Title

Prevalence and Predictors of Sleep-Disordered Breathing in Men Participating in the Multicenter AIDS Cohort Study

Journal

CHEST Journal, 163(3)

ISSN

0012-3692

Authors

Punjabi, Naresh M
Brown, Todd T
Aurora, R Nisha
et al.

Publication Date

2023-03-01

DOI

10.1016/j.chest.2022.10.030

Peer reviewed

CHEST

Prevalence and Predictors of Sleep-Disordered Breathing in Men Participating in the Multicenter AIDS Cohort Study

Naresh M. Punjabi, MD, PhD; Todd T. Brown, MD, PhD; R. Nisha Aurora, MD; Sanjay R. Patel, MD; Valentina Stosor, MD; Joshua Hyong-Jin Cho, MD, PhD; Gypsyamber D'Souza, PhD; and Joseph B. Margolick, MD, PhD

BACKGROUND: Data on the prevalence of sleep-disordered breathing (SDB) in people with HIV are limited. Moreover, whether the associations between SDB and age or BMI differ by HIV status is unknown.

RESEARCH QUESTION: Is SDB more prevalent in men with HIV than those without HIV, and do the predictors of SDB differ between the two groups?

STUDY DESIGN AND METHODS: Home polysomnography was used in the Multicenter AIDS Cohort Study to assess SDB prevalence in men with (n = 466; 92% virologically suppressed) and without (n = 370) HIV. SDB was defined using the oxygen desaturation index (ODI) and the apnea-hypopnea index (AHI), using four definitions: ≥ 5 events/h based on an ODI with a 3% (ODI_3) or 4% (ODI_4) oxygen desaturation, or an AHI with a 3% oxygen desaturation or EEG arousal (AHI_{3a}) or with a 4% oxygen desaturation (AHI_4).

RESULTS: SDB prevalence was similar in men with and without HIV using the ODI_3 and AHI_{3a} definitions. However, SDB prevalence was higher in men with than without HIV using the ODI_4 (55.9% vs 47.8%; $P = .04$) and the AHI_4 definitions (57.9% vs 50.4%; $P = .06$). Mild and moderate SDB were more common in men with than without HIV. Associations between SDB prevalence and age, race, and BMI were similar in men with and without HIV. Among men with HIV, viral load, CD4 cell count, and use of antiretroviral medications were not associated with SDB prevalence.

INTERPRETATION: SDB prevalence was high overall but greater in men with than without HIV using the ODI_4 threshold definition. Efforts to diagnose SDB are warranted in people with HIV, given that SDB is associated with daytime sleepiness and impaired quality of life.

CHEST 2023; 163(3):687-696

KEY WORDS: HIV; prevalence; sleep apnea; sleep-disordered breathing

ABBREVIATIONS: AHI = apnea-hypopnea index; AHI_4 = apnea-hypopnea index with ≥ 4% oxygen desaturation; AHI_{3a} = apnea-hypopnea index with ≥ 3% oxygen desaturation or EEG arousal; ESS = Epworth sleepiness scale; MACS = Multicenter AIDS Cohort Study; ODI = oxygen desaturation index; ODI_4 = oxygen desaturation index with ≥ 4% oxygen desaturation; ODI_3 = oxygen desaturation index with ≥ 3% oxygen desaturation; SDB = sleep-disordered breathing

AFFILIATIONS: From the Miller School of Medicine (N. M. P.), University of Miami, Miami, FL, the School of Medicine (T. T. B.), the Bloomberg School of Public Health (G. D. and J. B. M.), Johns Hopkins University, Baltimore, MD, the Robert Wood Johnson Medical School (R. N. A.), Rutgers University, New Brunswick, NJ, the School of Medicine (S. R. P.), University of Pittsburgh, Pittsburgh, PA, the Feinberg School of Medicine (V. S.), Northwestern University, Chicago, IL, and the David Geffen School of Medicine (J. H.-J. C.), University of California, Los Angeles, Los Angeles, CA.

CORRESPONDENCE TO: Naresh M. Punjabi, MD, PhD; email: npunjabi@miami.edu

DOI: https://doi.org/10.1016/j.chest.2022.10.030

Take-home Points

Study Question: Is sleep-disordered breathing (SDB) more prevalent in men with HIV than in men without HIV, and do the predictors of SDB differ between the two groups?

Results: In the Multicenter AIDS Cohort Study, prevalence of SDB was higher in men with HIV than in men without HIV. No differences between the two groups were noted in the predictors of SDB.

Interpretation: The finding that SDB was more common in men with HIV than in men without HIV indicates that an increased effort to identify SDB would have clinical value given that SDB treatment improves daytime function and quality of life.

Over the last three decades, HIV infection has become a chronic condition with a life expectancy that is comparable with that of people living without HIV.[1] However, improvement in survival in those with HIV has been associated with a concurrent increase in conditions such as chronic pulmonary disease,[2] type 2 diabetes mellitus,[3] and cardiovascular disease.[4] Disorders of sleep are pervasive, and previous studies suggest they may affect approximately 60% of people with HIV.[5-8] Data collected over the last two decades have shown that sleep-disordered breathing (SDB) is an important cause of medical morbidity and mortality.[9] SDB is relatively common and is characterized by recurrent episodes of partial or complete collapse of the upper airway during sleep,[10] leading to reduction in airflow, acute impairment of gas exchange, and recurrent arousals from sleep.

