Prevalence and Factors Associated With Sleep Disturbances Among Early-Treated HIV-Infected Persons

Nancy F. Crum-Cianflone,[1,3,4] Mollie Poehlman Roediger,[1,6] David J. Moore,[5] Braden Hale,[1,3,4] Amy Weintrob,[1,7] Anuradha Ganesan,[1,2] Lynn E. Eberly,[1,6] Erica Johnson,[1,8] Brian K. Agan,[1] and Scott Letendre[5]

[1]Infectious Disease Clinical Research Program, Uniformed Services University of the Health Sciences, and [2]Infectious Disease Clinic, National Naval Medical Center, Bethesda, Maryland; [3]HIV Clinic, Naval Medical Center San Diego, [4]Naval Health Research Center, San Diego, and [5]HIV Neurobehavioral Research Program, University of California, San Diego; [6]Division of Biostatistics, University of Minnesota, Minneapolis; [7]Infectious Disease Clinic, Walter Reed Army Medical Center, Washington DC; and [8]Infectious Disease Service, San Antonio Military Medical Center, Texas

Background. Sleep disturbances are reportedly common among persons infected with human immunodeficiency virus (HIV), but recent data, including comparisons with HIV-uninfected persons, are limited.

Methods. We performed a cross-sectional study among early-treated HIV-infected military beneficiaries (n = 193) to determine the prevalence and factors associated with insomnia (Pittsburgh Sleep Quality Index [PSQI]) and daytime sleepiness (Epworth Sleepiness Scale [ESS]). Data were compared with HIV-uninfected persons (n = 50) matched by age, sex, race or ethnicity, and military rank.

Results. Forty-six percent of HIV-infected persons had insomnia (PSQI >5), and 30% reported daytime drowsiness (ESS ≥10). The prevalence of insomnia and daytime sleepiness was not significantly higher compared with the HIV-uninfected group (38% [$P = .30$] and 20% [$P = .18$], respectively). In the multivariate model, factors associated with insomnia among HIV infected patients included depression (odds ratio [OR], 16.8; 95% confidence interval [CI], 2.0–142.1; $P = .01$), increased waist size (OR, 2.7; 95% CI, 1.4–5.1; $P = .002$), and fewer years of education (OR, 0.8; 95% CI, .7–.95; $P = .006$). Neurocognitive impairment (diagnosed in 19% of HIV-infected participants) was not associated with insomnia; however, HIV-infected persons with insomnia were 3.1-fold more likely to have a decline in activities of daily living than those without insomnia (23% vs 9%; $P = .01$). Only 18% of HIV-infected persons reported using a sleep medication at least weekly.

Conclusions. HIV-infected persons have a high prevalence of insomnia, but among an early-treated cohort this rate was not significantly higher compared with HIV-uninfected persons. Factors associated with insomnia among HIV-infected patients include depression and increased waist size. Prompt diagnosis and treatment of sleep disturbances are advocated and may improve quality of life.

Sleep disturbances among persons infected with human immunodeficiency virus (HIV) were recognized early in the HIV epidemic [1], with changes in sleep structure being one of the earliest and most consistent physiologic changes noted [2]. Although the prevalence of sleep disturbances is reportedly high among HIV-infected persons [3–8], few studies exist in the literature during the highly active antriretroviral therapy (HAART) era. Recent studies have largely focused on the impact of specific antiretroviral agents (eg, efavirenz) on sleep quality [9–13], or the impact of weight gain and lipohypertrophy on obstructive sleep apnea (OSA) [14–16]. The most recent study performed to assess the overall prevalence of insomnia in a well-defined HIV cohort found a prevalence rate of 73% [7]; however, this study had no control group and was conducted over 15 years ago.

The pathophysiology of sleep disturbances among HIV-infected patients is unclear, but may be related to the ability of HIV to infect the central nervous system

Received 13 September 2011; accepted 6 January 2012; electronically published 19 March 2012.

Correspondence: Nancy Crum-Cianflone, MD, MPH, c/o Clinical Investigation Department (KCA), Infectious Diseases Division, Naval Medical Center San Diego, 34800 Bob Wilson Dr, Ste 5, San Diego, CA 92134-1005 (nancy.crum@med.navy.mil).

Clinical Infectious Diseases 2012;54(10):1485–94
Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2012.
DOI: 10.1093/cid/cis192

(CNS), impact of antiretroviral medications, CNS opportunistic infections, mental health issues, and substance abuse [17, 18]. Regardless of its etiology, insomnia is clinically important in this population for several reasons, including its potential impact on quality of life, adherence to antiretroviral medications, and cognition [7, 8, 19].

Our aim was to determine the prevalence of sleep disturbances in the late HAART era among HIV-infected persons and compare this rate to a matched HIV-negative control group. In this study, we evaluated the factors associated with insomnia among HIV-infected persons and the association between insomnia and cognitive function, as well as activities of daily living (ADLs).

METHODS

Study Design and Participants

We performed a cross-sectional study among 200 HIV-infected and 50 HIV-uninfected persons who were 18–50 years of age. Participants were US military beneficiaries (active duty members, retirees, or dependents); active duty members are HIV seronegative on entry into military service and undergo mandatory HIV testing every 1–5 years. Given the routine screening and open access to care for military beneficiaries, our HIV cohort consisted of patients with early diagnosed and managed HIV infection.

HIV-infected patients were offered enrollment on presentation for routine care at HIV subspecialty clinics in 3 US geographic areas (San Diego, California; Washington, DC; and San Antonio, Texas). HIV-uninfected persons were enrolled at primary health care clinics. Exclusion criteria were current or recent suicidal ideation and the presence of an acute medical condition that could impact the participant's ability to complete the study (eg, febrile illness or any new onset or worsening condition deemed by patient's physician that could acutely impact sleep or neurocognitive functioning).

