CD^{4+} T Cell Count, Sleep, Depression, and Anxiety in People Living With HIV: A Growth Curve Mixture Modeling

Yirong Shi, MSN, RN • Chongming Yang, PhD* • Liumei Xu, BSN, RN • Yun He, BSM • Hui Wang, BSM • Jing Cao, BSN, RN • Min Wen, BSN, RN • Weimei Chen, BSN, RN • Baohong Wu, RN • Suqing Chen, RN • Huiwen Chen, RN

Abstract

We investigated changes in CD^{4+} T cell counts related to sleep quality, depression, anxiety, and sociodemographic variables in heterogeneous groups of people living with HIV in a 6-month prospective study. Our longitudinal study involved 247 ambulatory patients living with HIV and using antiretroviral therapy. Sleep quality, anxiety, depression, and CD^{4+} T cell counts were assessed three times at 3-month intervals. Growth curve mixture modeling was conducted to explore changes over time. A two-class mixture model with logarithmic change pattern fit the data best. For the majority of the sample (89.1%), anxiety, depression, and sleep quality did not change when CD^{4+} T cells increased. For a small proportion of the sample (11.9%), sleep quality, anxiety, and depression deteriorated when CD^{4+} T cells decreased. Marital status and alcohol use affected the classification significantly. Health care professionals should provide relevant services to people living with HIV with decreasing CD^{4+} T cell counts.

Key words: anxiety, CD^{4+} T cells, depression, growth mixture modeling, HIV, sleep

Psychiatric co-morbidities of depression, anxiety, and sleep disorders have aroused increasing interest in the care of the approximately 1.2 million people living with HIV (PLWH) in China. A recent meta-analysis of 27 studies of more than 9,000 PLWH demonstrated that high levels of sleep disturbances affected approximately 58% of this population (Wu, Wu, Lu, Guo, & Li, 2015). Depression and anxiety are of particular concern among PLWH who are on antiretroviral therapy. The prevalence of depression among PLWH has been estimated at 40% (Lowther, Selman, Harding, & Higginson 2014;

Uthman, Magidson, Safren, & Nachega, 2014). Anxiety is also common, at 28%, as reported in another meta-analysis (Lowther et al., 2014).

A number of studies have shown associations between sleep disorders, depression, and anxiety. These symptoms are co-morbid or even reciprocally causal, as one disorder can seriously affect a patient's mental states, which, in turn, affects the prognoses (Rogers et al., 2018; Sherr, Clucas, Harding, Sibley, & Catalan, 2011). Specifically, patients with sleep disorders often develop anxiety and depression, and depressed patients often experience anxiety symptoms. Although frequently co-occurring, sleep problems, depression, and anxiety may be best understood as three separate disorders. The separation of these conditions is supported by several studies that have suggested an independent course of sleep quality, depression, and anxiety (Jackson, Sztendur, Diamond, Byles, & Bruck, 2014; Meerlo, Havekes, & Steiger, 2015; Watanabe et al., 2011). However, several studies have shown that the CD^{4+} T cell count of PLWH is a common influencing factor of all three (Duko, Geja, Zewude, & Mekonen, 2018; Olisah, Adekeye, & Sheikh, 2015; Redman, Karstaedt, & Scheuermaier, 2018).

Yirong Shi, MSN, RN, is a Staff Nurse, Department of Nursing, the Third People's Hospital of Shenzhen, Shenzhen, China. Chongming Yang, PhD, is a Statistical Consultant, Brigham Young University, Provo, Utah, USA. Liumei Xu, BSN, RN, is a Head Nurse, AIDS Outpatient, the Third People's Hospital of Shenzhen, Shenzhen, China. Yun He, BSM, is a Director, AIDS Outpatient, the Third People's Hospital of Shenzhen, Shenzhen, China. Hui Wang, BSM, is Director, Infection Unit 1, the Third People's Hospital of Shenzhen, Shenzhen, China. Jing Cao, BSN, RN, is Director, Nursing, the Third People's Hospital of Shenzhen, Shenzhen, China. Min Wen, BSN, RN, is Vice Director of Nursing, the Third People's Hospital of Shenzhen, Shenzhen, China. Weimei Chen, BSN, RN, is a Staff Nurse, AIDS Outpatient, the Third People's Hospital of Shenzhen, Shenzhen, China. Baohong Wu, RN, is a Staff Nurse, AIDS Outpatient, the Third People's Hospital of Shenzhen, Shenzhen, China. Suqing Chen, RN, is a Staff Nurse, AIDS Outpatient, the Third People's Hospital of Shenzhen, Shenzhen, China. Huiwen Chen, RN, is a Staff Nurse, AIDS Outpatient, the Third People's Hospital of Shenzhen, Shenzhen, China.