The health consequences of SDB are numerous.[9] If untreated, it leads to daytime sleepiness, cognitive dysfunction, impaired work performance, and decrements in health-related quality of life.[11] Those affected by SDB often are unaware of the associated symptoms.[10,11] Observational and experimental evidence also suggests that SDB contributes to the development of systemic hypertension, cardiovascular disease, and abnormal glucose metabolism,[12-14] as well as to depression, fatigue, and impaired driving performance. Early recognition and appropriate therapy can influence these outcomes favorably and can improve quality of life.[15,16]

In most of those affected with SDB, the disease remains undiagnosed, indicating a need for greater awareness among health-care professionals. Risk factors for SDB in the general population include older age, male sex, central obesity, postmenopausal status, and the presence of craniofacial or oropharyngeal abnormalities.[10,11] In recent years, a few studies have examined the prevalence of SDB in people with HIV, with generally inconclusive results, in part because of the small sample sizes and lack of polysomnography-derived assessments.[7,17-21] Therefore, the current study was conducted in the Multicenter AIDS Cohort Study (MACS),[22] which includes men with and without HIV, to examine whether HIV is an independent predictor of prevalent SDB. Additionally, the current study assessed whether known risk factors for SDB, such as age and BMI, differentially influence[18,23] the prevalence of SDB in men with and without HIV.

Study Design and Methods

Study Sample

The MACS is a longitudinal cohort study of the natural and treated history of HIV infection in men who have sex with men. The cohort was recruited at sites in Baltimore, Maryland, and Washington, DC; Chicago, Illinois; Pittsburgh, Pennsylvania, Columbus, Ohio; and Los Angeles, California; the details of recruitment have been reported previously.[22,24] The cohort includes men with and without HIV, with four waves of enrollment (1984-1985, 1987-1991, 2001-2003, and 2010-2017). Semiannual visits are conducted with the cohort using standardized interviews that include assessment of health behaviors (eg, smoking status, use of recreational drugs and alcohol, medications), physical examination, anthropometry, and blood and urine sample collection for storage and laboratory testing, including measurement of T-cell percentages and counts and of plasma HIV RNA concentration. From March 2018 through June 2019, cohort participants were invited to enroll for assessment of sleep with home polysomnography. All participants who agreed to participate in this study provided informed consent, and the protocol was approved by an institutional review board at each of the study sites.

Protocol for Home Polysomnography

The protocol for home polysomnography and participant instruction have been described in detail.[25] Briefly, home polysomnography was conducted using a self-applied portable sleep recorder (Nox A1; Nox Medical), which collects a frontal EEG with the following derivations: AF4, AF3, AF7, and AF8. Additional physiologic data including recording of the frontalis muscle electromyogram, the ECG, right and left anterior tibialis electromyogram, nasal airflow, oxygen saturation, and chest and abdominal respiratory movement. Before each participant's overnight sleep study, the sleep study recorder was packaged along with the necessary attachments, which included the EEG, ECG, and electromyogram cables, a wireless Nonin oximeter, a nasal cannula for assessments of airflow, and respiratory impedance belts for recording of chest and abdominal

movements. During the MACS study visit before the home sleep study, each participant was trained on how to use the Nox A1 recorder, and his preferred bedtime and wake time were ascertained to configure the start and stop time for data collection for one night of recording. Instructional videos were developed along with notecards placed in the package to help participants complete the hookup of the Nox A1 recorder at home without the assistance of an onsite technician. After completion of the home sleep study, the Nox A1 recorder was returned to the study site. The digital data from the Nox A1 recorder were downloaded to a personal computer and transmitted to a central reading facility for manual scoring. Quality control measures for the home polysomnography study have been described.[25] Home polysomnography was considered successful if all signals were present for at least 3 hours.

Analysis of Sleep Data

Results from each sleep study were assessed for sleep architecture using standard criteria.[26] Sleep was classified as stage wake, non-rapid eye movement (N1, N2, and N3) sleep, or rapid eye movement sleep based on 30-s intervals. For the assessment of disordered breathing events, apneas were identified if airflow was absent or nearly absent for at least 10 s. Apneas were classified further as obstructive if chest or abdominal wall movement was noted or central if no such movement was observed. Hypopneas were identified when a reduction of ≥ 30% in airflow for at least 10 s was noted, along with a 4% decrease in oxygen saturation. An alternative definition of hypopnea also was used requiring a 3% decrease in oxygen saturation or an arousal on the EEG.

