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SCIENTIFIC INVESTIGATIONS

Diagnostic performance of screening tools for the detection of obstructive sleep apnea in people living with HIV

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Study Objectives: Many people living with human immunodeficiency virus (PLWH) have undiagnosed obstructive sleep apnea (OSA), which may contribute to commonly reported fatigue and the high cardiovascular disease burden in this population. Our objective was to assess the utility of traditional OSA screening tools (STOP-BANG, Berlin Questionnaire, and Epworth Sleepiness Scale) for detecting OSA in PLWH.

Methods: Adult PLWH were recruited from sleep/ human immunodeficiency virus clinics and the community into a larger clinical trial that included completion of these questionnaires before in-laboratory polysomnography. Discriminatory performance of these screening tools was assessed using area under receiver operating characteristic curves (AUC). The reference standard for the primary analysis was OSA based on an apnea-hypopnea index ≥ 5 events/h using recommended "1A"-criteria (hypopnea with 3% desaturation and/or arousal). Secondary analyses explored acceptable "1B"-criteria (hypopnea with 4% desaturation) and/or higher apnea-hypopnea index cut-offs (≥ 15 events/h).

Results: 120 PLWH were included (mean age: 50 ± 11 years; body mass index: 27 ± 4 kg/m^2, 84% male) and OSA was diagnosed in 75% using 1A-criteria. In the primary analysis, the discriminatory performance of the 3 screening tools was low (AUCs 0.58 to 0.70) and similar across the tools ($P \geq .14$). In secondary analyses, STOP-BANG showed moderate-high discriminatory ability (AUCs 0.77–0.80) and performed significantly better ($P \leq .008$) than the Berlin Questionnaire or Epworth Sleepiness Scale (AUCs 0.53–0.62).

Conclusions: OSA was highly prevalent in our cohort of PLWH. Although STOP-BANG could reasonably identify moderate-severe OSA, the tools were not reliable for mild disease. Specifically, the questionnaires perform poorly for PLWH with mild OSA manifesting with arousals, yet such people may be at risk of fatigue/sleepiness and impaired memory consolidation.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Title: Obstructive Sleep Apnea Endotypes and Impact on Phenotypes of People Living with HIV (PLWH/OSA); Identifier: NCT03575143; URL: https://clinicaltrials.gov/ct2/show/NCT03575143

Keywords: obstructive sleep apnea, screening, HIV, people living with HIV

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BRIEF SUMMARY

Current Knowledge/Study Rationale: People living with human immunodeficiency virus (PLWH) commonly complain of fatigue and are at risk for cardiovascular disease. Obstructive sleep apnea (OSA) is reported to be common in PLWH, could explain these consequences, yet is rarely diagnosed and treated.

Study Impact: OSA was found commonly in our cohort of PLWH, yet traditional screening metrics may miss OSA in PLWH. While the impact of OSA treatment in PLWH remains to be studied, researchers and clinicians should be aware that commonly used OSA screening tools lack sensitivity and specificity in this population for the detection of some patients with OSA.

INTRODUCTION

Treatment of human immunodeficiency virus (HIV) with antiretroviral therapy (ART) is extremely effective at preventing progression to acquired immunodeficiency syndrome (AIDS) and opportunistic infections. Where widely available, ART has resulted in dramatically improved survival and life expectancy. While more work needs to be done on disease prevention and availability of ART, there has been increasing focus on management of symptoms and comorbidities in people living with HIV (PLWH). Fatigue and sleep problems are commonly encountered in PLWH. For example, fatigue is very commonly reported by PLWH even while HIV viral loads are suppressed and with normal CD4 counts.[1,2] In addition, nearly half of HIV-infected adults report poor sleep quality.[3] Coronary artery disease, diabetes mellitus, and nonalcoholic fatty liver disease are now recognized as important complications of HIV/ART.[4]

Obstructive sleep apnea (OSA) is a very common disease worldwide that is also reported to be common in PLWH. Patil and colleagues[5] found that 70% of participants infected with HIV in their cohort had OSA (using apnea-hypopnea index [AHI] 3% criteria and considering an AHI >5 events/h). Although OSA was similarly prevalent in their control group, this finding suggests that the majority of PLWH have OSA.

The PLWH who also had OSA were younger and substantially leaner (as assessed by body mass index [BMI]) than the non-HIV controls in this study—and therefore would have been expected to have a lower prevalence of OSA. Only 12% of the patients with OSA in the Patil study were obese, suggesting traditional risk factors for OSA may differ in PLWH. OSA might also be an important contributor to fatigue in PLWH. For example, witnessed apnea, a fairly specific marker of OSA, was a predictor for clinically relevant fatigue in PLWH.[6] Not only do PLWH complain of fatigue, but in the study by Patil they also complained with equal frequency of daytime sleepiness (defined as Epworth Sleepiness Score [ESS] ≥ 11).

