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Associations between widespread pain and sleep quality in people with HIV

Short title: Pain and sleep in HIV infection

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Abstract

Background: We investigate the association of widespread pain with sleep quality among people with HIV (PWH) and HIV-negative controls.

Setting: UK-based cohort.

Methods: Pain information was collected through a pain mannikin identifying affected body sites; pain was classified as widespread if pain was reported in ≥4 of 5 body regions and in ≥7 of 15 body sites, and as regional otherwise. Sleep was assessed a median of 3.2 years later though 7-night actigraphy and through self-reported assessments of sleep quality. Chi-squared tests, Kruskal-Wallace tests and linear/logistic regression considered associations between pain extent and sleep quality.

Results: Of the 414 participants, 74 (17.9%) reported widespread and 189 (45.7%) regional pain. Whilst there were few clear associations between actigraphy outcomes and pain extent, those with widespread and regional pain consistently reported poorer sleep quality on all self-reported measures than those with no pain. Median (interquartile range) insomnia severity index and Patient-reported Outcomes Measurement Information System (PROMIS) for sleep disturbance and sleep-related impairment scores were 12 (7-16), 55.3 (48.0-58.9) and 57.2 (48.9-61.3) respectively for those with widespread pain, 8 (4-13), 51.2 (45.5-58.3) and 50.3 (43.6-56.1) for those with regional pain, and 5 (2-9), 47.9 (42.9-54.3) and 45.5 (41.4-50.3) for those with no pain (all p-values 0.0001). Associations remained strong after adjustment for HIV status and other confounders, and were reduced but remained significant, after adjustment for depressive symptoms.

Conclusions: Widespread pain was not associated with objective measures of sleep but was strongly associated with self-reported assessments of sleep quality in PWH.

Key words: HIV; sleep disturbance; widespread pain; actigraphy; insomnia

Introduction

The widespread use of antiretroviral treatment (ART) has meant that people with HIV (PWH) in many parts of the world now have a near-normal life expectancy [1,2]. However, PWH are ageing and, as a result, the prevalence of age-associated co-morbidities and use of concomitant medications has increased [3]. Moderate or severe pain is commonly reported among PWH and is associated with poorer quality-of-life [4-6], including poor sleep quality [7].

In the general population, there is a well-established bi-directional association between pain and sleep quality [8] with pain known to both disrupt sleep and to result from poor sleep quality or insufficient sleep duration. The current consensus appears to be, however, that poor sleep quality is a stronger predictor of future pain than pain is of future sleep quality [9]. Many possible causal mechanisms have been proposed for an association in this direction, including both biological and psychological mechanisms [8,10]. In particular, a reduction in sleep quantity is reported to be temporarily linked to elevated levels of inflammatory and immunological markers, including IL-6 and CRP [9]. This is of particular relevance for PWH, given the detrimental impact of HIV infection on the same type of inflammatory and immunological markers [11]. However, few studies have considered objectively assessed measures of sleep quality in this particular population, nor have they assessed whether associations with pain differ by type of sleep assessment.

In the present analysis, we describe the associations with pain and both objectively and subjectively measured sleep quality among PWH and HIV-negative controls in the Pharmacokinetic and clinical Observations in PeoPle over fifty (POPPY) Study in the UK and Ireland.

Methods

POPPY is a prospective cohort study at seven clinical sites in the UK and one in Ireland that aims to investigate the impact of HIV on the development and outcomes of comorbidities and pharmacotherapy among older PWH [12]. Three sub-groups are studied within POPPY: older PWH (≥50 years old), younger PWH (<50 years old) and older HIV-negative (≥50 years old) people. Eligible PWH participants acquired HIV through sexual transmission (either sex between men or sex between men and women – those acquiring HIV through other routes, including injection drug use, were excluded), were cisgender, and were either of white or black African ethnicity. Those recruited to the younger group of PWH were frequency-matched to the group of older PWH on gender, ethnicity, sexual orientation and participating clinic. HIV-negative participants were required to have a documented negative HIV test; this group was frequency-matched to the older PWH group on age, gender, ethnicity, sexual orientation and geographical location (in or out of London).