Two metrics were calculated from the home sleep study to assess the prevalence of SDB. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. The oxygen desaturation index (ODI) was defined as the number of desaturation episodes of ≥ 3% during sleep. For AHI and ODI, a more stringent threshold of 4% decline also was used for defining an oxygen desaturation event. As a result of the different criteria, the following SDB metrics were derived: (1) ODI with 3% oxygen desaturation (ODI_3), (2) ODI with 4% oxygen desaturation (ODI_4), (3) AHI with 3% oxygen desaturation or EEG arousal (AHI_{3a}), and (4) AHI with ≥ 4% oxygen desaturation (AHI_4). Prevalent SDB was characterized with these metrics using the commonly used clinical cut point of ≥ 5 events/h for the ODI and AHI. SDB severity was categorized further based on conventional cut points as mild (5.0-14.9 events/h), moderate (15.0-29.9 events/h), and severe (≥ 30 events/h). In addition, a self-administered scale of sleepiness, the Epworth sleepiness scale (ESS),[27] was completed by participants during the scheduled MACS visit before the sleep assessment. An ESS score of ≥ 11 was considered to indicate daytime sleepiness.[27]

Statistical Analyses

The proportion of the sample with SDB was determined using the different definitions described above (ODI_3, ODI_4, AHI_{3a}, and AHI_4). The prevalence of SDB with daytime sleepiness (ESS ≥ 11) also was examined, along with analyses that were stratified by HIV status. To account for demographic and anthropometric differences between men with and without HIV, adjusted estimates of SDB prevalence, along with adjusted ORs and 95% CIs, comparing men with and without HIV were determined using multivariable logistic regression models. These estimates were derived using White race, median age (57.5 years), and median BMI (27.5 kg/m^2) of the cohort of men with and without HIV. Additional analyses comparing categories of SDB severity (ie, none, mild, moderate, and severe) were conducted using multinomial regression models. In all multivariable models, age, BMI, and race were included to assess the association between HIV status and prevalent SDB. Analyses were completed using the Stata version 17.0 software (Stata, Inc.), and statistical significance was set at an α value of 0.05.

Results

The study sample consisted of 836 participants with complete data for demographics, anthropometry, and sleep. The cohort included 466 men with HIV (55.7%) and 370 men without HIV (44.3%). Table 1 summarizes the demographics, anthropometry, and prevalent medical conditions by HIV status. Men with HIV were younger and had a slightly lower BMI than men without HIV. Men with HIV also included greater proportions of non-White participants and of current individuals who smoke than those without HIV. Although waist circumference was lower in men with than without HIV infection, waist to hip ratio and neck circumference were similar between the two groups. BMI was correlated highly with waist circumference (Pearson $r = 0.87$; 95% CI, 0.85-0.89) and neck circumference (Pearson $r = 0.76$; 95% CI, 0.73-0.79), with no differences in these correlations between men with and without HIV (data not shown). In men with HIV, the median CD4 cell count was 702/μL, with 94.1% showing viral suppression with viral load of < 200 copies/mL. Antiretroviral therapy use was nearly universal in men with HIV (98.5%), with most regimens based on integrase inhibitors (47.3%), nonnucleoside reverse transcriptase inhibitors (24.6%), and protease inhibitors (20.5%).

Table 2 summarizes estimates of SDB prevalence using the four definitions of SDB (ODI_3, ODI_4, AHI_{3a}, and AHI_4), after adjustments for differences in age, BMI, and race. SDB prevalence was high overall, but similar between men with and without HIV if the ≥ 3% threshold of oxygen desaturation was used for ODI (83.0% vs 80.6%; $P = .40$) or AHI (88.1% vs 85.8%; $P = .33$). When a higher threshold of oxygen desaturation (ie, ≥ 4%) was used to define SDB-related events, prevalence of SDB remained high in both groups, but was significantly greater in men with than without HIV. For example, a greater proportion of men with HIV had an ODI ≥ 5 events/h with a 4% desaturation than did men without HIV (57.0% vs 47.5%; $P = .04$), with an adjusted OR of 1.47 (95% CI, 1.07-2.00). Using the AHI definition requiring 4% oxygen desaturation, SDB prevalence was 58.6% and 49.9% in men with and without HIV, respectively (adjusted OR, 1.42; 95% CI, 1.05-1.94). Although the prevalence of SDB in participants reporting daytime sleepiness (ESS ≥ 11) was considerably lower

TABLE 1] Study Population Characteristics

Variable	Men With HIV (n = 466)	Men Without HIV (n = 370)	*P* Value
Age, y	54.9 ± 10.9	60.8 ± 11.7	< .001
BMI, kg/m^2	27.2 ± 5.0	27.9 ± 5.6	.04
Waist circumference, cm	97.7 ± 13.7	102.5 ± 15.1	< .001
Waist to hip ratio	0.99 ± 0.08	0.99 ± 0.07	.45
Neck circumference, cm	39.8 ± 3.3	40.0 ± 3.4	.52
Race			
White	57.1	76.8	< .001
Black	32.4	18.1	. . .
Other	10.5	5.1	. . .
Smoking status			
Never	33.2	34.3	< .001
Former	44.0	53.3	. . .
Current	22.8	12.4	. . .
CD4 cell count, /μL	702 (516-906)	…	. . .
HIV viral load, copies/mL	1 (1-20)	…	. . .
HIV viral load < 200 copies/mL	94.1	…	. . .
Antiretroviral therapy	98.5	…	. . .
Integrase inhibitors	47.3	…	. . .
NNRTI	24.6	…	. . .
Protease inhibitors	20.5	…	. . .

