Understanding and managing disordered sleep in people with HIV

Luxsena Sukumaran, Karine Scheuermaier, Caroline A Sabin, Nomathemba Chandiwana, Francesc Xavier Gómez-Olivé, Malcolm von Schantz, Dale E Rae, Alan Winston

People with HIV experience higher burden of cardiometabolic, mood, and cognitive disorders. Poor-quality and insufficient sleep are both associated with increased risk for these comorbidities and are more common in people with HIV. Although previous reviews have explored the prevalence and risk factors for sleep complaints in people with HIV, few have differentiated these complaints by potential underlying causes. Disordered sleep in people with HIV might arise from HIV-specific sleep disruptors, including direct effects of the virus, chronic inflammation, and antiretroviral treatment. There is also evidence that sleep is more fragile in people with HIV and some common sleep disorders, such as obstructive sleep apnoea, chronic insomnia, and circadian rhythm disorders, might be particularly problematic in people with HIV. Understanding how HIV uniquely disrupts sleep physiology could inform the development of tailored, mechanism-based management strategies to improve sleep health in people with HIV.

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Institute for Global Health, University College London, London, UK (L Sukumaran PhD, Prof C A Sabin PhD); **Wits Sleep Laboratory, Brain Function Research Group, Department of Physiology, School of Biomedical Sciences, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa** (Prof K Scheuermaier MD); **Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa** (N Chandiwana MD); **Desmond Tutu Health Foundation, Cape Town, South Africa** (N Chandiwana MD); **MRC/Wits Rural Public Health and Health Transitions Research Unit, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa** (Prof F X Gómez-Olivé MD PhD); **Faculty of Health and Life Sciences, Northumbria University, Newcastle-upon-Tyne, UK** (Prof M von Schantz PhD); **Health through Physical Activity, Lifestyle and Sport Research Centre and Division of Physiological Sciences, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa** (Prof D E Rae PhD); **Department of Infectious Disease, Imperial College London, London, UK** (Prof A Winston MD)

Correspondence to:
Luxsena Sukumaran, Institute for Global Health, University College London, London WC1N 1DP, UK
luxsena.sukumaran.19@ucl.ac.uk

Introduction

Widespread use of antiretroviral therapy (ART) has transformed HIV infection from a life-limiting condition to a manageable chronic disease, increasing life expectancy to a similar level as the general population.[1] Despite this success, people with HIV continue to experience higher burden of non-communicable diseases than the general population,[2] including mental health problems[3] and sleep disturbances,[4] which contribute to multimorbidity burden.

Sleep problems are a well documented consequence of living with HIV and were identified during the early years of the HIV epidemic.[5] People with HIV commonly experience either formal sleep disorders, such as insomnia disorder or obstructive sleep apnoea,[6] as defined by the International Classification of Sleep Disorders,[7] or poor quality sleep that falls short of the formal criteria for a sleep disorder yet still impacts daytime function. At least part of this additional burden appears to be caused by particular fragility of sleep in people with HIV, making the consequences of sleep disorders more severe.[8] Although both types of sleep disorders are relevant to people with HIV, the primary focus of this Review is on disordered sleep, a term we use to encompass these undifferentiated or subclinical sleep problems (panel 1), due to their high prevalence and frequent under-recognition in clinical care and research.

In early clinical assessment and many published studies, sleep quality questionnaires are often chosen for their ease of use. They are also the most documented tools used for reports of disordered sleep in HIV cohorts. A systematic review and meta-analysis found that 58% of people with HIV reported disordered sleep.[9] A direct comparison with lifestyle-matched people without HIV concluded an increased risk of insomnia in people with HIV with an adjusted odds ratio of 5·3.[10]

The persistent pathophysiology of disordered sleep among people with HIV, even when viral suppression has been achieved with ART, is not well characterised. Sleep disturbances can be influenced by HIV-specific factors that combine with or add to psychological and environmental factors affecting the general population. These include immune responses to the virus (characterised by immune activation, chronic inflammation, and neurotoxic effects within the CNS),[11] the psychosocial impact of living with a stigmatised condition,[12] insufficient social support,[13] and adverse effects of antiretroviral medications.[14] These factors all likely contribute to the considerable heterogeneity in the prevalence and severity of sleep issues among people with HIV. Applying the Sleep Health framework proposed by the National Sleep Foundation,[15] which encompasses dimensions such as sleep regularity, satisfaction, alertness, timing, efficiency, and duration, could provide a more nuanced and holistic understanding of these challenges. This broader perspective is relevant given that many individuals experience subclinical but functionally substantial sleep impairments that do not meet diagnostic thresholds. Unresolved sleep problems, whether formally diagnosed disorders or disturbances across those dimensions, have significant clinical implications, including increased risk of cardiometabolic disease, psychiatric disorders, and cognitive impairment.[16,17]

The prevalence and risk factors associated with sleep disturbances in people with HIV are documented. However, evidence does not often differentiate sleep complaints according to underlying causes and mechanisms, without which treatment approaches can either be too generalised, leading to suboptimal outcomes, or withheld due to an absence of differential diagnosis or of an understanding of the importance of sleep. Elucidating both the distinctiveness and the commonalities of mechanisms that drive sleep disturbances can inform the development of better targeted clinical guidelines and personalised care strategies, which will lead to better outcomes and improved quality-of-life for people with HIV. In this Review, we characterise disordered sleep in people with HIV, investigate underlying mechanisms, and determine whether (and to what extent) their disordered sleep differs from that observed in populations without

***Panel 1*: Differentiating between sleep disorders and disordered sleep**

Sleep disorders

Sleep disorders are clinically defined conditions, such as insomnia disorder and obstructive sleep apnoea, that meet diagnostic criteria outlined in medical guidelines (eg, The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision or International Classification of Sleep Disorders, Third Edition).