Corresponding author: Chongming Yang, e-mail: chongming_yang@email.byu.edu

Sleep and CD^{4+} T Cells

Research into the relationship between sleep quality and CD^{4+} T cells in PLWH has shown inconsistent results. Some studies have found a negative relationship: poor

sleep quality was associated with higher CD^{4+} T cell counts (Redman, et al., 2018). Others found no relationship (Nokes & Kendrew, 2001), whereas some studies found a positive relationship (Oshinaike et al., 2014; Seay et al., 2013), which seems to be the most likely scenario because as viral loads decrease and CD^{4+} T cell counts improve, and the overall health and sleep quality of PLWH should improve. Higher CD^{4+} T cell counts and poor sleep quality may reveal an underlying immune mechanism involved in the pathophysiology of HIV-related poor sleep quality. Gay et al. (2015), for example, showed an association between poor sleep quality in treated PLWH and cytokine levels/cytokine polymorphisms, which suggested that poor sleep quality in treated PLWH may have been caused by underlying immune activation.

Chronic immune activation was found in treated and well-controlled PLWH. Okulicz et al. (2015) found that later timing of treatment relative to seroconversion (>12 months) was associated with a higher percentage of effector CD^{4+} T cells expressing the human leukocyte antigen–DR isotype activation marker. In addition, the relationship between sleep quality and CD^{4+} T cells in PLWH differed in different ethnic groups. For PLWH of African descent in South Africa and in the San Francisco Bay Area, the relationship between sleep quality and CD^{4+} T cells was negative, whereas in Nigeria and the Caribbean, the relationship was positive (Seay et al., 2013). With such conflicting findings, it was difficult to ascertain the expected relationships between sleep quality and CD^{4+} T cells in Chinese PLWH.

Depression, Anxiety, and CD^{4+} T Cells

Researchers have explored the relationship between depression, anxiety, and CD^{4+} T cells in PLWH. Some studies suggested that a lower CD^{4+} T cell count independently contributed to depression and anxiety (Cui, Wang, & Qu, 2018; Varghese, 2013). In addition, as CD^{4+} T cells are sensitive indicators of the therapeutic effect of antiretroviral therapy and immune function, a decrease in CD^{4+} T cells suggests poor immune function, making the body susceptible to secondary infection. Knowing this may leave patients feeling that their treatment will be unsuccessful, thus resulting in anxiety and depression. However, other studies have found that a reduction in the number of CD^{4+} T cells is not associated with depressive symptoms (Fincham, Smit, Carey, Stein, & Seedat, 2008).

Depression and anxiety produce a nonspecific stress response mainly through the neuroendocrine–immune axis (Cui, Wang, & Qu, 2018). Sleep, anxiety, and depression were found to be associated with immune activation in PLWH (Gay et al., 2015; Wibbeler, Reichelt,

Husstedt, & Evers, 2012). Through this mechanism, CD^{4+} T cells are expected to be associated with anxiety and depression in PLWH.

Sleep, Depression, Anxiety, and CD^{4+} T Cells

Few studies have explored the relationship among sleep quality, depression, anxiety, and CD^{4+} T cells simultaneously; most have focused on the effects of CD^{4+} T cells on just one or two of these conditions. The general conclusion is that an individual's sleep quality and levels of depression and anxiety mainly stem from his/her inflammatory response and immune suppression (Byun, Gay, & Lee, 2016; Wibbeler et al., 2012). It is important to note that CD^{4+} T cells are inflammatory and immunosuppressive factors and seem to regulate sleep quality, depression, and anxiety dynamically in PLWH (Chen et al., 2017; Suzuki et al., 2017).

Background

Inconsistency in these findings might be ascribed to a nonexistent causal mechanism between CD^{4+} T cells and sleep quality, anxiety, and depression or to methodologic variations, including sampling methods (i.e., large normative samples vs. small clinical samples, cross-sectional studies vs. longitudinal studies, or included and omitted co-variates in models).

