Clinical Importance of HIV and Depressive Symptoms Among Veterans with HIV Infection

Amy M. Kilbourne, PhD, MPH, Amy C. Justice, MD, PhD, Bruce L. Rollman, MD, MPH, Kathleen A. McGinnis, MS, Linda Rabeneck, MD, MPH, Sharon Weissman, MD, Susan Smola, MBA, Richard Schultz, PhD, Jeff Whittle, MD, MPH, Maria Rodriguez-Barradas, MD

OBJECTIVE: To compare the clinical importance (association with illness severity and survival) of depressive and HIV symptoms among veterans with HIV infection.

DESIGN: Cross-sectional study; survival analysis.

SETTING: Infectious Disease Clinics at 3 VA Medical Centers.

PARTICIPANTS: HIV-infected patients ($N = 881$) and their health care providers from June 1999 through July 2000.

MEASUREMENTS AND MAIN RESULTS: Depressive symptoms were assessed using the 10-item Centers for Epidemiologic Studies Depression Scale (CES-D). Patient baseline survey included an HIV Symptom Index measuring the frequency and bother of 20 common symptoms. Providers were surveyed on patients' illness severity, and survival data were obtained from VA death records. Of 881 patients, 46% had significant depressive symptoms ($\text{CES-D} \geq 10$). Increasing depression symptom severity was associated with increasing HIV symptom frequency ($P < .001$) and bother ($P < .001$). Multiple regression results revealed that having moderate or severe depressive symptoms was not associated with provider-reported illness severity or survival. However, HIV symptoms were significantly associated with provider-reported illness severity ($P < .01$) and survival ($P = .05$), after adjusting for moderate and severe depressive symptoms, CD4 cell count/ mm^3 , viral load, age, race, and antiretroviral use.

CONCLUSIONS: Depression, while common in this sample, was not associated with illness severity or mortality after adjusting for HIV symptoms. HIV symptoms are associated with severity of illness and survival regardless of patients' severity of depressive symptoms. This suggests that equal medical consideration

should be given to HIV symptoms presented by HIV-infected patients regardless of their depression status, rather than automatically attributing medical complaints to depression.

KEY WORDS: HIV/AIDS; symptoms; depression.

J GEN INTERN MED 2002;17:512-520.

The clinical importance of coexisting HIV and depressive symptoms remains elusive in the era of highly active antiretroviral therapy (HAART). It is well documented that depressed patients with HIV disease report more somatic symptoms than do nondepressed patients with HIV disease.¹⁻⁵ Furthermore, a number of somatic symptoms, including wasting and neurologic symptoms, are associated with poorer health-related quality of life,⁶⁻⁹ worse functional status,^{6,7,10} and mortality^{6,7,11,12} in patients with HIV infection.

Yet clinicians are given little guidance as to what to do in response to symptoms reported by depressed patients with HIV infection. For example, should clinicians first treat the depression and observe whether the somatic symptom (e.g., dizziness, pain) resolves, or should they also search for medical causes of the symptom? The answer may hinge on whether the association between somatic symptoms and outcomes (e.g., disease progression, mortality)¹³⁻¹⁸ is different in patients with co-occurring depressive symptoms. If the association between somatic symptoms and outcomes is as strong in patients with depressive symptoms as in those without depressive symptoms, then providers should consider possible medical causes of the somatic symptoms as well as treat the depressive symptoms.

Thus, determining whether HIV symptoms are clinically significant among HIV-infected patients with co-occurring depressive symptoms is crucial in selecting the best treatment options for the patient. Prior research suggests that providers may not follow up with patients if they assume the symptoms are attributed to a psychiatric condition.¹⁹ Yet previous studies examining the role of depression in HIV illness progression and survival did not control for a comprehensive array of symptoms.^{2-5,13-18} Our study objectives are to determine the clinical importance of HIV and depressive symptoms by determining whether depressive or HIV symptoms are associated with illness severity and 1-year survival among a cohort of HIV-infected patients exposed to HAART.

METHODS

We used baseline survey data from the Veterans Aging Cohort 3 Site Study (VACS 3), a longitudinal study of

Received from the VA Pittsburgh Center for Health Equity Research and Promotion (AMK, ACJ, KAM, SS), the University of Pittsburgh Center for Research on Health Care, School of Medicine, Division of General Internal Medicine (AMK, ACJ, BLR), and the University of Pittsburgh Center for Social and Urban Research (RS), Pittsburgh, Pa; Division of Gastroenterology, Department of Medicine, University of Toronto (LR), Toronto, Canada; the Department of Medicine, Baylor College of Medicine (MR-B), and the VA Medical Center (MR-B), Houston, Tex; the Hospital of Saint Raphael (SW), New Haven, Conn; and the Department of Internal Medicine, Geriatric and General Medicine, Kansas University Medical Center, and Kansas City VA Medical Center (JW), Kansas City, Kan.

Data from this manuscript were presented at the Veterans Affairs Health Services Research and Development Annual Meeting, March 23, 2000, Washington D.C.