For this nested POPPY-Sleep sub-study, additional inclusion criteria required that participants have been previously enrolled in the main POPPY study and be able to wear a fingertip oximetry device and wrist actigraph. The only exclusion criterion was an investigator's judgement that the participant was unlikely to adhere to study procedures. Potential participants were identified without regard to sleep symptoms and all participants provided written informed consent. The protocol was approved by the UK National Health Service Health Research Authority and local ethics committees and/or institutional review boards.

The POPPY dataset includes information on socio-demographics, pharmacotherapy, family history, medical history, healthcare utilisation and quality-of-life. The POPPY dataset is linked to the UK Collaborative HIV Cohort (UK sites [13]) and to the UCD ID Cohort

(Dublin [14) for historic data on ART and longitudinal data on CD4 counts and HIV RNA. Pain information was collected through self-completed questionnaires and through a pain mannikin identifying affected body sites; pain was classified as widespread based on the 2019 American College of Rheumatology fibromyalgia criteria [15], in which widespread pain was defined if the presence of pain was reported in at least four of the five body regions [(1) left and (2) right shoulder/upper arm/lower arm; (3) left and (4) right hip/upper leg/lower leg, and (5) neck/upper back/lower back] and also in at least 7 of 15 distinct body sites.

Procedures

Participants wore a wrist actigraph (ActiGraph wGT3X-BT®, ActiGraph Corporation) against their skin on their non-dominant wrist for 7 nights. Devices were fitted at the time of the POPPY-Sleep visit, at which time participants also received a Sleep Diary and an information sheet about the actigraphy device. During the day, participants were requested to keep the actigraphy device exposed to light and not to wear it under clothing for accurate light meter data, although it was understood that this may not always be possible. Participants were asked to wear the device continuously until the time of return (a minimum of 7 days later) unless they were engaged in contact sports or had contact with water (bathing, swimming) when they were asked to remove the watch to avoid damage. The Sleep Diary included questions about each night's sleep (to be completed first thing the following morning) and about whether the participant had gone to work in the day, had been sick, had removed the actigraphy device or had taken any daytime naps (to be completed prior to bed each evening).

All actigraphy data and Sleep Diaries were transmitted initially to the co-ordinating centre in London, where the Sleep Diary was reviewed for accuracy and completeness. If any information was missing, site staff attempted to complete the diary by asking the participant

about any incomplete information. Both datasets were then transmitted to the Sleep Reading Center (SRC). Actigraphy data were scored at the SRC using ActiLife 6® and summary measurements for each participant were generated, including: average sleep duration, sleep efficiency (percentage of time in bed spent asleep), sleep fragmentation index, and wake after sleep onset (WASO).

Self-reported assessments of sleep quality were assessed through questionnaires. These included the insomnia severity index (ISI), a validated, 7-item, self-reported questionnaire designed to detect insomnia, with a score classification of no clinically significant insomnia (0-7), subthreshold insomnia (8-14), and clinically significant insomnia (15-28) [16]. The International Restless Legs Syndrome Study Group questionnaire for RLS assessment in epidemiologic studies [17] is a 4-item questionnaire, with 3 dichotomous yes/no questions targeted at RLS symptoms, and 1 question to assess the frequency of such symptoms; participants who responded yes to all three symptoms were considered to have RLS. We also collected the Patient-Reported Outcomes Measurement Information System questionnaires for sleep disturbance (PROMIS-SD) and sleep-related impairment (PROMIS-SRI) [18, 19].