Recruitment into the HIV arm was balanced across the participants' current HIV status: "earlier" (<6 years of infection, no prior AIDS-defining condition, and $CD4^+$ cell count nadir >200 cells/mm^3) and "later" (not meeting all 3 criteria). Of the 200 original study participants, 193 (97%) provided complete sleep and neuropsychological test data and were included in this analysis. In the majority (n = 185), HIV infection had been diagnosed >6 months before study enrollment. HIV-uninfected participants (required to have an HIV-negative enzyme-linked immunosorbent assay test within the last year) were frequency matched to the HIV-infected participants by age (<35 vs 35–50 years), sex, race or ethnicity (white vs other), and military rank (officer vs enlisted vs other; retirees and dependents were placed in the "other" category). All participants provided written informed consent, and the study was approved by a central military institutional review board.

Main Outcomes

Insomnia and daytime sleepiness were the main outcomes examined. Each participant completed the Pittsburgh Sleep Quality Index (PSQI), a 19-item questionnaire that assesses 7 sleep components (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of hypnotics, and daytime dysfunction) during the prior month, and insomnia was defined as a global score of >5 (sensitivity of 90% and specificity of 87% in the general population [20]). An Epworth Sleepiness Scale (ESS) score of ≥10 indicated daytime sleepiness [21].

Additional Data Collected

Factors potentially associated with sleep outcomes were collected including demographics, military rank and duty status, education, self-reported substance use (tobacco, alcohol, and illicit drugs), and history of serious head trauma. A self-assessment of sleep problems (categorized as present or absent, and if present having very little effect, mild effect, moderate effect, or severe effect on daily activities), and self-assessment of cognitive impairment were obtained via participant questionnaires. The Beck Depression Inventory (BDI) II (depression defined as a BDI score ≥20) and a modified version of the Activities of Daily Living (ADL) Questionnaire (a decline was defined as a reduction from prior best to current score in ≥2 items) were performed [22, 23]. HIV-infected participants completed questionnaires on lipodystrophy and peripheral neuropathy [24]. Lipoatrophy was defined as an affirmative response to loss of fat in the face, arms, or legs. Fat gain in the abdominal area was used as potential indicator of lipohypertrophy and referred to as increased waist size.

Participants underwent a comprehensive battery of standardized neuropsychological tests (administration time, 3.5–4 hours) derived from prior work [25] and composed of 9 measures shown to be sensitive to HIV-associated neurocognitive disorders. Neuropsychological tests were scored by trained psychometrists, and a global deficit score (GDS) of ≥0.5 was defined as neurocognitive impairment [26].

Clinical data were abstracted from medical records among HIV-infected participants, including body mass index (BMI), fasting lipid levels, and medical conditions. The metabolic syndrome was defined by modified Adult Treatment Panel III guidelines [27] and diabetes and hypertension by physician diagnoses. HIV-specific data were collected, including date of HIV seropositivity, history of AIDS-defining conditions [28], $CD4^+$ cell counts (including nadir $CD4^+$ cell counts), HIV RNA levels, and antiretroviral therapy.

Statistical Analyses

Participant characteristics were summarized by HIV status. Descriptive statistics are presented as means with standard deviations (SDs), or counts with proportions, as appropriate. Two-sample *t* tests were used to compare means, and χ^2 tests were used to compare proportions across HIV-infected vs HIV-uninfected groups. Univariate and multivariate associations of factors (listed above) with insomnia were determined by logistic regression. Odds ratios (OR) for the prevalence of insomnia were estimated with 95% confidence intervals (CIs). Factors with a *P* value $\leq$ .10 in univariate models were initially included in the multivariate model and were then eliminated using backward selection. Linear regression and the Pearson correlation coefficient were used to explore the relationship between the PSQI score and BDI score. All *P* values were 2-sided, and *P* values $<$ .05 were considered significant. Analyses were conducted using SAS software, version 9.2 (SAS Institute) and *R* software, version 2.9.

RESULTS

Study Characteristics of HIV-Infected Persons

We evaluated 193 HIV-infected persons with a mean age of 36 years (SD, 9), 95% were male, and 50% were white (Table 1). The mean BMI was 27.5 kg/m^2 (SD, 4.5), and 25% were obese. Lipodystrophy was noted among 52%, metabolic syndrome in 26%, depression (BDI, $\geq$20) in 7%, and diabetes in 3%. The mean time from HIV seropositivity to study enrollment was 7 years (SD, 6), 6% had a prior AIDS-defining condition, and 15% had a CD4$^+$ cell count nadir of $<$200 cells/mm^3. The mean CD4$^+$ count at enrollment was 587 cells/mm^3; 66% of patients were receiving HAART, and 55% had an undetectable HIV RNA level.

Prevalence of Sleep Disturbances Among HIV-Infected Persons

Eighty-nine HIV-infected persons (46.1%; 95% CI, 39.0%–53.2%) had insomnia based on the PSQI ($>$5) (Table 2). The mean amount of sleep per night reported was 6.5 hours (SD, 1.3) with 46% reporting $<$7 hours of sleep on average per night. Subjective sleep quality was reported as ''bad'' among 23%. Sleep latency was $>$60 minutes on $\geq$3 nights per week among 12% of HIV-infected persons and 31–60 minutes at least weekly among 19%, for a total of 31% having an extended sleep latency. Some amount of daytime dysfunctioning due to sleepiness was reported by 53% of patients. On the ESS, 29.5% of HIV-infected persons (95% CI, 23.0%–36.0%) had evidence of daytime drowsiness (score, $\geq$10). Finally, 18% reported taking a medication for sleep at least weekly.