Perhaps because PLWH with OSA are younger and thinner than those without HIV and OSA, or because common OSA symptoms like fatigue/tiredness are ascribed to HIV, few PLWH have been evaluated for OSA. In multiple practice settings including the Veterans Aging Cohort Study (VACS), an urban clinic, and an academic University Center for AIDS Research clinic, only about 4% of PLWH were diagnosed with OSA.[7,8] Although OSA is often underdiagnosed in general, in the same Veterans Cohort the rate of OSA diagnosis in non-HIV was 12.4%. Thus, few patients or providers consider OSA in PLWH, although OSA may contribute to many comorbidities in these patients. To facilitate better identification of PLWH with likely OSA, it is important to determine the reliability of commonly used questionnaires for screening for OSA in PLWH.

Based on all of the above, we sought to evaluate the diagnostic utility of commonly used screening tools for OSA in PLWH.

METHODS

Study design

This was a prospective cohort study of PLWH taking part in a larger clinical trial (NCT03575143). The study was approved by the UCSD Human Research Protection Program (#180160), and all participants gave written informed consent.

Participants

Based on the parent study, eligible participants were those with HIV and viral suppression (RNA < 200 copies/mL), ages 18-65 years, and BMI 20–35 kg/m^2 who were recruited through physician referral, interest forms, support groups, and flyers in San Diego. Those recruited were English language speakers (based on other requirements of the study). Exclusion criteria included: pregnancy, already on effective therapy and adherent to treatment for OSA, another known sleep fragmenting disorder—other than insomnia—such as periodic limb movement disorder or narcolepsy.

Data collection and questionnaires

At a baseline, in-person visit age, height, weight, and neck circumference were obtained. Three questionnaires frequently used for screening OSA were completed by participants prior to overnight sleep recording, which occurred within 0–14 days after the baseline visit.

STOP-BANG

The STOP-BANG was developed to identify OSA in those undergoing elective procedures[9] and has been validated in a number of populations.[10] The tool relies on signs and symptoms of OSA, as well as objective data such as BMI and age. It ranges from 0 to 8, with a score of ≥ 3 typically being used to identify those at high risk of moderate to severe OSA,[10] although in patients with severe obesity a cut-off of ≥ 4 may be preferable.[11]

Berlin Questionnaire

The Berlin Questionnaire was developed to identify patients in primary care settings likely to have OSA.[12] Similar to STOP-BANG, it relies on the medical history, demographics, and signs and symptoms of OSA. A score of ≥ 2 positive categories (range 0–3 positive categories) has been used to identify those at high risk of OSA.

Epworth Sleepiness Scale

The ESS measures subjective daytime sleepiness by asking participants their likelihood of falling asleep in 8 different scenarios.[13] Although less commonly used as a screening tool for OSA, since excessive sleepiness is a common symptom of OSA, the ESS has potential value to identify patients with high risk of OSA.[14] It is scored on a scale of 0–24, with scores ≥ 11 denoting excessive daytime sleepiness.

Polysomnography

Participants underwent in-laboratory, attended polysomnography (Nihon Khoden America, Irvine, CA) and were instrumented in the standard fashion with electroencephalogram, electrooculogram, and chin electromyogram for sleep staging; nasal pressure transducer and thermistor for air flow; respiratory impedance belts at the thorax and abdomen for respiratory effort; electrocardiogram for heart rate; and pulse oximetry. Studies were scored by an experienced single registered polysomnography technologist. The AHI was primarily quantified using American Academy of Sleep Medicine (AASM) recommended criteria "AHI3A" (ie, 1A criteria—hypopnea defined as a > 30% decrement in nasal pressure with 3% desaturation and/or an arousal). In addition, we also quantified the "AHI4" based on the AASM acceptable criteria (ie, 1B, "Medicare"—hypopnea as > 30% decrease in nasal pressure with 4% desaturation). OSA severity was categorized as mild (AHI ≥ 5 events/h and < 15 events/h), moderate (AHI ≥ 15 events/h and < 30 events/h), and severe (AHI ≥ 30 events/h).

Reference standard

There is increasing evidence that even patients with mild OSA that is associated with arousals rather than hypoxemia (ie, AHI3A ≥ 5 and < 15 events/h), can suffer from, and substantially benefit from OSA therapy with regard to daytime sleepiness, fatigue, and low energy.[15,16] Thus, for the primary analysis we used "any OSA" based on the recommended criterion (ie, AHI3A ≥ 5 events/h) as the reference standard. For secondary analyses, we further used the AHI4 ≥ 5 events/h and the AHI3A/AHI4 ≥ 15 events/h (ie, moderate-severe OSA) as reference standards.