Address correspondence and requests for reprints to Dr. Kilbourne: VA Pittsburgh Center for Health Equity Research and Promotion, (130-U) University Drive C, Pittsburgh, PA 15240 (e-mail: Amy.Kilbourne@med.va.gov).

HIV-infected veterans from infectious disease clinics at 3 VA Medical Centers in Houston, Cleveland, and Manhattan. Further information on VACS 3 is available elsewhere.²⁰ We collected baseline data from patients and their providers between June 1999 and July 2000. We approached all HIV-infected patients currently attending the infectious disease clinic at 1 of the 3 sites and asked them to self-complete a survey that included questions on depressive and HIV symptoms at the time of their clinic appointment. Patients were paid \$10 to complete the survey. We obtained informed consent from all patients participating in this study, and the Human Subjects Committees at all participating sites as well as the University of Pittsburgh institutional review board reviewed and approved VACS 3.

We asked providers to complete a survey regarding their patients' severity of illness and overall disease severity. We collected laboratory data (including CD4 cell count and viral load) using the electronic medical record system with the assistance of the VA Information Resources Management at each site.

MEASURES

Depressive Symptoms

We assessed depressive symptoms in the patient survey using the 10-item version of the Centers for Epidemiologic Studies Depression Scale (CES-D; see Appendix A).²¹ The CES-D has been widely used in studies of the relationship between HIV and depression.^{2,3,13,14,22} We used the CES-D 10-item survey rather than a more comprehensive instrument such as the Diagnostic Interview Schedule in order to minimize respondent burden. Patients screened positive for significant depressive symptoms if they obtained a standard cut point of 10 or more out of a possible 30 points. This cut point in the 10-item CES-D has a sensitivity of 96% and specificity of 100% when compared to the CES-D 20-item survey in a sample of older adults in primary care.²¹ While the CES-D 10-item survey has not been directly compared to clinical diagnoses of major depression, the sensitivity and specificity of the CES-D 20-item survey has been reported to average 80% and 70%, respectively, compared to formal diagnostic interview.²³

We also identified veterans who experienced more-severe depressive symptoms by distinguishing those scoring greater than or equal to 15 out of 30 on the CES-D 10-item survey. We derived this cut point from a previously established higher cut point used in the CES-D 20-item survey,²⁴ representing the top 25th percentile of the score distribution. Therefore, we classified those scoring 0 to 9 as having a mild level of depressive symptoms, 10 to 14 as moderate depressive symptoms, and ≥ 15 representing severe depressive symptoms.

Symptom Frequency and Bother

Veterans completed the HIV Symptom Index to ascertain symptom frequency and bother.^{25,26} This symptom

index measures the frequency and bother of 20 common and bothersome symptoms. The development and validation of the HIV Symptom Index has been described elsewhere by Justice et al.²⁶ The HIV Symptom Index asked whether respondents experienced any one of 20 common symptoms within the past 4 weeks. If they did experience the symptom, patients were asked what the relative level of bother was for each symptom, based on a Likert scale (see Appendix A). Patients who skipped a particular symptom were assumed to not have that symptom. Patients were defined as having a symptom if they reported experiencing it, and were defined as having a "bothersome symptom" if they reported the particular symptom as "it bothers me" or "it bothers me a lot."

Demographics and Laboratory Data

Patient age and race data were available from the VA administrative files and confirmed by patient and provider report. Antiretroviral (ARV) medication use, including current number of ARV prescriptions at the time of the survey, was obtained from the VA national pharmacy data file. We collected data on CD4 cell count per cubic millimeter (mm^3) and viral load (copies per mL) from computerized laboratory records at each site, using lab results collected nearest to the patient survey date.

Outcomes: Severity of Illness and Mortality

For severity of illness, we asked providers how sick their patients were at the time of the visit using a 5-point Likert scale (0 = not sick, 1 = somewhat sick, 2 = moderately sick, 3 = very sick, and 4 = near death), based on a provider clinical judgment question developed and validated by Charlson et al.²⁷ Physician overall assessment of severity of illness using a Likert scale response has been demonstrated to be highly predictive of short-term (in-hospital) and long-term (6-month and 1-year) mortality.^{28,29}

Mortality was ascertained from the Beneficiary Identification and Records Locator Subsystem (BIRLS) Death File, a VA administrative database containing records on all beneficiaries. Fisher et al. (1995) reported a high accuracy rate for BIRLS data in ascertaining mortality.³⁰ Additionally, death information was obtained from administrative inpatient files and from investigators at each VACS 3 site.

Analyses

We first determined the association between depression and symptom frequency among HIV-infected veterans by comparing the prevalence of each symptom and each bothersome symptom among HIV-infected patients with mild, moderate, and severe depressive symptoms. We then compared the total count of symptoms and bothersome symptoms by adding together the total number of symptoms experienced regardless of bother level, and then adding the total number of bothersome symptoms for each patient.²⁶

Some of the symptoms in the HIV Symptom Index are similar to the depressive symptoms in the CES-D 10-item survey. Previous studies used reduced versions of the CES-D that excluded the somatic symptoms or symptoms that correlated with HIV symptoms.^{1,13} Therefore, we created an alternative HIV Symptom Index for the bivariate and multivariate analyses that excluded the following symptoms most highly correlated with CES-D score: sadness ($r = .68$), anxiety ($r = .61$), sleep problems ($r = .56$), fatigue ($r = .52$), and memory loss ($r = .48$). We also created a reduced CES-D score based on the 5 remaining affective symptoms (feeling bothered, effort, hopeful, happy, and lonely) for the multivariate analysis.