On the self-reported questionnaire, 69 persons (36%) responded affirmatively to the question, ''Do you feel that you have a problem sleeping?'' of whom 24 (35%) stated that the problem had a moderate or severe impact on their life. Among HIV-infected persons with insomnia, these percentages were 72% and 38%, respectively.

Prevalence of Sleep Disturbances Among HIV-Infected vs HIV-Uninfected Persons

Among the 50 HIV-uninfected persons evaluated, the mean age was 35 years (SD, 9), 96% were male, and 50% were white (Table 1). HIV-uninfected persons were similar to the HIV-infected persons except that they were more likely to be of Hispanic or ''other'' ethnicity and less likely to meet criteria for depression (Table 1).

The prevalence of insomnia in the HIV-uninfected group was 38.0% (95% CI, 24.1%–51.9%), which was not statistically significantly different compared with the HIV-infected cohort (*P* = .30). There were also no differences in any of the 7 components of the PSQI between groups (Table 2), nor in daytime sleepiness of HIV-uninfected (20.0%; 95% CI, 8.5%–31.5%) vs HIV-infected persons (*P* = .18). HIV-infected and HIV-uninfected persons had similar rates of use of sleep medications $\geq$1 times/week (18% vs 16%; *P* $>$ .79).

Factors Associated With Sleep Disturbances Among HIV-Infected Persons

In the univariate analyses, factors associated with a insomnia (PSQI $>$5) included fewer years of education (OR, 0.8 per year; 95% CI, .7–.9; *P* = .005), obesity (OR, 2.3; 95% CI, 1.0–4.9; *P* = .04), increased waist size (OR, 3.0; 95% CI, 1.7–5.5; *P* $<$ .001), current cigarette use (OR, 2.8; 95% CI, 1.3–6.4; *P* = .01), history of serious head trauma (OR, 3.1; 95% CI, 1.4–6.9; *P* = .006), depression (OR, 17.6; 95% CI, 2.3–137.6; *P* = .006), and peripheral neuropathy (OR, 2.1; 95% CI, 1.3–4.0; *P* = .02) (Table 3). The military rank of officer (OR, 0.3; 95% CI, .1–.9; *P* = .04) was associated with a lower prevalence of insomnia, compared with enlisted rank. There were no significant associations between HIV-specific factors including HAART use (including efavirenz-containing regimens) and sleep. In the final multivariate model (Table 4), factors associated with insomnia based on the PSQI included depression (OR, 16.8; 95% CI, 2.0–142.1; *P* = .01), increased waist size (OR, 2.7; 95% CI, 1.4–5.1; *P* = .002), and fewer years of education (OR, 0.8 per year; 95% CI, .7–.95; *P* = .006).

Regarding the association of insomnia and depression by BDI scores among HIV-infected persons, insomnia was present in 37% of those without depression, 71% with mild depression, 89% with moderate depression, and 93% with severe depression (*P* $<$ .001). Moreover, higher BDI scores were significantly associated with higher PSQI scores (*r* = 0.57; *P* $<$ .001). Regarding antidepressant use, antidepressants were being taken by 7 (50%) of the 14 participants with a BDI $\geq$20, and 20 (11%) of the 179 with a BDI $<$20. Among participants with a BDI $<$20, those who were taking

Table 1. Study Population Characteristics by HIV Status

Characteristic	No. (%)[a]		
	HIV Infected (n = 193)	HIV Uninfected (n = 50)	*P* Value
Demographics			
Age, mean (SD), y	35.9 (8.6)	35.1 (9.2)	.57
Male sex	184 (95.3)	48 (96.0)	.84
Race			<.001
White	96 (49.7)	25 (50.0)	
Black	56 (29.0)	4 (8.0)	
Hispanic	26 (13.5)	9 (18.0)	
Other	15 (7.8)	12 (24.0)	
Military characteristics			
Rank			.68
Officer	16 (8.3)	5 (10.0)	
Enlisted	119 (61.7)	33 (66.0)	
Not applicable	58 (30.1)	12 (24.0)	
Duty status			.14
Active	135 (69.9)	38 (76.0)	
Retired	52 (26.9)	9 (18.0)	
Dependent	6 (3.1)	2 (4.0)	
Other	0 (0.0)	1 (2.0)	
Education			
Total, mean (SD), y	14.4 (2.3)	13.6 (1.7)	.03
Highest completed level			.05
Less than high school	1 (0.5)	1 (2.0)	
High school diploma or equivalent	125 (64.8)	39 (78.0)	
Bachelor's degree	36 (18.7)	9 (18.0)	
Higher degree (eg, master's, PhD)	30 (15.5)	1 (2.0)	
Beck Depression Inventory (BDI)			
Total score, mean (SD)	5.9 (7.6)	2.7 (3.6)	.004
Depression (BDI ≥20)	14 (7.3)	0 (0.0)	…
Medical conditions			
Hypertension	54 (28.0)	2 (4.0)	<.001
Diabetes	6 (3.1)	1 (2.0)	>.68
HIV history			
Duration of HIV seropositivity, mean (SD), y	7.2 (6.3)	…	…
Prior AIDS-defining condition	12 (6.2)	…	…
Patients with ''later'' HIV infection[b]	96 (49.7)	…	…
Current $CD4^+$ count, mean (SD), cells/mm^3	586.8 (230.1)	…	…
Nadir $CD4^+$ count, mean (SD), cells/mm^3	343.2 (166.6)	…	…
Current HIV RNA, undetectable (≤50 copies/mL)	105 (55.3)	…	…
Current HAART use	127 (65.8)	…	…

Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; SD, standard deviation.

[a] Unless otherwise specified, values represent no. (%) of participants.