Analysis

Continuous data are reported as means ± standard deviation (SD), and categorical data are reported as percentages and absolute numbers, unless stated otherwise. Discriminatory performance of the screening tools was assessed by calculating the area under the empiric receiver operating characteristic curve (AUC) for each tool and comparing them based on the DeLong method.[17] Discriminatory ability was considered low, moderate, high based on AUC values of ≤ 0.7, 0.7–0.8, ≥ 0.8, respectively.[18] For each tool, we further calculated the sensitivity, specificity, and positive/negative predictive values (+bootstrapped 95% confidence intervals) for various threshold values with a special focus on commonly used cut-offs (ie, STOP-BANG score ≥ 3, Berlin Questionnaire ≥ 2 positive categories, ESS ≥ 11). Analyses were performed using R (3.6.1) including the pROC package, using P values < .05 to denote statistical significance.

RESULTS

Participants and polysomnography results

In total, 120 PLWH met eligibility criteria and were included in this study. Participants were middle-aged, predominantly male, and overweight, with a diverse racial background and one quarter identifying as Hispanic (**Table 1**). Twenty-two participants reported a prior diagnosis of OSA. Overall, OSA was present in 90 participants (75%) based on an AHI3A ≥ 5 events/h (28 mild, 20 moderate, 42 severe) and in 69 participants (58%) based on an AHI4% ≥ 5 events/h (24 mild, 16 moderate, 29 severe). **Table 2** summarizes the estimated prevalence of OSA in the underlying PLWH population based on different severity levels. Of note, 8 of 28 participants diagnosed with mild OSA using the AHI3A criteria had an ESS > 10.

Table 1—General characteristics.

	Overall	Based on AHI3A ≥ 5 events/h		
		OSA	No OSA	
	n = 120[a]	n = 90[a]	n = 30[a]	P[b]
Demographics				
Age (years)	53 [41 to 57]	54 [47 to 58]	46 [32 to 53]	< .001
Female sex	18 (15%)	12 (13%)	6 (20%)	.39
BMI (kg/m^2)	27.7 [24.9 to 29.9]	28.1 [25.4 to 30.5]	25.1 [22.6 to 28.5]	.006
Race				.33
White	75 (62%)	60 (67%)	15 (50%)	
Black or African American	19 (16%)	13 (14%)	6 (20%)	
American Indian/Alaska Native	5 (4.2%)	4 (4.4%)	1 (3.3%)	
Asian	1 (0.8%)	0 (0%)	1 (3.3%)	
More than one race	16 (13%)	10 (11%)	6 (20%)	
Native Hawaiian or Other Pacific Islander	1 (0.8%)	1 (1.1%)	0 (0%)	
Unknown / not reported	3 (2.5%)	2 (2.2%)	1 (3.3%)	
Hispanic ethnicity	30 (25%)	24 (27%)	6 (20%)	.63
Sleep Apnea Severity				
AHI3A (/h)	17 [5 to 42]	27 [13 to 50]	3 [2 to 4]	< .001
AHI4 (/h)	8 [2 to 28]	14 [6 to 39]	1 [1 to 2]	< .001
SpO_2 nadir (%)	86.0 [80.8 to 89.0]	84.5 [80.0 to 86.0]	89.0 [87.2 to 90.0]	< .001
Screening Instruments				
STOP-BANG score (n = 108)	3 [2 to 5]	4 [3 to 5]	2 [2 to 4]	.002
Berlin Questionnaire score (n = 116)				.090
0	24 (21%)	16 (18%)	8 (29%)	
1	42 (36%)	30 (34%)	12 (43%)	
2	29 (25%)	22 (25%)	7 (25%)	
3	21 (18%)	20 (23%)	1 (3.6%)	
Epworth score (n = 118)	7.0 [5.0 to 11.8]	8.0 [5.0 to 12.2]	7.0 [5.0 to 8.0]	.20

[a]Median [25–75%]; n (%). [b]Wilcoxon rank sum test; Fisher's exact test. AHI3A = apnea-hypopnea index with hypopneas based on a 3% oxygen desaturation or arousal, AHI4 = apnea-hypopnea index with hypopneas based on a 4% oxygen desaturation, BMI = body mass index.

Table 2—Estimated prevalence of OSA in PLWH based on different OSA severity definitions and levels.

	Prevalence (95% Confidence Interval)			
	Any OSA	Mild OSA	Moderate OSA	Severe OSA
	AHI ≥ 5 events/h	AHI ≥ 5 & < 15 events/h	AHI ≥ 15 & < 30 events/h	AHI ≥ 30 events/h
Recommended "AASM" AHI3A	75% (66 to 82)	23% (16 to 32)	17% (11 to 25)	35% (27 to 44)
			52% (42 to 61)	
Acceptable "Medicare" AHI4	58% (48 to 66)	20% (14 to 29)	13% (8 to 21)	24% (17 to 33)
			38% (29 to 47)	

AHI = apnea-hypopnea index, AHI3A = apnea-hypopnea index with hypopneas based on a 3% oxygen desaturation or arousal, AHI4 = apnea-hypopnea index with hypopneas based on a 4% oxygen desaturation, OSA = obstructive sleep apnea, PLWH = people living with human immunodeficiency virus.