Values are presented as percentages, mean ± SD, or median (interquartile range), unless otherwise indicated. NNRTI = nonnucleoside reverse transcriptase inhibitor.

overall, it was still higher in men with than without HIV, regardless of the metric used to define SDB (ie, ODI or AHI), the threshold of oxygen desaturation (≥ 3% or ≥ 4%), or the inclusion of an arousal for scoring hypopneas. For example, using the ≥ 4% oxygen desaturation threshold for ODI and AHI, the adjusted ORs for

TABLE 2] Adjusted[a] Prevalence of SDB by HIV Status

Definition of SDB	Men With HIV (n = 466)	Men Without HIV (n = 370)	Adjusted[a] OR (95% CI)
ODI ≥ 5 events/h			
3% desaturation (ODI_3)	83.0	80.6	1.17 (0.81-1.69)
4% desaturation (ODI_4)	57.0	47.5	1.47 (1.07-2.00)
AHI ≥ 5 events/h			
3% desaturation or arousal (AHI_{3a})	88.1	85.8	1.23 (0.82-1.81)
4% desaturation (AHI_4)	58.6	49.9	1.42 (1.05-1.94)
SDB with daytime sleepiness (ESS ≥ 11)			
ODI ≥ 5 events/h			
3% desaturation (ODI_3)	17.1	11.4	1.60 (1.07-2.40)
4% desaturation (ODI_4)	11.2	6.4	1.83 (1.12-2.99)
AHI ≥ 5 events/h			
3% desaturation or arousal (AHI_{3a})	17.5	13.2	1.39 (0.94-2.05)
4% desaturation (AHI_4)	11.8	7.1	1.74 (1.09-2.77)

Data are presented as percentage, unless otherwise indicated. AHI = apnea-hypopnea index; AHI_4 = apnea-hypopnea index with ≥ 4% oxygen desaturation; AHI_{3a} = apnea-hypopnea index with ≥ 3% oxygen desaturation or EEG arousal; ESS = Epworth sleepiness scale; ODI = oxygen desaturation index; ODI_4 = oxygen desaturation index with ≥ 4% oxygen desaturation; ODI_3 = oxygen desaturation index with ≥ 3% oxygen desaturation; SDB = sleep-disordered breathing.
[a]Adjusted for age, BMI, and race.

prevalent SDB with daytime sleepiness were 1.83 (95% CI, 1.12-2.99) and 1.74 (95% CI, 1.09-2.77), respectively.

The distribution of SDB severity (ie, none, mild, moderate, and severe) based on the ≥ 3% threshold for oxygen desaturation was similar by HIV status regardless of whether ODI or AHI was used to define SDB (Table 3). However, if the oxygen desaturation threshold was made more stringent (ie, ≥ 4%), significantly higher proportions of men with HIV had mild and moderate SDB using both ODI and AHI. Specifically, using the ODI_4 definition for SDB, the adjusted ORs for mild and moderate disease relative to no SDB were 1.46 (95% CI, 1.03-2.07) and 1.84 (95% CI, 1.15-2.95), respectively. Similarly, if the AHI_4 definition was used, the adjusted ORs for mild and moderate disease were 1.45 (95% CI, 1.02-2.06) and 1.67 (95% CI, 1.04-2.67), respectively. The proportions of men with HIV who had mild and moderate SDB and daytime sleepiness were higher than those in men without HIV for all metrics used to define SDB (ie, ODI_3, ODI_4, and AHI_4) except AHI_{3a} (Table 4). The percentages of hypopneas (ie, number of hypopneas per total number of disordered breathing events) were similar between men with and without HIV infection and also were similar for all metrics used to define SDB.

To determine whether known risk factors for SDB (eg, age, BMI, and race) were associated differentially with prevalence of SDB in men with and without HIV, multivariable models with interaction terms between these variables and HIV status were evaluated. No statistically significant interactions were present between these variables and HIV status (e-Table 1). Additionally, to determine whether having a detectable HIV viral load affected the prevalence of SDB, the 430 men with HIV (92.2%) who had an undetectable viral load (< 200 copies/mL) were compared with the 36 men with HIV (7.8%) who had a viral load of ≥ 200 copies/mL. No significant associations were observed for SDB prevalence based on ODI_3, AHI_{3a}, ODI_4, or AHI_4. The strongest association between viral load and SDB prevalence was for ODI_3, for which the adjusted OR was 2.42 (95% CI, 0.90-6.50) comparing those with a viral

