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Cobalamin level is related to self-reported and clinically rated mood and to syndromal depression in bereaved HIV-1$^+$ and HIV-1$^-$ homosexual men

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Abstract

Objective: An examination of the relationship of plasma cobalamin (vitamin B_{12}) level to overall psychological distress, specific mood states, and major depressive disorder was conducted in 159 bereaved men (90 HIV-1$^+$ and 69 HIV-1$^-$). **Methods:** The relationship of a continuous measure of cobalamin level to psychological distress was examined, while controlling for HIV-1 serostatus, life stressors, social support, and coping styles. **Results:** Of this sample, 23.9% were either overtly or marginally cobalamin deficient; however, the deficiency rate was not significantly different by HIV-1 serostatus. Cobalamin level was inversely related to self-reported overall distress level and specifically to depression, anxiety, and confusion subscale scores, as well as to clinically rated depressed and anxious mood. Lower plasma cobalamin levels also were associated with the presence of symptoms consistent with major depressive disorder. **Conclusion:** These findings suggest that cobalamin level may be physiologically related to depressed and anxious mood level, as well as to syndromal depression.

Keywords: Cobalamin; Depression; Anxiety; Distress, HIV-1 infection; Vitamin B_{12}

Introduction

Cobalamin (vitamin B_{12}) is an important micronutrient that is involved in many aspects of physiological functioning, including DNA synthesis, red blood cell production, and myelin synthesis. There are well-documented laboratory abnormalities and clinical sequelae associated with cobalamin deficiency, including fatigue [1,2], macrocytosis and pernicious anemia, peripheral neuropathy, and progressive demyelination, particularly of the spinal cord [3,4]. Moreover, various neuropsychological changes have been linked to cobalamin deficiency, such as confusion, memory impairment, and slowed information processing [3,5], as well as the clinical syndrome of dementia [6,7].

Cobalamin deficiency has also been found to be related to psychiatric disturbance in some [1,4,8,9], but not all, studies [10,11]. Lower cobalamin levels have been noted to be associated with increased overall psychological distress [6,12], as well as with specific mood states, including depressed [1,13], anxious, and irritable mood [14]. Regarding depressed mood, in some reports, cobalamin deficiency has been found to be associated specifically with psychotic depression [8,9,15]. Several investigators have noted that depression [16,17] and psychotic symptoms [18–20] are reversible with cobalamin supplementation. In fact, in a review of the psychiatric literature from the 1920s to the 1980s, Hector and Burton [14] found 16 studies demonstrating improvement of symptoms of mood disturbance and other psychiatric symptoms with cobalamin supplementation.

Numerous studies examining nutritional status in HIV-1 infected patients have found that abnormally low values of specific micronutrients are a relatively frequent occurrence in this population. Herbert et al. [21] reported that cobalamin deficiency is common and may be present in about 50% of HIV-1$^+$ individuals,

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whereas other studies have reported slightly lower deficiency rates of 25% of asymptomatic HIV-1$^+$ individuals [5] and 27% of AIDS patients [22]. Several factors may account for increased micronutrient deficiencies (such as cobalamin) in HIV-1$^+$ individuals, including inadequate intake and/or absorption, defective nutrient utilization, increased excretion, and increased metabolic demand due to infection. In addition, alcoholism can lead to cobalamin deficiency through poor diet (lack of intake) and/or alcohol's antagonism of cobalamin absorption [3].

The present investigation examined the relationship of cobalamin level to psychological distress level and to the presence of depressive and anxiety disorders in HIV-1$^+$ and HIV-1$^-$ individuals, and to potential differences by HIV-1 serostatus. Based on prior research, it was hypothesized that cobalamin levels would be inversely related to self-reported overall psychological distress, and to the specific mood states of depression, anxiety, anger, fatigue, and confusion, while being positively related to vigor. Furthermore, it was expected that the inverse relationship between cobalamin and depressed and anxious mood levels would be maintained on clinical rating scales. In addition, it was predicted that low cobalamin levels would be associated with a higher frequency of depressive and anxiety disorders, and specifically with major depressive disorder. Because our prior work [23–26] has demonstrated the importance of utilizing a stressor–support–coping (SSC) model in accounting for variance in psychological distress, we included negatively rated stressful life-event burden, social support availability, and four coping styles as controls for potentially confounding effects on distress. In addition, pyridoxine (vitamin B_6) level was controlled for in these analyses, as our prior work has demonstrated a relationship between pyridoxine level and distress [27,28], thus better allowing for differentiation of the specific micronutrient effect of cobalamin.