Statistical analysis

Measures of sleep quality were compared in those without pain, with regional and widespread pain using Kruskal-Wallis tests or Chi-squared tests, as appropriate. We then used linear and logistic regression to compare the sleep outcomes in the three groups after controlling for HIV status. For the self-reported assessments of sleep, further analyses were performed which included additional adjustment for i) demographic factors (age, gender, ethnicity, mode of HIV acquisition and educational attainment), ii) recreational drug or alcohol use and any reported medication for pain relief or sleep, iii) depressive symptom scores (as numerical variables) as assessed by either the CES-D and PHQ-9 questionnaires. Analyses were also

repeated in the subset of PWH only. All analyses were performed using SAS v9.3 (SAS Institute Inc., Cary, NC).

Results

Of the 474 participants in POPPY-SLEEP, 414 also had pain information recorded from the pain manikin at the baseline visit. Characteristics of these 414 study participants are reported in Table 1. Of the 310 (74.9%) PWH, 281 (91.5%) had a viral load ≤50 copies/ml, and the median current and nadir CD4+ T-cell counts were 605 (470, 790) and 190 (94, 290) cells/mm^3, respectively. Longitudinal data on ART use was available for 303 PWH among whom the median (IQR) duration on ART was 10.6 (5.3, 17.1) years.

Participants reported pain at a median of 2 (interquartile range 0-4) of the 15 body sites, with the most frequently reported pain sites being the upper leg (left: 29.0%; right: 28.5%), lower leg (left: 26.3%; right 23.7%), lower back (29.5%), upper back (18.8%) and shoulders (left: 17.4%, right: 17.9%). Participants reported pain in a median (IQR) of 1 (0, 3) regions of the body. Overall, 74 participants (17.9%) reported widespread pain, and 189 (45.7%) regional pain. Pain relief medication use was reported by 68 (16.4%) of the cohort.

The POPPY-Sleep visit occurred at a median of 3.2 (2.5, 3.8) years after the initial study visit. Actigraphy assessments, overall and stratified by the extent of pain, are reported in Table 2. In general, there were few clear associations with pain extent and where these did exist, associations appeared to be somewhat counter-intuitive. For example, those reporting widespread pain had the least amount of sleep fragmentation and had the highest sleep maintenance efficiency. Results from multivariable linear regression analyses confirmed a

lack of association between these measures and either widespread or regional pain (data not shown).

Self-reported sleep measures are shown in Table 3. In contrast to actigraphy assessments, those with regional or widespread pain were consistently more likely to meet the criteria for insomnia and RLS, and also report poorer sleep quality than those with no pain. Associations with widespread and regional pain generally remained strong, even after adjustment for HIV status, demographic and lifestyle confounders, and recreational drug/alcohol use as well as the receipt of pain relief and sleep medication (Table 4). Furthermore, associations were reduced, but remained significant, after adjustment for depressive symptoms as assessed by either the CES-D or PHQ-9 questionnaire (Table 5).

Results were similar when analyses were restricted to the subgroup of PWH only (data not shown).

Discussion

In this large cohort of PWH, we found that regional and widespread pain were both strongly associated with self-reported measures of sleep quality. In contrast, no strong associations were seen with actigraphy assessments.

In the general population, an association between sleep and chronic pain is well established. In a large meta-analysis of 37 studies [20], the pooled prevalence of diagnosed sleep disorders (based on polysomnography or clinical diagnosis) among adults with chronic pain ($\geq$3 months) was 44%; those with chronic pain had worse sleep onset latency and efficiency, time awake after onset and recurrent awakening compared to controls. Whilst the association has, until relatively recently, been assumed to be bi-directional, the consensus view is now

that the effect of sleep on pain exacerbation may be stronger than that of pain on sleep [9, 21], with poor sleep quality having been shown to strongly predict the onset of new pain or new widespread pain over periods of 3-17 years, even after controlling for other confounders [22-25]. Further evidence for a causal association in this direction is provided from a randomised trial of either opioid or non-opioid therapy, in which those with higher sleep disturbance scores at baseline experienced less improvement of pain over follow-up, regardless of the intervention received [26].