Given the inconsistent findings and few available longitudinal studies, we aimed to explore the dynamic relationship among sleep, anxiety, depression, and CD^{4+} T cells in a sample of Chinese PLWH using growth curve mixture modeling (Nagin, 2005) to identify subgroups of participants with dynamic changes in sleep, depression, anxiety, and CD^{4+} T cells. This modeling technique differed from the majority of techniques previously used that did not have longitudinal and mixture distribution components. We could not hypothesize how the potential subgroups would change dynamically before the data analysis.

Methods
Participants and Procedure

Participants were patients of the Hospital of Infectious Diseases outpatient clinic in Shenzhen, China. The Hospital of Infectious Diseases Ethics Committee approved this study. After signing informed consent forms, the participants voluntarily filled out a paper-and-pencil version of the measures from January to June 2017. Eligibility criteria for the study included the following: ages 18 years or older, diagnosed with HIV infection, and currently receiving health care from the clinic. Adult patients were selected for

the study because treatments were different for patients younger than 18 years. Exclusion criteria included AIDS-related cognitive impairment or complications diagnosed by a physician working in a hospital.

A total of 247 participants were selected for the study, including 236 (95.5%) men and 11 (4.5%) women. The average age was 30.6 years ($SD = 6.7$), and the range was a minimum of 18 years and maximum of 52 years. Education attainments ranged from elementary school or less ($n = 3$, 1.2%), middle school ($n = 51$, 20.6%), high school or vocational schools ($n = 90$, 36.4%), to college or higher ($n = 103$, 41.7%). Marital statuses were unmarried ($n = 160$, 64.8%), divorced ($n = 17$, 6.9%), and married ($n = 70$, 28.3%). At the time of the study, 214 (86.6%) were employed full time and 33 (13.4%) were unemployed. Participants were grouped by monthly income into less than ¥3,000 ($n = 32$, 13.0%), ¥3,000–5,000 ($n = 129$, 52.2%), and greater than ¥5,000 ($n = 86$, 34.8%). Seventy-eight (31.6%) were cigarette smokers, 92 (37.2%) used alcohol, and 77 (31.2%) used a sexual stimulant. HIV infections were contracted through homosexual behaviors ($n = 128$, 51.8%), heterosexual behaviors ($n = 47$, 19.0%), bisexual behaviors ($n = 47$, 19.0%), unknown sources ($n = 18$, 7.4%), and drug use, blood infusion, or mother to child ($n = 7$, 2.8%).

Participants completed their first assessments at the first visit and provided contact information for follow-up. The second assessment was performed 3 months later. Of the 247 participants assessed the first time, 242 (98.0%) participated in the second assessment. The final assessment was completed 6 months later, with 220 participants (89.1%) remaining in the study. An attrition rate of 10.9% was not worrisome for the analysis (Collins, Schafer, & Kam, 2001).

Measurement

Participant sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), which includes seven items ranked from 0 to 3. The PSQI Global score ranges from 0 to 21. A global PSQI score of 5 indicates normal sleep quality, whereas a score of greater than 5 indicates poor sleep quality (Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989).

The Hospital Anxiety and Depression Scale was used to assess participant depressive and anxiety symptoms (Zigmond & Snaith, 1983). The scale is mainly a screening tool for anxiety and depression in patients in hospitals. It has been translated into many languages and is widely used. The Chinese version has been found to have good reliability and validity, with sensitivity of

anxiety and depression at 70% and 82%, respectively, and specificity at 68% and 94%, respectively (Liang, 2000). The Hospital Anxiety and Depression Scale consisted of 14 items, 7 of which assess anxiety and 7 of which assess depression. The scores of the two subscales of anxiety/depression are divided into three groups: 0 to 7 (classified as asymptomatic), 8 to 10 (classified as suspicious), and 11 to 21 (classified as affirmative).

In our study, sum scores of these scales were not directly analyzed or modeled. Instead, anxiety, depression, and sleep quality were treated as latent constructs (alternatively referred to as factors or latent variables) measured by the original scale items in the probability models (Yang, Nay, & Hoyle, 2009). The scores of these latent constructs (with 0 means at the first measure) were derived from the probability models to partition out measurement errors and biases of raw sum scores (Wright, 1999).