Methods

Subjects

The sample consisted of 159 bereaved homosexual men (90 HIV-1$^+$ and 69 HIV-1$^-$) who were evaluated at the baseline of a randomized clinical trial of a bereavement support group intervention. Within the 6 months prior to enrollment, subjects experienced the loss of a close friend or intimate partner to AIDS and reported a negative impact of this loss. Exclusion criteria at entry were: (1) CD4 cell count <50 cells/mm^3; (2) HIV-1 related opportunistic infection or tumor requiring treatment at enrollment; (3) dependence on alcohol or other psychoactive substances within the past 6 months; (4) intravenous substance use within the past 2 years; (5) history of or current major psychiatric disorder likely to make a subject ineligible for the support group intervention (e.g., HIV-1 associated dementia, psychosis, or bipolar affective disorder); and (6) use of prescribed immunostimulants.

Procedures and measures

Following informed consent, subjects completed psychosocial questionnaires, a structured clinical interview for psychopathology, a medical history and physical examination, and phlebotomy, while fasting, 30 minutes after insertion of a peripheral indwelling venous catheter.

Independent measure

Plasma cobalamin level and status. Plasma cobalamin level was examined as a continuous measure. In this study, the normal range was defined as 240 to 1000 pg/ml, marginal deficiency as 200 to 240 pg/ml, and overt deficiency as <200 pg/ml. Cobalamin level was determined by a radioisotope dilution assay [29].

Dependent measures—psychological distress

Self-reported mood state. A 65-item self-report measure, the Profile of Mood States (POMS [30]), was used to measure overall psychological distress with subscales for depression-dejection, tension-anxiety, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. Subjects used a five-point rating scale to describe their mood over the prior week. Overall distress was measured as the POMS total mood disturbance score (TMD), which is a composite score of the sum of the other five subscales minus the vigor-activity subscale score.

Clinical rating scales. The Structured Interview Guide for the Hamilton Anxiety and Depression Rating Scales (SIGH-AD [31]) is an examiner-administered clinical mood rating scale containing the 17-item Hamilton Rating Scale for Depression (HRSD [32]) and the 14-item Hamilton Anxiety Rating Scale (HARS [33]). This instrument has been modified for patients with HIV-1 infection and has subscale scores for each scale excluding the somatic items, allowing a differentiation of a subset of mood symptoms that may be expected to be more specifically related to mood state than to HIV-1 infection itself.

Syndromal depression and anxiety. The Structured Clinical Interview for DSM-III-R Axis I disorders (nonpatient version), modified for the HIV-1 infected (SCID-NP-HIV [34]), was used to interview subjects for current depression and anxiety disorders including: major depressive disorder (MDD); dysthymic disorder; panic disorder; generalized anxiety disorder; and adjustment disorder with depressed or with anxious mood.

Control variables

Negative life stressors. Major life events occurring over the prior 6 months were measured as the number of negatively rated events using our modification of the

Life Experiences Survey [35]. Additional modifications reported previously [24] were made for homosexual men with HIV-1 related concerns.

Social support. Perceived available social support was measured with the six-item short form of the Social Support Questionnaire-6 [36], which assesses the total number of potentially available supportive persons listed across items.

Coping style. The 52-item dispositional COPE [37], was used to measure 13 behaviorally specific coping strategies. As described in our prior work [24–26], for the purpose of data reduction, factor analysis generated four coping variables represented by two composite scores ("active coping" and "disengagement/denial") and two single subscales ("focus on and venting of emotion" and "turning to religion").

Albumin. Serum albumin level was measured by standard rate nephelometry [38]. Normal values were 3.5 to 5.5 g/dl, and subjects with albumin values of <3.5 g/dl were excluded from the study due to inadequate general nutritional status.

Pyridoxine (vitamin B_6). Plasma pyridoxine status was determined by a bioassay of erythrocyte transaminase activity [39] and was used as a continuous variable. Results were reported as an activity coefficient (AC), with higher values of the activity coefficient indicating lower levels of pyridoxine activity. Normal values were an AC < 1.85.

CDC staging. 1993 Centers for Disease Control and Prevention clinical staging [40], determined by a medical history and physical examination, was used to characterize HIV-1 disease progression in the sample.