[b] ≥6 years of HIV infection, prior AIDS-defining condition, or CD4 nadir ≤300 cells/mm^3.

antidepressants had a 6-fold higher odds of insomnia than those who were not (OR 6.6; 95% CI, 2.1–20.7; $P = .001$), whereas those with a BDI ≥20 had a 21-fold higher odds of insomnia relative to those with a BDI <20, regardless of whether or not they were taking antidepressants (OR, 21.4; 95% CI, 2.7–168.1; $P = .004$). Among those with a BDI ≥20, it was impossible to compare those taking with those not taking an antidepressant, because all participants in this group who were not taking an antidepressant had insomnia.

Associations between increased waist size and components of the PSQI and ESS were also examined. HIV-infected participants with increased waist size were at increased odds

Table 2. Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) Scores Among HIV-Infected and HIV-Uninfected Persons

Parameter	No. (%)[a]		*P* Value
	HIV Infected (n = 193)	HIV Uninfected (n = 50)	
PSQI, mean total score (SD)	6.0 (4.1)	5.2 (3.7)	.22
Insomnia (PSQI >5)	89 (46.1)	19 (38.0)	.30
Subjective sleep quality			.29
Very good	56 (29.0)	19 (38.0)	
Fairly good	92 (47.7)	20 (40.0)	
Fairly bad	37 (19.2)	11 (22.0)	
Very bad	8 (4.1)	0 (0.0)	
Sleep latency			.57
<15 min + not during past month	58 (30.1)	20 (40.0)	
16–30 min + less than once/wk	75 (38.9)	18 (36.0)	
31–60 min + once or twice/wk	37 (19.2)	7 (14.0)	
>60 min + ≥3 times/wk	23 (11.9)	5 (10.0)	
Sleep duration			.69
>7 h	104 (53.9)	26 (52.0)	
6–7 h	40 (20.7)	14 (28.0)	
5–6 h	34 (17.6)	7 (14.0)	
<5 h	15 (7.8)	3 (6.0)	
Amount of sleep per night, mean (SD), h	6.5 (1.3)	6.5 (1.3)	.95
Habitual sleep efficiency			.61
≥85%	131 (67.9)	34 (68.0)	
75%–84%	27 (14.0)	10 (20.0)	
65%–74%	17 (8.8)	3 (6.0)	
<65%	18 (9.3)	3 (6.0)	
Sleep disturbances			.51
None	15 (7.8)	7 (14.0)	
1–9	132 (68.4)	32 (64.0)	
10–18	38 (19.7)	10 (20.0)	
19–27	8 (4.1)	1 (2.0)	
Use of sleeping medication			>.99
Not during past month	140 (72.5)	37 (74.0)	
Less than once/wk	19 (9.8)	5 (10.0)	
Once or twice/wk	14 (7.3)	3 (6.0)	
≥3 times/wk	20 (10.4)	5 (10.0)	
Daytime dysfunction			.33
Never; no problem at all	91 (47.2)	26 (52.0)	
Once or twice; only a very slight problem	62 (32.1)	19 (38.0)	
1–2 times/wk; somewhat of a problem	36 (18.7)	5 (10.0)	
≥3 times/wk; very big problem	4 (2.1)	0 (0.0)	
ESS score, mean (SD)	7.5 (4.4)	6.6 (3.6)	.19
Sleepy, ESS ≥10	57 (29.5)	10 (20.0)	.18
Very sleepy, ESS ≥18	4 (2.1)	0 (0.0)	.58

Abbreviations: ESS, Epworth Sleepiness Scale; HIV, human immunodeficiency virus; SD, standard deviation.

[a] Unless otherwise specified, values represent no. (%) of participants.

for loud snoring (OR, 4.2; 95% CI, 1.7–10.2; $P = .001$), daytime dysfunction (OR, 2.3; 95% CI, 1.2–4.8; $P = .02$), and daytime sleepiness (ESS ≥10; OR, 2.0; 95% CI, 1.1–3.7; $P = .03$).

Finally, we examined whether HIV infection itself was associated with insomnia. In a multivariate model that included ethnicity, years of education, positive depression