Performance of screening tools

Results of the primary analysis are shown in **Figure 1** and **Table 3**. When using "any OSA" (ie, AHI3A ≥ 5 events/h) as the reference standard, the discriminatory performance of the 3 screening tools was low (AUCs 0.58 to 0.70) and similar across the tools ($P \geq .14$). **Table 4** shows the sensitivity/specificity and positive/negative predictive values for various thresholds. With commonly used thresholds, the STOP-BANG (≥ 3) had modest sensitivity (76%) and specificity (62%), the Berlin Questionnaire (≥ 2) had low sensitivity (48%) and modest specificity (71%), and the ESS (≥ 11) showed high specificity (80%) but very low sensitivity (32%).

In secondary analyses (**Table 3**), the STOP-BANG showed moderate-high discriminatory ability (AUCs 0.77–0.80) for the detection of any OSA when using the acceptable AHI definition (ie, AHI4 ≥ 5 events/h) or for the detection of moderate-severe OSA using either AHI definition (ie, AHI3A/AHI4 ≥ 15 events/h). Moreover, in these secondary analyses, the STOP-BANG showed significantly higher discriminatory power than both the Berlin Questionnaire or the ESS ($P \leq .008$), both of which had very low discriminatory power (AUCs 0.53 to 0.62). Details about sensitivity/specificity and positive/negative predictive values for various thresholds from these analyses are shown in the supplemental material.

DISCUSSION

In our cohort of middle-aged and mostly overweight (although not obese) men, OSA was very common. Moreover, we found that commonly used screening tools for OSA were not particularly sensitive or specific for the diagnosis of OSA using the currently recommended scoring criteria. Taken together, our findings suggest the need for better screening tools for this population or consideration of diagnostic testing in those with appropriate symptoms regardless of screening tool results.

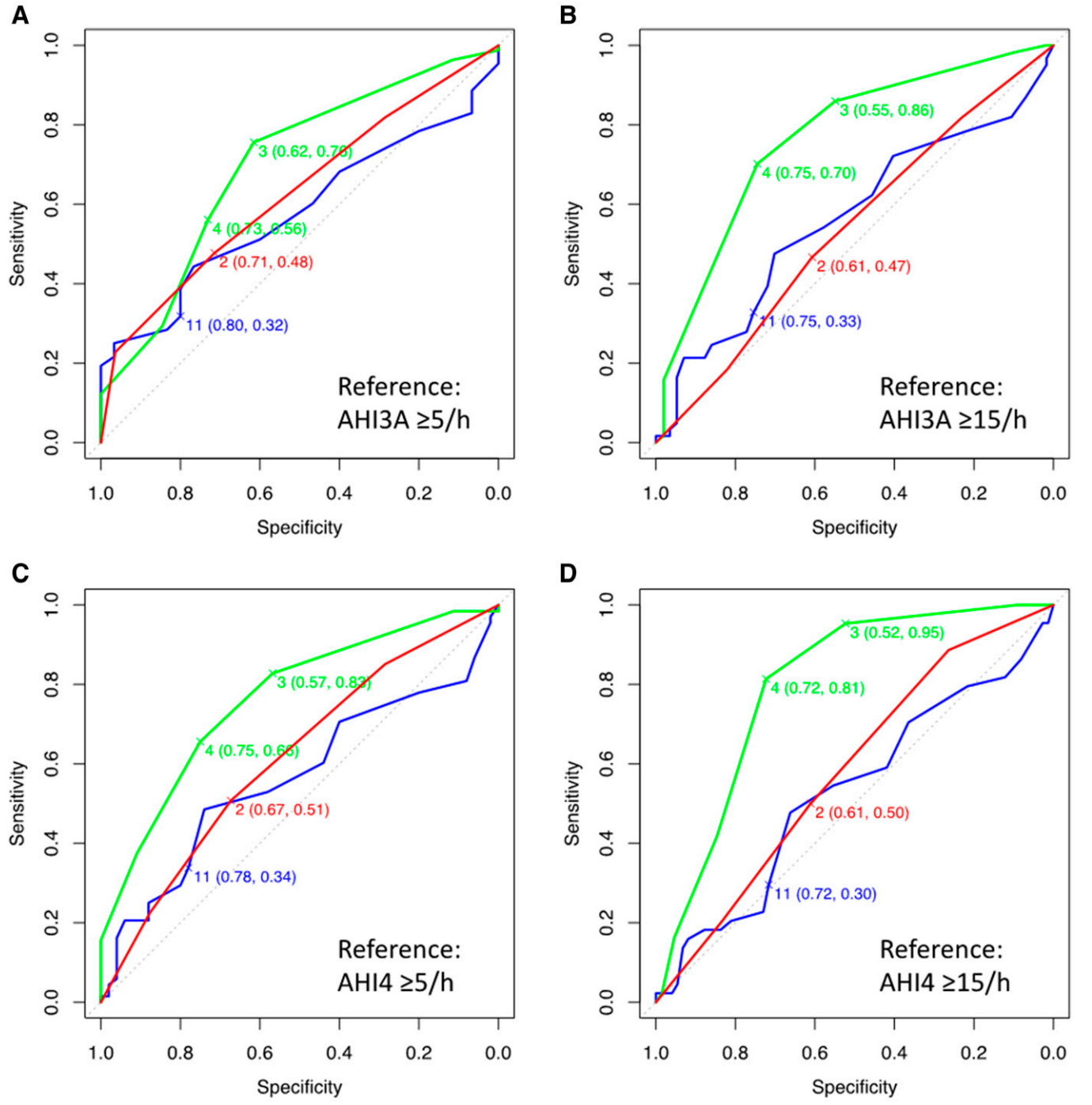
Our patients were largely drawn from our public university Center for AIDS Research (CFAR) affiliated HIV Medicine Clinic. Similar to other reports, we found that OSA was very prevalent, even using conservative diagnostic criteria (eg, AHI4 ≥ 15 events/h). Using a definition that may better capture arousal from sleep, our results are similar to Patil and colleagues, who found that 72% of their participants had an AHI ≥ 5 events/h. Their participants were all men and had a similar mean age (49.9 years) and BMI (25.4 kg/m^2) as our cohort. We note, too, that our cohort had 18 women, of whom 12 (67%) had OSA as well. While definitive data regarding the true prevalence of OSA in HIV are lacking, particularly in women, OSA appears common in PLWH. And, consistent with prior reports, most of our participants were not diagnosed with OSA nor were they treated for OSA.