Disordered sleep

Disordered sleep refers to sleep that is disturbed or irregular in timing and what the patient experiences as unsatisfactory or non-restorative but does not meet the criteria for a formal sleep disorder. It can involve the following:

- Fragmentation (frequent arousals or difficulty maintaining sleep throughout the night)
- Altered sleep architecture (changes in the proportion of time spent in different sleep stages, particularly reduced non-rapid eye movement stage 3 and rapid eye movement sleep)
- Daytime dysfunction (impairments in daytime function, such as excessive fatigue, daytime sleepiness or reduced alertness, which is attributed to poor quality sleep)

Poor sleep and sleep disturbances

Poor sleep and sleep disturbances are general, more subjective terms often used interchangeably in the literature to describe any deviation from normal or restorative sleep. These can refer to:

- Episodic or chronic difficulties falling or staying asleep
- Perceived low quality of sleep
- Symptoms of either disordered sleep or an undiagnosed sleep disorder

Although these terms overlap, sleep disorder implies a clinical diagnosis, disordered sleep suggests dysfunction without formal diagnosis, and poor sleep or sleep disturbances are general descriptors that can encompass either.

HIV. Additionally, we seek to bridge the knowledge gap between health-care providers across three key groups: those responsible for treating and managing HIV, specialists at sleep disorder referral centres, and general practitioners who have the primary responsibility for managing sleep disorders in the majority of individuals globally, irrespective of HIV-status. Finally, we identify gaps in current research and outline priorities to guide future studies, which could inform future guidelines for sleep management in people with HIV. Although our primary emphasis is on disordered sleep, we also include discussion of selected formal sleep disorders, specifically those with a convincing or plausible HIV-specific mechanism of action. In contrast disorders such as restless leg syndrome, narcolepsy, and hypersomnia, for which little or no evidence of HIV-related differences currently exists, fall outside the scope of this Review.

Most common sleep disorders and disordered sleep in people with HIV

Insomnia disorder

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision (DSM-5-TR) defines insomnia disorder as difficulty initiating or maintaining sleep or waking too early at least 3 nights per week, resulting in dissatisfaction with the quantity or quality of sleep, and substantial daytime distress or impairment.[18] Importantly, the symptoms should be present for at least 3 months and should not be explained by other sleep disorders, mental or physical conditions, or substance or medication use. In the general population, insomnia is the most common sleep disorder, with an estimated prevalence of 10–30%.[19] However, the DSM-5-TR criteria can be difficult to apply in people with HIV due to the high prevalence of comorbidities[2,3] and the side-effects of ART regimens,[20] including fatigue, mood changes, and cognitive impairment, which can overlap with or mask a formal diagnosis of insomnia disorder. It can therefore be challenging for clinicians to accurately distinguish sleep disorders from other conditions, potentially leading to underdiagnosis or misdiagnosis with respect to the DSM-5-TR criteria. Given these limitations, most studies of people with HIV focus on insomnia symptoms rather than a differential diagnosis of insomnia disorder. Studies using these criteria suggest higher prevalence of insomnia symptoms among people with HIV than what might be observed in the general population. A UK-based matched-control study found that people with HIV older than 50 years had higher risk of insomnia disorder (adjusted odds ratio 5·3), compared with matched counterparts without HIV.[10] Similarly, a large US-based study reported that women with HIV were 17% more likely to report insomnia symptoms than women without HIV.[21] These data suggest that greater understanding and clearer definition of the dimensions of insomnia disorder in people with HIV should be a future research priority.

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is the second most common sleep disorder in the general population. It is characterised by repeated episodes of upper airway collapse during sleep, which causes partial (hypopnoea) or complete (apnoea) obstruction of airflow.[22] These events lead to oxygen desaturation and sleep fragmentation, which drive the key symptoms of OSA, including excessive daytime sleepiness and cognitive impairment. OSA severity is measured using the apnoea-hypopnoea index, which records the number of events per hour of sleep. An apnoea-hypopnoea index score of 5–14 is diagnostic of mild OSA, 15–29 is diagnostic of moderate OSA, and 30 or more is diagnostic of severe OSA. Studies using polysomnography to assess risk for sleep apnoea report a prevalence of mild to moderate

subclinical sleep-disordered breathing of up to 70% among people with HIV.[23] Traditional risk factors for OSA include obesity, male sex, age older than 50 years, and a neck circumference more than 43 cm in men and more than 41 cm in women.[24] However, in people with HIV, chronic inflammation and weight gain associated with ART contribute to OSA risk, potentially altering its presentation compared with the general population. OSA in people with HIV can involve distinct pathophysiological mechanisms, with these established risk factors possibly being less predictive of OSA in this population.[25] The evidence on the impact of HIV serostatus on OSA is mixed. The Multicenter AIDS Cohort Study reported differences in prevalence using specific scoring criteria (eg, oxygen desaturation index 4% and apnoea-hypopnoea index 4%),[23] whereas other studies found no significant differences by HIV status.[10] However, recently reported data suggest that severe OSA in people with HIV might be associated with more severe sleep disruption (more waking after sleep onset and lower sleep efficiency) in people with HIV compared with people without HIV.[26] This finding highlights the need for more nuanced and mechanistic studies to determine the impact of HIV infection on OSA risk and presentation. Given the potential for atypical OSA manifestations in people with HIV, and the independent association of OSA with increased cardiometabolic disease and mortality,[27] there is an urgent need to address the evidence gap of risk factors for OSA in people with HIV.