CD^{4+} T cell counts were completed by an automatic biochemical analyzer and its supporting reagents and detected by FACSCanto flow cytometry (BD Company, USA). Participant CD^{4+} T cell counts were assessed at the first treatment, and at 3 and 6 months. Due to the large range of the variable, CD^{4+} T cell counts were categorized into three levels ($<200 = 1$, $200–350 = 2$, $>350 = 3$) using the cutoff scheme for PLWH in another study (Mao et al., 2015).

Data Analysis

The data were analyzed and modeled in two steps. First, measurement properties of anxiety, depression, and sleep quality were examined with confirmatory factor analyses. The measurement model included three factors (sleep quality, anxiety, and depression) reflected by indicators for each time point. Measurement invariance in the factor loadings over time was tested by comparing a model with any equality constraints with the model that had factor loadings constrained to be equal over time. Second, latent scores of the factors were obtained from the constrained model. This approach can decrease the subsequent model size and computation time (Yang, Nay, & Hoyle, 2009). Missing data (3.6% at 3 months, 11.7% at 6 months) were accounted for by expectation maximization of the sample correlation matrix with maximum likelihood estimation.

In the second step, latent growth mixture modeling of four processes was carried out, including the latent scores for anxiety, depression, sleep quality, and CD^{4+} T cell variables. This modeling technique identifies heterogeneous subgroups with different change trajectories; modeling a whole sample may fail to discover any changes because upward and downward changes could

be balanced out. Social demographic variables, such as age, gender, marriage, education, uses of cigarettes, alcohol, and sexual stimulants, were included as time-invariant co-variates of the latent categorical class variable, so that classification was simultaneously affected by these variables.

Models of different classes with various change patterns were estimated separately first and then compared in terms of information criteria, likelihood ratio tests, and a classification quality index—entropy. The best fit model was selected based on a combination of (a) the smallest Bayesian information criterion (BIC), the Akaike's information criterion, and the sample size-adjusted BIC; (b) the likelihood ratio test to compare model with k class and k-1 class; (c) entropy values (Muthén, 2004); and (d) substantive criteria (Nagin, 2005), including that the size of the smallest class was greater than 5% of the sample (Nasserinejad, van Rosmalen, de Kort, & Lesaffre, 2017; Nylund, Asparouhov, & Muthén, 2007).

Through this modeling, average changes and variances of these four processes were captured respectively with two latent factors: the intercept (initial status) and slope (change rate). The mean of the intercept factor can be interpreted as the average value at the initial measurement, whereas the mean of the slope factor is interpreted as the average change rate across time. Variances of the intercept and slope factors, respectively, indicate how much the participants differed at the first measurement and how much their change rates differed.

The confirmatory factor analyses and growth mixture modeling were carried out using the latent variable modeling program Mplus (v8.2; Muthén & Muthén, 2017).

Results

Confirmatory Factor Analysis and Measurement Properties of Scales

The measurement properties of the scales were examined with confirmatory factor analyses. The measurement model for the confirmatory factor analyses fit the data satisfactorily ($\chi^2_{(1341)} = 1{,}789.89; p < .01$; comparative fit index = .93; Tucker-Lewis index = .93; root-mean-square error of approximation = .04). The factor loadings and reliabilities of the scales in the study are listed in Table 1.

The numbers suggest that the latent variables were measured well with the scales. The intercorrelations of the three latent variables ranged from .01 to .90. The correlations between anxiety and depression were .82, .89, and .90, respectively, for the three measurement times. Compared with this model, the model with factor loadings

constrained to be equal across three measurements were not a poorer fit for the data, as indicated by a chi-square difference test ($\chi^2_{(30)} = 27.91; p = .58$). This implies that the measurements of sleep quality, anxiety, and depression were not biased by the scales over time.

Growth Curve Mixture Modeling

Three growth mixture models were estimated with 1–3 classes specified. The information criteria, entropy, and likelihood ratio tests are listed in Table 2.

Bayesian information criteria has been found to perform generally better than other information criteria, such as the Akaike information criterion or the sample-size adjusted BIC (Nylund, et al., 2007). The BIC suggested that the two-class model was slightly better than the three-class model. Based on the smallest BIC and interpretability of the result, we chose the two-class model as optimal. The model identified 89.1% of the participants for the first class and 10.9% for the second. Parameter estimates for the two-class model are listed in Table 3.