We used multivariate logistic regression analysis to determine whether having moderate or severe depressive symptoms was independently associated with provider-reported severity of illness, controlling for HIV symptom count, in which we modeled the probability of being moderately or very sick, compared to those who were not or somewhat sick.

Cox proportional hazards modeling was used to determine the impact of depressive and HIV symptoms on survival (up to 1 year), using the patients' last visit date as the censor date. Hazard ratios were generated from the Cox model that represent the mortality risk of patients with a given exposure (e.g., significant depressive symptoms) divided by those without the given exposure (no significant depressive symptoms). We assessed the predictive value of the Cox model using the C statistic,³¹ which is an estimate of the probability that in any pairwise comparison of individuals in the dataset, the individual with the longer predicted survival would actually survive longer.

In both the multivariate logistic and Cox models, we adjusted for CD4 count ($<200/\text{mm}^3$ or $\geq 200/\text{mm}^3$) viral load (<500 or ≥ 500 copies), age (<50 , ≥ 50 years), race (nonwhite or white), and ARV use (0, 1, 2, 3, 4, 5, or ≥ 6 ARV prescriptions). For the logistic and Cox regression models, the symptom count variable was normally distributed; hence transformation was not necessary. We also checked for multicollinearity between symptom count, CES-D score, and the other variables using Spearman-Brown correlation coefficients, and all correlations were less than 0.60.

To determine whether the exclusion of overlapping CES-D and HIV symptoms changed our results, we reran the logistic and Cox regression models using both the full and reduced HIV Symptom Index and CES-D score. We also added the interaction between CES-D score (<10 , ≥ 10) and HIV symptom count to determine whether the association between symptoms and severity of illness differed by CES-D score.

We repeated our regression analyses using International Classification of Diseases (ICD)-9 data for depression from the VA computerized medical record system. HIV-infected patients with ICD-9 codes for depression within the past 3 years of the patient survey date were identified using the VA computerized electronic medical record, based on previously established ICD-9 codes from the

Veterans Health Study³² and Druss and Rosenheck, 2000.³³ ICD-9 codes included depression—single episode (296.2x), depression—recurrent episode (296.3x), depressive disorder (311, 309.10), and neurotic depression (300.4).

RESULTS

Between June 1999 and July 2000, 1,038 HIV-infected patients presented for care at the 3 VA Infectious Disease Clinics; of those, 915 patients were approached. Excluding refusals ($N = 34$), 881 patients completed surveys, representing 85% of the HIV-infected clinic population at the 3 sites. Of the 881, 99% were male, 55% were African American, 87% were currently taking antiretroviral medications, and the mean age was 49 years (Table 1). Over a quarter (27%) of patients had a CD4 count of less than 200 cells/ mm^3 and 46% had a viral load of <500 RNA copies. Twenty-two percent were considered at least moderately sick by their health care provider (Table 1).

The median CES-D score among the participants was 9 (Table 2). Approximately half (46%) of the sample had moderate depressive symptoms (CES-D score: ≥ 10), of whom 23% had severe depressive symptoms (CES-D ≥ 15). Only 57% of patients with severe depressive symptoms were recognized as depressed by their provider. In contrast, almost a quarter (24%) of patients without significant depressive symptoms were considered depressed by their

Table 1. Descriptive Characteristics and Symptom Prevalence

Demographic Characteristics	n	%
Gender		
Female	11	1
Male	870	99
Race/ethnicity		
African American	480	55
Latino, other	106	12
White	295	33
Mean age, y ($\pm$ SD)	49 (9)	
Current antiretrovirals, n		
0	116	13
1	36	4
2	248	28
3	350	40
4	83	9
5	27	3
≥ 6	21	2
CD4 cell count/ mm^3 (n missing = 6)		
0–199	235	27
≥ 200	640	73
Viral load (n missing = 7)		
<500 copies	406	46
≥ 500 copies	468	54
Provider-reported patient severity of illness (n missing = 81)		
Not sick	266	33
Somewhat sick	361	45
Moderately sick	143	18
Very sick	30	4

Table 2. Symptoms, Comorbidities, and Severity of Illness in Veterans with HIV/AIDS Cohort Study: Patients by Depression Category (N = 881)

