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Trajectories of sleep disturbance severity in HIV-infected and uninfected Veterans

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Keywords

HIV-RNA; sleep disturbance

Sleep disturbance has been described at all stages of HIV infection since the early days of the epidemic. A physiologic association between HIV infection and sleep disturbance is plausible: HIV infection can lead to immune dysregulation in the brain that may alter the production of sleep-inducing cytokines (Zager, Andersen, Ruiz, Antunes, & Tufik, 2007). However, the relationship between sleep disturbance and markers of HIV severity (CD4+ T cell count and HIV-RNA) remains unclear. Some have described an association between increased CD4+ T cell count/decreased HIV-RNA and improvement in sleep disturbance (Seay et al., 2013), while others have reported no such association (Crues et al., 2003). Antiretroviral therapy (ART), particularly efavirenz and the integrase inhibitors, has also been associated with sleep disturbance. Individuals on efavirenz frequently report vivid dreams or nightmares, difficulty falling asleep, and frequent night awakenings. These symptoms often resolve within the first month of use but persist in some patients (Nunez et al., 2001).

In the general population, multimorbidity, polypharmacy, and aging are important drivers of sleep disturbance. Multimorbidity is the norm for people living with HIV infection (PLWH), and many of these comorbidities are associated with sleep disturbance (Redeker et al., 2010), particularly mental health comorbidities including depression, post-traumatic stress disorder (PTSD), and alcohol and drug abuse. Physical comorbidities are also important, including coronary artery disease, diabetes, liver disease (including hepatitis C virus infection, cirrhosis, and end stage liver disease), peripheral vascular disease, chronic kidney disease, cerebrovascular disease, cancer, heart failure, chronic obstructive pulmonary disease, and obstructive sleep apnea. Smoking (de Souza Lopes, Robaina, & Rotenberg, 2012), pain (Menefee et al., 2000), and elevated body mass index (BMI; Young et al., 2002) are also common in PLWH and are positively associated with sleep disturbance. Polypharmacy has also been linked to sleep disturbance (Edelman et al., 2013).

To our knowledge, the role of HIV in determining patterns of sleep disturbance severity over time has not been explored. We fit trajectory models to repeated measures of sleep disturbance severity in PLWH and uninfected individuals, and explored predictors of trajectory membership.

Methods

Sample

The Veterans Aging Cohort Study (VACS) is a longitudinal, prospective, multisite observational study of HIV-infected and uninfected Veterans enrolled at eight Veterans Health Administration (VHA) medical centers. Veterans with HIV were matched one to one

with uninfected Veterans by age, race/ethnicity, site of clinical care, and gender (Justice et al., 2006). In addition to permitting access to their electronic health records (EHR), VACS participants completed a health care survey at baseline and at yearly follow-up visits. We included all VACS participants who completed an enrollment survey (June 2002 through August 2012) and followed them through a maximum of 6 years. VACS recruitment is updated annually. Therefore, while all participants completed a baseline survey, the follow-up surveys depended on the year of recruitment: a participant recruited in the first year of the study would have a baseline survey as well as all follow-up surveys. A participant recruited in the third year of the study would have a baseline survey and would have then completed follow-up survey 3 in their first follow-up year. They would not be able to complete either the first or second follow-up surveys. Because information on sleep disturbance was not collected at the fifth follow-up survey, data from that survey were excluded from the analysis.

Independent Variable

We defined HIV infection as the presence of Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for HIV during at least two out-patient or one in-patient encounter.

Dependent Variable

Our primary outcome was severity of sleep disturbance assessed using the HIV Symptom Index (Justice et al., 2001). The index elicits the frequency and severity of discomfort associated with 20 symptoms commonly associated with HIV as follows: *The following questions ask about symptoms you might have had during the past four weeks. Please fill in the circle of the one response that best describes how much you have been bothered by each symptom.* If the symptom was present, participants were prompted to indicate the degree of severity, based on a 5-point Likert scale. The sleep disturbance symptom reads: *Difficulty falling or staying asleep.* Severity was assessed using the same questions and the full range of responses: 1 = *does not experience the symptom*, 2 = *experiences the symptom but without bother*, 3 = *bothered a little by this symptom*, 4 = *bothered*, and 5 = *experiences a lot of bother with the symptom*. Sleep disturbance symptoms were elicited on the VACS survey at baseline and at follow-up visits 1–4 and 6, enabling us to model sleep disturbance severity trajectories over time.