Circadian rhythm sleep disorders

Sleep is governed by a finely tuned power balance between two physiological processes, the sleep homoeostat (sleep pressure that grows during wakefulness and dissipates during sleep) and the circadian oscillator (our internal body clock that maintains near-24-hour rhythms in physiology and behaviour). During the day, the circadian drive for wakefulness peaks in the evening, referred to as the wake maintenance zone. Once this peak has passed, and homoeostatic sleep pressure is at its highest, the balance between the two processes allows sleep initiation.[28] Circadian rhythm sleep disorders reflect a misalignment between these processes. According to DSM-5-TR, these disorders are characterised by a pattern of sleep disruption that results in excessive daytime sleepiness, insomnia symptoms, and clinically significant daytime distress or impairment. The most common circadian rhythm sleep disorder is delayed sleep phase disorder, where an individual's natural sleep period is substantially later than the social norm, resulting in difficulties initiating sleep at night and waking up in the morning at a socially acceptable hour. The conflict between the sleep schedule dictated by the disorder and social norms often leads to chronic sleep deprivation. By contrast, advanced sleep phase disorder is marked by an abnormally early natural sleep period. Although shift work represents a separate circadian rhythm sleep disorder stemming from imposed work at night, it is beyond the scope of this Review. Chronic circadian misalignment, a hallmark of these disorders, has been linked to increased risk for a range of physical and mental health conditions.[29,30] The relationship between circadian phase and sleep phase has also been shown to weaken with ageing, further complicating sleep regulation in older adults.[31] Although few studies have examined circadian rhythm sleep disorders in people with HIV, emerging evidence suggests that circadian dysregulation might represent a distinct mechanism contributing to sleep disturbances in this population. For instance, a study of older rural-dwelling African adults found that those with HIV exhibited later dim-light melatonin onset (a marker of circadian phase) compared with those without HIV, but similar sleep timing compared to those without HIV, indicating greater circadian misalignment.[32] Although these findings need to be replicated in other groups, they are consistent with many of the general sleep disturbances described in this Review.

Disordered sleep

Many of the sleep issues reported in people with HIV do not fit within the established diagnostic categories for formal sleep disorders. Characteristics of disordered sleep include fragmentation, altered sleep architecture, daytime dysfunction, and subjective dissatisfaction with sleep, all of which are often described in terms of poor sleep quality. A National Sleep Foundation consensus panel has identified measures of sleep continuity or fragmentation (time to fall asleep, number of awakenings longer than 5 minutes, cumulative time spent awake in the night, and low sleep-efficiency) as key indicators of low sleep-quality.[33] Such disturbances can reduce overall sleep duration or interfere with sleep architecture, both of which reduce the restorative capacity of sleep. Sleep architecture, assessed by polysomnography, refers to the proportions of time spent in non-rapid eye movement (NREM) sleep stage 1 (NREM1), sleep stage 2 (NREM2), and sleep stage 3 (NREM3) as well as rapid eye movement (REM) stage sleep. Appropriately structured sleep in adults comprises approximately 5% in NREM1, 50% in NREM2, 20% in NREM3, and 25% in the REM stage,[34] however these proportions can vary with age, particularly for NREM1 and NREM3, as well as the incidence of wake after sleep onset.[35] The deep sleep stage (NREM3) is particularly important for memory consolidation processes, such as synaptic depotentiation, but also for physiological processes, such as growth hormone secretion, whereas the REM stage is associated with procedural memory, emotional processing, and appetite control.[36,37] Notably, multiple studies have shown that individuals with HIV, regardless of insomnia or OSA symptoms, experience reduced NREM3 sleep (as low as 5% of total sleep time)[38] compared with those without HIV, even in the absence of a known sleep disorder.[38–40]