Table 3. Factors Associated With Insomnia Among HIV-Infected Persons

Factor	Insomnia, No. (%)[a]		Univariate Models	
	Yes (n = 89)	No (n = 104)	OR (95% CI)	*P* Value
Age, mean (SD), y	36.1 (8.6)	35.7 (8.6)	1.01 (.97–1.04)	.74
Sex				
Female	6 (6.7)	3 (2.9)	2.43 (.59–10.03)	.22
Male	83 (93.3)	101 (97.1)	1.0	…
Race				
White	41 (46.1)	55 (52.9)	1.0	…
Black	32 (36.0)	24 (23.1)	1.79 (.92–3.48)	.09
Hispanic	11 (12.4)	15 (14.4)	0.98 (.41–2.36)	.97
Other	5 (5.6)	10 (9.6)	0.67 (.21–2.11)	.50
Military characteristics				
Rank				
Officer	3 (3.4)	13 (12.5)	0.25 (.07–.93)	.04
Enlisted	57 (64.0)	62 (59.6)	1.0	…
Not applicable	29 (32.6)	29 (27.9)	1.09 (.58–2.04)	.79
Duty status				
Active	60 (67.4)	75 (72.1)	1.0	…
Retired	24 (27.0)	28 (26.9)	1.07 (.56–2.04)	.83
Dependent	5 (5.6)	1 (1.0)	6.25 (.71–54.93)	.10
Other	0 (0.0)	0 (0.0)	…	…
Education				
Total, mean (SD), y	13.9 (2.2)	14.8 (2.4)	0.83 (.72–0.94)	.005
Highest completed level				
Less than high school	1 (1.1)	0 (0.0)	…	…
High school/diploma	69 (77.5)	56 (53.8)	2.71 (1.19–6.19)	.02
Bachelor's degree	10 (11.2)	26 (25.0)	0.85 (.30–2.40)	.75
Higher degree (eg, master's, PhD)	9 (10.1)	21 (20.2)	1.0	…
HIV history				
Duration of HIV seropositivity, mean (SD), y	7.3 (6.2)	7.1 (6.4)	1.00 (.96–1.05)	.84
HIV status (''later'' vs ''earlier'')[b]	45 (50.6)	51 (49.0)	1.06 (.60–1.87)	.83
Prior AIDS-defining condition	7 (7.9)	5 (4.8)	1.69 (.52–5.52)	.39
Laboratory results				
$CD4^+$ count, mean (SD) cells/mm^{3c}	567.9 (218.5)	603.3 (239.6)	0.97 (.91–1.03)	.29
Nadir $CD4^+$ count, mean (SD) cells/mm^{3c}	325.7 (157.6)	358.2 (173.3)	0.94 (.86–1.03)	.18
HIV RNA, undetectable (≤50 copies/mL)	47 (52.8)	58 (57.4)	0.83 (.47–1.47)	.52
Current HAART regimen contains efavirenz	33 (55.9)	41 (61.2)	0.78 (.38–1.57)	.48
HAART use and HIV RNA status				
ARV naive	22 (24.7)	36 (34.6)	0.76 (.39–1.46)	.41
Off ARVs, not naive	7 (7.9)	1 (1.0)	8.97 (1.03–73.06)	.05
On HAART, HIV RNA >50 copies/mL	14 (15.7)	10 (9.6)	1.73 (.71–4.27)	.23
On HAART, HIV RNA ≤50 copies/mL	46 (51.7)	57 (54.8)	1.0	…
Lipids and other CVD risk factors				
BMI, mean (SD), kg/m^2	28.3 (5.0)	26.8 (3.9)	1.08 (1.01–1.15)	.03
BMI category				
Normal weight (18.5 ≤ BMI <25)	25 (28.7)	37 (35.9)	1.0	…
Overweight (25 ≤ BMI <30)	33 (37.9)	47 (45.6)	1.04 (.53–2.04)	.91
Obese (BMI ≥30)	29 (33.3)	19 (18.4)	2.26 (1.05–4.88)	.04
Total cholesterol ≥200 mg/dL	25 (28.1)	20 (19.2)	1.64 (.84–3.21)	.15
LDL cholesterol ≥130 mg/dL	19 (21.3)	16 (15.4)	1.49 (.72–3.11)	.29
HDL cholesterol ≤35 mg/dL	19 (21.3)	28 (26.9)	0.74 (.38–1.44)	.37
Triglycerides ≥150 mg/dL	34 (38.2)	33 (31.7)	1.33 (.73–2.41)	.35

Table 3 continued.

Factor	Insomnia, No. (%)[a]		Univariate Models	
	Yes (n = 89)	No (n = 104)	OR (95% CI)	*P* Value
Metabolic syndrome	29 (32.6)	21 (20.2)	1.91 (0.99–3.67)	.05
Hypertension	30 (33.7)	24 (23.1)	1.69 (.90–3.19)	.10
Diabetes	5 (5.6)	1 (1.0)	6.13 (.70–53.48)	.10
Fat distribution				
Lipoatrophy	23 (25.8)	21 (20.2)	1.38 (.70–2.70)	.35
Increased waist size	49 (55.1)	30 (28.8)	3.02 (1.67–5.48)	<.001
Lipodystrophy	58 (65.2)	43 (41.3)	2.65 (1.48–4.76)	.001
Smoking status				
Never	38 (42.7)	59 (56.7)	1.0	…
Former	29 (32.6)	33 (31.7)	1.36 (.72–2.60)	.34
Current	22 (24.7)	12 (11.5)	2.85 (1.26–6.42)	.01
Comorbid conditions				
Serious head injury[d]	22 (24.7)	10 (9.6)	3.09 (1.37–6.94)	.006
Significant medical conditions[e]	38 (42.7)	32 (30.8)	1.68 (.93–3.03)	.09
Depression (BDI ≥20)	13 (14.6)	1 (1.0)	17.62 (2.26–137.6)	.006
Depression category				
Normal (BDI ≤9)	56 (62.9)	97 (93.3)	1.0	…
Mild (BDI 10–15)	12 (13.5)	5 (4.8)	4.16 (1.39–12.41)	.01
Mild-moderate (BDI 16–19)	8 (9.0)	1 (1.0)	13.86 (1.69–113.7)	.01
Moderate-severe (BDI ≥20)	13 (14.5)	1 (1.0)	22.51 (2.87–176.7)	.003
Disruption in ADLs (≥2 items indicating a decline from best to worst)	20 (22.5)	9 (8.7)	3.06 (1.31–7.13)	.01
Any history of peripheral neuropathy symptoms	36 (40.4)	25 (24.0)	2.15 (1.16–3.98)	.02
Average alcohol use during past year				
Never	13 (14.9)	17 (16.3)		
0–1 drinks/wk	33 (37.9)	44 (42.3)	1.00 (.42–2.30)	.96
2–5 drinks/wk	38 (43.7)	36 (34.6)	1.38 (.59–3.24)	.46
6–12 drinks/wk	2 (2.3)	5 (4.8)	0.52 (.09–3.14)	.48
>12 drinks/wk	1 (1.1)	2 (1.9)	0.65 (.05–8.02)	.74
Current illicit drug use	6 (6.7)	1 (1.0)	7.44 (.88–63.02)	.07

Abbreviations: ADLs, activities of daily living; ARV, antiretroviral; BDI, Beck Depression Inventory; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HAART, highly active antiretroviral therapy; HDL, high density lipoprotein; HIV, human immunodeficiency virus; LDL, low density lipoprotein; OR, odds ratio; SD, standard deviation.