Covariates

To better understand the independent association between HIV and membership in sleep disturbance severity trajectories, the models adjusted for baseline sleep disturbance risk factors with known associations in the general population. These included demographic characteristics (age at baseline, gender, and race/ethnicity); ICD-9-CM codes for PTSD; measures of pain (pain severity between 0 and 10) and smoking status (current, former, and never smoker); depressive symptoms (Patient Health Questionnaire PHQ-2); and the Alcohol Use Disorders Identification Test (AUDIT-C), where we defined hazardous alcohol use as a score of at least 4 for men and at least 3 for women. Medications were identified using VHA pharmacy data, and the model also adjusted for a count of unique medications (excluding antiretrovirals) prescribed within 90 days of the completion of each survey. To

account for serial correlation within individuals, we used generalized estimating equations with auto-regressive correlation. Our results were generated from a multivariable model that retained only those variables that had previously demonstrated associations with sleep disturbance severity in this study sample (Womack et al., 2016).

Of the Veterans living with HIV, we identified use of ART, based on use of any of the following: protease inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors, entry inhibitors, and CCR5 receptor antagonists. We identified efavirenz as a separate covariate. Values of CD4+ T cell count and HIV-RNA closest to survey date were used.

Ethical Considerations

All participants signed a voluntary informed consent. The parent study was approved by both the VA Connecticut Healthcare System Institutional Review Board and by the Yale University Human Investigation Committee. The current study was added to both protocols.

Statistical Analysis

We sought to identify distinct functional trajectories of sleep disturbance severity over the survey waves (baseline and follow-ups 1–4 and 6) using a form of latent class analysis. Trajectory modeling concurrently estimates each participant's probabilities for membership in multiple trajectories, with highest probability determining assignment to a specific trajectory. We used PROC TRAJ in SAS software (SAS institute) to fit semiparametric (discrete) mixture models to this longitudinal data using the maximum likelihood method. We tested between two and six classes to determine the optimal number of trajectories using the following criteria: Bayesian information criterion, model fit, and a requirement that each trajectory group include a minimum of 10% of the analytic sample.

Within the context of trajectory modeling, we evaluated the association between HIV and membership in each trajectory by modeling the self-reported severity of sleep disturbance using ordinal values of 0 through 4 as a zero-inflated Poisson distribution with adjustment for covariates that had been previously established as being associated with severity of sleep disturbance in this study sample (Womack et al., 2016). The same covariates were included in each trajectory model, and their odds ratios represent the association between presence of that covariate at baseline and membership in a given trajectory, relative to membership in the no sleep disturbance trajectory. All analyses were performed using SAS 9.4. Statistical significance was defined as a two-sided p -value < 0.05 .

Results

We included all VACS participants ($N = 7,515$), 50% of whom had HIV. The sample was composed predominantly of Black (65%) and non-Hispanic (9%) men (95%; Table 1). Relative to uninfected counterparts, PLWH were younger (49 ± 9 years vs. 50 ± 10 years, $p < 0.0001$), had lower BMI (26 ± 4 kg/m² vs. 30 ± 6 kg/m², $p < 0.0001$), were more likely to have liver (54% vs. 30%, $p < 0.0001$) or renal (5% vs. 3%, $p = 0.0003$) disease, and less likely to have heart failure (2% vs. 3%, $p = 0.003$), sleep apnea (1% vs. 3%, $p < 0.0001$), PTSD (8% vs. 12%, $p < 0.0001$), drug use/abuse (24% vs. 27%, $p = 0.006$), coronary artery

disease (8% vs. 12%, $p < 0.0001$), diabetes (12% vs. 22%, $p < 0.0001$), or peripheral vascular disease (2% vs. 3%, $p = 0.0002$). Relative to uninfected Veterans, those with HIV infection were less likely to report hazardous alcohol use (median [IQR]: 2[1, 5] vs. 3[1, 5], $p = 0.001$, respectively). Among Veterans with HIV infection, the mean CD4+ T cell count was 410 ± 287 cells/mm³ and mean HIV-RNA was $37,013 \pm 170,242$ copies/mL. Eighty percent of the Veterans with HIV were started on ART within 90 days of the baseline survey, and 28% were on efavirenz.