While we reported strong associations with self-reported sleep quality, including assessments of insomnia and sleep-related quality of life, associations could not be detected with objectively assessed actigraphy data. These findings are consistent with studies from the general population, in which reported associations between sleep and pain differ depending on the dimension of sleep that is assessed. For example, Tang and colleagues reported that whilst pre-sleep pain was a predictor of poorer sleep efficiency calculated based on sleep diary entries, it was not a significant predictor of subsequent sleep efficiency as estimated by actigraphy [27]. Afolalu's meta-analysis confirmed that changes in insomnia symptoms, but not sleep quantity, were associated with the risk of developing a pain condition [9]. Associations between pain and sleep have also been reported in cohorts of people with other chronic conditions. Conley et al [28] conducted a cross-sectional study of 173 people with heart failure. Insomnia symptoms, sleep duration, poor sleep quality, use of sleep medications, napping and daytime sleepiness were all associated with increased pain. In particular, those with the longest sleep duration (which included those with insomnia) had more pain, and the researchers noted that associations between pain and sleep differed depending on the presence of insomnia and sleep duration. Our findings emphasise the importance of patient-reported measures of sleep disturbance when attempting to determine the impact of sleep on outcomes.

Studies that have related pain and sleep in PWH are more limited. Correlates of poor sleep quality in treated PWH included the presence of peripheral neuropathy [29,30]. Among 139 PWH in South Africa, both pain in the previous month and current pain were associated with poorer sleep quality [7].

Hypothesised mechanisms that underly the complex relationship between sleep deficiency and chronic pain include both neuronal and non-neuronal components of the opioid, monoaminergic, orexinergic, immune, melatonin and endocannabinoid systems, the hypothalamus-pituitary-adrenal axis and adenosine and nitric oxide signalling, as reviewed by Haack [8]. It has also been reported that non-restorative sleep is associated with higher morning pain catastrophizing (negative cognitive and emotional responses that result in heightened attention to pain) which, in turn, predicts afternoon pain severity [10]. A reduction in sleep quantity appears to be temporarily linked to elevated levels of inflammatory and immunological markers, including IL-6 and CRP [9]. Research is ongoing within the POPPY study to investigate biomarker associations with sleep patterns, and thus future analyses will consider a possible mediating effect of these for the relationship between sleep and pain. Such information is essential if we are to develop effective interventions that are acceptable to PWH.

The clinical implications of our findings remain unclear – whilst there is some evidence to support approaches to reducing pain, including in PWH, it is unclear whether these will result in improvements in sleep quality. Furthermore, whilst it is intriguing to speculate that increased recognition and management of sleep disorders in PWH may have a beneficial impact on sleep quality and mental health, and ultimately reduce some of the need for pain medication in this group, whether interventions to improve sleep quality will lead to a reduction in pain remains unclear. In a large meta-analysis, Afolalu reported that whilst there

was substantial evidence that sleep deterioration has a negative effect on pain-related health outcomes, there was insufficient evidence to suggest a clear positive effect of sleep improvement on pain [9]. Our aim in the present manuscript was not to understand the reasons for poor sleep in this group. However, further analyses of this cohort, including more detailed investigation of the biological and clinical mechanisms underlying any pain, may support the identification of appropriate management strategies which may have a positive impact on not only the pain itself, but also sleep.

Our study benefits from a large sample of PWH which is broadly representative of older PWH in western European settings, where the population is optimally treated for their HIV (with high levels of viral suppression), which has allowed us to describe the extent of pain as well as sleep quality. In comparison to many earlier studies, our study also benefits from the inclusion of appropriately selected HIV-negative controls with similar characteristics to the older PWH in the study, allowing us to determine the role of HIV infection in both outcomes. Whilst our analyses have considered associations between pain assessed at the baseline study visit, with sleep assessment on average 3.2 years later, associations that we can draw regarding causality are limited and we cannot rule out the possibility that we may have failed to control for unmeasured confounding. Furthermore, it is possible that pain patterns may have changed within individuals over the period between assessment. Although we might expect regional pain to be transient, widespread pain is more likely to be persistent and, if anything, would be more likely to increase in prevalence rather than decrease as people age. Thus our reported prevalence of widespread pain, and its associations with sleep may be under-estimated. Our analyses used an approach to define widespread pain based on both the number of sites affected and the variation of these across the body, following the latest (2019) American College of Rheumatology/Fibromyalgia criteria [15]. However, this is a broad definition and does not allow us to examine pain phenotypes in greater detail. We also note

