



Sleep Disturbance Among HIV-Infected and Uninfected Veterans

Julie A. Womack, *VA Connecticut Healthcare System*
Terrence E. Murphy, *Yale School of Medicine*
Harini Bathulapalli, *VA Connecticut Healthcare System*
Kathleen M. Akgun, *VA Connecticut Healthcare System*
Cynthia Gibert, *George Washington University*
Ken M. Kunisaki, *University of Minnesota Medical School*
[David Rimland](#), *Emory University*
Maria Rodriguez-Barradas, *Baylor College of Medicine*
H. Klar Yaggi, *VA Connecticut Healthcare System*
Amy C. Justice, *VA Connecticut Healthcare System*

Only first 10 authors above; see publication for full author list.

Journal Title: Journal of Acquired Immune Deficiency Syndromes
Volume: Volume 74, Number 4
Publisher: Lippincott, Williams & Wilkins | 2017-04-01, Pages E117-E120
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1097/QAI.0000000000001264
Permanent URL: <https://pid.emory.edu/ark:/25593/s8tk5>

Final published version: <http://dx.doi.org/10.1097/QAI.0000000000001264>

Copyright information:

©2017 Wolters Kluwer Health, Inc.

Accessed February 27, 2021 1:47 PM EST



HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2017 April 01; 74(4): e117–e120. doi:10.1097/QAI.0000000000001264.

Sleep Disturbance Among HIV Infected and Uninfected Veterans

Julie A. Womack^{1,2}, Terrence E. Murphy³, Harini Bathulapalli^{1,3}, Kathleen M. Akgün^{1,3}, Cynthia Gibert⁴, Ken M. Kunisaki⁵, David Rimland⁶, Maria Rodriguez-Barradas⁷, H. Klar Yaggi^{1,3}, Amy C. Justice^{1,3}, and Nancy S. Redeker²

¹VA Connecticut Healthcare System, West Haven, CT

²Yale School of Nursing, West Haven, CT

³Yale School of Medicine, New Haven, CT

⁴Veterans Affairs Medical Center and Department of Medicine, George Washington University, Washington, DC

⁵Minneapolis Veterans Affairs Healthcare System and University of Minnesota Medical School, Minneapolis, MN

⁶Veterans Affairs Medical Center and Emory University School of Medicine, Atlanta, GA

⁷Medical Service, Michael E. De Bakey Veterans Affairs (VA) Medical Center and Department of Medicine, Baylor College of Medicine, Houston, TX

To the Editors

Although sleep disturbance has been observed at all stages of HIV infection,¹⁻⁴ the nature of the association between HIV and sleep disturbance has not been rigorously evaluated in the current treatment era. We explored the longitudinal associations between HIV status and self-reported occurrence or severity of sleep disturbance, with adjustment for demographics, comorbidities, and polypharmacy.

We used the Veterans Aging Cohort Study (VACS), a longitudinal, prospective observational study of HIV infected and uninfected Veterans enrolled at eight Veterans Health Administration (VHA) medical centers: Atlanta, Baltimore, Brooklyn and Manhattan, Bronx, Houston, Los Angeles, Pittsburgh, and Washington DC. HIV infected Veterans were matched one to one with uninfected Veterans by age, race/ethnicity, site of clinical care, and sex.⁵ Data for this analysis included electronic health-record (EHR) data and self-report questionnaires completed by participants at enrollment (baseline) (June 2002 through August 2012) and through six years of follow-up.

Correspondence: Julie A. Womack, PhD, CNM, APRN, VAMC, 950 Campbell Avenue, Building 35A, West Haven, CT 06516, Fax (203)737-2414, julie.womack@yale.edu.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

Conflict of Interest: All authors declare that they have no conflict of interest.

We defined HIV infection as the presence of Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for HIV during least two outpatient visits or one inpatient event that were confirmed in the immunology case registry of the VHA.⁶

Our primary outcomes were sleep disturbance and its severity. Both were assessed on an annual basis using the self-completed HIV Symptom Index⁷ over a follow-up period of six years. The Index elicits the frequency and severity of discomfort for 20 symptoms commonly associated with HIV. If the symptom was present, participants were prompted to indicate the degree of severity, based on a five-point Likert scale (0=does not experience the symptom, 1=experiences the symptom but without bother, 2=bothered a little by this symptom, 3=bothered, and 4=experiences a lot of bother with the symptom). Sleep disturbance was dichotomized as occurrence (a non-zero response on the Likert scale), or non-occurrence (a zero response on the Likert scale). Severity was assessed using the ordinal range of responses. Sleep disturbance symptoms were elicited on the survey at baseline and at follow-up visits in years 1-4 and 6, facilitating the longitudinal modeling of sleep disturbance and its severity.