Antiretroviral medication and multivitamin use. Antiretroviral medication and multivitamin use were recorded as separate categorical variables (yes/no).

Constitutional symptoms. 1993 CDC stage defining constitutional symptoms (fever, diarrhea, fatigue, night sweats, and weight loss of >10% of body weight) were noted as being present or absent at assessment.

Substance use. Self-report of alcohol and other psychoactive substance use was recorded by class of substance (alcohol, marijuana, opioids, cocaine, amphetamines, sedatives, hallucinogens, and others). Frequency of use over the past 6 months was rated as follows: 0 = never/none; 1 = tried or rarely used; 2 = monthly or less; 3 = less than weekly, but more than monthly; 4 = less than daily, but more than weekly; 5 = daily or more.

Statistical methods

All calculations were done with SAS, version 6.12 [41]. Differences in the frequency of cobalamin deficiency by HIV-1 serostatus were calculated by a chi-square test and serostatus differences in mean cobalamin level were calculated using a Student's *t*-test. The relationship of cobalamin level and psychological distress, controlling for HIV-1 serostatus and psychosocial factors (life stressors, social support, and coping style), was estimated using multiple regression analysis. To examine the relationship of cobalamin level to major depressive disorder, a logistic regression model was used, including the aforementioned control variables.

Significant relationships between cobalamin level and distress were confirmed by post hoc multiple regression analyses including controls for other factors that could affect distress level or cobalamin level: pyridoxine activity; prescribed antiretroviral medication use; constitutional symptoms; weight loss; and multivitamin use. In addition, tests for the influence of substance use were conducted for alcohol or other psychoactive substances showing a Spearman rank-order correlation of $p < 0.20$ (to avoid type II error) with any of the outcome measures.

Results

The sample was composed of HIV-1^+ and HIV-1^- homosexual men who were Caucasian (65%), Hispanic (23%), African American (9%), or of other/mixed ethnicity (3%). Generally, they were in their 30s and 40s (mean age = 38.34 years, SD = 9.14), well-educated (mean years = 14.72, SD = 2.30), and had a modal annual income of $20,000 to $29,999. The HIV-$1^+$ subjects were predominantly early symptomatic (n = 68), with fewer asymptomatic (n = 17) and late symptomatic (n = 5) subjects. The mean CD4 cell count for the HIV-1^+ subjects was 369 cells/mm^3 (SD = 251), indicative of moderate immunological progression (i.e., 1993 CDC stage 2, 200 to 499 cells/mm^3).

Plasma cobalamin levels in the sample ranged from 42 to 1917 pg/ml, with a mean of 433 pg/ml (SD = 274), which is in the normal range (median = 359 pg/ml). The high end of the range of cobalamin level was due to several subjects with super-normal cobalamin levels, likely related to cobalamin supplementation. Of the total sample, 15.7% displayed overt cobalamin deficiency (8.2% HIV-1^+ and 7.5% HIV-1^-) and an additional 8.2% showed marginal levels of deficiency (5.6% of HIV-1^+ and 2.6% of HIV-1^-), totaling 23.9%. There was no statistically significant difference in mean cobalamin level between the HIV-1^+ and HIV-1^- groups [$t(157) = 1.03$, $p = 0.30$]. Likewise, there was no difference in the frequency of overt or marginal deficiency by HIV-1 serostatus [$\chi^2(1) = 0.34$, $p = 0.85$]. The mean albumin level in the total sample was 4.05 g/dl (SD = 0.24) and the mean pyridoxine activity coefficient was 1.61 (SD = 0.37) — both within the normal range.

Self-reported levels of psychological distress, as measured by the POMS total mood disturbance score (TMD) ranged from –21 to 179, with a mean of 44.69 (SD = 38.38), a level indicative of mild distress, as would be expected in a bereaved population. The multiple regression analysis results on the TMD revealed that the analytical model, including cobalamin level, HIV-1

Table 1
Multiple regression models β-coefficients and (standard error) for POMS TMD and subscales[a]