Mechanisms underlying disordered sleep in people with HIV

Direct effects of HIV infection and immune activation

Primary HIV-infection (the acute phase of HIV infection) is characterised by systemic immune activation, which can drive increased NREM sleep duration and more fragmented NREM sleep. In the early stages of primary HIV-infection, HIV crosses the blood–brain barrier, disrupting glial cell function, which can lead to sleep alterations.[41,42] These alterations might also be linked to the neurotoxic effects of HIV glycoproteins such as gp120, gp41, and transactivator of transcription (Tat) protein. For instance, elevated Tat protein concentrations have been shown to contribute to delays in the rest–activity cycle and circadian phase.[32,43] Although scarce, evidence suggests that HIV neurotoxicity can disrupt neurotransmitter systems, including dopamine and glutamate pathways, resulting in poor sleep quality and impairments in sleep–wake regulatory mechanisms.[11] Despite viral suppression on ART, chronic immune activation can persist, with delayed ART initiation linked to greater immune activation.[44] The immune response in both acute and chronic HIV infection can disrupt sleep regulation, primarily through cytokine-mediated modulation of sleep homoeostasis. HIV-related immune responses are more prevalent in low-income and middle-income countries, where a greater proportion of individuals with HIV are diagnosed and commence treatment late. A later onset of ART is associated with a reconstitution of more activated CD4 and higher chronic immune activation.[44] Although no consensus definition of chronic immune activation exists, many groups have described elevated plasma concentrations of C-reactive protein, cytokines (eg, IL-1, TNF-α, IL-6, and IFN-α), and abnormal expression of immune markers on CD4 and CD8 cells (eg, HLA-DR, CD-38, and PD-1). Using these markers, several studies have suggested that persistent immune activation and inflammation are linked to disordered sleep,[45–48] which can further exacerbate immune dysregulation by impairing functionality of regulatory CD4 cells.[49] In a study in people without HIV with depression and systemic inflammation, treatment with a blocker of the pro-inflammatory cytokine TNF-α (infliximab) decreased wake after sleep onset and improved sleep quality.[50] Thus, it might be important to explore such anti-inflammatory strategies as potential therapeutic targets for disordered sleep in HIV (figure 1).

ART

The use of ART combinations, including efavirenz (a non-nucleoside reverse transcriptase inhibitor), has been largely phased out worldwide due to their association with adverse events, including neuropsychiatric symptoms and sleep disturbances. However, many people with HIV remain on efavirenz-containing regimens. Elevated plasma concentrations of efavirenz and its 8-OH-metabolite have been linked

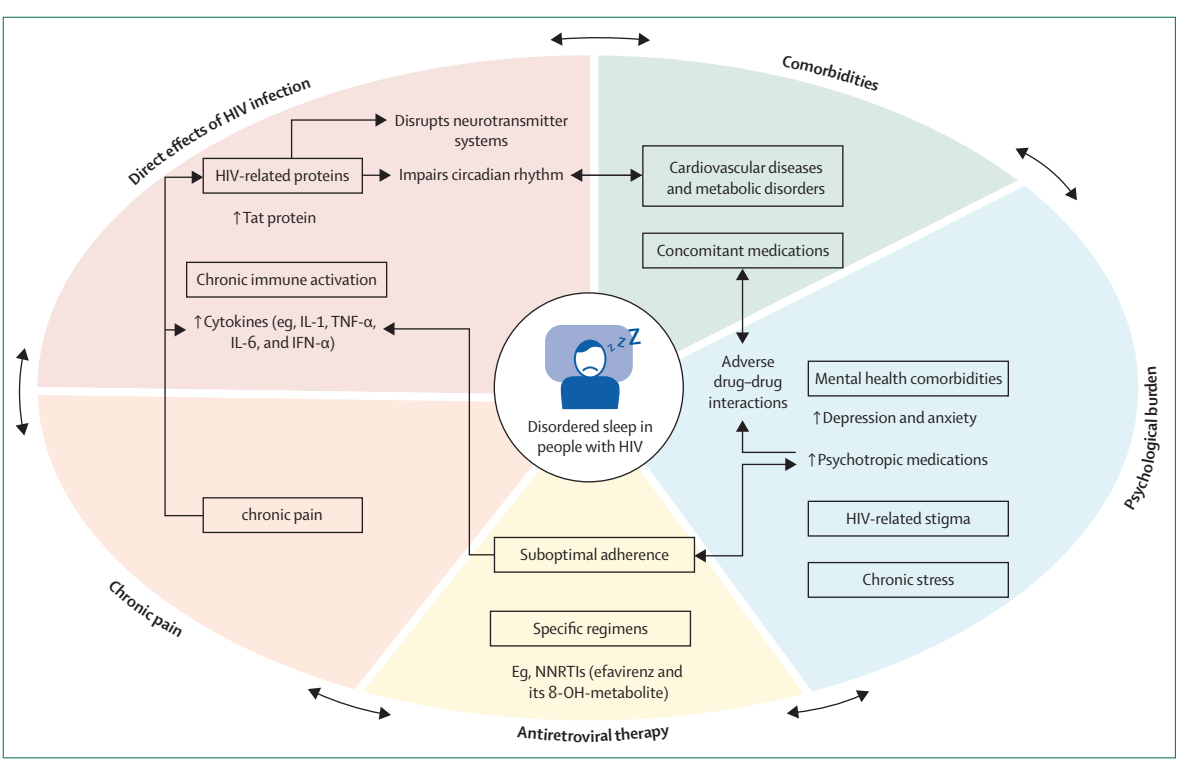

Figure 1: **Potential mechanisms and interplay of factors contributing to disordered sleep in people with HIV**
Tat=transactivator of transcription. Figure created with BioRender.com.

to longer sleep-onset latency times and more sleep fragmentation.[51,52] Studies using polysomnography have reported reduced sleep efficiency and diminished REM stage and NREM3 sleep in individuals treated with efavirenz, even among those without prior sleep disorders.[39] Clinically significant symptoms of sleep disturbance is an indication to move away from an efavirenz-containing ART regimen where possible.