We focused mostly on OSA as defined by the AASM Recommended criteria (ie, 1A, 3% or arousal for hypopneas). This definition will result in a higher prevalence of disease compared to more stringent 4% oxygen desaturation criteria (ie, 1B or Medicare). While this reflects a broader debate in the field, we have argued that no one outcome captures all the clinical relevance of OSA.[19] Broadly speaking, it may be that 4% arousals and/or metrics such as the hypoxic burden reflect risk of cardiovascular disease, while arousal-based definitions of disease might be more important for neurocognitive consequences.[20,21] In PLWH, fatigue is a clinically relevant outcome, hence our focus on this arousal-based criteria. We note that a substantial fraction of participants found to have an AHI3A in the mild range (≥ 5 and < 15 events/h) did have an ESS score >10, suggesting excessive daytime sleepiness.

Several lines of evidence suggest that untreated OSA might have a negative impact on PLWH, especially as this population ages and combats obesity.[22] As above, fatigue and sleep complaints are common in PLWH.[6] Untreated moderate and severe OSA has been associated with high levels of inflammation and viral load.[23] However, it remains to be seen whether diagnosis and treatment of OSA will improve symptoms and other outcomes. Our work suggests that clinicians and researchers should not rely solely on STOP-BANG, Berlin Questionnaire, and ESS for diagnosis of OSA, or for consideration of further diagnostic testing.

Some groups have suggested that HIV is a risk factor for OSA. Proposed mechanisms include upper airway narrowing due to lipodystrophy (a side effect of earlier ART regimens[24]) or chronic inflammation of the upper airway predisposing to collapse and/or inhibiting upper airway reflexes and muscle

Figure 1—Receiver operating characteristic curves of the 3 instruments.



Receiver operating characteristic curves of the 3 instruments (STOP-BANG green; Berlin Questionnaire red, Epworth Sleepiness Score blue) using different reference standards: (**A**) AHI3A ≥ 5 events/h (primary analysis); (**B**) AHI3A ≥ 15 events/h; (**C**) AHI4 ≥ 5 events/h; (**D**) AHI4 ≥ 15 events/h. Commonly used thresholds for each instrument are marked by an "x" followed by the "threshold value (specificity, sensitivity)". For more details about the sensitivity/specificity of various thresholds see Table 4 and the supplemental material. AHI3A = apnea-hypopnea index with hypopneas based on a 3% oxygen desaturation or arousal, AHI4 = apnea-hypopnea index with hypopneas based on a 4% oxygen desaturation.

responsiveness.[25] Previous work suggesting HIV is a risk factor for OSA relied on case-control studies, and very few actually measured the physiology. In our recent report, we found little evidence to suggest major differences in OSA pathogenesis in those with and without HIV, accounting for sex, age, and BMI.[26]

OSA is increasingly recognized as a heterogenous disorder with both anatomical and nonanatomical factors important for

Table 3—Area under the receiver operating curve (AUC) for each instrument and the *P* values for comparisons of AUC's across instruments.