Variables	Total mood disturbance	Depression-dejection	Tension-anxiety	Anger-hostility	Vigor-activity	Fatigue-inertia	Confusion-bewilderment
Cobalamin level	−0.02	−0.01	−0.004	−0.004	0.003	−0.003	−0.004
	(0.01)	(0.003)	(0.002)	(0.003)	(0.002)	(0.002)	(0.001)
	0.02*	0.05*	0.05*	0.09	0.10	0.13	0.01**
HIV-1 serostatus	3.92	1.29	1.35	0.34	−0.27	−0.36	1.02
	(5.66)	(1.84)	(1.15)	(1.41)	(1.08)	(1.06)	(0.77)
	0.49	0.48	0.24	0.81	0.80	0.74	0.19
Negative life stressor count	0.17	0.08	0.04	0.07	0.08	−0.04	0.05
	(0.48)	(0.16)	(0.10)	(0.12)	(0.09)	(0.09)	(0.07)
	0.73	0.62	0.70	0.58	0.41	0.65	0.46
Social support availability	−0.14	−0.02	−0.03	−0.04	0.02	−0.04	0.01
	(0.27)	(0.09)	(0.05)	(0.07)	(0.05)	(0.05)	(0.04)
	0.61	0.79	0.64	0.58	0.71	0.41	0.76
Active coping	−0.44	−0.19	−0.05	−0.03	0.06	−0.06	−0.04
	(0.24)	(0.08)	(0.05)	(0.06)	(0.05)	(0.04)	(0.03)
	0.07	0.01**	0.27	0.61	0.15	0.17	0.28
Disengagement and denial	1.65	0.60	0.24	0.30	−0.08	0.21	0.24
	(0.50)	(0.16)	(0.10)	(0.12)	(0.10)	(0.09)	(0.07)
	0.001***	0.0003***	0.02*	0.02*	0.43	0.03*	0.0006***
Focus on and venting of emotion	3.02	0.94	0.49	0.97	−0.01	0.27	0.34
	(0.94)	(0.30)	(0.19)	(0.23)	(0.18)	(0.18)	(0.13)
	0.002**	0.002**	0.01**	0.0001***	0.97	0.13	0.008**
Turning to religion	−1.29	−0.37	−0.23	−0.21	0.18	−0.11	−0.20
	(0.67)	(0.22)	(0.14)	(0.17)	(0.13)	(0.12)	(0.09)
	0.05*	0.09	0.10	0.22	0.15	0.38	0.03*
Intercept	39.76	16.74	11.61	0.26	7.59	11.03	7.71
	(24.61)	(8.00)	(5.00)	(6.12)	(4.70)	(4.61)	(3.34)
Model F	6.41	7.16	3.85	4.80	1.75	2.42	5.32
	0.0001***	0.0001***	0.0004***	0.0001***	0.09	0.02*	0.0001***
R^2 (% variance accounted for)	0.25	0.28	0.17	0.20	0.09	0.11	0.22

[a] Data presented as β-coefficient, standard error (in parentheses), and p-value.
* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$. Error $df = 150$; N = 159.

serostatus, and our SSC model control variables significantly predicted overall psychological distress ($p = 0.0001$). Cobalamin level was inversely related to overall distress level ($p = 0.02$) and accounted for 4% of the variance in this measure (see Table 1).

When examining the POMS subscales to determine the relationships with specific mood states, cobalamin level was significantly inversely associated with the depression-dejection ($p = 0.05$), tension-anxiety ($p = 0.05$), and confusion-bewilderment ($p = 0.01$) scores, after controlling for HIV-1 serostatus and the psychosocial variables.

On the total HRSD, scores ranged from 0 to 28, with a mean of 7.74 (SD = 5.71), which is also within the normal, nonclinical range. In the multiple regression analysis, the analytical model with cobalamin level and control variables was significantly associated with clinically rated depressed mood level ($p = 0.007$). Within this model, cobalamin level was inversely related to depressed mood ($p = 0.01$) and accounted for 4% of the variance on this measure. When omitting the somatic items from the HRSD total score, the model continued to be associated with depressed mood ($p = 0.03$), with cobalamin level retaining its significant inverse relationship with this outcome measure ($p = 0.009$) (see Table 2).

Scores on the total HARS ranged from 0 to 39, with a mean of 6.78 (SD = 6.46), which is within the normal, nonclinical range. The multiple regression analysis showed that the analytical model with cobalamin level and control variables was significantly associated with clinically rated anxious mood level ($p = 0.002$), with cobalamin level inversely related ($p = 0.003$) and accounting for 6% of the variance on this measure. When omitting the somatic items from the HARS score, the model continued to be associated with anxious mood ($p = 0.004$), with cobalamin level retaining its significant inverse relationship with anxious mood level ($p = 0.005$) (see Table 2).