TABLE 3] Adjusted[a] Prevalence of SDB Severity by HIV Status

	AHI, Events/h			
SDB Metric	< 5.0	5.0-14.9	15.0-29.9	≥ 30.0
ODI_3				
Total no.	187	315	205	132
Men without HIV	19.9	42.1	25.1	12.9
Men with HIV	17.2	40.0	27.7	15.0
OR (95% CI)	. . .	1.10 (0.74-1.62)	1.27 (0.82-1.98)	1.35 (0.80-2.26)
ODI_4				
Total no.	407	252	111	66
Men without HIV	53.3	28.6	12.0	6.0
Men with HIV	43.2	34.0	17.8	4.9
OR (95% CI)	. . .	1.46 (1.03-2.07)	1.84 (1.15-2.95)	1.00 (0.54-1.82)
AHI_{3a}				
Total no.	143	305	223	165
Men without HIV	14.7	42.6	26.6	16.1
Men with HIV	12.1	37.3	29.4	21.1
OR (95% CI)	. . .	1.06 (0.69-1.62)	1.34 (0.84-2.12)	1.59 (0.95-2.64)
AHI_4				
Total no.	387	257	111	81
Men without HIV	50.6	29.2	11.6	8.4
Men with HIV	41.7	35.0	16.0	7.4
OR (95% CI)	. . .	1.45 (1.02-2.06)	1.67 (1.04-2.67)	1.07 (0.62-1.83)

Data are presented as percentage, unless otherwise indicated. AHI = apnea-hypopnea index; AHI_4 = apnea-hypopnea index with ≥ 4% desaturation; AHI_{3a} = apnea-hypopnea index with ≥ 3% desaturation or arousal; ODI_4 = oxygen desaturation index with ≥ 4% desaturation; ODI_3 = oxygen desaturation index with ≥ 3% desaturation; SDB = sleep-disordered breathing.
[a]Adjusted for age, BMI, and race.

TABLE 4] Adjusted Prevalence[a] of SDB Severity in Participants With an Epworth Sleepiness Scale Score of ≥ 11 by HIV Status

SDB Metric	AHI, Events/h			
	< 5.0	5.0-14.9	15.0-29.9	≥ 30.0
ODI_3				
Total no.	31	66	45	29
Men without HIV	20.4	41.7	31.0	6.9
Men with HIV	7.3	52.2	23.4	17.1
OR (95% CI)	. . .	3.50 (1.28-9.49)	2.12 (0.72-6.20)	6.95 (1.85-26.0)
ODI_4				
Total no.	78	57	20	16
Men without HIV	56.4	30.3	7.9	5.4
Men with HIV	35.0	37.6	21.6	5.8
OR (95% CI)	. . .	2.00 (0.90-4.43)	4.43 (1.30-15.1)	1.71 (0.45-6.50)
AHI_{3a}				
Total no.	21	64	48	29
Men without HIV	9.2	45.5	30.8	14.5
Men with HIV	5.0	42.6	27.2	25.1
OR (95% CI)	. . .	1.71 (0.55-5.26)	1.61 (0.49-5.26)	3.16 (0.86-11.5)
AHI_4				
Total no.	69	61	25	16
Men without HIV	49.8	29.2	17.1	3.8
Men with HIV	32.7	40.8	18.8	7.6
OR (95% CI)	. . .	2.12 (0.94-4.78)	1.67 (0.58-4.81)	3.07 (0.77-12.1)

Data are presented as percentage, unless otherwise indicated. AHI = apnea-hypopnea index; AHI_4 = apnea-hypopnea index with ≥ 4% desaturation; AHI_{3a} = apnea-hypopnea index with ≥ 3% desaturation or arousal; ODI_4 = oxygen desaturation index with ≥ 4% desaturation; ODI_3 = oxygen desaturation index with ≥ 3% desaturation; SDB = sleep-disordered breathing.
[a]Adjusted for age, BMI, and race.

load of > 200 copies/mL with those with a viral load of < 200 copies/mL, but all associations based on 4% desaturation were similar between the two groups (e-Table 2). The use of different antiretroviral medication classes, including protease inhibitors, integrase inhibitors, and nonnucleoside as well as nucleoside reverse transcriptase inhibitors, was not associated significantly with the prevalence or severity of SDB in men with HIV (data not shown).

Discussion

Using full-montage home polysomnography in the MACS, the current study found that men with HIV showed a higher prevalence of SDB than men without HIV, based on the 4% oxyhemoglobin desaturation threshold for defining SDB-related events even after accounting for known risk factors for SDB such as age, BMI, and race. The higher prevalence of SDB in men with HIV was the result of a greater proportion of men who demonstrated mild or moderate SDB. Associations of age, BMI, and race with SDB prevalence were examined separately for men with and without HIV and were found to be similar between the two groups. Finally, among men with HIV, prevalence and severity of SDB were not associated significantly with CD4 cell counts or the type of antiretroviral therapy.

Only two previous studies have attempted to examine the prevalence of SDB in people with HIV by objective testing, one by overnight oximetry and one by polysomnography. First, in the Pharmacokinetics and Clinical Observations in People Over Fifty Study,[28] which conducted overnight oximetry and used an ODI (based on 4% desaturation) of ≥ 5 events/h to define SDB, only 7.3% of people with HIV older than 50 years (n = 219) demonstrated SDB and only 7.6% of similarly aged men without HIV recruited from sexual health clinics (n = 118) demonstrated SDB. Second, in a previous study carried out at one MACS clinical site, the prevalence of SDB,[17] defined as an AHI of ≥ 5 events/h on in-laboratory polysomnography, was high. SDB was