Prevalence of Depression (n Missing = 19)	CES-D 10-item Score			P Value*
Median CES-D score, 9 (SD = 6.7; range: 0–29)	<10	10–14	≥15	
Patients by depression category, n	467	194	201	
By depression category, %	54	23	23	
Reported by provider as depressed, %	24	37	57	<.001
Depressed based on ICD-9 code for depression, past 3 y [†] , %	20	33	55	<.001
Mean symptom count, n (±SD) (20 symptoms)				
Symptoms	7.6 (5.0)	12.5 (5.3)	15.1 (4.6)	<.001
Bothersome symptoms	2.2 (2.9)	5.7 (4.4)	9.5 (4.7)	<.001
Mean symptom count, n (±SD) (15 symptoms) [‡]				
Symptoms	5.4 (3.8)	8.8 (4.2)	10.6 (3.9)	<.001
Bothersome symptoms	1.6 (2.2)	3.9 (3.4)	6.1 (3.7)	<.001
Mean CD4 cell count/mm ³ , n (±SD) (n missing = 11)	369 (252)	393 (270)	381 (274)	.53
With viral load <500 copies, %	49	43	45	.22
Provider-reported patient severity of illness level (n missing = 96), %				<.001
Moderately sick or very sick	18	22	31	
Not sick or somewhat sick	82	78	69	

* P values obtained based on 1-way ANOVA for provider-reported depression (symptom counts are approximately normally distributed). For symptom count, bothersome symptom counts, CD4 cell count/mm³, P values were based on nonparametric Wilcoxon test for trend. For provider-reported severity of illness, P value was based on χ^2 .

[†] HIV-infected patients with ICD-9 codes for depression within the past 3 years of the patient survey date were identified using the VA computerized electronic medical record and included depression—single episode (296.2x), depression—recurrent episode (296.3x), depressive disorder (311, 309.10), and neurotic depression (300.4).

[‡] Excluding sadness, anxiety, sleep problems, fatigue, and memory loss—5 symptoms most highly correlated with CES-D score.

providers. Those with moderate or severe depressive symptoms were more likely to have an ICD-9 code for depression within the past 3 years ($P < .001$). Overall agreement beyond chance between patient self-reported moderate or severe depressive symptoms and provider report of depression and ICD-9 code was poor ($\kappa = 0.24$, $\kappa = 0.25$ respectively).

Increasing severity of depressive symptoms was associated with increasing frequency of each HIV symptom (Fig. 1); in all cases, the P value based on the Cochran trend test was $<.001$. Increasing level of depressive symptoms was also associated with an increasing mean count of HIV symptoms and bothersome HIV symptoms (Table 2; $P < .001$ based on 1-way ANOVA). After excluding the 5 HIV Symptom Index symptoms most highly correlated with CES-D symptoms, the dose-response association was still evident for increasing level of depression and symptom count and bothersome symptom count ($P < .001$).

Although median CD4 cell count/mm³ and viral load did not significantly differ between depressive symptom severity levels based on the Wilcoxon nonparametric test (Table 2), both severely and moderately depressed patients were more likely to be considered at least moderately sick than nondepressed patients ($P < .001$; Table 2).

Regression Results

Univariate regression analyses revealed that an increased HIV symptom count and having severe depressive symptoms ($P < .001$) were significantly associated with provider-reported illness severity (Table 3). In other words,

before adjustment, those with severe depression (CES-D score >15) were twice as likely to be moderately or very sick according to providers ($P < .001$). HIV symptom count was independently associated with provider-reported severity of illness ($P < .01$), after adjusting for depressive symptoms, CD4 cell count, viral load, age, race, and antiretroviral use (Table 3). Hence, after adjustment, the odds of being moderately or very sick were 6% higher for each additional symptom. Having moderate or severe depressive symptoms was not independently associated with being moderately or very sick after adjustment.

Survival

After 12 months of follow-up, 53 (7%) of HIV-infected veterans in VACS 3 died. Unadjusted Cox proportional hazards modeling revealed that both HIV symptom count ($P < .01$) and severe depressive symptoms ($P < .05$) were associated with mortality (Table 4). After further adjusting for CD4 cell count, viral load, age, race, and antiretroviral use, the association of HIV symptom count with mortality approached significance ($P = .05$). That is, based on the hazard ratio, the risk of mortality was 3% higher with each additional symptom. There was no association between depressive symptoms and mortality after adjustment. The C statistic of the multivariate Cox model was 0.74, indicating a 74% probability that the HIV-infected patient with the longer predicted survival was in fact the one who survived longer.

The association between HIV symptoms and provider-reported sickness and mortality remained significant even

FIGURE 1. Symptom frequency by depression severity level. In all cases, differences in symptom frequency were significant at $P < .001$ based on Cochran Test for Trend.

when symptoms overlapping with the CES-D were excluded (data not shown). There was no significant interaction between CES-D score and HIV symptom count (data not shown). In addition, using ICD-9 diagnostic codes for depression in multivariate models instead of CES-D score produced similar results.