Of the total sample of 159 subjects, 26 (16.4%) met DSM-III-R criteria for a current major depressive disorder (MDD) diagnosis or had bereavement-related depressive symptoms consistent with the diagnosis of MDD. Of this subsample, a significantly higher proportion had cobalamin levels that were in the overtly or marginally deficient ranges (42%), compared with only 20% of subjects not meeting MDD criteria [$\chi^2(1) =$

Table 2
Multiple regression models β-coefficients and (standard error) for HRSD and HARS[a]

Variables	HRSD (with somatic items)	HRSD (without somatic items)	HARS (with somatic items)	HARS (without somatic items)
Cobalamin level	−0.004	−0.004	−0.005	−0.003
	(0.002)	(0.001)	(0.002)	(0.001)
	0.01**	0.009**	0.003**	0.005**
HIV-1 serostatus	1.77	1.06	1.88	0.91
	(0.91)	(0.83)	(1.02)	(0.60)
	0.05*	0.21	0.07	0.13
Negative life stressor count	0.06	0.09	0.14	0.07
	(0.08)	(0.07)	(0.09)	(0.05)
	0.44	0.23	0.10	0.20
Social support availability	−0.03	−0.04	−0.06	−0.04
	(0.04)	(0.04)	(0.05)	(0.03)
	0.44	0.34	0.25	0.18
Active coping	−0.05	−0.03	−0.01	−0.01
	(0.04)	(0.03)	(0.04)	(0.03)
	0.23	0.43	0.76	0.77
Disengagement and denial	0.07	−0.004	0.08	0.05
	(0.08)	(0.07)	(0.09)	(0.05)
	0.39	0.96	0.39	0.35
Focus on and venting of emotion	0.18	0.22	0.25	0.15
	(0.15)	(0.14)	(0.17)	(0.10)
	0.24	0.11	0.14	0.14
Turning to religion	0.02	0.02	−0.05	−0.06
	(0.11)	(0.10)	(0.12)	(0.07)
	0.86	0.81	0.67	0.39
Intercept	10.94	9.21	7.13	4.76
	(3.96)	(3.63)	(4.42)	(2.60)
Model F	2.79	2.21	3.34	2.99
	0.007**	0.03*	0.002**	0.004**
R^2 (% variance accounted for)	0.13	0.11	0.15	0.14

[a] Data presented as β-coefficient, standard error (in parentheses), and p-value.
* $p \leq 0.05$; ** $p \leq 0.01$. Error $df = 150$; N = 159.

5.79, $p = 0.02$]. In a logistic regression analysis predicting the presence or absence of MDD, cobalamin level was a significant predictor ($p = 0.005$), controlling for HIV-1 serostatus and our SSC model control variables (see Table 3).

The data for the remaining depression and anxiety disorders were not analyzed due to the small number of subjects meeting criteria and insufficient statistical power for analyses: dysthymic disorder (n = 1); adjustment disorder with depressed mood (n = 3); adjustment disorder with anxious mood (n = 3); panic disorder (n = 1); and generalized anxiety disorder (n = 2).

Table 3
Logistic regression model solution for major depressive disorder

Variables	β-coefficient	p value
Cobalamin level	7.76	0.005**
HIV-1 serostatus	0.24	0.62
Negative life stressor count	0.12	0.73
Social support availability	0.11	0.74
Active coping	1.36	0.24
Disengagement and denial	0.59	0.44
Focus on and venting of emotion	0.01	0.97
Turning to religion	0.01	0.97
Intercept	0.37	0.54
Model χ^2	16.26	0.04*

* $p \leq 0.05$; ** $p \leq 0.01$.