	AUC (95% Confidence Interval)			*P* Value		
AHI Definition and Cutoff	**STOP-BANG**	**Berlin Questionnaire (Berlin-Q)**	**Epworth Score (ESS)**	**STOP-BANG vs Berlin-Q**	**STOP-BANG vs ESS**	**ESS vs Berlin-Q**
Primary analysis						
AHI3A ≥ 5 events/h	0.70 (0.58 to 0.82)	0.63 (0.53 to 0.74)	0.58 (0.47 to 0.68)	.19	.14	.32
Secondary analysis						
AHI3A ≥ 15 events/h	0.77 (0.68 to 0.86)	0.54 (0.44 to 0.64)	0.56 (0.46 to 0.67)	< .001	.001	.89
AHI4 ≥ 5 events/h	0.77 (0.68 to 0.85)	0.62 (0.52 to 0.72)	0.57 (0.46 to 0.67)	.008	.003	.31
AHI4 ≥ 15 events/h	0.80 (0.72 to 0.88)	0.59 (0.48 to 0.69)	0.53 (0.42 to 0.64)	< .001	< .001	.35

AHI = apnea-hypopnea index, AHI3A = apnea-hypopnea index with hypopneas based on a 3% oxygen desaturation or arousal, AHI4 = apnea-hypopnea index with hypopneas based on a 4% oxygen desaturation.

Table 4—Performance characteristics of the different instruments for varying thresholds.

Threshold	Sensitivity	(95% CI)	Specificity	(95% CI)	PPV	(95% CI)	NPV	(95% CI)
STOP-BANG								
1	0.99	(0.96 to 1)	0.00	(0 to 0)	0.76	(0.75 to 0.76)	0.00	(0 to 0)
2	0.96	(0.93 to 1)	0.12	(0 to 0.23)	0.77	(0.75 to 0.8)	0.50	(0 to 1)
*3	0.76	(0.66 to 0.84)	0.62	(0.42 to 0.81)	0.86	(0.8 to 0.93)	0.44	(0.33 to 0.58)
4	0.56	(0.45 to 0.67)	0.73	(0.58 to 0.88)	0.87	(0.79 to 0.94)	0.35	(0.27 to 0.43)
5	0.29	(0.2 to 0.4)	0.85	(0.69 to 0.96)	0.86	(0.74 to 0.97)	0.28	(0.23 to 0.32)
6	0.12	(0.06 to 0.2)	1.00	(1 to 1)	1.00	(1 to 1)	0.27	(0.25 to 0.28)
7	0.02	(0 to 0.06)	1.00	(1 to 1)	1.00	(1 to 1)	0.25	(0.24 to 0.25)
Berlin Questionnaire								
1	0.82	(0.74 to 0.9)	0.29	(0.14 to 0.43)	0.78	(0.74 to 0.83)	0.33	(0.17 to 0.52)
*2	0.48	(0.38 to 0.59)	0.71	(0.54 to 0.86)	0.84	(0.76 to 0.92)	0.30	(0.24 to 0.37)
3	0.23	(0.14 to 0.32)	0.96	(0.89 to 1)	0.95	(0.84 to 1)	0.28	(0.26 to 0.31)
Epworth Sleepiness Score								
1	0.97	(0.92 to 1)	0.00	(0 to 0)	0.74	(0.73 to 0.75)	0.00	(0 to 0)
2	0.95	(0.91 to 0.99)	0.00	(0 to 0)	0.74	(0.73 to 0.74)	0.00	(0 to 0)
3	0.89	(0.82 to 0.94)	0.07	(0 to 0.17)	0.74	(0.71 to 0.76)	0.17	(0 to 0.4)
4	0.83	(0.75 to 0.91)	0.07	(0 to 0.17)	0.72	(0.69 to 0.75)	0.11	(0 to 0.29)
5	0.78	(0.69 to 0.86)	0.20	(0.07 to 0.33)	0.74	(0.7 to 0.78)	0.24	(0.09 to 0.4)
6	0.68	(0.58 to 0.77)	0.40	(0.23 to 0.57)	0.77	(0.71 to 0.83)	0.30	(0.19 to 0.42)
7	0.60	(0.5 to 0.7)	0.47	(0.3 to 0.63)	0.77	(0.7 to 0.84)	0.29	(0.19 to 0.38)
8	0.51	(0.41 to 0.62)	0.60	(0.43 to 0.77)	0.79	(0.71 to 0.87)	0.30	(0.22 to 0.37)
9	0.44	(0.34 to 0.56)	0.77	(0.6 to 0.9)	0.85	(0.76 to 0.94)	0.32	(0.26 to 0.38)
10	0.39	(0.28 to 0.49)	0.80	(0.67 to 0.93)	0.85	(0.76 to 0.95)	0.31	(0.26 to 0.36)
*11	0.32	(0.22 to 0.42)	0.80	(0.67 to 0.93)	0.83	(0.71 to 0.94)	0.29	(0.24 to 0.33)
12	0.28	(0.19 to 0.39)	0.83	(0.7 to 0.97)	0.84	(0.71 to 0.96)	0.29	(0.24 to 0.33)
13	0.25	(0.16 to 0.34)	0.97	(0.9 to 1)	0.96	(0.86 to 1)	0.31	(0.28 to 0.34)
14	0.22	(0.14 to 0.31)	0.97	(0.9 to 1)	0.95	(0.84 to 1)	0.30	(0.27 to 0.33)
15	0.19	(0.11 to 0.28)	1.00	(1 to 1)	1.00	(1 to 1)	0.30	(0.28 to 0.32)