Dolutegravir, a second-generation integrase strand transfer inhibitor, has now widely replaced efavirenz. Dolutegravir has also been associated with sleep disturbances,[53] although to a lesser extent than efavirenz.[54] Strategies to mitigate these effects of sleep disturbances include morning dosing, avoiding an abacavir-containing nucleoside backbone within the ART regimen (which can exacerbate the sleep effects of dolutegravir-containing regimens), and switching to alternative second-generation integrase strand transfer inhibitor where available, although supporting evidence for all these strategies remains scarce.[55]

Although adverse effects, including on sleep, have been reduced in the modern ART era, they are important given the lifelong nature of ART. The successful global roll-out of initially efavirenz-containing and now dolutegravir-containing ART regimens, both of which are associated with sleep disturbances, supports the need for more detailed understanding of the effects of ART on sleep, and how sleep disturbances might be mitigated in people on ART.

Comorbidities and concomitant medication

As people with HIV age, they might experience higher incidence of several non-infectious comorbidities compared with people without HIV. These include cardiometabolic comorbidities, renal and bone disease, respiratory problems, depression, and conditions affecting the CNS, some of which are not only associated with, but are also influenced by, sleep disorders.[16] Studies suggest that OSA and sleep disturbances, specifically insomnia symptoms, play an independent role in increasing the risk of cardiovascular disease in people with HIV.[56] In 2022, The American Heart Association incorporated sleep health into its Life's Essential Eight framework, underscoring the importance of addressing sleep disturbances as a modifiable cardiovascular disease risk-factor among people with HIV.[57] There is a notable gap in our understanding of the mechanisms driving the increased prevalence of comorbidities in people with HIV but they are thought to include chronic immune activation that persists even with viral suppression. This immune dysregulation, combined with social, lifestyle, and environmental factors, can further contribute to multisystem decline or frailty, both of which are strongly linked to disordered sleep, as suggested by a preprint paper.[58] HIV can also alter circadian regulation, which can contribute to the development and progression of comorbidities, particularly cardiometabolic conditions.[59]

The increasing prevalence of comorbidities in people with HIV has resulted in a rise in polypharmacy. The use of multiple medications, including antidepressants, sedatives, antipsychotics, beta blockers, and anticholinergic drugs, can negatively impact sleep quality. A greater understanding of the mechanisms through which ART and non-ART medications interact and contribute to disordered sleep is required to develop individualised treatment approaches.

Psychological burden

The unique challenges associated with living with HIV, such as concerns about long-term health, the emotional toll of ongoing management, and the stigma associated with the condition, can heighten psychological distress. Chronic stress has been linked to both disordered sleep and immune dysregulation.[60] The burden of HIV-related stigma varies globally but intersects with factors such as gender, sexual orientation, religion, and cultural norms, further exacerbating mental health issues and sleep disturbances. HIV-related stigma and insufficient social support can negatively impact sleep quality, largely through their associations with loneliness, psychological distress, and depression.[13,61,62] Depression is not only more common in people with HIV, but is also one of the strongest predictors of poor sleep quality in any population.[63,64] Depression has also been linked to suboptimal ART adherence,[65] which has been independently linked to poor sleep quality.[64] Access to mental health care services is often scarce, further contributing to untreated psychological distress and disordered sleep, especially in regions where stigma (relating to both HIV and mental health issues) remains a major barrier to seeking care. In settings where pharmacological interventions are available, common psychotropic medications prescribed to manage these conditions, such as antidepressants and anxiolytics, might also impact sleep. Substance and alcohol use can also contribute, through their direct effects on sleep or through their interaction with mental health and ART adherence. Given the complex interplay between mental health, stigma, and disordered sleep, a holistic approach that addresses all these factors is essential for improving sleep outcomes in people with HIV.

Chronic pain

Chronic pain, typically defined as lasting for more than 3–6 months,[66] is common among people with HIV, with rates as high as 83%,[67] compared with 34% in the general population.[68] Although no direct relationships have been reported between chronic pain and sleep as monitored by actigraphy in people with HIV,[69] self-reported sleep disturbances, including poorer sleep quality and insomnia symptoms, are associated with pain,[13,69,70] which might be explained by the immune dysregulation triggered by the HIV infection itself.[70] For instance, markers of inflammation, such as IL-6, remain elevated

in people with suppressed viral loads and are associated with increased pain sensitivity.[71] Emerging evidence highlights the complex interaction between CD4 cell counts, pain, and sleep quality, showing that higher CD4 counts are associated with poorer sleep quality, particularly in the absence of pain in people with HIV who had low CD4 counts when starting ART.[72] These findings underscore the importance of addressing pain and sleep disturbances in tandem and suggest that immunological recovery alone might not guarantee improved sleep quality in people with HIV.

Clinical management of disordered sleep in people with HIV

Disordered sleep in people with HIV combines manifestations of classical sleep disorders with atypical features related to HIV. Thus, a therapeutic approach beyond conventional sleep disorder treatments is likely required. This process can be complicated by the fact that HIV management and sleep disorder investigations tend to involve physicians with different types of expertise. The clinical strategies required to manage the substantial issues of both sleep disorders and disordered sleep might be distinct from those used in the general population, owing to the links between sleep symptoms, comorbidities, and ART. Sleep disorders, such as insomnia and OSA, are common yet often underdiagnosed and undertreated in people with HIV, suggesting a need for greater awareness among primary health care providers around the importance of treating poor sleep. Thus, tailored clinical pathways that account for the unique interplay of HIV-related factors are needed. An evaluation, published in 2024, of a multidimensional programme for insomnia in people with HIV showed improvements in sleep and overall wellness,[73] offering a promising model for holistic, context-specific care.