In each of the respective post hoc multiple regression analyses adding, individually, pyridoxine activity, prescribed antiretroviral medication use, weight loss, constitutional symptoms, multivitamin supplementation, and alcohol or other psychoactive substance use (by type) as additional control variables, along with HIV-1 serostatus and the SSC model control variables, these models continued to be significantly associated with each of the mood outcome measures. Moreover, cobalamin level retained its level of statistical significance. As expected, subjects taking a multivitamin supplement were less likely to have cobalamin levels in the overtly or marginally deficient range (Fisher's exact test, $p = 0.04$) than subjects not taking a multivitamin supplement. Of interest, there was a significant inverse Spearman's correlation of cobalamin level with frequency of alcohol use in the previous 6 months ($r = -0.25$, $p = 0.002$). A Student's t-test between subjects who were overtly or marginally cobalamin deficient versus those with normal

cobalamin levels revealed that there was a higher mean frequency of alcohol use in subjects with marginal or deficient cobalamin levels [$t(156) = 2.00$, $p = 0.05$]. The mean frequency of alcohol use in subjects who had marginal or deficient cobalamin levels was "less than weekly, more than monthly," and was "monthly or less" in those with adequate or super-normal cobalamin levels.

Discussion

The findings of this investigation demonstrate a relationship between plasma cobalamin level and psychological distress on both self-report and clinical rating scale measures. This relationship was maintained when controlling for other factors that may influence mood state, such as HIV-1 serostatus, our SSC model variables (life stressor burden, social support availability, coping styles), pyridoxine activity, antiretroviral medication use, multivitamin use, constitutional symptoms, and the frequency of alcohol and other specific psychoactive substance use. When partitioning distress into its component mood states, relationships between cobalamin and depressed, anxious, and confused mood levels were uncovered. The finding that these associations existed while testing cobalamin level as a continuous measure suggests that levels of this micronutrient within the normal range may also have effects on mood, and that this relationship, therefore, is not restricted to deficiency states.

The association of plasma cobalamin level with three measures of depression—self-reported depressed mood on the POMS, clinically rated depressed mood on the HRSD (with and without somatic items), and diagnosis of major depressive disorder (allowing symptoms related to bereavement)—provides striking evidence supporting this relationship. Of those individuals who had symptoms consistent with major depressive disorder, the prevalence of marginal or deficient cobalamin levels was 42%, compared with only 20% in subjects not meeting criteria for major depression. The findings of this study are consistent with prior research reporting a relationship between cobalamin level and depression [1,13]. The maintenance of this association across the spectrum of depressed mood, from depressed mood within the normal, nondiagnosable range to clinically relevant depressed mood consistent with psychiatric disorder, suggests that this relationship is important across a wide range of depressed mood.

A relationship between plasma cobalamin level and anxious mood level was also supported in this study, as measured by both self-report and clinical rating. However, due to a low numbers of subjects meeting criteria for syndromal anxiety, the latter could not be examined and should be explored in future studies. Nevertheless, the fact that the association was maintained across both self-reported and clinically rated anxiety suggests that the observed relationship was not accounted for by a methodological bias in mood assessment. These data also imply that either of these mood rating measures may be adequate in detecting this relationship. The finding of the relationship of anxious mood with low levels of this micronutrient is consistent with an earlier report [14], but has not yet been adequately documented.

The association between plasma cobalamin level and confusion may be related to neuropsychological impairment and, in turn, a demyelinating process that may account for the decreased cognitive performance in cobalamin-deficient individuals [5,42] and may eventually lead to a clinical dementia [7]. This relationship may be more prominent in HIV-1^+ subjects, who are at increased risk for developing neuropsychological impairment related to HIV-1 infection of the brain, which is known to be a demyelinating process related to tumor necrosis factor-alpha secretion by activated HIV-1 infected macrophages [43,44]. However, neuropsychological testing would be required to determine whether this self-reported confusion is only a subjective complaint, or whether it is indicative of a detectable change in cognitive functioning.

There were no significant associations between plasma cobalamin level and angry/irritable mood, fatigue, or vigorous mood in this investigation. The lack of such findings may have been due to the somewhat smaller range of variance on these subscale scores and, hence, there may not have been sufficient power to uncover statistically significant relationships. Nevertheless, the lack of a significant association with fatigued mood state is surprising, given that a relationship between cobalamin level and fatigue has been frequently noted in the literature [1,2,4]. However, it is possible that fatigued mood state as measured by the POMS may represent a closer approximation of an individual's subjective level of mental, rather than physical, fatigue as noted in other research.