present in 86.7% of men without HIV (n = 60), 70.7% of men with HIV who were virologically suppressed (n = 58), and 73.2% of men who were not suppressed (n = 41). However, differences among the three groups were not significant after adjusting for BMI. Thus, neither of the two previous studies found a difference in prevalence of SDB by HIV status. The current study extended this limited body of literature by analyzing a larger study group within one well-defined cohort and demonstrated a higher prevalence of SDB in men with HIV independent of other known risk factors for SDB such as age, BMI, and race based on definitions that used a 4% threshold for oxyhemoglobin desaturation. Given that there can be substantial night-to-night variability in AHI, future studies assessing SDB in people with HIV should consider multinight testing by leveraging novel technologies for home testing. However, it should be noted that any misclassification of SDB burden because of night-to-night variability in SDB is likely be nondifferential with respect to HIV status, and thus would lead to underestimation of differences between men with and without HIV infection. Consequently, the differences in SDB prevalence by HIV status found in this study are likely to be valid.

The relatively low SDB prevalence in the Pharmacokinetics and Clinical Observations in People Over Fifty Study is the result of the use of overnight oximetry without concurrent EEG monitoring, which in the current study allowed for determining the total sleep time and identification of arousals. It is well known that using total sleep time instead of time in bed to calculate ODI and AHI, and including EEG arousals for scoring hypopneas, can increase these values and lead to higher prevalence of SDB. This could account in part for the higher prevalence of SDB in the present study compared with the Pharmacokinetics and Clinical Observations in People Over Fifty Study. Although the prevalence of SDB in the current study was comparable with that previously reported in a smaller subset of MACS participants,[17] the larger sample size likely uncovered the higher SDB prevalence in men with HIV not noted in the previous study.

The current study also found that the prevalence of SDB with daytime sleepiness was higher in men with than without HIV infection after accounting for age, BMI, and race. Daytime sleepiness is a common symptom of SDB and is the result of the independent effects of SDB-related arousals and cyclical hypoxemia. Recurrent arousals lead to daytime sleepiness by disrupting nocturnal sleep continuity, which impairs the excitability of wake-promoting neurons in the locus coeruleus and facilitates the development of daytime sleepiness.[29,30] Intermittent hypoxemia also can contribute to the development of daytime sleepiness through oxidative injury of the basal forebrain and brainstem, leading to impaired ability to maintain wakefulness.[31] The reasons why only some people with SDB manifest daytime sleepiness are not known, but could be related to the duration and severity of the SDB exposure, to variability in subjective experience and reporting on the subjective scales (eg, the ESS) used to assess daytime sleepiness, or both.

Despite the high prevalence of SDB in people with HIV compared with those without HIV, SDB has been underdiagnosed in both people with and people without HIV. For example, in the Veterans Aging Cohort Study,[18] the diagnosis rates in men with and without HIV were only 3.9% and 12.4%, respectively. In that study, veterans with HIV were more likely to report SDB-related symptoms such as tiredness and fatigue, and younger age and lower BMI were associated with a higher prevalence of SDB. In the current study, although prevalence of SDB with associated sleepiness was greater in men with than those without HIV, no statistically significant interactions were noted between HIV status and age, race, or BMI. Thus, the influence of known risk factors for SDB was similar in men with and without HIV. Furthermore, in men with HIV, no significant association was noted between HIV viral load and SDB prevalence. However, it should be noted that the number of men with HIV and detectable RNA concentrations was quite small. In the previous study, which specifically recruited men not receiving antiretroviral therapy, SDB prevalence was associated independently with having a viral load of $>$ 10,000 copies/mL,[23] but this could not be evaluated in the present study because it included only 12 men with such viral loads.

The pathophysiologic factors for why men with HIV have a greater prevalence of SDB than men without HIV is not known. Physiologic assessments of upper airway collapsibility in people with HIV are limited. In a study of 17 people with HIV who had moderate to severe SDB and an age-, sex-, and BMI-matched group who had SDB but not HIV, no differences were observed in various physiologic traits associated with a higher predisposition for SDB,[32] namely active and passive upper airway critical closing pressure, arousal threshold, and loop gain. These limited data suggest that other mechanisms may explain the greater prevalence in men with than without HIV. Given the lack of a differential

effect of anatomic factors (eg, BMI and neck and waist circumferences) on SDB prevalence in the current study, nonanatomic factors such as upper airway muscle responsiveness and ventilatory control are worth assessing in people with and without HIV. It is also possible that the lower diffusing capacity of the lung in people with HIV also may contribute to oxyhemoglobin desaturation episodes and thus worse hypoxemia and a greater number of disordered breathing episodes during sleep.[33] Considering the observation from the current study that the higher SDB prevalence in men with HIV was driven by mild and moderate disease, HIV-induced dysfunction of the upper airway needs to be assessed further using methods that include the physiologic as well as anatomic basis of upper airway collapse during sleep.