Disordered sleep cannot be addressed in isolation from broader social, economic, and cultural contexts. Globally, access to diagnostic tools and treatments for sleep disorders varies widely. Even in many high-income settings, access to advanced diagnostics and specialised sleep clinics is scarce. Substantial resource barriers, including minimal access to diagnostic equipment, trained specialists, and even basic sleep-health education, are common problems in both higher-income and lower-income countries. Sleep disturbances can be dismissed as a trivial concern, delaying diagnosis and intervention. In low-resource settings, improving sleep health among people with HIV requires pragmatic strategies that account for local health-care constraints, with formal diagnostic tools like actigraphy and polysomnography often being inaccessible due to cost, availability, or infrastructure limitations. In such contexts, validated screening tools, such as the Insomnia Severity Index and Pittsburgh Sleep Quality Index, can support initial clinical assessment. Where digital infrastructure exists, app-based or SMS-delivered cognitive behavioural therapy for insomnia can offer scalable solutions, particularly where trained therapists are scarce, provided that resources exist for an informed diagnosis and follow-up. Additionally, screening for sleep disturbances along with other comorbidities and integrating sleep-health education (panel 2) into existing HIV-care platforms can aid frontline health workers and reduce stigma around sleep complaints.

In most settings, people with HIV are not routinely screened for sleep issues, however primary care physicians can play an important role by routinely including sleep in discussions about lifestyle factors. Standardised screening tools, such as the Pittsburgh Sleep Quality Index (for disordered sleep), the Insomnia Severity Index (for insomnia), and the Berlin questionnaire (for OSA), are easy to administer and can help pinpoint individuals who might benefit from further evaluation or a sleep intervention. Other validated tools, including the Patient-Reported Outcomes Measurement Information System Sleep Disturbance and Sleep-Related Impairment questionnaires, can also be useful. Given the little evidence to recommend one screening tool over others in people with HIV, the choice should be based on practical considerations, including ease of administration and time availability. Physicians also require targeted training to recognise the unique sleep

Panel 2: Healthy sleep practices to be discussed with all patients with sleep complaints

- Keep regular bedtimes and wake times: irregularity leads to being exposed to light at a time when the body clock is very sensitive and can delay its timing and decrease the amplitude of the wake and sleep signals, resulting in frequent awakenings or difficulty maintaining sleep throughout the night
- Optimise light exposure (seeking out light in the morning and avoiding in the late evening): this helps keep the body clock aligned with Earth's light–dark cycle and have a strong amplitude of our circadian rhythms
- Get some form of physical activity every day, if possible around the same time of day: physical activity helps keep the body clock aligned with Earth's light–dark cycle (though this is less powerful than light exposure)
- Sleep environment: dim or dark, temperature controlled around 19°C, remove sources of noise—if not possible, use a source of white noise to cover the changes in noise levels (eg, a fan)
- Reduce alcohol consumption
- Do not watch screens at night: light emitted from screens delays the body clock and thus sleep timing and can result in sleeping at the wrong time with respect to one's body clock, making sleep more fragmented with a shorter sleep duration
- Do not consume stimulants (eg, nicotine and caffeinated drinks) after midday

challenges faced by people with HIV, including the sleep-related side-effects of commonly used ART regimens and the increased burden of mental health comorbidities. In health-care systems where referrals to sleep specialists are possible but restricted, primary care physicians need to be educated about and mindful of these specific vulnerabilities.

Clear clinical guidelines and collaborative care models can facilitate the integration between primary care and sleep specialists, ensuring that sleep disturbances are identified and managed through multidisciplinary clinical teams, considering clinical, lifestyle, and psychological factors. The clinical management of poor sleep can be conceptualised as a structured, stepwise pathway (figure 2), designed to help clinicians initiate and navigate sleep discussions, with emphasis on HIV-specific factors that should be assessed. As with other sleep complaint investigations, the first step is to rule out specific sleep disorders through screening and appropriate diagnostic pathways. Subsequent evaluations should focus on identifying other potential sleep disruptors that might be more complex and more important for people with HIV. Clinicians should adopt a treat and reassess approach, addressing modifiable contributors, such as chronic pain, depression, alcohol, recreational drugs, and suboptimal ART, before attributing sleep disturbances to a primary sleep disorder. However, where sleep problems persist after these factors have been addressed, the toolkit will essentially be the same as that for insomnia disorder. This stepwise pathway reflects the iterative and sometimes non-linear nature of real-world care, where clinicians might revisit earlier stages as new information arises or the individual's needs evolve. This stepwise approach captures the complexity of managing sleep disturbances in people with HIV. Although alternative decision-making models (such as the so-called decision blob, proposed by the French Sleep Research and Medicine Society[75]) offer useful perspectives, this stepwise approach was chosen for its relevance to the broader HIV-care context.