[a] Unless otherwise specified, values represent no. (%) of participants.

[b] ''Later'' HIV is defined as ≥6 years of HIV infection, prior AIDS-defining condition, or CD4 nadir ≤300 cells/mm^3.

[c] OR is given per 50 cells/mm^3.

[d] History of seizures, serious head trauma or concussion, or loss of consciousness for >30 min.

[e] History of any of the following conditions: hepatitis C, clinical AIDS, cardiac disease, cerebrovascular disease, hypertension, diabetes, cirrhosis, or renal failure.

score (BDI ≥20), and HIV status (negative vs positive), HIV infection was not associated with insomnia ($P = .70$). Additionally, using the outcome of total PSQI score, there was also no association with HIV status in a multivariate linear regression model ($P = .44$) (data not shown).

Impact of Insomnia Among HIV-Infected Persons

We examined neurocognitive impairment (GDS ≥0.5), which was present in 36 (19%) of the HIV-infected participants. There was no association found between sleep and overall neurocognitive impairment by GDS (Table 5). We also evaluated 7 individual neuropsychological domains, and found only 1 to be associated—those with impaired verbal fluency were less likely to have insomnia (OR, 0.4; 95% CI, .2–.9; $P = .03$).

We studied the association between PSQI score and self-reported cognitive impairment (''Do you feel that you have a problem with memory loss or cognitive functioning?''); among those with insomnia, 43% reported memory loss compared with 16% without insomnia (OR, 3.8; 95% CI, 2.0–7.4; $P < .001$). This finding remained after excluding participants with depression. Finally, we examined the

Table 4. Multivariate Analysis of Factors Associated With Insomnia (PSQI >5) Among HIV-Infected Persons

	Insomnia, No. (%)[a]		Final Multivariate Model	
Factor	Yes (N = 89)	No (N = 104)	OR (95% CI)	*P* Value
Total education, mean (SD), y	13.9 (2.2)	14.8 (2.4)	0.82 (.71–.95)	.006
Increased waist size	49 (55.1)	30 (28.8)	2.70 (1.43–5.10)	.002
Depressed (BDI ≥20)	13 (14.6)	1 (1.0)	16.79 (1.98–142.4)	.01
Current illicit drug use	6 (6.7)	1 (1.0)	8.07 (.91–71.41)	.06

Abbreviations: BDI, Beck depression inventory; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation.

[a] Unless otherwise specified, values represent no. (%) of participants.

presence of insomnia and ADLs; 22% of participants with insomnia reported a decline in ADLs in ≥2 items compared with 9% of those without insomnia (OR, 3.1; 95% CI, 1.3–7.1; $P = .01$).

DISCUSSION

This study represents one of the largest epidemiologic studies of the prevalence of insomnia among HIV-infected persons that included a frequency-matched HIV-negative control group [6, 29]. We found that HIV-infected persons have a high prevalence of sleep disturbances (insomnia and daytime sleepiness) as measured by standardized questionnaires. Despite the high prevalence of insomnia, HIV-infected persons did not have a statistically significantly higher rate compared with matched HIV-uninfected persons. These data suggest that in the HAART era, patients with early-diagnosed, early-treated HIV infection may have similar rates of sleep disturbances as the general population.

Data from prior studies among HIV-infected persons found higher rates of insomnia (up to 73%) and suggested that this group was at elevated risk for sleep disturbances compared with the general population [3–7, 29–31]. However, these studies were conducted in the pre-HAART era when patients often had concurrent opportunistic diseases, and studies included a number of illicit drug users. Our population consisted of HIV-infected persons with free access to antiretroviral therapy, few AIDS-related conditions, and low rates of illicit drug use.

The strongest factor associated with insomnia among HIV-infected persons in our study was depression. This finding is consistent with other studies [7, 32], and exemplifies that psychological morbidity is a major factor in insomnia among HIV-infected patients. Given the

Table 5. Associations Between Insomnia and Neurocognitive Impairment Among HIV-Infected Persons

	Insomnia, No. (%)		Univariate Models	
Parameter	Yes (n = 89)	No (n = 104)	OR (95% CI)	*P*
Global deficit score ≥ 0.5	16 (18.0)	20 (19.2)	0.92 (.44–1.91)	.82
Area of neurocognitive impairment				
Verbal fluency	10 (11.2)	24 (23.1)	0.42 (.19–.94)	.03
Abstraction/executive functioning	18 (20.2)	18 (17.3)	1.21 (.59–2.50)	.60
Speed of information processing	9 (10.1)	8 (7.7)	1.35 (.50–3.66)	.56
Attention/working memory	20 (22.5)	23 (22.1)	1.02 (.52–2.01)	.95
Learning	15 (16.9)	26 (25.0)	0.61 (.30–1.24)	.17
Recall	18 (20.2)	18 (17.3)	1.21 (.59–2.50)	.60
Motor speed and dexterity	20 (22.5)	23 (22.1)	1.02 (.52–2.01)	.95

Neurocognitive tests included estimates of premorbid functioning (Wechsler Test of Adult Reading [WTAR]), verbal fluency (Letter Fluency [FAS], category fluency [animals], and action fluency [verbs]), attention/working memory (Paced Auditory Serial Addition Task [PASAT], Wechsler Adult Intelligences Scale III [WAIS-III] Digit Span), visuospatial functioning (Judgment of Line Orientation Tests [JLOT], form H; Hooper Visual Organization Test [HVOT]), speeded information processing (WAIS-III Symbol Search; WAIS-III Digit Symbol; Trail Making Test [TMT] A; Stroop Word and Color Tests), learning and recall (Hopkins Verbal Learning Test-R [HVLT-R]; Brief Visuospatial Memory Test-R [BVMT-R]; Memory for Intentions Screening Test [MIST]), abstraction/executive functioning (Wisconsin Card Sorting Tests [WCST] 64 card version; TMT B; Stroop Word and Color Tests), motor speed and dexterity (Grooved Pegboard Test [both hands]), and accuracy of reporting (Hiscock Digit Memory Test [HDMT]). Impairment was defined as a domain deficit score >0.5 or global deficit score ≥0.5.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

bidirectional relationship between sleep and depression, management of one condition may improve the other. For example, treating depression might improve sleep quality, and the treatment of sleep disturbances may decrease the incidence of depression [32].