that eligible participants for the sleep component were those who were believed (by the study investigators) to be able to adhere to study procedures. Any bias that this may introduce is, however, believed to be small given all procedures for the POPPY-sleep sub-study (such as study questionnaires, actigraphy and overnight oximetry) would not be considered to be much more onerous to the study procedures for the main POPPY study (such as cognitive testing, bone densitometry assessments and study questionnaires). Finally, our study sample only includes those acquiring HIV through sexual routes and of white or black African ethnicity; generalisability of our findings to other populations must therefore be undertaken with caution.

In conclusion, we report strong associations between widespread and regional pain and sleep quality among PWH. Pain and sleep have been identified by PWH as priority concerns to be addressed in routine HIV care [31], and our data support the need for clinicians to assess PWH for these conditions. Given the increasing focus on the maintenance of the highest possible quality-of-life in this population that is living and aging with HIV [31], our findings also demonstrate the need for intervention studies to inform best practices on how to improve sleep quality and reduce pain in PWH.

Appendix,http://links.lww.com/QAI/B483

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Table 1: Characteristics of POPPY-SLEEP participants with pain data available

		N (%)
Number of participants		414 (100.0)
HIV status	Positive	310 (74.9)
	Negative	104 (25.1)
Gender	Male	343 (82.9)
	Female	71 (17.2)
Sexuality/risk group	MSM	310 (74.9)
	Heterosexual	104 (25.1)
Race	White	373 (90.1)
	Black African	41 (9.9)
Work status	Employed/student	221 (53.4)
	Unemployed/off sick	98 (23.7)
	Other/unknown	95 (23.0)
Age (years)	Median (IQR)	54 (50, 60)
BMI (kg/m^2)	Median (IQR)	25.3 (22.9, 28.3)
Educational level	O-levels or lower	100 (24.2)
	A-levels	63 (15.2)
	Higher education/unknown	251 (60.6)
Year of baseline visit	2013	61 (14.7)
	2014	186 (44.9)
	2015	157 (37.9)
	2016	10 (2.4)

Table 2: Summary of sleep parameters (median (IQR), assessed via actigraphy, stratified by extent of pain

		Overall	Pain			
			None	Regional	Widespread	p-value[1]
Sleep parameter	n		151	189	74	
Fragmentation index	Average	12.76 (9.53, 16.15)	12.84 (9.73, 16.83)	13.30 (9.76, 16.15)	11.22 (8.12, 14.42)	0.01
	Standard deviation	7.96 (6.34, 10.10)	7.56 (6.12, 10.03)	8.46 (6.71, 10.27)	7.88 (5.93, 9.60)	0.12
Maintenance efficiency	Average	89.12 (85.21, 91.82)	89.10 (84.68, 91.54)	88.79 (84.98, 91.58)	90.40 (86.30, 93.26)	0.04
(%)	Standard deviation	3.55 (2.38, 4.94)	3.58 (2.32, 4.85)	3.59 (2.48, 5.20)	3.19 (2.23, 4.54)	0.23
Sleep duration (mins)	Average	424 (384, 459)	424 (389, 459)	421 (383, 450)	440 (384, 475)	0.19
	Standard deviation	55 (38, 81)	50 (35, 74)	56 (40, 82)	62.5 (41, 91)	0.04
Sleep onset latency	Average	7 (6, 9)	7 (6, 9)	7 (6, 9)	7 (6, 9)	0.46
(mins)	Standard deviation	3 (2, 5)	3 (2, 5)	3 (2, 5)	4 (2, 6)	0.11
Wake after sleep onset	Average	53 (38, 73)	53 (40, 75)	55 (39, 73)	47.5 (32, 65)	0.07
(mins)	Standard deviation	19 (13, 27)	18 (13, 27)	19 (13, 28)	16.5 (12, 26)	0.38