The standard first-line intervention for insomnia disorder is cognitive behavioural therapy for insomnia, which has minimal adverse effects and has shown efficacy, including in people with HIV.[76] However, the physiological consequences of HIV infection and side-effects of ART and concomitant medications might adversely affect sleep in ways where behavioural change might be insufficient, thus transcending the definition and potentially the standard treatment protocol of insomnia disorder. In some instances, sleep physicians

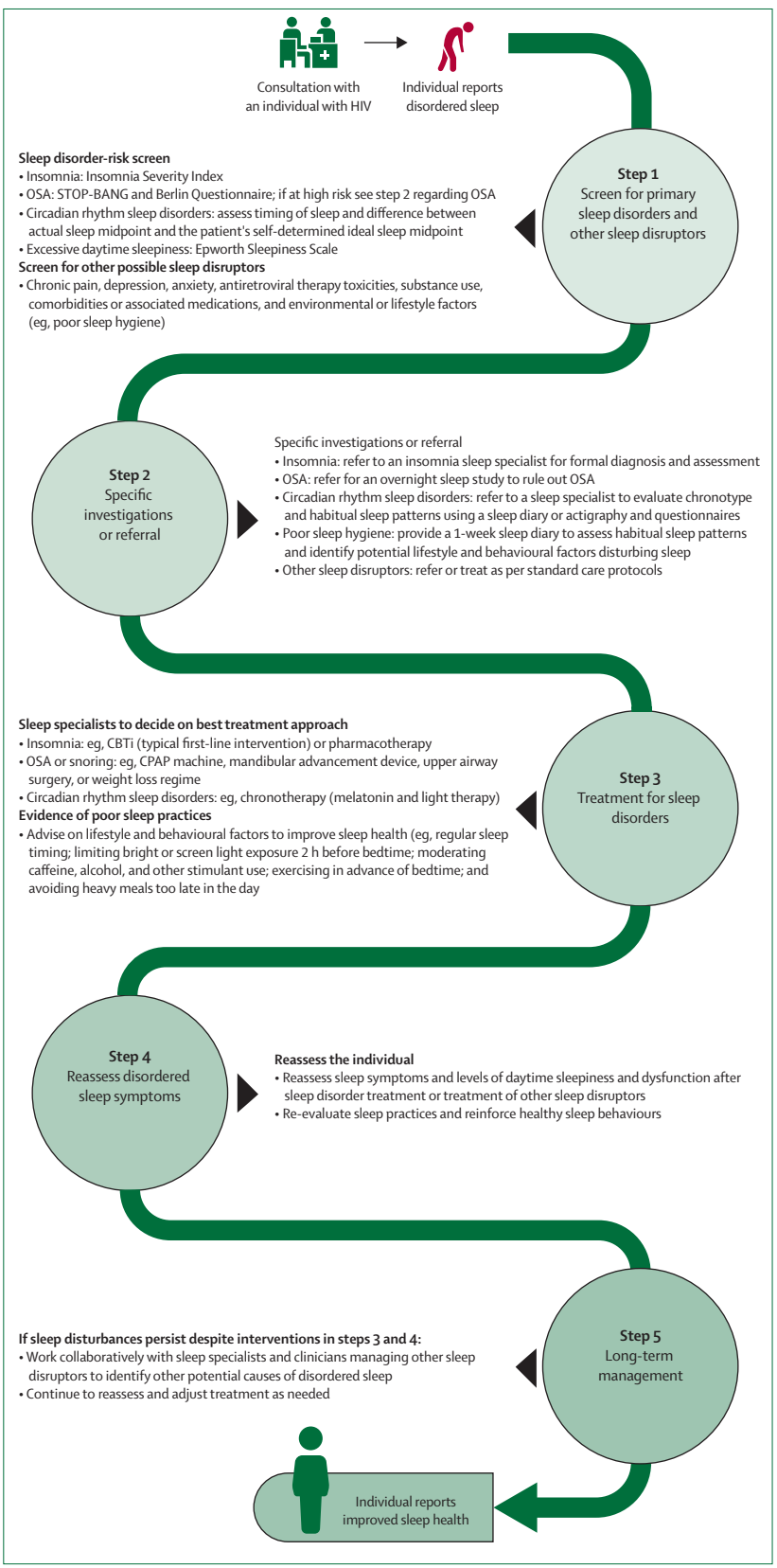

Figure 2: **Clinical decision-making for disordered sleep in people with HIV**
Sleep hygiene is defined as set of behavioural and environmental recommendations intended to promote healthy sleep.[74] CBTi=cognitive behavioural therapy for insomnia. CPAP=continuous positive airway pressure. OSA=obstructive sleep apnoea.

might consider pharmacological therapies to address insomnia symptoms.[77] Although dual orexin receptor antagonists[78] have shown promise, careful monitoring for potential drug–drug interactions with HIV-protease inhibitors is required.[79] Other options, such as zaleplon, have also been shown to improve symptoms of both insomnia and depression in people with HIV.[80] However, access to these medications can be scarce, particularly in resource-constrained settings. The efficacy and safety of long-term pharmacotherapy for insomnia in people with HIV, particularly when cognitive behavioural therapy for insomnia has failed, represents an important area for future research.