Increased waist size was associated with sleep disturbances in our study. Prior studies have associated increases in BMI, as well as waist and neck circumferences with disordered night breathing and OSA [14–16]. Although we found an association with increased waist size and insomnia or daytime sleepiness, the exact etiology of this association is unclear, because we did not perform formal sleep studies. In addition to OSA, there are other potential mechanisms (eg, difficulty in achieving a comfortable sleeping position) by which abdominal adiposity may cause insomnia.

Regarding HIV-specific factors, we did not find an association between insomnia and HAART use in either direction. Antiretroviral agents with high CNS penetration effectiveness scores may be protective of HIV's effects on the CNS. On the other hand, some drugs may be associated with adverse sleep effects (eg, efavirenz, raltegravir), especially at higher plasma levels [4, 9, 11–13, 31, 33]. We found no relationship between stable, long-term efavirenz use and insomnia.

The impact of sleep disturbances may be several-fold. HIV-infected persons with insomnia reported a decline in performance of ADLs. We did not find a relationship between sleep and measured cognitive impairment (by neuropsychological tests) but did note an association with self-reported cognitive difficulties. A prior study conducted in the pre-HAART era showed an association between insomnia and cognitive impairment as measured using abbreviated testing [7]. The divergence of findings may be due to the differences in neuropsychological tests used or to the fact that the prior study was conducted in the pre-HAART era when HIV perhaps played a more direct role in both sleep and cognitive issues. Despite a high prevalence of insomnia among HIV-infected persons, only 17% were regularly using a medication for sleep. Prior studies have also noted that most patients with insomnia remain untreated and often have a poor understanding of available treatment options [7, 34].

Our study had several potential limitations. Sleep disturbances were diagnosed based on questionnaire data rather than polysomnograms; however, we used standardized instruments [20, 21] comparable to those used in other studies, and some experts suggest that self-reported data may be more representative of sleep issues [8]. The cross-sectional study design did not allow for assessing the temporal relationship between insomnia and factors (eg, depression and reduction in ADLs), nor for the assessment of whether sleep disturbances were transient or chronic in nature. Although we used an HIV-negative control group, our study was not powered to estimate small differences in insomnia rates between the 2 groups; the current study was performed concurrently with an evaluation of neurocognitive deficits among HIV-infected vs HIV-uninfected persons and the sample size was based on this objective. However, the 8% difference in the prevalence of insomnia between the 2 groups (46% vs 38%) may not be of enough clinical significance to warrant a larger study. Further, our rates of insomnia in the HIV-uninfected group were similar to those in prior reports [35–37]. Because our study was conducted among a cohort of military beneficiaries with early-diagnosed, early-managed HIV infection, results may not be generalizable to other HIV populations. Finally, we found that increased waist size was associated with sleep disturbances; however, whether this was due to abdominal lipohypertrophy was not confirmed by objective measures such as dual-energy x-ray absorptiometry scans.

Our study had several strengths. This study is one of the largest to date among HIV-infected patients and included an HIV-negative control group [4, 7]. The study used validated measures for both insomnia and daytime sleepiness, which are quick and inexpensive to implement into clinical practice [20, 21]. Furthermore, the study evaluated a comprehensive set of sociodemographic characteristics and clinical factors and also included evaluations of neurocognitive functioning and daily activities.

In summary, insomnia and daytime sleepiness are common among HIV-infected persons, but in the setting of early HIV diagnosis and management, the prevalence of these disorders does not seem higher than matched HIV-uninfected persons. Among HIV-infected persons, depression and increased waist size were significantly associated with insomnia. Prompt diagnosis and treatment of sleep disturbances are advocated and may improve quality of life.

Notes

Acknowledgments. All authors contributed to the content of the manuscript and concurred with the decision to submit it for publication.

Disclaimer. The content of this publication is the sole responsibility of the authors and does not necessarily reflect the views or policies of the National Institutes of Health or the Department of Health and Human Services, the Department of Defense, or the Departments of the Army, Navy, or Air Force. Mention of trade names, commercial products, or organizations does not imply endorsement by the US Government.

Financial support. This work was supported by the Infectious Disease Clinical Research Program, a Department of Defense program executed through the Uniformed Services University of the Health Sciences (grant number HU0001-05-2-0011). This project has been funded in whole, or in part, with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, under Inter-Agency Agreement Y1-AI-5072. Support was also obtained from the National Institute of Mental Health (grant P30 MH62512 to UCSD HIV Neurobehavioral Research Center).