A major strength of the current study is that men without HIV were recruited from the same underlying risk group as men with HIV (ie, men older than 18 years who have sex with men). However, men without HIV were not matched individually with those with HIV. In the first MACS enrollment period (1984-1985), which was by far the largest enrollment, men were enrolled on a volunteer basis without knowledge of HIV status because no HIV test was available. In later MACS enrollment periods (1987-1990, 2001-2003, and 2010-2017), an attempt was made to obtain a wide distribution of ages for both men with and men without HIV. At the time of the sleep assessments, the MACS population was not necessarily generalizable to all men who have sex with men for two reasons: (1) cohort enrollment bias and (2) survivor bias that resulted from being in the cohort for numerous years, during which no effective antiretroviral treatment was available and many with HIV died of AIDS. MACS participants also are not representative of men living with HIV because many of the men were untreated for HIV for several years and many MACS participants have received older forms of antiretroviral treatment that are more toxic than currently used agents. Differences between men in the MACS who participated in the current study and those who did not were minor and not likely to affect the generalizability of the current results.[25]

Interpretation

Although the pathophysiologic basis of SDB in people with HIV needs further study, the clinical impact of SDB is known. Daytime sleepiness,[34] impaired quality of life,[16] and hypertension[35] are established SDB-related outcomes that are responsive to positive airway pressure therapy. Clinical and epidemiologic data also show that SDB is associated independently with cardiovascular consequences, including myocardial infarction, heart failure, and stroke.[36] Considering the effects of SDB on sleepiness and quality of life, case identification of SDB in people with HIV whose disease remains undiagnosed is of clinical value given the associated improvements with positive airway pressure therapy. Conventional strategies used for diagnosing SDB with portable home testing can be used in people with HIV because there is no evidence that diagnostic accuracy of such approaches varies as a function of HIV status.

Funding/Support

Data in this manuscript were collected by the Multicenter AIDS Cohort Study (MACS), now the MACS/WIHS Combined Cohort Study (MWCCS). The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH). N. M. P. was supported by NIH grants HL146709, HL11716, and HL075078. MWCCS was supported by the following: Baltimore Clinical Research Site (CRS) [Grant U01-HL146201 (T. T. B. and J. B. M.)]; Data Analysis and Coordination Center [Grant U01-HL146193 (G. D., Stephen Gange, and Elizabeth Golub)]; Chicago-Northwestern CRS [Grant U01-HL146242 (Steven Wolinsky)]; Los Angeles CRS [Grant U01-HL146333 (Roger Detels and Matthew Mimiaga)]; Pittsburgh CRS (Jeremy Martinson and Charles Rinaldo). The MWCCS is funded primarily by the National Heart, Lung, and Blood Institute, with additional cofunding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Institute on Aging, National Institute of Dental and Craniofacial Research, the National Institute of Allergy and Infectious Diseases, the National Institute of Neurological Disorders and Stroke, the National Institute of Mental Health, the National Institute on Drug Abuse, the National Institute of Nursing Research, the National Cancer Institute, the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Deafness and Other Communication Disorders, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Minority Health and Health Disparities, and in coordination and alignment with the research priorities of the National Institutes of

Health, Office of AIDS Research. MWCCS data collection also is supported by Grants UL1-TR003098 (Johns Hopkins University Institute for Clinical and Translational Research) and UL1-TR001881 (University of California, Los Angeles, Clinical and Translational Science Institute).

Financial/Nonfinancial Disclosures

The authors have reported to *CHEST* the following: N. M. P. received research grant support from Philips Respironics and Resmed for work unrelated to this manuscript; S. R. P. has received research funding through his institution from Bayer Pharmaceuticals, Philips Respironics, Respicardia, and Sommetrics unrelated to this work; and has served as a consultant to Bayer Pharmaceuticals, NovaResp Technologies, Philips Respironics, and Powell Mansfield, Inc. T. T. B. has served as a consultant to ViiV Healthcare, Merck, Gilead Sciences, Janssen, and Theratechnologies. None declared (N. A., V. S., J. J.-J. C., G. D., J. B. M.).

Acknowledgments

Author contributions: N. M. P. is the guarantor of the paper, taking responsibility for the integrity of the work as a whole. All authors contributed to the design, collection and analysis of the data, and writing of the manuscript.

Additional information: The e-Tables are available online under "Supplementary Data."