DISCUSSION

Depressive symptoms were common in our sample, with almost a quarter of HIV-infected veterans with severe depressive symptoms. Increasing depression symptom severity was associated with both symptom frequency and

Table 3. Provider-reported Severity of Illness (Moderately or Very Sick): Logistic Regression Results (N = 780)

	Unadjusted Results		Adjusted Results*	
	Odds Ratio	95% CI	Odds Ratio	95% CI
HIV symptom count (0–20)	1.07 [†]	1.04 to 1.10	1.06 [‡]	1.02 to 1.10
CES-D Score (reference = 0–9)				
10–14	1.33	0.86 to 2.66	0.98	0.60 to 1.62
>15	2.08 [†]	1.39 to 3.11	1.61	0.98 to 2.66
CD4 cell count <200 (reference = CD4 count ≥200)	3.50 [†]	2.45 to 5.00	3.02 [†]	2.06 to 4.44
Viral load ≥500 copies (reference = <500 copies)	2.65 [†]	1.84 to 3.81	2.23 [†]	1.50 to 3.31
Age, y <50 (reference = age ≥50)	0.97	0.69 to 1.36	1.17	0.80 to 1.69
Nonwhite (reference = white)	1.16	0.80 to 1.66	1.34	0.89 to 2.00
Antiretroviral medications (reference = 0), n				
1	0.41	0.11 to 1.46	0.56	0.15 to 2.12
2	0.81	0.45 to 1.43	0.93	0.50 to 1.72
3	1.07	0.63 to 1.81	1.04	0.59 to 1.86
4	1.13	0.56 to 2.29	1.15	0.54 to 2.45
5	3.09 [§]	1.22 to 7.80	2.31	0.83 to 6.38
≥6	1.52	0.49 to 4.76	1.12	0.34 to 3.74

* Log likelihood ratio = 95; df = 13.

[†] $P < .001$.

[‡] $P < .01$.

[§] $P < .05$.

Table 4. Time to Death: Cox Proportional Hazards Model Results (N = 780)

	Unadjusted Results		Adjusted Results*	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
HIV symptom count (0–20)	1.03 [†]	1.01 to 1.05	1.02 [‡]	1.00 to 1.05
CES-D score (reference = 0–9)				
10–14	2.03 [§]	1.02 to 4.02	1.52	0.74 to 3.14
>15	2.22 [§]	1.14 to 4.30	1.50	0.69 to 3.25
CD4 cell count <200 (reference = CD4 count ≥200)	3.36	1.93 to 5.86	2.74 [†]	1.54 to 4.90
Viral load ≥500 copies (reference = <500 copies)	3.69	1.84 to 7.38	2.97 [†]	1.44 to 6.13
Age, y <50 (reference = age ≥50)	1.20	0.69 to 2.09	1.43	0.81 to 2.51
Nonwhite (reference = white)	1.04	0.59 to 1.86	1.04	0.58 to 1.88
Antiretroviral medications (reference = 0), n				
1	0.82	0.16 to 4.05	1.16	0.23 to 5.86
2	0.88	0.33 to 2.35	1.21	0.45 to 3.26
3	0.96	0.38 to 2.38	0.99	0.39 to 2.50
4	1.40	0.47 to 4.17	1.24	0.41 to 3.75
5	0.61	0.07 to 5.09	0.49	0.06 to 4.15
≥6	1.42	0.29 to 7.06	1.14	0.23 to 5.76

* Censor date is patients' last visit date; C-Statistic = 0.74.

[†] P < .01.

[‡] P = .05.

[§] P < .05.

^{||} P < .001.

higher mean symptom count not only for symptoms considered affective (e. g., anxiety) but also for "physical" (somatic) symptoms.

The high prevalence of depression, and its association with HIV-related symptoms is not surprising, and is consistent with previous studies of medical patients in general^{34,35} and of HIV-infected patients in care in particular.^{16,22,36} Previous studies report a depression prevalence of near 50% among HIV-infected patients presenting for care,^{36,37} similar to what we found.

Yet depressive symptoms among the patients in our sample were not significantly associated with survival after adjusting for HIV symptoms and other factors (CD4 cell count, viral load, age, race, and ARV use). In contrast, HIV symptoms were independently associated with provider-reported severity of illness and survival, whereas depressive symptoms were not associated with these outcomes after adjustment.

To our knowledge, this is the first report to compare the role of depressive and HIV symptoms on mortality using a validated HIV Symptom Index that included a comprehensive array of symptoms. While our results are consistent with other reports that suggest depressive symptoms are not associated with HIV illness progression,^{14–16} other studies suggest the opposite.^{13,17,18} Prior research in both the pre- and post-HAART era that assessed the impact of depressive symptoms on HIV disease progression and mortality controlled for relatively few HIV-related symptoms. Lyketsos et al. found that depression had no independent effect on AIDS-free survival time and overall mortality among men enrolled in the Multicenter AIDS Cohort Study. HIV symptoms (having "any" versus "none" out of 6 symptoms) were significantly associated with time

to AIDS.¹⁴ Symptoms measured by Lyketsos et al. (1993) included diarrhea, fatigue, fever, rash, thrush, and weight loss.

In contrast, among a sample of women with HIV infection, Ickovics et al. found an association between depressive symptoms (based on the CES-D excluding somatic symptoms related to HIV) and mortality, controlling for symptom count based on 6 HIV-related symptoms (oral thrush, diarrhea, fever, memory problems, neuropathy, weight changes).¹³ These differences in findings may be gender related, given that our study and the work by Lyketsos et al. were based primarily on a male population. Hence, potential gender differences regarding the clinical importance of symptoms should be explored in future research.