The finding that there was no difference in the prevalence of cobalamin deficiency between HIV-1^+ and HIV-1^- individuals in this investigation also was somewhat unexpected. This is likely to be related to stage of HIV-1 disease being predominantly non-AIDS and, therefore, subjects not having many of the complicating conditions that impair micronutrient absorption and uptake. Although the etiology of cobalamin deficiency was not examined in this sample, two factors were found to be associated with the presence of lower values of this micronutrient: a lack of multivitamin supplementation and a greater frequency of alcohol use. In regard to alcohol use, this finding was noteworthy, given that the frequency of self-reported alcohol use in this study was generally within the normal range, and that the mean self-reported frequency of use was "less than weekly, but more than monthly." Only three subjects in the sample met criteria for alcohol abuse at the time of the assess-

ment, as defined by the SCID-NP-HIV, and there were no subjects who met criteria for alcohol dependence, as this was a study exclusion criterion. Therefore, this finding suggests that alcohol use within the normal range (i.e., outside of abuse or dependence) may have a clinically significant influence on plasma cobalamin levels.

A note of caution in interpreting the findings of this study is that this sample was comprised of bereaved homosexual men, and hence, these findings may not be generalizable to other populations. This could potentially account for some of the discrepancy between these findings and those of other researchers who reported no association of cobalamin to mood in other populations where bereavement status was not identified [10,11]. However, bereavement is an unlikely source of this micronutrient deficiency, because weight loss—the most likely mediator—was controlled for as a global nutritional status variable. Moreover, our prior work has noted similar frequencies of cobalamin deficiency in other HIV-1^+ and HIV-1^- populations in which bereavement status was unidentified [5,42]. Furthermore, the addition of our SSC model controls for psychological distress level in this study may have also accounted for the uncovering of significant findings herein, especially given that several of these variables had significant relationships with the outcome measures (e.g., use of active coping being associated with lower levels of depressed mood). Moreover, cobalamin level only accounted for a small, although significant, percentage of the variance in distress in these analyses. Last, folate levels were not measured in this study. This may be an important variable to control for in future work due to the relationship between cobalamin and folate in 1-carbon fragment metabolism, and the fact that some laboratory abnormalities and clinical sequelae, such as macrocytic anemia and peripheral neuropathy, can result from either or both of these micronutrient deficiencies [45]. In addition, folate levels have been associated with depressed mood and, specifically, the duration of a depressive episode [15] and lack of response to antidepressant treatment [46,47].

Although the proportion of HIV-1^+ subjects with overt or marginal plasma cobalamin deficiency was not statistically greater than that of the HIV-1^- subjects in this study, several points may be of particular relevance for the HIV-1^+ population. Low cobalamin levels may potentiate HIV-1 associated vacuolar myelopathy, neuropsychological impairment, minor cognitive-motor disorder, and dementia. *S*-adenosyl methionine is a universal methyl-group donor involved in myelin synthesis and has been linked to affective disorders [48]. It is involved, as is methylcobalamin, in the synthesis of methionine from 5-methyltetrahydrofolate, which transfers its methyl group to homocysteine, forming methionine in a complex reaction catalyzed by cobalamin-dependent methionine synthase. Methionine is related to resistance to demyelinating disease processes such as HIV-1 infection of the central nervous system [49]. In addition, peripheral neuropathy, anemia, stomatitis, lipid abnormalities, and lack of appetite, all of which are common occurrences in HIV-1 infected individuals, may also be increased by cobalamin deficiency. Furthermore, cobalamin deficiency has been found to be related to decreased immune functioning, such as decreased CD4/CD8 ratios [50], decreased CD4 cell count over time [51], decreased lymphocyte proliferation [52], more rapid disease progression [53], and an increased risk for mortality, referable to HIV-1 conditions [53,54]. Hence, monitoring cobalamin levels in the cerebrospinal fluid may provide clinically relevant data regarding neurological functioning [55].

Although the data from this study do not address the issue of therapeutic supplementation, findings on the effects of cobalamin supplementation from other studies are promising. There have been no reported toxic effects related to the use of cobalamin supplementation [3,45]. Research has shown reversal of several psychiatric symptoms [14], cognitive difficulties [42,56], clinical neurological symptoms [4,6,57], and a case of apparent HIV-1 associated dementia [58] when cobalamin levels were restored to normal. Further studies are needed to determine whether cobalamin supplementation would reverse the mood state disturbances identified in this study in both HIV-1^+ and HIV-1^- individuals, and to determine optimal supplementation dosages, frequency, routes of administration, and whether supplementation in individuals having plasma cobalamin levels within the normal range would also prove to be of therapeutic benefit.

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