The two classes are profiled in Figures 1 and 2. For the majority of the sample (Class 1, $n = 220$, 89.1%), CD^{4+} T cells increased, whereas anxiety, depression, and sleep quality remained unchanged over time. For a small proportion of the sample (Class 2, $n = 27$, 10.9%), CD^{4+} T cells decreased, whereas depression and anxiety increased, and sleep quality deteriorated over time.

Mixture modeling also revealed that latent class membership was found to be affected by marital status and alcohol use ($\beta = .41; p < .05$; confidence interval $[CI]_{95\%}$: 0.11–1.44 and $\beta = .18; p < .01$; $CI_{95\%}$: 0.03–1.16, respectively), based on a logistic regression with Class 2 as a reference. These implied that those who were married or using alcohol had, respectively, 40.6% ($CI_{95\%}$: 11%–144%) and 17.7% ($CI_{95\%}$: 0.03%–116%) higher odds of falling into the second class than singles or non-alcohol users.

Discussion

We applied latent growth curve mixture modeling to explore how a change in CD^{4+} T cell count was associated with sleep quality, depression, and anxiety in a sample of PLWH from Shenzhen, China. When CD^{4+} T cells decreased, sleep quality, depression, and anxiety deteriorated. However, when CD^{4+} T cells increased, sleep quality, depression, and anxiety remained unchanged. All changes in the small class of the sample were nonlinear. There was similarity in the changes of anxiety and depression in both classes. In addition, the second class tended to have higher percentages of married participants and alcohol users.

Table 1. Standardized Factor Loadings and Reliabilities (ω) of Scales

Scale	Item Content	Time 1	Time 2	Time 3
Sleep quality	Sleep quality	.77	.74	.77
	Sleep time	.72	.69	.72
	Sleep efficiency	.61	.58	.61
	Sleep disorder	.63	.60	.63
Anxiety	I feel nervous or in pain	.74	.73	.73
	I feel a little scared, as if I felt that something terrible happened	.77	.76	.77
	My heart is full of troubles	.79	.78	.79
	I can sit comfortably and easily	.72	.71	.72
	I feel a trembling fear	.77	.77	.77
	I am a little restless, as if I feel that I have to be active	.65	.65	.65
	I suddenly have a fear	.77	.77	.77
Depression	I am still interested in things that I have been interested in the past	.62	.65	.65
	I can laugh and see the interesting side of things	.65	.69	.69
	I am happy	.75	.78	.79
	I feel that people seem to be dull	.60	.63	.63
	I lost interest in my appearance (dressing myself)	.67	.70	.70
	I am happy with the future	.56	.59	.59
	I can enjoy a good book or a good radio or TV show	.62	.65	.65

Note. Scores of some items are reverse coded to reflect anxiety and depression. Scale reliabilities (ω) were .78, .75, and .78 for sleep quality, .90, .89, and .89 for anxiety, and .83, .85, and .85 for depression, respectively, at three measurements.

The finding that a decrease in CD^{4+} T cells over time was associated with deterioration of sleep quality and an increase in depression and anxiety in PLWH was consistent with other studies (Mohammed, Mengistie, Dessie, Godana, 2015; Wibbeler et al., 2012). However, the conclusion that CD^{4+} T cell counts independently influenced factors affecting sleep quality, depression, and anxiety in PLWH was not supported by our study, as the

Table 2. Comparison of the Two-Class Model With the Three-Class Model

Model	BIC	AIC	ABIC	Number of Parameters	Entropy	LRT Value	*p*-Value	Smallest Class %	Count
Class 1	7,904.10	7,658.44	7,682.20	70	NA	NA	NA	NA	NA
Class 2	**4,426.51**	**4,173.84**	**4,198.27**	72	.93	19.62	.87	10.9	27
Class 3	4,492.78	4,183.96	4,213.82	88	.96	12.19	.99	1	2

Note. ABIC = sample-size adjusted BIC; AIC = Akaike Information Criterion; BIC = Bayesian information criterion; LRT = likelihood ratio test; NA = not applicable.