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Norman SE, Resnick L, Cohn MA, Duara R, Herbst J, Berger JR. Sleep disturbances in HIV-seropositive patients. JAMA **1988**; 260:922.
2. White JL, Darko DF, Brown SJ, Miller JC, Hayduk R, Kelly T. Early central nervous system response to HIV infection: sleep distortion and cognitive-motor decrements. AIDS **1995**; 9:1043–50.
3. Wiegand M, Moller AA, Schreiber W, Krieg J C, Fuchs D, Wachter H. Nocturnal sleep EEG in patients with HIV infection. Eur Arch Psychiatry Clin Neurosci **1991**; 240:153–8.
4. Moeller AA, Oechsner M, Backmund HC, Popescu M, Emminger C, Holsboer F. Self-reported sleep quality in HIV infection: correlation to the stage of infection and zidovudine therapy. J Acquir Immune Defic Syndr **1991**; 4:1000–3.
5. Norman SE, Chediak AD, Freeman C, Kiel M, Cohn MA. Sleep disturbances in men with asymptomatic human immunodeficiency (HIV) infection. Sleep **1992**; 15:150–5.
6. Darko DF, McCutchan JA, Kripke DF, Gillin JC, Golshan S. Fatigue, sleep disturbance, disability, and indices of progression of HIV infection. Am J Psychiatry **1992**; 149:514–20.
7. Rubinstein ML, Selwyn PA. High Prevalence of insomnia in an outpatient population with HIV infection. J Acquir Immune Defic Syndr Hum Retrovirol **1998**; 19:260–5.
8. Reid S, Dwyer J. Insomnia in HIV infection: a systematic review of prevalence, correlates, and management. Psychosom Med **2005**; 67:260–9.
9. Núñez M, de Requena DG, Gallego L, Jimenez-Nacher I, Gonzalez-Lahoz J, Soriano V. Higher efavirenz plasma levels correlate with development of insomnia. J Acquir Immune Defic Syndr **2001**; 28:399–400.
10. Gallego L, Barreiro P, del Rio R, Gonzalez de Requena D, Rodriguez-Albarino A, Soriano V. Analyzing sleep abnormalities in HIV-infected patients treated with efavirenz. Clin Infect Dis **2004**; 38:430–2.
11. Nguyen A, Calmy A, Delhumeau C, et al. Swiss HIV Cohort Study. A randomized crossover study to compare efavirenz and etravirine treatment. AIDS **2011**; 25:57–63.
12. Waters L, Fisher M, Winston A, Higgs C, Hadley W, Garvey L. A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine. AIDS **2011**; 25:65–71.
13. Moyle G, Fletcher C, Brown H, Mandalia S, Gazzard B. Changes in sleep quality and brain wave patterns following initiation of an efavirenz-containing triple antiretroviral regimen. HIV Med **2006**; 7:243–7.
4. Lo Re V 3rd, Schutte-Rodin S, Kostman JR. Obstructive sleep apnoea among HIV patients. Int J STD AIDS **2006**; 17:614–20.
15. Dorey-Stein Z, Amorosa VK, Kostman JR, Lo Re V 3rd, Shannon RP. Severe weight gain, lipodystrophy, dyslipidemia, and obstructive sleep apnea in a human immunodeficiency virus−infected patient following highly active antiretroviral therapy. J Cardiometab Syndr **2008**; 3:111–14.
16. Brown TT, Patil SP, Jacobson LP, et al. Anthropometry in the prediction of sleep disordered breathing in HIV-positive and HIV-negative men. Antivir Ther **2010**; 15:651–9.
17. Omonuwa TS, Goforth HW, Preud'homme X, Krystal AD. The pharmacologic management of insomnia in patients with HIV. J Clin Sleep Med **2009**; 5:251–562.
18. Vosvick M, Gore-Felton C, Ashton E, Koopman C, Fluery T, Israelski D. Sleep disturbances among HIV-positive adults: the role of pain, stress, and social support. J Psychosom Res **2004**; 57:459–63.
19. Zammit GK, Weiner J, Damato N, Sillup GP, McMillan CA. Quality of life in people with insomnia. Sleep **1999**; 22(suppl 2): S379–85.
20. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res **1989**; 28:193–213.
21. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep **1991**; 14:540–5.
22. Beck AT, Steer RA, Brown GK. Beck depression inventory-second edition manual. San Antonio: The Psychological Corporation, **1996.**
23. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist **1969**; 9:179–86.
24. Cherry CL, Wesselingh SL, Lal L, McArther JC. Evaluation of a clinical screening tool for HIV-associated sensory neuropathies. Neurology **2005**; 65:1778–81.
25. Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C, Vaida F. CHARTER Group. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology **2010**; 75:2087–96.
26. Carey CL, Woods SP, Gonzalez R, Conover E, Marcotte TD, Grant I. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. J Clin Exp Neuropsychol **2004**; 26:307–19.
27. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (Adult Treatment Panel III). JAMA **2001**; 285:2486–97.
28. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep **1992**; 41:1–19.
29. Perkins DO, Leserman J, Stern RA, Baum SF, Liao D, Golden RN. Somatic symptoms and HIV infection: relationship to depressive symptoms and indicators of HIV disease. Am J Psychiatry **1995**; 152: 1776–81.
30. Cohen FL, Ferrans CE, Vizgirda V, Kunkle V, Cloninger L. Sleep in men and women infected with human immunodeficiency virus. Holist Nurs Pract **1996**; 10:33–43.
31. Nokes KM, Kendrew J. Correlates of sleep quality in persons with HIV disease. J Assoc Nurses AIDS Care **2001**; 12:17–22.
32. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? JAMA **1989**; 262:1479–84.
33. Eiden C, Peyriere H, Peytavin G, Reynes J. Severe insomnia related to high concentrations of raltegravir. AIDS **2011**; 25:725–7.
34. Ancoli-Israel S, Roth T. Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. Sleep **1999**; 22:S347–53.
35. Morin CM, LeBlanc M, Daley M, Gregoire JP, Mérette C. Epidemiology of insomnia: prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. Sleep Med **2006**; 7: 123–30.
36. Bixler EO, Kales A, Soldatos CR, Kales JD, Healey S. Prevalence of sleep disorders in the Los Angeles metropolitan area. Am J Psychiatry **1979**; 136:1257–62.
37. Sing CY, Wong WS. Prevalence of insomnia and its psychosocial correlates among college students in Hong Kong. J Am Coll Health **2010**; 59:174–82.