Finally, a delayed circadian phase, caused by physiological rather than environmental and lifestyle factors, has also been reported in people with HIV.[32] This circadian disruption potentially delays the time at which circadian physiology switches from the wake-promoting zone into the sleep-permitting zone, and can present as difficulties with sleep initiation when individuals attempt to sleep too early. In such cases, chronotherapy (which is based on carefully timed administration of light or melatonin) can offer promise, since limiting evening light exposure coupled with exogenous administration of melatonin in the early evening and exposure to light in the morning can advance circadian phase.[81]

Evidence gaps and considerations for research

Our understanding of sleep difficulties in people with HIV remains constrained by substantial evidence gaps, leading to frequent suboptimal management or even neglect of these challenges in clinical practice. A major challenge stems from the methodological heterogeneity across studies, particularly regarding sleep assessment tools. Many studies have relied predominantly on self-reported measures to assess sleep quality, which fail to classify disordered sleep into formal sleep disorders. This distinction is crucial, as it shapes both clinical decision-making and the development of appropriate evidence-based guidelines. The POPPY-Sleep substudy[48] and Multicenter AIDS Cohort study[23] highlight the importance of using both subjective and objective assessments to provide a more comprehensive understanding of disordered sleep, yet this dual approach remains underused. Future research should prioritise the development and validation of standardised assessment tools that integrate both self-reported and objective measures to better define and differentiate types of disordered sleep in people with HIV. Clearer differentiation is needed between primary insomnia and insomnia symptoms secondary to HIV-related factors. Frameworks that conceptualise sleep health along a continuum, rather than focusing solely on the presence of sleep disorders, could be valuable. Tools, such as RU-SATED[82] (which assesses regularity, satisfaction, alertness, timing, efficiency, and duration of sleep) and the Sleep Health Index,[83] offer broader perspectives on sleep health in the general population. However, these instruments have not yet been validated in people with HIV or in low-income and middle-income countries, such as South Africa where HIV prevalence is the highest worldwide. Further research should assess the relevance of sleep assessment tools, feasibility, and sensitivity to HIV-specific contributors in all settings.

Diagnosis of OSA is both important and straightforward for clinicians with access to sleep laboratories, however most clinicians do not have access to these laboratories. Therefore, developing and refining sensitive, practical tools to screen for OSA in people with HIV should be a research priority. Home-based sleep apnoea tests, which are commonly used in the general population and correlate well with polysomnography, show promise. Beyond OSA, many people with HIV report other forms of sleep disturbances that do not easily align with established diagnostic criteria, this reflects gaps in clinical and research frameworks and defines a research challenge of growing worldwide importance. With well-designed research protocols, it is feasible to disentangle how sleep problems in people with HIV relate to sleep architecture and circadian phase. Existing studies using these methodologies show promise for providing better mechanistic understanding of how HIV infection affects sleep. Further research is needed to investigate how HIV-specific immunological pathways impact sleep patterns and contribute to sleep disturbances. Additionally, given the lifelong use of ART, a clearer evidence base on how specific antiretroviral agents influence sleep and circadian physiology is required. This evidence should include pharmacological studies examining the impact of commonly used ART regimens on sleep health, and longitudinal studies assessing long-term sleep outcomes across different ART regimens. With the ongoing global de-diversification of ART regimes, comparative effectiveness studies and intervention trials are now more feasible and essential to determine whether modifying ART can improve sleep health without compromising HIV treatment efficacy.

These mechanistic studies will be able to inform the design of epidemiological studies of whether specific sleep interventions (eg, cognitive behavioural therapy for insomnia, sleep medication, chronotherapy, and modified administration of ARTs) can improve health and well-being, and ultimately life expectancy, in people with HIV both directly and by reducing comorbidities. This outcome would be consistent with the strong associations between disturbed sleep and circadian rhythms and non-communicable morbidity reported in the general population.[84]

Research should also prioritise populations often under-represented in research conducted in the northern hemisphere, including women and non-White populations, to ensure findings are applicable across diverse groups. Additionally, the roles of social

Search strategy and selection criteria

We searched PubMed and Web of Science from inception to Sept 13, 2024. Search terms included "Human Immunodeficiency Virus", "HIV*", "Sleep"[MeSH], "Insomnia", "Apnea" OR "Apnoea", "OSA", "Restless leg syndrome", "RLS", "RS", "Narcolepsy", "Circadian", "Parasomnia", "Risk factor*", "Associated factor*", "Predictor*", "Mechanisms", "Pathophysiology", "Etiology", "Aetiology", "Psychological", "Stress", "Mental health", "Anxiety*", "Depress*", "Fatigue*", "Inflamm*", "Immune activation", "Pain", "Antiretroviral therap*", "ART", "Socioeconomic", "Social", "Comorbid*", and "Neurodegenerat*". We also identified articles from reference lists of earlier reviews and through authors who have expertise in sleep health and/or HIV. Included studies were peer reviewed, published in English, assessed one or more sleep outcomes measured in adults (≥18 years) with HIV, measured sleep outcomes using subjective or objective measures, and reported factors associated with sleep outcomes during the study.

determinants, including stigma and socioeconomic status, on disordered sleep warrant further investigation to better understand and address disparities. Novel interventions targeting inflammation and circadian disruption could offer promising avenues for improving sleep health. As there is now an ageing population of people with HIV, addressing these evidence gaps will be imperative to developing targeted interventions that improve both sleep and overall health outcomes.

Contributors

This Review was designed and conducted by all authors. LS, KS, MvS, DER, and AW conceptualised the piece and drafted the initial version based on written and oral inputs from all authors. LS conducted the literature review. All authors reviewed the drafts and provided substantive feedback, with further revisions led by LS. KS, CAS, MvS, DER, and AW worked with LS to develop figures 1 and 2. All authors reviewed and approved the final version before submission. All authors had full access to the resources, materials, and information used in developing this work.

Declaration of interests

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