95% confidence intervals (CI) were estimated based on a bootstrap procedure ($N_{samples}$= 2,000). Commonly used cut-offs are marked by an asterisk (*).

pathogenesis.[27] The underlying physiology is important because it may impact disease manifestations and therefore may help determine which OSA screening tools work in a given population. For example, we recently reported very low specificity for STOP-BANG in those with posttraumatic stress disorder.[28] In people with posttraumatic stress disorder, we hypothesize that the low arousal threshold pathophysiology is common and may lead systematically to differences in screening compared to other populations (eg, lower rate of loud snoring or witnessed apneas).[29] Unlike posttraumatic stress disorder, our prior work suggests that the underlying physiology of OSA in PLWH does not differ from persons who are HIV seronegative. Thus, there should not be observed differences with screening tools in HIV and non-HIV populations. The sensitivity and specificity we found using these tools in PLWH are similar to that reported for STOP-BANG and Berlin Questionnaire in populations without HIV.[10,30] For example, if focused on only finding more moderate or severe "hypoxic" OSA, eg, AHI4 ≥ 15 events/h, in PLWH then STOP-BANG (which was developed based on AHI4) probably has reasonable performance.

Two limitations deserve mention. First, our participants were not chosen at random. It is likely that those who participated had symptoms/concerns that might suggest sleep apnea and they therefore sought participation in our study. As such, our sample may be enriched for those with OSA, and our study does not reflect the true prevalence of OSA in PLWH. However, our analyses regarding sensitivity and specificity are still useful although limited to the population studied. In particular, the positive predictive value and negative predictive value for these screening tests would likely change if applied to populations where the actual prevalence of OSA was different. For example, positive predictive value would likely be lower at the cut points we established if applied to populations with lower OSA prevalence.[30] Second, study results were limited by age and BMI range as per our parent study's inclusion criteria. Thus, our results may not be generalizable to older or heavier PLWH.

In summary, OSA was common in our cohort of PLWH. Although STOP-BANG performed the best in our cohort, none of the tools are completely reliable for the diagnosis of OSA, particularly when using the currently recommended arousal-based scoring criteria. While the impact of OSA treatment in PLWH remains to be studied, researchers and clinicians should be aware that commonly used OSA screening tools lack sensitivity and specificity in this population for the detection of some patients with OSA.

ABBREVIATIONS

ART, anti-retroviral therapy
AASM, American Academy of Sleep Medicine
AIDS, acquired immunodeficiency syndrome
AHI, apnea-hypopnea index
AHI3A, apnea-hypopnea index with hypopneas based on a 3% oxygen desaturation or arousal
AHI4, apnea-hypopnea index with hypopneas based on a 4% oxygen desaturation
AUC, area under receiver operating characteristic curve
BMI, body mass index
ESS, Epworth Sleepiness Scale
HIV, human immunodeficiency virus
OSA, obstructive sleep apnea
PLWH, people living with HIV
SD, standard deviation
STOP-BANG, snoring history, tired during the day, observed stop breathing while sleep, high blood pressure, BMI more than 35 kg/m^2, age more than 50 years, neck circumference more than 40 cm and male sex