Our findings suggesting that HIV symptoms are independently associated with severity and survival after controlling for depression are of potential clinical importance. Some have speculated that providers who consider physical symptoms to be depression related may be less willing to follow up and subsequently treat the symptom. In a survey of over 200 providers using patient scenarios, providers were less likely to believe that a patient with a prior psychiatric history who presented a new symptom had a potentially serious physical illness.¹⁹ This is perhaps due to the provider's perception that patients with depression exaggerate or somatize their physical symptoms,^{38,39} although this is not always the case.⁴⁰ Providers may also express different attitudes toward their depressed compared to nondepressed patients. In one study, patients identified as "difficult" by their providers were more likely to be depressed and more likely to seek care.⁴¹ In addition, the poor agreement between patient- and provider-reported

depression might potentially be problematic in that providers may assume that clinically significant symptoms are depression related among nondepressed patients. For HIV-infected patients in particular, providers who assume that symptoms are depression related might hesitate to prescribe a more complex antiretroviral regimen, especially if they feel that depression might hinder adherence to the medications.^{42,43}

We recognize the following limitations of this study. The cross-sectional nature of the data brings up the issue of temporal ambiguity by preventing us from determining whether depression leads to greater frequency and bother from symptoms and/or whether the greater frequency and bother from symptoms leads to depression. Distinguishing symptoms that may have psychological or physical origins can be difficult without longitudinal data on symptom progression. Cross-sectional data also prevented us from measuring changes in depressive symptoms, although other researchers have reported that mood tends to remain stable among HIV-infected patients, even with increased HIV illness severity.^{2,3,16}

Second, while we did not find a significant problem with collinearity, such findings comparing the clinical significance of depressive and HIV or other physical symptoms need to be interpreted with caution because of the potential for overlap between depressive and physical symptoms. Although we found no significant interaction between depressive symptoms and HIV symptom count, our power to detect such interactions was low. Because of the cross-sectional nature of the study, further studies are needed to confirm the degree to which depression might have an independent effect on prognosis, given that previous studies are conflicting or inconclusive on this issue.¹³⁻¹⁸

In addition, we employed the CES-D 10-item survey to identify depression, which has limited validity when compared to diagnostic criteria for major depression. While the CES-D 10-item survey was highly correlated with the CES-D 20, formal psychiatric interview remains the gold standard for diagnosing depression, and can better distinguish depressive symptoms attributed to physical or emotional illness. We attempted to mitigate the impact of the measure's low specificity by using 2 different cut points to distinguish patients with more moderate and severe depressive symptoms. We also performed analyses excluding symptoms that overlapped with the HIV Symptom Index, as well as using ICD-9 diagnostic codes to define depression, and similar results were obtained.

We had only 53 deaths for the survival analyses, which limited our power to detect differences in mortality. Our primarily male population that received care at 3 VA sites may limit the generalizability of our findings. Still, VACS 3 includes a large proportion of older, minority, HIV-infected patients, which is expected to become the predominant HIV-infected patient population in the near future.⁴⁴

In conclusion, our data suggest that HIV symptoms may have the same association with severity of illness and survival regardless of the patient's severity of depressive

symptoms. Therefore, if our results are generalizable, providers may want to consider possible physical problems associated with symptoms among patients with depression, and not assume the symptoms are somatic manifestations of depression. Providers may want to give equal consideration to clinical symptoms presented by HIV-infected patients, regardless of their depression status, rather than automatically attributing medical complaints to depression.

The primary funding sources were from a National Institute of Aging (NIA) Career Development Award, a Robert Wood Johnson Faculty Scholar Award, and an Inter-agency Agreement between the NIA, National Institute of Mental Health, and the Department of Veterans Affairs (Dr. Justice, PI). Dr. Rabeneck is the recipient of a VA Health Services Research and Development Advanced Research Career Development Award.

