also have been receiving mental health services elsewhere and these data were not captured in their clinical record at the study clinic. Because of incomplete medical charting, we could not reliably ascertain the utility of using PRIME-MD for improving the diagnosis of depression in routine HIV clinical practice. Additionally, although the PRIME-MD instrument was developed to provide diagnostic criteria for depression and has been validated, it is possible that participants who reported depression on PRIME-MD might not have met the criteria for clinical diagnosis of depression by a physician.[60] Furthermore, because no systematic interventions based on PRIME-MD results were implemented (i.e., clinicians were blinded to the patients' individual responses and could not use these data to assess and treat), we could not evaluate whether recognition and treatment of depressed patients at high risk for nonadherence could result in better immunologic and virologic outcomes, as has been suggested previously.[31]

Collection of depression, nonadherence, and other patient risk factor data in a confidential fashion through ACASI compared to other self-report instruments or specific interview methods has been reported in only a limited number of U.S. HIV cohort studies.[11,19,39] While findings to date tend to be consistent in cross-sectional versus longitudinal analyses of depression and adherence, the SUN cohort is one of few studies that provides ongoing data collection from a diverse cohort in a high-resource setting. This study underscores the observation that depression and adherence are dynamic processes that vary over time. One potential application for future research is to evaluate the real time integration of an ACASI-based PRIME-MD screening with an on-site behavioral health consultant or specific behavioral intervention and systematic monitoring of changes in adherence.

In summary, the use of a confidential standardized computer-based screening instrument identified depression in over 10% of men and over 20% of women prescribed HAART; these persons were in turn at higher risk of nonadherence to antiretroviral therapy and of not suppressing plasma HIV

replication. Our findings and those of others suggest that treating depression would not only improve quality of life but would also likely improve survival by increasing adherence to HAART, viral suppression, and CD4 cell counts. Improvement in health outcomes for the HIV-infected community through systematic attention to depression can also achieve one of the goals of the current United States HIV/AIDS strategy.[61] Although we could not determine whether depression was underdiagnosed in our population, we believe our findings provide further compelling evidence for ensuring that contemporary HIV-infected patients who are engaged in care are regularly screened for depression and treated, if indicated.

Acknowledgments

Disclaimer: The findings and conclusions of this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

We wish to thank the SUN Study participants, who have devoted their time and effort to this research project. We also wish to thank the SUN Study Investigators: Kathleen Wood, Rose Baker, and Cheryl Akridge, Cerner Corporation, Vienna, Virginia; John Hammer, Tara Kennedy, Barbara Widick, and Billie Thomas, Denver Infectious Disease Consultants, Inc., Denver, Colorado; Ken Lichtenstein and Joslyn Axinn, National Jewish Medical and Research Center, Denver, Colorado; Keith Henry, Jason Baker, Rachel Prosser, Edie Gunderson, Miki Olson, and John Hall, Hennepin County Medical Center, Minneapolis, Minnesota; Frank Rhame, Mark Olson, and Eve Austad, Abbott-Northwestern Hospital, Minneapolis, Minnesota; Mark Sannes, Meaghan Morton, and Cheri Murch, Park-Nicollet Institute, Minneapolis, Minnesota; Charles Carpenter, Susan Cu-Uvin, Kenneth Mayer, Erna Milunka Kojic, Jennifer Florczyk, Sheila Tumilty, and Patricia D'Aiello, The Miriam Hospital, Providence, Rhode Island; and Nur Onen, E. Turner Overton, Don Connor, Sara Hubert, and David Coughlin, Washington University School of Medicine, St. Louis, Missouri. We also would like to thank Dr. Joan S. Chmiel for her comments on the earlier version of the manuscript, and Dr. Carl Armon for technical assistance in preparation of the final manuscript.

Funding: The Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN) is funded by the Centers for Disease Control and Prevention.

Author Disclosure Statement

No competing financial interests exist.

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