REFERENCES

1. Fredericksen RJ, Edwards TC, Merlin JS, et al. Patient and provider priorities for self-reported domains of HIV clinical care. *AIDS Care.* 2015;27(10):1255–1264.
2. Payne BA, Hateley CL, Ong EL, et al. HIV-associated fatigue in the era of highly active antiretroviral therapy: Novel biological mechanisms? *HIV Med.* 2013;14(4):247–251.
3. Allavena C, Guimard T, Billaud E, et al. COREVIH-Pays de la Loire Troubles du Sommeil Study Group. Prevalence and risk factors of sleep disturbance in a large HIV-infected adult population. *AIDS Behav.* 2016;20(2):339–344.
4. Lakey W, Yang LY, Yancy W, Chow SC, Hicks C. Short communication: from wasting to obesity: Initial antiretroviral therapy and weight gain in HIV-infected persons. *AIDS Res Hum Retroviruses.* 2013;29(3):435–440.
5. 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.
6. Goswami U, Baker JV, Wang Q, Khalil W, Kunisaki KM. Sleep apnea symptoms as a predictor of fatigue in an urban HIV clinic. *AIDS Patient Care STDS.* 2015;29(11):591–596.
7. Kim DJ, Westfall AO, Chamot E, et al. Multimorbidity patterns in HIV-infected patients: The role of obesity in chronic disease clustering. *J Acquir Immune Defic Syndr.* 2012;61(5):600–605.
8. Kunisaki KM, Akgün 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.
9. Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: A tool to screen patients for obstructive sleep apnea. *Anesthesiology.* 2008;108(5):812–821.
10. Pivetta B, Chen L, Nagappa M, et al. Use and performance of the STOP-Bang Questionnaire for obstructive sleep apnea screening across geographic regions: A systematic review and meta-analysis. *JAMA Netw Open.* 2021;4(3):e211009.
11. Chung F, Yang Y, Liao P. Predictive performance of the STOP-Bang score for identifying obstructive sleep apnea in obese patients. *Obes Surg.* 2013;23(12):2050–2057.
12. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med.* 1999;131(7):485–491.
13. Johns MW. A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. *Sleep.* 1991;14(6):540–545.
14. Kreitinger KY, Lui MMS, Owens RL, et al. Screening for obstructive sleep apnea in a diverse bariatric surgery population. *Obesity (Silver Spring).* 2020;28(11):2028–2034.
15. Wimms AJ, Kelly JL, Turnbull CD, et al.MERGE trial investigators. Continuous positive airway pressure versus standard care for the treatment of people with mild obstructive sleep apnoea (MERGE): A multicentre, randomised controlled trial. *Lancet Respir Med.* 2020;8(4):349–358.
16. Weaver TE, Mancini C, Maislin G, et al. Continuous positive airway pressure treatment of sleepy patients with milder obstructive sleep apnea: Results of the CPAP Apnea Trial North American Program (CATNAP) randomized clinical trial. *Am J Respir Crit Care Med.* 2012;186(7):677–683.
17. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics.* 1988;44(3):837–845.
18. Hosmer DW, Lemeshow S, eds. *Applied Logistic Regression.* New York: John Wiley and Sons; 2000.

19. Edwards BA, Redline S, Sands SA, Owens RL. More than the sum of the respiratory events: Personalized medicine approaches for obstructive sleep apnea. *Am J Respir Crit Care Med.* 2019;200(6):691–703.
20. Azarbarzin A, Sands SA, Taranto-Montemurro L, et al. The sleep apnea-specific hypoxic burden predicts incident heart failure. *Chest.* 2020; 158(2):739–750.
21. Djonlagic I, Guo M, Matteis P, Carusona A, Stickgold R, Malhotra A. Untreated sleep-disordered breathing: Links to aging-related decline in sleep-dependent memory consolidation. *PLoS One.* 2014;9(1):e85918.
22. Johnson AS, Hall HI, Hu X, Lansky A, Holtgrave DR, Mermin J. Trends in diagnoses of HIV infection in the United States, 2002-2011. *J Am Med Assoc.* 2014;312(4):432–434.
23. Brigham EP, Patil SP, Jacobson LP, et al. Association between systemic inflammation and obstructive sleep apnea in men with or at risk for HIV infection. *Antivir Ther.* 2014;19(8):725–733.
24. Epstein LJ, Strollo PJ Jr, Donegan RB, Delmar J, Hendrix C, Westbrook PR. Obstructive sleep apnea in patients with human immunodeficiency virus (HIV) disease. *Sleep.* 1995;18(5):368–376.
25. 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.
26. Orr JE, Edwards BA, Schmickl CN, et al. Pathogenesis of obstructive sleep apnea in people living with HIV. *J Appl Physiol.* 2021;131(6):1671–1678.
27. Owens RL, Edwards BA, Eckert DJ, et al. An integrative model of physiological traits can be used to predict obstructive sleep apnea and response to non positive airway pressure therapy. *Sleep.* 2015;38(6):961–970.
28. Lyons R, Barbir LA, Owens R, Colvonen PJ. STOP-BANG screener vs objective obstructive sleep apnea testing among younger veterans with PTSD and insomnia: STOP-BANG does not sufficiently detect risk. *J Clin Sleep Med.* 2022; 18(1):67–73.
29. El-Solh AA, Lawson Y, Wilding GE. Impact of low arousal threshold on treatment of obstructive sleep apnea in patients with post-traumatic stress disorder. *Sleep Breath.* 2021;25(2):597–604.
30. Abrishami A, Khajehdehi A, Chung F. A systematic review of screening questionnaires for obstructive sleep apnea. *Can J Anaesth.* 2010;57(5): 423–438.

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