REFERENCES

1. Kalichman SC, Rompa D, Cage M. Distinguishing between overlapping somatic symptoms of depression and HIV disease in people living with HIV-AIDS. *J Nerv Ment Dis*. 2000;188:662-70.
2. Lyketsos CG, Hoover DR, Guccione M, et al. Depressive symptoms over the course of HIV infection before AIDS. *Soc Psychiatry Psychiatr Epidemiol*. 1996;31:212-9.
3. Lyketsos CG, Hoover DR, Guccione M, et al. Changes in depressive symptoms as AIDS develops. The Multicenter AIDS Cohort Study. *Am J Psychiatry*. 1996;153:1430-7.
4. Griffin KW, Rabkin JG, Remien RH, Williams JB. Disease severity, physical limitations and depression in HIV-infected men. *J Psychosom Res*. 1998;44:219-27.
5. Hoover DR, Saah AJ, Bacellar H, et al. Signs and symptoms of "asymptomatic" HIV-1 infection in homosexual men. Multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr*. 1993;6:66-71.
6. Justice AC, Rabeneck L, Hays RD, Wu AW, Bozzette SA. Sensitivity, specificity, reliability, and clinical validity of provider-reported symptoms: a comparison with self-reported symptoms. Outcomes Committee of the AIDS Clinical Trials Group. *J Acquir Immune Defic Syndr*. 1999;21:126-33.
7. Justice AC, Chang CH, Rabeneck L, Zackin R. Clinical importance of provider-reported HIV symptoms compared with patient-report. *Med Care*. 2001;39:397-408.
8. Lorenz KA, Shapiro MF, Asch SM, Bozzette SA, Hays RD. Associations of symptoms and health-related quality of life: findings from a national study of persons with HIV infection. *Ann Intern Med*. 2001;134:854-60.
9. Cunningham WE, Shapiro MF, Hays RD, et al. Constitutional symptoms and health-related quality of life in patients with symptomatic HIV disease. *Am J Med*. 1998;104:129-36.
10. Wilson IB, Cleary PD. Clinical predictors of declines in physical functioning in persons with AIDS: results of a longitudinal Study. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997;16:343-9.
11. Wilson IB, Roubenoff R, Knox TA, Spiegelman D, Gorbach SL. Relation of lean body mass to health-related quality of life in persons with HIV. *J Acquir Immune Defic Syndr*. 2000;24:137-46.
12. Wheeler DA, Gilbert CL, Launer CA, et al. Weight loss as a predictor of survival and disease progression in HIV infection. Terry Bein community programs for clinical research on AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;18:80-5.
13. Ickovics JR, Hamburger ME, Vlahov D, et al. Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women: longitudinal analysis from the HIV Epidemiology Research Study. *JAMA*. 2001;285:1466-74.

14. Lyketsos CG, Hoover DR, Guccione M, et al. Depressive symptoms as predictors of medical outcomes in HIV infection. Multicenter AIDS Cohort Study. *JAMA*. 1993;270:2563-7.
15. Lyketsos CG, Federman EB. Psychiatric disorders and HIV infection: impact on one another. *Epidemiol Rev*. 1995;17:152-64.
16. Rabkin JG, Goetz RR, Remien RH, Williams JB, Todak G, Gorman JM. Stability of mood despite HIV illness progression in a group of homosexual men. *Am J Psychiatry*. 1997;154:231-8.
17. Burack JH, Barrett DC, Stall RD, Chesney MA, Ekstrand ML, Coates TJ. Depressive symptoms and CD4 lymphocyte decline among HIV-infected men. *JAMA*. 1993;270:2568-73.
18. Leserman J, Jackson ED, Petitto JM, et al. Progression to AIDS: the effects of stress, depressive symptoms, and social support. *Psychosom Med*. 1999;61:397-406.
19. Graber MA, Bergus G, Dawson JD, Wood GB, Levy BT, Levin I. Effect of a patient's psychiatric history on physicians' estimation of probability of disease. *J Gen Intern Med*. 2000;15:204-6.
20. Smola S, Justice AC, Wagner J, Rabeneck L, Weissman S, Rodriguez-Barradas M. Veterans aging cohort three-site study (VACS 3): overview and description. *J Clin Epidemiol*. 2001;54(suppl 1):61-76.
21. Andresen EM, Carter WB, Malmgren JA, Patrick DK. Screening for depression in well older adults: evaluation of a short form of the CES-D. *Am J Prev Med*. 1994;10:77-84.
22. Low-Beer S, Chan K, Yip B, et al. Depressive symptoms decline among persons on HIV protease inhibitors. *J Acquir Immune Defic Syndr*. 2000;23:295-301.
23. Mulrow CD, Williams JW Jr, Gerety MB, Ramirez G, Montiel OM, Kerber C. Case-finding instruments for depression in primary care settings. *Ann Intern Med*. 1995;122:913-21.
24. Zich JM, Attkisson CC, Greenfield TK. Screening for depression in primary care clinics: the CESD and the BDI. *Int J Psychiatry Med*. 1990;20:259-77.
25. Symptom Index HIV. AIDS Clinical Trials Group (ACTG) of the National Institute of Allergy and Infectious Disease. Available at: http://www.fstrf.org/qol/adult_ql.html. Accessed May 8, 2002.
26. Justice AC, Holmes W, Gifford AL, et al. Development and validation of a self-completed HIV symptom index. *J Clin Epidemiol*. 2001;54(suppl 1):77-90.
27. Charlson ME, Sax FL, MacKenzie R, Fields SD, Braham RL, Douglas RG. Assessing illness severity: does clinical judgment work? *J Chronic Dis*. 1986;39:439-52.
28. Knaus WA, Harrell FE, Lynn J, et al. The SUPPORT prognostic model: objective assessments of survival for seriously ill hospitalized adults. *Ann Intern Med*. 1995;122:191-203.
29. McKlish DK, Powell SH. How well can physicians estimate mortality in a medical intensive care unit? *Med Decis Making*. 1989;9:125-32.
30. Fisher SG, Weber L, Goldberg J, et al. Mortality ascertainment in the veteran population: alternatives to the National Death Index. *Am J Epidemiol*. 1995;141:242-50.
31. Harrell FE Jr, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modeling strategies for improved prognostic prediction. *Stat Med*. 1984;3:143-52.
32. Office of Quality and Performance, Veterans Health Administration and the Health Quality Assessment Project, Center for Health Quality, Outcomes and Economic Research. Health Status and Outcomes of Veterans: Physical and Mental Component Summary Scores: Veterans SF-36 1999 Large Health Survey of Veteran Enrollees Executive Report. Washington, DC: Department of Veterans Affairs; 2000.
33. Druss BG, Rosenheck RA. Locus of mental health treatment in an integrated service system. *Psychiatr Serv*. 2000;51:890-2.
34. Kroenke K, Spitzer RL, Williams JB, et al. Physical symptoms in primary care. Predictors of psychiatric disorders and functional impairment. *Arch Fam Med*. 1994;3:774-9.
35. Katon W, Sullivan M, Walker E. Medical symptoms without identified pathology: relationship to psychiatric disorders, childhood and adult trauma, and personality traits. *Ann Intern Med*. 2001;134:917-25.
36. Lyketsos CG, Hutton H, Fishman M, Schwartz J, Treisman GJ. Psychiatric morbidity on entry to an HIV primary care clinic. *AIDS*. 1996;10:1033-9.
37. Sherbourne CD, Hays RD, Fleishman J, et al. Impact of psychiatric condition on health-related quality of life in persons with HIV infection. *Am J Psychiatry*. 2000;157:248-54.
38. Gerber PD, Barrett JE, Barrett JA, et al. The relationship of presenting physical complaints to depressive symptoms in primary care patients. *J Gen Intern Med*. 1992;7:170-3.
39. Mechanic D. Effects of psychological distress on perceptions of physical health and use of medical and psychiatric facilities. *J Human Stress*. 1978;4:26-32.
40. Suh T, Gallo JJ. Symptom profiles of depression among general medical service users compared with specialty mental health service users. *Psychol Med*. 1997;27:1051-63.
41. Hahn SR, Kroenke K, Spitzer RL, et al. The difficult patient: prevalence, psychopathology, and functional impairment. *J Gen Intern Med*. 1996;11:1-8.
42. Bangsberg DR, Moss A. When should we delay highly active antiretroviral therapy? *J Gen Intern Med*. 1999;14:446-8.
43. Centers for Disease Control and Prevention. Update: trends in AIDS incidence, deaths, and prevalence—United States, 1996. *Morb Mortal Wkly Rep*. 1997;46:165-73.