The latent class analysis was based on 4 distinct trajectories in both the combined and HIV-only samples (Figure 1). Group 1 represented no sleep disturbance (No Sleep Disturbance Trajectory), Group 2 demonstrated increasing severity (Worsening Trajectory), Group 3 demonstrated decreasing severity (Recovery Trajectory), and Group 4 demonstrated a constant, elevated severity of sleep disturbance (Relentless Sleep Disturbance Trajectory). The No Sleep Disturbance Trajectory was the reference category for all associations with explanatory variables. In the combined sample, the No Sleep Disturbance trajectory included 18.6% of the sample, the Worsening Trajectory 13.5%, the Recovery Trajectory 23.2%, and the Relentless Trajectory 44.8%. The corresponding percentages in the group with HIV infection were similar: 16.6%, 13.3%, 23.8%, 46.3%, respectively.

HIV infection was independently associated with membership in the Recovery Trajectory (Odds ratio [OR] 1.32; 95% CI 1.07, 1.63; $p = 0.007$), but not with membership in other trajectories (HIV and Worsening Trajectory [0.97; 0.75, 1.25; $p = 0.80$]; HIV and Relentless Sleep Disturbance Trajectory [1.00; 0.82, 1.21; $p = 0.97$]).

In analyses restricted to individuals with HIV, we found that when we included variables for ART, HIV-RNA, and CD4+ T cell count in the same model, none was significantly associated with membership in any of the trajectory groups. Because this lack of significance might arise from collinearity among these variables, we then explored the following pairs of HIV-specific variables: CD4+ T cell count and HIV-RNA, and CD4+ T cell count and ART. When we excluded HIV-RNA and included ART classes and CD4+ T cell count, we found that neither protease inhibitors (1.08; 0.76, 1.54; $p = 0.66$) nor NRTIs (1.33; 0.88, 2.02; $p = 0.17$) nor NNRTIs (0.83; 0.59, 1.16; $p = 0.26$) were associated with being in the Recovery Trajectory. When we removed NNRTIs and substituted efavirenz, there was still no significant association with membership in the Recovery Trajectory (1.14; 0.40, 1.42; $p = 0.24$). However, when we included HIV-RNA and CD4+ T cell count, we found that membership in the Recovery Trajectory was less likely for those with a baseline HIV-RNA greater than 1,000 copies/mL (0.73; 0.54, 0.99; $p = 0.04$). CD4+ T cell count lower than 200 cells/mL (1.19; 0.86, 1.64; $p = 0.27$) and CD4+ T cell count between 200 and 500 cells/mL (1.19; 0.94, 1.63; $p = 0.41$) were not associated with trajectory membership.

Discussion

In this large, longitudinal dataset of matched HIV-infected and uninfected Veterans, we identified four separate sleep disturbance trajectories: No Sleep Disturbance Trajectory, Worsening Trajectory, Recovery Trajectory, and the Relentless Sleep Disturbance Trajectory.

HIV infection was associated with the Recovery Trajectory. In models restricted to individuals with HIV infection: those with HIV-RNA at baseline greater than 1,000 copies/mL were less likely to be in the Recovery Trajectory than those with undetectable HIV-RNA. In contrast, neither CD4+ T cell count nor use of ART was associated with membership in any of the sleep disturbance trajectories. This suggests that viral control may play a more important role than CD4+ T cell count or specific classes of medications in determining the trajectory of sleep disturbance severity for those recently diagnosed with HIV infection.