References

1. Ghosn J, Taiwo B, Seedat S, Autran B, Katlama C. HIV. *Lancet*. 2018;392(10148):685-697.
2. Cribbs SK, Crothers K, Morris A. Pathogenesis of HIV-related lung disease: immunity, infection, and inflammation. *Physiol Rev*. 2020;100(2):603-632.
3. Sarkar S, Brown TT. Diabetes in people with HIV. *Curr Diab Rep*. 2021;21(5):13.
4. So-Armah K, Benjamin LA, Bloomfield GS, et al. HIV and cardiovascular disease. *Lancet HIV*. 2020;7(4):e279-e293.
5. Allavena C, Guimard T, Billaud E, et al. Prevalence and risk factors of sleep disturbances in a large HIV-infected adult population. *J Int AIDS Soc*. 2014;17(4 suppl 3):19576.
6. Allavena C, Guimard T, Billaud E, et al. Prevalence and risk factors of sleep disturbance in a large HIV-infected adult population. *AIDS Behav*. 2016;20(2):339-344.
7. Chen CC, Lin CY, Chen YC, Ko WC, Li CY, Ko NY. High sleep-related breathing disorders among HIV-infected patients with sleep complaints. *Sleep Med*. 2020;75:218-224.
8. Chen YC, Chen CC, Strollo PJ Jr, et al. Differences in sleep disorders between HIV-infected persons and matched controls with sleep problems: a matched-cohort study based on laboratory and survey data. *J Clin Med*. 2021;10(21):5206.
9. Ralls F, Cutchen L. A contemporary review of obstructive sleep apnea. *Curr Opin Pulm Med*. 2019;25(6):578-593.
10. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc*. 2008;5(2):136-143.
11. Gottlieb DJ, Punjabi NM. Diagnosis and management of obstructive sleep apnea: a review. *JAMA*. 2020;323(14):1389-1400.
12. Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol*. 2017;69(7):841-858.
13. Salman LA, Shulman R, Cohen JB. Obstructive sleep apnea, hypertension, and cardiovascular risk: epidemiology, pathophysiology, and management. *Curr Cardiol Rep*. 2020;22(2):6.
14. Reutrakul S, Mokhlesi B. Obstructive sleep apnea and diabetes: a state of the art review. *Chest*. 2017;152(5):1070-1086.
15. McMahon JP, Foresman BH, Chisholm RC. The influence of CPAP on the neurobehavioral performance of patients with obstructive sleep apnea hypopnea syndrome: a systematic review. *WMJ*. 2003;102(1):36-43.
16. Jing J, Huang T, Cui W, Shen H. Effect on quality of life of continuous positive airway pressure in patients with obstructive sleep apnea syndrome: a meta-analysis. *Lung*. 2008;186(3):131-144.
17. Patil SP, Brown TT, Jacobson LP, et al. Sleep disordered breathing, fatigue, and sleepiness in HIV-infected and -uninfected men. *PLoS One*. 2014;9(7):e99258.
18. Kunisaki KM, Akgun KM, Fiellin DA, et al. Prevalence and correlates of obstructive sleep apnoea among patients with and without HIV infection. *HIV Med*. 2015;16(2):105-113.
19. Owens RL, Hicks CB. A wake-up call for human immunodeficiency virus (HIV) providers: obstructive sleep apnea in people living with HIV. *Clin Infect Dis*. 2018;67(3):472-476.
20. Chen YC, Lin CY, Li CY, Zhang Y, Ko WC, Ko NY. Obstructive sleep apnea among HIV-infected men in the highly active antiretroviral therapy era: a nation-wide longitudinal cohort study in Taiwan, 2000-2011. *Sleep Med*. 2020;65:89-95.
21. Asgari S, Najafi A, Sadeghniiat K, Gholamypour Z, Akbarpour S. The association between body mass index and risk of obstructive sleep apnea among patients with HIV. *J Res Med Sci*. 2021;26:123.
22. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR Jr. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. *Am J Epidemiol*. 1987;126(2):310-318.
23. 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(4):651-659.
24. Detels R, Jacobson L, Margolick J, et al. The multicenter AIDS Cohort Study, 1983 to. *Public Health*. 2012;126(3):196-198.
25. Punjabi NM, Brown T, Aurora RN, et al. Methods for home-based self-applied polysomnography: the Multicenter AIDS Cohort Study. *Sleep Adv*. 2022;3(1):zpac011.
26. Berry RB, Brooks R, Gamaldo C, et al. AASM scoring manual updates for 2017 (version 2.4). *J Clin Sleep Med*. 2017;13(5):665-666.
27. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540-545.
28. Kunisaki KM, De Francesco D, Sabin CA, et al. Sleep disorders in human immunodeficiency virus: a substudy of the Pharmacokinetics and Clinical Observations in People Over Fifty (POPPY) Study. *Open Forum Infect Dis*. 2021;8(1):ofaa561.
29. Li Y, Panossian LA, Zhang J, et al. Effects of chronic sleep fragmentation on wake-active neurons and the hypercapnic arousal response. *Sleep*. 2014;37(1):51-64.
30. Zhu Y, Fenik P, Zhan G, Xin R, Veasey SC. Degeneration in arousal neurons in chronic sleep disruption

modeling sleep apnea. *Front Neurol*. 2015;6:109.

31. Veasey SC, Davis CW, Fenik P, et al. Long-term intermittent hypoxia in mice: protracted hypersomnolence with oxidative injury to sleep-wake brain regions. *Sleep*. 2004;27(2):194-201.
32. Orr JE, Edwards BA, Schmickl CN, et al. Pathogenesis of obstructive sleep apnea in people living with HIV. *J Appl Physiol (1985)*. 2021;131(6):1671-1678.
33. Kunisaki KM, Nouraie M, Jensen RL, et al. Lung function in men with and without HIV. *AIDS*. 2020;34(8):1227-1235.
34. Lal C, Weaver TE, Bae CJ, Strohl KP. Excessive daytime sleepiness in obstructive sleep apnea. Mechanisms and clinical management. *Ann Am Thorac Soc*. 2021;18(5):757-768.
35. Seravalle G, Grassi G. Sleep apnea and hypertension. *High Blood Press Cardiovasc Prev*. 2022;29(1):23-31.
36. Yeghiazarians Y, Jneid H, Tietjens JR, et al. Obstructive sleep apnea and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021;144(3):e56-e67.