[1]p-value obtained from Kruskal-Wallis test; [2]p-value obtained from ANOVA

Table 3: Self-reported sleep parameters stratified by extent of pain

Sleep parameter		Total	Pain			
			None	Regional	Widespread	p-value[1]
	n	414	151	189	74	
ISI	Median (IQR)	7 (3, 13)	5 (2, 9)	8 (4, 13)	12 (7, 16)	0.0001
No clinically significant insomnia (0-7)		208 (51.9)	101 (68.7)	89 (48.1)	19 (26.8)	
Sub-threshold insomnia (8-14)		119 (29.7)	32 (21.8)	60 (32.8)	27 (38.0)	
Clinically significant insomnia (15-28)		74 (18.5)	14 (9.5)	35 (19.1)	25 (35.2)	0.0001
RLS	n (%)	61 (15.0)	14 (9.4)	31 (16.8)	16 (21.9)	0.03
Insomnia	n (%)	74 (18.5)	14 (9.5)	35 (19.1)	25 (35.2)	0.0001
PROMIS-SD T-score	Median (IQR)	51.2 (45.5, 57.3)	47.9 (42.9, 54.3)	51.2 (45.5, 58.3)	55.3 (49.0, 59.4)	0.0001
PROMIS-SRI T-score	Median (IQR)	48.9 (43.6, 56.1)	45.5 (41.4, 50.3)	50.3 (43.6, 56.1)	57.2 (48.9, 61.3)	0.0001

[1]p-value obtained from Kruskal-Wallis test or Mann-Whitney U test, as appropriate

Table 4: Results from multivariable regression models to investigate independent associations of HIV and extent of pain with each self-reported sleep parameter and abnormal ODI: Model 1 – main effects only; Model 2 – including additional adjustment for age, gender, ethnicity, HIV exposure group and educational attainment; Model 3 – including additional adjustment for substance use, pain relief and sleep medication.

Sleep parameter		Model 1		Model 2		Model 3	
	Parameter	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SD)	p-value
ISI (continuous)	HIV	2.29 (0.66)	0.0006	2.42 (0.74)	0.001	2.12 (0.73)	0.004
	Non-widespread pain	2.45 (0.64)	0.0001	2.44 (0.64)	0.0002	2.29 (0.64)	0.0004
	Widespread pain	5.29 (0.84)	0.0001	5.35 (0.87)	0.0001	4.37 (0.90)	0.0001
PROMIS-SD T-score	HIV	2.76 (0.96)	0.004	3.75 (1.06)	0.0005	3.47 (1.07)	0.001
	Non-widespread pain	3.14 (0.92)	0.0007	3.08 (0.92)	0.0009	2.85 (0.92)	0.002
	Widespread pain	5.87 (1.21)	0.0001	5.53 (1.25)	0.0001	4.55 (1.30)	0.0005
PROMIS-SRI T-score	HIV	4.66 (0.96)	0.0001	4.58 (1.07)	0.0001	4.31 (1.09)	0.0001
	Non-widespread pain	3.94 (0.92)	0.0001	3.96 (0.93)	0.0001	3.83 (0.94)	0.0001
	Widespread pain	8.68 (1.21)	0.0001	8.84 (1.25)	0.0001	8.10 (1.32)	0.0001
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
RLS	HIV	1.01 (0.53, 1.94)	0.98	1.26 (0.61, 2.61)	0.54	1.29 (0.62, 2.71)	0.50
	Non-widespread pain	1.94 (0.99, 3.80)	0.05	1.84 (0.93, 3.64)	0.08	1.81 (0.91, 3.61)	0.09
	Widespread pain	2.70 (1.23, 5.94)	0.01	2.34 (1.03, 5.30)	0.04	2.28 (0.96, 5.40)	0.06
Insomnia	HIV	3.58 (1.57, 8.17)	0.002	3.50 (1.43, 8.55)	0.006	3.25 (1.31, 8.06)	0.01
	Non-widespread pain	2.17 (1.11, 4.23)	0.02	2.16 (1.10, 4.25)	0.03	2.04 (1.03, 4.05)	0.04
	Widespread pain	4.60 (2.18, 9.68)	0.0001	5.03 (2.31, 10.97)	0.0001	3.68 (1.62, 8.36)	0.002