Strengths

Our study was a large, longitudinal analysis of self-reported sleep disturbance severity in a matched cohort of HIV-infected and uninfected Veterans. The individuals living with HIV infection included in this analysis had high CD4+ T cell counts at baseline, allowing us to explore sleep disturbance in a relatively healthy population, reflecting the nature of the current epidemic.

Limitations

The primary limitation of the analysis was our reliance on a single question to assess sleep disturbance. A more refined approach using established questionnaires or physical assessment may have yielded different results. Incorporating actigraphy and polysomnography into future analyses would help to characterize sleep patterns in this population and to determine if HIV infection has an impact on physiologic measures of sleep.

Conclusion

Our results demonstrate that HIV plays a role in patterns of sleep disturbance severity over time, and that viral control may play a role in the amelioration of sleep disturbance for PLWH. Research is required to more fully explore this hypothesis and to precisely quantify the relative associations of HIV-RNA and inflammation with effective treatment of sleep disturbance for PLWH.

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Figure 1.
 Trajectories of sleep disturbance severity among HIV-infected and uninfected Veterans.
 O: No Sleep Disturbance Trajectory, 18.6%
 +: Worsening Trajectory, 13.5%
 Δ: Recovery Trajectory, 23.2%
 X: Relentless Sleep Disturbance Trajectory, 44.8%

Table 1

Sample Characteristics by HIV Status at Baseline (N = 7,515)

Patient Characteristics (% unless otherwise noted)	HIV infected N = 3,728	HIV uninfected N = 3,787	P-value
Sleep disturbance	61	58	0.01
Sleep disturbance severity ^a	2 (0, 3)	2 (0, 3)	0.26
Age (years) ^b	49 (9)	50 (10)	< 0.0001
Race/ethnicity			0.0001
White	19	23	
Black	67	63	
Hispanic	9	10	
Other	4	4	
Men	97	92	< 0.0001
Body mass index ^b	26 (4)	30 (6)	< 0.0001
CD4+ T cell count (cells/mm ³) ^b	410 (287)	NA	–
HIV-RNA (copies/mL) ^b	37,013 (170,242)	NA	–
Pain score ^a	0 (0, 2)	0 (0, 4)	< 0.0001
Depressive symptoms (PHQ-2 score) ^a	4 (1, 9)	3 (0, 8)	0.15
Alcohol use (AUDIT-C score) ^a	2 (1, 5)	3 (1, 5)	0.001
Heart failure	2	3	0.003
Chronic obstructive pulmonary disease	5	5	0.27
Other chronic lung conditions	8	9	0.05
Sleep apnea	1	3	< 0.0001
Post-traumatic stress disorder	8	12	< 0.0001
Coronary artery disease	5	8	< 0.0001
Diabetes	12	22	< 0.0001
Liver disease	54	30	< 0.0001
Peripheral vascular disease	2	3	0.0002
Renal disease	5	3	0.0003
Cerebrovascular disease or stroke	0.8	1	0.05
Cancer	5	5	0.83

Patient Characteristics (% unless otherwise noted)	HIV infected <i>N</i> = 3,728	HIV uninfected <i>N</i> = 3,787	<i>P</i> -value
Drug use or abuse	24	27	0.006
Any antiretroviral medications	81	NA	NA
Nonantiretroviral medication count ^b	8 (6)	8 (6)	0.34
Benzodiazepine use	8	10	0.003
Z-drug use	2	3	0.79
Opiate use	21	22	0.88
SSRI use	19	19	0.58
Other antidepressant use	16	18	0.03
Efavirenz use	28	NA	NA

Note. *p*-values based on chi-square statistic (%), *t*-test (mean), or the Wilcoxon (median); a = Median (Interquartile range); b = Mean (standard deviation); NA = not available; PHQ2 = patient health questionnaire-2; SSRI = selective serotonin reuptake inhibitor; count = number of prescriptions for a medication from the date of the survey plus/minus 90 days. AUDIT-C = Alcohol Use Disorders Identification Test, short version.