Covariates were selected *a priori* based on prior sleep disturbance research and data availability. Baseline demographic information included age, sex, and race/ethnicity. All other covariates were updated at each annual assessment. We identified ICD-9-CM codes one year before and six months after baseline for the following conditions: coronary artery disease, diabetes, liver disease (any of hepatitis B or C, cirrhosis, end stage liver disease), peripheral vascular disease, renal disease, cerebrovascular disease (including stroke), cancer, heart failure, COPD, other chronic lung diseases, obstructive sleep apnea, PTSD, and drug use or abuse.

Body mass index (BMI; weight in kilograms/height in meters²) and pain (pain level between 0 and 10) were identified using vital sign data. We categorized BMI according to WHO criteria: underweight (BMI<18.5), normal weight (18.5–24.9), overweight (25-29.9), and obese (BMI ≥ 30). Smoking status was categorized as current, former and never smoker. From survey data, we used the Patient Health Questionnaire PHQ-2 to assess depressive symptoms.⁸ Using the Alcohol Use Disorders Identification Test (AUDIT-C),⁹⁻¹¹ we defined hazardous alcohol use as a score of ≥ 4 for men and ≥ 3 for women. For these time-updated variables, values within 90 days of each survey date were used. If multiple values occurred within this time period, the one closest to the survey date was used.

We included a count of unique medications (excluding antiretrovirals) prescribed within 90 days of each survey date over the six year follow-up period. Use of selective serotonin reuptake inhibitors (SSRIs), other antidepressants, benzodiazepines, and hazardous opiate use (≥ 120 morphine equivalents per day) were coded as dichotomous indicator variables. Among HIV infected individuals, we identified use of antiretroviral therapy (ART) within the same time window, as well as a separate marker of efavirenz use, given its historical association with sleep disturbance.¹² CD4 count and HIV-RNA were also time-updated, and the values closest to survey date were used. Time was quantified as a count variable ranging from 1 through 6 representing the baseline survey and the successive waves of follow-up that we included in the study.

Descriptive characteristics were calculated at baseline: continuous variables with means and standard deviations (SD) or with medians and interquartile ranges (IQR) and dichotomous variables with the percent of observations. Each characteristic was compared between Veterans with and without HIV infection.

Clinical and demographic characteristics plausibly associated with the presence or severity of sleep disturbance were tested in multivariable longitudinal models that employed generalized estimating equations with an autoregressive correlation structure. Approximately 7% of observations were missing. Because we believed the missingness to be at random, ten imputations of the entire longitudinal dataset were created with a full conditional specification. The associations of clinical and demographic factors with occurrence of sleep disturbance were modeled using logistic regression. We assessed model fit using discrimination (C-statistic) and calibration (Hosmer-Lemeshow chi-square statistic). Severity of sleep disturbance was modeled with a negative binomial distribution. Separate models of each outcome were fit to the combined sample and to the subgroup of HIV infected individuals. To discern whether the effect of polypharmacy was due to the number of medications taken or to the inclusion of certain classes of medications that might be particularly associated with sleep disturbance, we also included indicators of use of the following medication classes: benzodiazepines, Z-drugs (non-benzodiazepine sleep medications), hazardous opiate use, SSRIs, and other antidepressants. All analyses were performed using SAS version 9.4. Because of the large number of analyses, p-values from multivariable models were adjusted for multiple comparisons using the Hochberg method.¹³

We included all VACS participants (N=7,515). The sample was composed predominantly of Black (65%) and non-Hispanic (90%) men (95%) of whom 50% were HIV infected. Relative to their uninfected counterparts, HIV infected individuals were younger (49±9 years vs 50±10 years, $p<0.0001$), had a 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 disease (5% vs 3%, $p=0.0003$), 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%, $P=0.0002$). There were no differences between HIV infected and uninfected individuals in terms of COPD (5% vs 5%, $p=0.27$), other chronic lung conditions (8% vs 9%, $p=0.05$), cerebrovascular disease or stroke (0.8% vs 1%, $p=0.05$), and cancer (5% vs 5%, $p=0.83$). HIV infected Veterans had lower AUDIT C scores (median [IQR]: 2[1, 5] vs 3[1, 5], $p=0.001$) and fewer prescriptions for benzodiazepines (8% vs 10%, $p=0.003$) and other antidepressants (16% vs 18%, $p=0.03$). Prescriptions for opiates (HIV infected: 21% vs uninfected: 22%, $p=0.88$), SSRIs (19% for both, $p=0.58$) and Z-drugs (2%, and 3%, respectively; $p=0.79$) did not differ by HIV status. Depressive symptom scores were similar in both groups (HIV infected median 4 [IQR: 1, 9] and HIV uninfected median 3 [IQR 1, 5]) Among HIV infected Veterans, the mean CD4 count was 410±287 (cells/mm³) and mean HIV-RNA was 37,013±170,242 (copies/mL). Eighty percent were on ART within 90 days of the baseline survey, and 28% were on efavirenz.