Table 3. Parameter Estimates (95% Confidence Intervals) of Latent Growth Curve Modeling

Parameter	Group	Class 1		Class 2	
		Intercept	Slope	Intercept	Slope
Mean	Anxiety	0.03 (−0.06 to 0.12)	−0.01 (−0.07 to 0.05)	−0.30 (−0.83 to 0.23)	0.50 (0.06 to 0.95)
	Depression	−0.03 (−0.10 to 0.05)	−0.01 (0.045 to 0.06)	0.27 (−0.13 to 0.67)	0.44 (0.13 to 0.74)
	Sleep quality	−0.02 (−0.10 to 0.07)	0.02 (−0.04 to 0.08)	0.21 (−0.16 to 0.57)	−0.64 (−0.91 to −0.36)
	CD^{4+} T cell	2.17 (2.04 to 2.30)	0.21 (0.16 to 0.26)	2.27 (1.49 to 3.06)	−0.71 (−1.20 to −0.22)
Variance	Anxiety	0.34 (0.25 to 0.42)	0.16 (0.12 to 0.20)	0.34 (0.25 to 0.42)	0.16 (0.12 to 0.20)
	Depression	0.27 (0.20 to 0.34)	0.17 (0.13 to 0.21)	0.27 (0.20 to 0.34)	0.17 (0.13 to 0.21)
	Sleep quality	0.14 (0.06 to 0.21)	0.15 (0.10 to 0.19)	0.14 (0.06 to 0.21)	0.15 (0.10 to 0.19)
	CD^{4+} T cell	0.21 (0.11 to 0.32)	−0.06 (−0.12 to 0.00)	0.21 (0.11 to 0.32)	−0.06 (−0.12 to 0.00)

increase in CD^{4+} T cells was not associated with improvement in sleep quality, depression, and anxiety of the majority of PLWH in our study. The association in only a small proportion of the sample and irrelevance in the large proportion of the sample cast some doubt on the causal effects of CD^{4+} T cells or the underlying causal mechanism the CD^{4+} T cell count reflected, especially in light of inconsistent previous findings. As an essential element of causality, cross-sectional correlations between CD^{4+} T cells and anxiety, depression, and sleep (available upon request) did not support or reflect the causal linkage.

Disregarding the weak or nonexistent causal mechanism, the inconsistency might have also stemmed from the following reasons. First, our study was a longitudinal study that reflected the changing trends of CD^{4+} T cells with sleep, depression, and anxiety, rather than showing cross-sectional correlations. The growth mixture model in our study identified the development trends of hidden subgroups and individual differences in the growth trend, as opposed to other studies that focused on whole sample shifts (Zhou, Gao, Wang, Song, & Yu, 2014). A growth modeling of the whole sample of our study would not reveal the change patterns identified through the growth mixture model. Second, we also explored the relationship between changes in CD^{4+} T cells and sleep, depression, and anxiety, whereas most other studies focused on the effects of CD^{4+} T cells on sleep, depression, or anxiety (Seay et al., 2013; Zeinab, Mohammad, & Hassan, 2016). However, CD^{4+} T cells, sleep quality, depression, and anxiety could interact with one another (Allavena et al., 2016; Barroso, Leserman, Harmon, Hammill, & Pence, 2015). As a strength, we included all variables in a longitudinal design.

Can sleep quality, depression, and anxiety influence CD^{4+} T cell count? Our modeling did not explicitly test this question. However, the literature has generally suggested that CD^{4+} T cells influence sleep quality, depression, and anxiety by a certain mechanism. Many factors can influence the fluctuation in CD^{4+} T cell counts, such as mood, physical status, or tiredness (Yi et al., 2014). Over time, CD^{4+} T cell counts would imply the determinant effects of patient viral loads. In a reverse logic, if quality sleep or the improvement of depression or anxiety could reduce the HIV load and thus increase CD^{4+} T cell counts, HIV would not pose any serious health problems.

Figure 1. Change patterns of Class 1 ($n = 220$, 89.1%).