Table 5: Results from multivariable regression models to investigate independent associations of HIV and widespread pain with each self-reported sleep parameter and abnormal ODI with additional adjustment for 1) CES-D and 2) PHQ-9. CES-D scores were available for 392 individuals (median 10, IQR 3-19) with PHQ-9 scores available for 393 (3, IQR 1-9).

Sleep parameter	Model 1 – CES-D			Model 2 – PHQ-9		
	Parameter	Estimate (SE)	p-value	Parameter	Estimate (SE)	p-value
ISI (continuous)	HIV	1.25 (0.66)	0.06	HIV	1.09 (0.62)	0.08
	Non-widespread pain	1.62 (0.63)	0.01	Non-widespread pain	1.67 (0.60)	0.005
	Widespread pain	2.66 (0.91)	0.004	Widespread pain	2.69 (0.85)	0.002
	CES-D (/unit higher)	0.18 (0.03)	0.0001	PHQ-9 (/unit higher)	0.43 (0.05)	0.0001
PROMIS-SD T-score	HIV	1.52 (0.95)	0.11	HIV	1.20 (0.92)	0.19
	Non-widespread pain	1.91 (0.91)	0.04	Non-widespread pain	2.18 (0.87)	0.01
	Widespread pain	2.42 (1.31)	0.07	Widespread pain	2.62 (1.25)	0.04
	CES-D (/unit higher)	0.24 (0.04)	0.0001	PHQ-9 (/unit higher)	0.59 (0.07)	0.0001
PROMIS-SRI T-score	HIV	2.86 (0.95)	0.003	HIV	2.58 (0.92)	0.005
	Non-widespread pain	2.70 (0.91)	0.003	Non-widespread pain	2.74 (0.87)	0.002
	Widespread pain	4.73 (1.30)	0.0003	Widespread pain	4.49 (1.24)	0.0003
	CES-D (/unit higher)	0.27 (0.04)	0.0001	PHQ-9 (/unit higher)	0.64 (0.07)	0.0001

		OR (95% CI)	p-value		OR (95% CI)	p-value
RLS	HIV	0.79 (0.39, 1.62)	0.52	HIV	0.89 (0.44, 1.79)	0.74
	Non-widespread pain	1.60 (0.79, 3.27)	0.20	Non-widespread pain	1.68 (0.84, 3.35)	0.14
	Widespread pain	1.75 (0.70, 4.28)	0.22	Widespread pain	1.70 (0.70, 4.13)	0.24
	CES-D (/unit higher)	1.04 (1.01, 1.07)	0.005	PHQ-9 (/unit higher)	1.06 (1.01, 1.11)	0.02
Insomnia	HIV	2.29 (0.97, 5.37)	0.06	HIV	2.39 (1.00, 5.67)	0.05
	Non-widespread pain	1.64 (0.80, 3.36)	0.18	Non-widespread pain	1.91 (0.92, 3.96)	0.08
	Widespread pain	2.03 (0.85, 4.81)	0.11	Widespread pain	2.25 (0.94, 5.38)	0.07
	CES-D (/unit higher)	1.06 (1.03, 1.08)	0.0001	PHQ-9 (/unit higher)	1.14 (1.09, 1.20)	0.0001