Among HIV infected individuals, 61% experienced sleep disturbance, compared with 58% of uninfected ($p=0.01$). The full range of severity scores was observed in both groups, who shared a common median of two (bothered a little by this symptom).

In unadjusted models, HIV infection was associated with sleep disturbance (odds ratio (OR)= 1.13; 95% CI: 1.03, 1.24, $p=0.01$) but not its severity (relative risk (RR) =1.03; 95% CI: 0.98, 1.08, $p=0.32$). In multivariable models with adjustment for multiple comparisons, HIV was associated with neither outcome (sleep disturbance OR: 1.08; 1.01, 1.15, $p=0.39$; severity: RR: 1.02; 95% CI: 0.99, 1.04, $p=0.98$).

Variables associated with increased risk of sleep disturbance included (Table 1) depressive symptom score (OR: 3.56; 95% CI: 3.14, 4.04, $p<0.0001$), female sex (1.75; 1.47, 2.08, $p<0.0001$), pain (1.06; 1.03, 1.08, 0.0006); liver disease (1.13; 1.06, 1.20, $p=0.0068$), PTSD (1.81; 1.60, 2.04, $p<0.0001$), hazardous alcohol use (1.15; 1.07, 1.23, $p=0.0014$), current smoking (1.20; 1.10, 1.30, $p=0.0007$); and higher medication count (1.06; 1.05; 1.08, $p<0.0001$). Variables protective against sleep disturbance included age over 65 years (0.78; 0.69, 0.87, $p=0.0007$), Black race (0.64; 0.60, 0.69, $p<0.0001$), and Hispanic ethnicity (0.76; 0.68, 0.85, $p<0.0001$). When the five indicators for specific medication classes were included in the model, only hazardous opiate use was not associated with sleep disturbance. After controlling for these specific medication classes, medication count retained the significance of its association (1.04; 1.03, 1.06, $p=0.003$).

Results for sleep disturbance were similar in the analyses restricted to HIV infected Veterans. Of note, none of the HIV-specific variables (CD4 count (1.00; 1.00, 1.00, $p=0.95$), HIV-RNA (1.00; 1.00, 1.00, $p=0.90$), ART use (1.02; 0.92, 1.14, $p=0.95$), and efavirenz use (0.96; 0.88, 1.05, $p=0.94$)) were associated with occurrence of sleep disturbance.

The C-statistics for the combined and HIV-only samples were 0.78 and 0.77 and both exhibited good calibration per the Hosmer and Lemeshow Goodness-of-Fit statistic.¹⁴

The explanatory variables used to model the association between HIV infection and sleep disturbance severity were virtually identical to those utilized for the dichotomized outcome. Severity was also modeled in combined and HIV infected only samples.

Strengths

This longitudinal study explored self-reported sleep disturbance and severity in a large matched cohort of HIV infected and uninfected Veterans. Adjustment for comorbid conditions and medication counts helped differentiate the relative contributions of chronic disease and polypharmacy. It is notable that the HIV infected individuals included in this analysis had a high CD4 count at baseline, accurately reflecting the relatively good health of persons comprising the current epidemic.

The question of the generalizability of our results to populations outside of the VA is pertinent. A recent study explored the overlap between Veterans receiving care in the Veterans Health Administration and civilian cohorts found that VHA enrollees had similar demographic and health characteristics as individuals with Medicaid, Medicare, or private

insurance coverage. These results suggest that research done within the VHA may be generalizable to other clinical populations.¹⁵

Limitations

The primary limitation of this study was its reliance on a single question from the HIV Symptom Index to assess sleep disturbance. The self-reported outcome essentially reflected degree of severity rather than its true occurrence. Any non-reporting of sleep disturbance might therefore reflect patients' focus on other issues that were of greater concern at that moment. Future studies will include the use of validated sleep questionnaires and physiologic measures of sleep (actigraphy or polysomnography) for a more in-depth understanding of the nature and severity of the sleep disturbance. The dichotomization of the outcome may have decreased our power to detect sleep disturbance, but this limitation is attenuated by the large sample size and the fact that results from the full range of outcome values from the Symptom Index scale did not differ substantively from those of the dichotomized outcome. While selection bias is always a concern in any observational study, the matching of HIV infected and uninfected participants by age, race, and gender does address potential imbalance in those important confounders. Lastly, because this study was observational, we make no claims of causality.