Limitations

Our study was limited in the following aspects. First, the study did not probe into the genetic or biomolecular

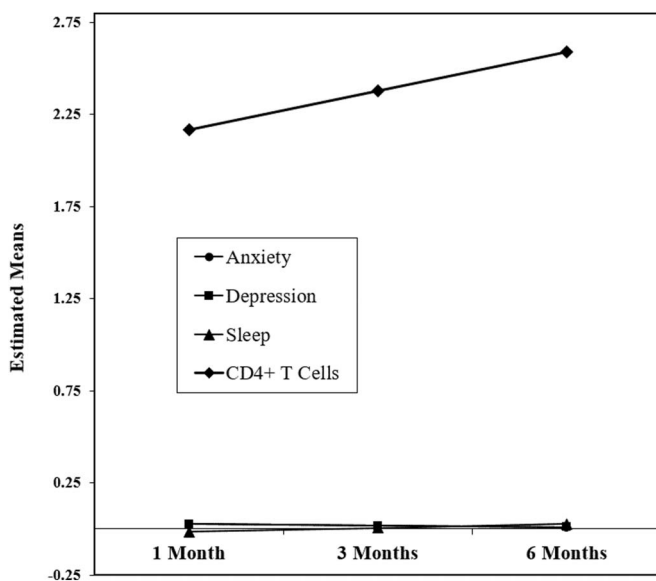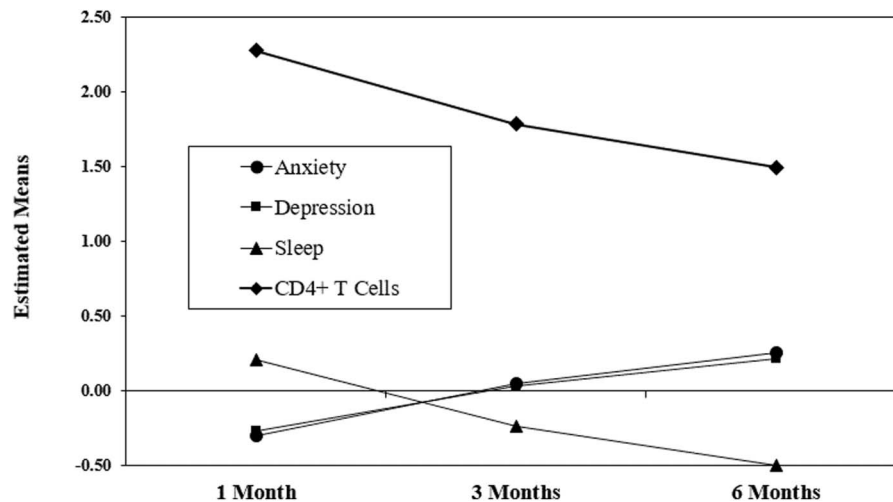**Figure 2.** Change patterns of Class 2 ($n = 27$, 10.9%).

level, and thus, any causal relationship among CD^{4+} T cells and sleep quality, depression, and anxiety could not be firmly concluded. Second, we did not probe what adverse events the participants could anticipate in the future and how optimistic they felt about their prognoses from a biopsychosocial perspective (Borrell-Carrió, Sucbman, & Epstein, 2004). Including such variables may help differentiate any cognitive or personality confounding effects from that of CD^{4+} T cells. Third, there might be better approaches to deal with the CD^{4+} T cells variable with a huge variance and flat distribution, such as cutting into more categories instead of only the three used in our study or applying other appropriate models to the original variable. Finally, depression may be measured more sensitively with the widely used Center for Epidemiologic Studies - Depression Scale.

Conclusion

An increase of CD^{4+} T cells over time may not be associated with the sleep quality, depression, and anxiety of PLWH; however, a decrease in CD^{4+} T cells over time is accompanied by deterioration of sleep quality and an increase in depression and anxiety in a small proportion of PLWH. The practical implication is that health care professionals need to be vigilant for symptoms of depression, anxiety, and sleep disorders in PLWH with decreasing CD^{4+} T cell counts and promptly provide additional counseling or treatment.

Disclosures

The authors report no real or perceived vested interests related to this article that could be construed as a conflict of interest.

Key Considerations

❍ Health care professionals may improve service quality by providing extra care for anxiety, depression, and sleep disorders in PLWH with decreasing CD^{4+} T cell counts.

❍ Methodologically, a biopsychosocial approach is better than a pure biomedical one to examine and understand the relationships between CD^{4+} T cells, sleep quality, anxiety, and depression in PLWH.

❍ Statistically, mixture modeling that identifies heterogeneous subgroups with different change patterns may provide unexpected insights.

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