APPENDIX A

Symptom and Depression Measures

The following questions ask about symptoms you might have had during the past 4 weeks. Please circle the one response that best describes how much you have been bothered by each symptom.

HIV Symptom Index	I have this symptom and...				
	I do not have this symptom	It doesn't bother me	It bothers me a little	It bothers me	It bothers me a lot
a. Fatigue or loss of energy?*	1	2	3	4	5
b. Fevers, chills, or sweats?	1	2	3	4	5
c. Feeling dizzy or lightheaded?	1	2	3	4	5
d. Pain, numbness, or tingling in the hands or feet?	1	2	3	4	5
e. Trouble remembering?*	1	2	3	4	5
f. Nausea or vomiting?	1	2	3	4	5
g. Diarrhea or loose bowel movements?	1	2	3	4	5
h. Felt sad, down, or depressed?*	1	2	3	4	5
i. Felt nervous or anxious?*	1	2	3	4	5
j. Difficulty falling or staying asleep*	1	2	3	4	5
k. Skin problems, such as rash, drying, or itching?	1	2	3	4	5
l. Cough or trouble catching your breath?	1	2	3	4	5
m. Headache?	1	2	3	4	5
n. Loss of appetite or change in the taste of food?	1	2	3	4	5
o. Bloating, pain, or gas in your stomach?	1	2	3	4	5
p. Muscle aches or joint pain?	1	2	3	4	5
q. Problems with having sex, such as loss of interest or lack of satisfaction?	1	2	3	4	5
r. Changes in the way your body looks, such as fat deposits or weight gain?	1	2	3	4	5
s. Problems with weight loss or wasting?	1	2	3	4	5
t. Hair loss or changes in the way your hair looks?	1	2	3	4	5

CES-D 10-item Survey

For each of these statements, please indicate how often you felt this way during the past week.

During the past week...	I have this symptom and...			
	Rarely (<1 day)	Some/little (1–2 days)	Much (3–4 days)	Most (5–7 days)
a. I was bothered by things that usually don't bother me	1	2	3	4
b. I had trouble keeping my mind on what I was doing*	1	2	3	4
c. I felt that everything I did was an effort	1	2	3	4
d. I felt depressed*	1	2	3	4
e. I felt hopeful about the future	1	2	3	4
f. I felt fearful*	1	2	3	4
g. My sleep was restless*	1	2	3	4
h. I was happy	1	2	3	4
i. I felt lonely	1	2	3	4
j. I could not get "going"*	1	2	3	4

* These symptoms were excluded to create CES-D 5 and HIV symptom 15-item index.