Conclusion

Our results demonstrate that while sleep disturbance is more common among HIV infected individuals, its higher incidence may be driven by numerous factors known to cause sleep disturbance in the general population, rather than from HIV-specific factors. Until we have guidelines for treatment of sleep disturbance among HIV infected individuals, we recommend avoiding the use of sleep medications and routine use of CBT-I¹⁶ and/or CAM therapies. Patients may benefit from a provider's review of their medications and subsequent elimination of those not central to their goals of care. Future studies should include physiologic measures of sleep, such as those measured with actigraphy and polysomnography. Those techniques will more clearly characterize sleep patterns in this population and enhance evaluation of the association between HIV infection and sleep disturbance.

Acknowledgments

Funding: This study was funded by the following:

The Yale Center for Sleep Disturbance in Acute and Chronic Conditions (NIH/NINR P20 NR013126)

Veterans Aging Cohort Study funded by: National Institute on Alcohol Abuse and Alcoholism (U10 AA 13566) and VHA Public Health Strategic Health Core Group.

The Yale Claude D. Pepper Older Americans Independence Center (NIH/NIA P30AG021342).

References

1. Norman SE, Resnick L, Cohn MA, Duara R, Herbst J, Berger JR. Sleep disturbances in HIV-seropositive patients. *Jama*. Aug 19.1988 260(7):922.
2. Norman SE, Chediak AD, Freeman C, et al. Sleep disturbances in men with asymptomatic human immunodeficiency (HIV) infection. *Sleep*. Apr; 1992 15(2):150–155. [PubMed: 1579789]

3. White JL, D DF, Brown SJ, Miller JC, Hayduk R, Kelly T, Mitler MM. Early central nervous system response to HIV infection: sleep distortion and cognitive-motor decrements. *AIDS (London, England)*. 1995; 9:1043–1050.
4. Wiegand M, Moller AA, Schreiber W, et al. Nocturnal sleep EEG in patients with HIV infection. *European archives of psychiatry and clinical neuroscience*. 1991; 240(3):153–158. [PubMed: 1827600]
5. Justice AC, Dombrowski E, Conigliaro J, et al. Veterans Aging Cohort Study (VACS): Overview and description. *Medical care*. Aug; 2006 44(8 Suppl 2):S13–24. [PubMed: 16849964]
6. Fultz SL, Skanderson M, Mole LA, et al. Development and verification of a “virtual” cohort using the National VA Health Information System. *Medical care*. Aug; 2006 44(8 Suppl 2):S25–30. [PubMed: 16849965]
7. Justice AC, Holmes W, Gifford AL, et al. Development and validation of a self-completed HIV symptom index. *Journal of clinical epidemiology*. Dec; 2001 54(Suppl 1):S77–90. [PubMed: 11750213]
8. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire*. *JAMA*. Nov 10; 1999 282(18):1737–1744. [PubMed: 10568646]
9. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. *Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test*. *Archives of internal medicine*. Sep 14; 1998 158(16):1789–1795. [PubMed: 9738608]
10. Bradley KA, McDonell MB, Bush K, Kivlahan DR, Diehr P, Fihn SD. The AUDIT alcohol consumption questions: reliability, validity, and responsiveness to change in older male primary care patients. *Alcoholism, clinical and experimental research*. Nov; 1998 22(8):1842–1849.
11. Bradley KA, Bush KR, Epler AJ, et al. Two brief alcohol-screening tests From the Alcohol Use Disorders Identification Test (AUDIT): validation in a female Veterans Affairs patient population. *Archives of internal medicine*. Apr 14; 2003 163(7):821–829. [PubMed: 12695273]
12. Gallego L, Barreiro P, del Rio R, et al. Analyzing sleep abnormalities in HIV-infected patients treated with Efavirenz. *Clin Infect Dis*. Feb 1; 2004 38(3):430–432. [PubMed: 14727217]
13. Hochberg Y, Benjamini Y. More powerful procedures for multiple significance testing. *Statistics in medicine*. Jul; 1990 9(7):811–818. [PubMed: 2218183]
14. Hosmer DW, aL S. A goodness-of-fit test for the multiple logistic regression model. *Communications in Statistics*. 1980; A10:1043–1069.
15. Wong ES, Wang V, Liu CF, Hebert PL, Maciejewski ML. Do Veterans Health Administration Enrollees Generalize to Other Populations? *Medical care research and review: MCRR*. Aug; 2016 73(4):493–507. [PubMed: 26589675]
16. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. Oct 15; 2008 4(5):487–504. [PubMed: 18853708]

Table

HIV and self-reported sleep disturbance: unadjusted and adjusted models.*

	Unadjusted		Adjusted Polypharmacy only		Adjusted Polypharmacy and specific sleep-related medications	
	Odds Ratio (95% CI)**	p‡	Odds Ratio (95% CI)**	p‡	Odds Ratio (95% CI)**	p‡
HIV	1.13 (1.03, 1.24)	0.01	1.08 (1.01, 1.15)	0.39	1.08 (1.01, 1.05)	0.55
Age	--	--	REF	REF	REF	REF
< 50 years of age			0.93 (0.87, 1.00)	0.65	0.94 (0.88, 1.01)	0.832
50 – 65 years of age			0.78 (0.69, 0.87)	0.0007	0.80 (0.72, 0.90)	0.008
> 65 years of age						
Race	--	--	REF	REF	REF	REF
White			0.64 (0.60, 0.69)	<0.0001	0.69 (0.64, 0.75)	0.003
Black			0.76 (0.68, 0.85)	<0.0001	0.79 (0.71, 0.89)	0.003
Hispanic			0.84 (0.72, 0.99)	0.69	0.90 (0.77, 1.06)	0.832
Other						
Female	--	--	1.75 (1.47, 2.08)	<0.0001	1.74 (1.46, 2.07)	0.003
Pain Score	--	--	1.06 (1.03, 1.08)	0.0006	1.06 (1.03, 1.08)	0.003
Depression§	--	--	3.56 (3.14, 4.04)	<0.0001	3.49 (3.08, 3.97)	0.003
Liver disease	--	--	1.13 (1.06, 1.20)	0.0068	1.11 (1.04, 1.18)	0.051
PTSD	--	--	1.81 (1.60, 2.04)	<0.0001	1.55 (1.37, 1.75)	0.003
Hazardous alcohol use	--	--	1.15 (1.07, 1.23)	0.0014	1.14 (1.07, 1.22)	0.003
Smoker	--	---	REF	REF	REF	REF
Never			1.05 (0.96, 1.14)	0.86	1.05 (0.97, 1.14)	0.832
Former			1.20 (1.10, 1.30)	0.0007	1.20 (1.10, 1.31)	0.003
Current						
Medication count	--	--	1.06 (1.05, 1.08)	<0.0001	1.04 (1.03, 1.06)	0.003

	Unadjusted		Adjusted Polypharmacy only		Adjusted Polypharmacy and specific sleep-related medications	
	Odds Ratio (95% CI)**	p [‡]	Odds Ratio (95% CI)**	p [‡]	Odds Ratio (95% CI)**	p [‡]
Benzodiazepine use	--	--	--	--	1.60 (1.42, 1.80)	0.003
Z-drug use	--	--	--	--	2.15 (1.74, 2.66)	0.003
Hazardous opiate use	--	--	--	--	1.05 (0.92, 1.18)	0.832
SSRI use	--	--	--	--	1.20 (1.10, 1.32)	0.003
Other antidepressant use	--	--	--	--	1.60 (1.46, 1.76)	0.003

* Variables included in the model but not significantly associated with self-reported sleep disturbance: underweight (body mass index < 18.5), normal weight (BMI between 18.5 and 25), overweight (BMI between 25 and 30), obesity (BMI ≥ 30), heart failure, COPD, other lung disease, drug use or abuse, coronary artery disease, diabetes, peripheral vascular disease, renal disease, cerebrovascular disease/stroke, cancer, sleep apnea, female × depression^{1/2}, female × depression, medication count × pain score, depression (PHQ-2), (medication count)² × pain score, depression (PHQ-2), survey wave, (baseline, follow-up 1-6)

** Model fit: C statistic: 0.78; Hosmer and Lemeshow Goodness-of-Fit > 0.05

[‡] Model fit: C statistic: 0.77; Hosmer and Lemeshow Goodness of Fit > 0.05

[‡] p values calculated by Hochberg to control for multiple comparisons

[§] square root of PHQ-2 score.