Sleep Disturbances in HIV Infection and their Biological Basis

Katie E. O'Brien[1], Natalie E. Riddell[1], F Xavier Gómez-Olivé[2, 3], Dale E. Rae[5], Karine Scheuermaier[5], Malcolm von Schantz[1 3 6]

[1]Faculty of Health and Medical Sciences, University of Surrey, Guildford GU2 7XH, UK

[2]MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), [3]School of Public Health, [4]School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[5]Division of Exercise Science and Sports Medicine, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

[6]Northumbria Centre for Sleep Research, Department of Psychology, Northumbria University, Newcastle-upon-Tyne, UK

Corresponding author :

Northumbria Centre for Sleep Research

Department of Psychology

Northumbria University

Newcastle-upon-Tyne NE1 8ST

UK

m.von.schantz@northumbria.ac.uk

Conflicts of interest

None

Acknowledgements

This work was supported by a Newton Fellowship from the Academy of Medical Sciences to FXGO and MvS

Summary

Antiretroviral therapy has significantly reduced morbidity and mortality in people living with HIV (PLWH). However, a direct consequence of higher survival is the development of ageing-related co-morbidities that have considerable potential to affect quality of life. Sleep disturbances in PLWH are a significant source of morbidity. A meta-analysis has estimated the prevalence of self-reported sleep disturbances in PLWH to be 58%, with commonly identified disturbances including insomnia, obstructive sleep apnoea and poor sleep quality. Not only do sleep disturbances impair daytime functioning, but chronic sleep disruption also associates with metabolic dysregulation and cardiometabolic disease. Therefore, an understanding of the pathogenesis of sleep disturbances in PLWH is important for reducing morbidity and improving quality of life. Several pathophysiological processes in HIV infection may cause sleep-wake dysregulation. In early infection stages, immunological changes such as expression of sleep-promoting cytokines could mediate sleep disturbances. Long term, chronic immune activation, in addition to side effects of antiretroviral therapy, may impact sleep homeostasis more severely, for example through increasing the risk of obstructive sleep apnoea. These sleep disturbances may further contribute to an inflammatory state, due to the bi-directional relationship between sleep and immunity. In summary, further elucidating the link between HIV, immune activation, and sleep is an underexplored avenue for minimising population morbidity and mortality.

Key words

AIDS; Antiretroviral treatment; Cellular immunity; Dopamine; Global health; Glutamate; HIV-associated neurocognitive disorders; Humoral immunity; Human immunodeficiency virus

Glossary of Terms

ANI	Asymptomatic neurocognitive impairment
ART	Antiretroviral therapy
CNS	Central nervous system
DA	Dopamine
DAT	Dopamine transporter
EFV	Efavirenz
EEG	Electroencephalography
HAD	HIV-associated dementia
HAND	HIV-associated neurocognitive disorder
HIV	Human immunodeficiency virus
IL-1 and -2	Interleukin 1 and 2
IFN	Interferon
MND	Mild neurocognitive disorder
MnPO	Median preoptic nucleus
NREM	Non-rapid eye movement
OSA	Obstructive sleep apnoea
PLWH	People living with HIV
PSG	Polysomnography
REM	Rapid eye movement
SNc	Substantia nigra pars compacta
SWS	Slow wave sleep
TAT	Transactivator of transcription
TNFα	Tumor necrosis factor alpha
VLPO	Ventrolateral preoptic nucleus

VTA	Ventral tegmental area

Introduction

With the development and implementation of anti-retroviral therapy (ART), the focus on human immunodeficiency virus (HIV) has shifted from patient survival to controlling ageing-related co-morbidities and improving quality of life. Sleep disturbances are a well-documented consequence of living with HIV, regardless of treatment status, although the effects of treatment do not invariably have a positive effect on sleep. A meta-analysis has estimated the prevalence of sleep disturbances in people living with HIV (PLWH) to be around 58% [1]. The types of sleep disturbances reported in PLWH are largely non-specific, manifesting as complaints of daytime fatigue and sleepiness in these individuals, as opposed to insomnia [2]. Where studies have been specific, commonly identified sleep disturbances in PLWH include insomnia, poor sleep quality, and obstructive sleep apnoea (OSA), which are associated with subsequent interference with daytime energy levels in PLWH [2].

Persistent sleep disturbances can have a significant impact on mental health, manifesting as debilitating fatigue, depression, anxiety, and cognitive impairment [3–5], as well as profound direct physiological consequences [6]. Extensive literature links long-term disturbed and mistimed sleep to metabolic diseases such as type 2 diabetes and cardiovascular disease [7], the pathophysiology of which is attenuated by the downstream metabolic effects of altered circadian rhythms [8]. In HIV specifically, poor sleep has been associated with medication regimes and disease progression [2]. Owing to PLWH having a high incidence of disordered sleep, it is logical to assume that their increased risk of developing co-morbidities may relate, at least in part, to the bi-directional relationship between sleep and inflammation [9]. This is highlighted by the evidence that PLWH have a two-fold increased risk for cardiometabolic syndrome, compared to HIV negative individuals [10]. This is thought to be driven by chronic inflammation, which has been linked to dyslipidaemia, hypertension and insulin resistance

[11]. This relationship also appears to be bi-directional, with dyslipidemia further contributing to the inflammatory profile [12]. Comorbidities not only impact quality of life for PLWH but contribute to population mortality.

Though the pathogenesis of sleep disturbances in PLWH is not well characterised, immune activation and the persistent inflammatory state as a consequence of HIV infection are thought to be key drivers [13]. This is based on an abundance of reports linking chronic inflammatory diseases, such as rheumatoid arthritis, with poor sleep quality [14]. To date, much of the research probing this relationship has focused on CD4+ T cell counts and viral load, which are markers of HIV disease progression *versus* efficiency of antiretroviral therapy (ART). Exploring more extensive immune parameters, in addition to exploration of objective sleep characteristics may further elucidate the relationship between sleep health and HIV. Understanding the mechanisms driving these sleep disturbances should be a priority in improving the quality of life of PLWH, as well as limit the development of co-morbidities driven by sleep disturbances. Given the high prevalence of sleep disturbances in PLWH, in the context of a modified immune background, we suggest that there could be aetiological mechanisms unique to HIV infection. However, current research is limited and results often conflicting. Therefore, this review intends to summarise current knowledge on how the immunopathology of HIV could provide a biological basis for sleep disturbances.

The Immune Response to HIV – Implications for Sleep Physiology

HIV is a retrovirus that induces an immune deficiency by infection and depletion of CD4+ T lymphocytes through persistent viral replication, eventually progressing to acquired immunodeficiency syndrome (AIDS), if untreated. The acute infection phase generally manifests as non-specific viral infection symptoms, including fatigue, fever, headaches, and

chills [15]. Generally, in acute viral infections, immune activation is a necessary and temporary response in order to eliminate infection and build immunity. However, in chronic infections such as HIV, persistent immune activation does not eliminate the virus and can in itself be pathological, likely contributing to the disease state [16]. One notable aspect of this is that the immune response in both the acute and chronic infection stages have the potential to disrupt sleep homeostasis, due to the role of cytokines in the modulation of sleep physiology [17].

Acute Immune Response and Sleep Disruption in HIV

Though there is no existing literature which describes sleep in the acute phase of HIV infection, we can hypothesise that sleep will be disturbed based on the well-established relationship between sleep and the acute phase response to infection. As with any acute infection, symptoms such as fever and lethargy are thought to be adaptive responses of the central nervous system (CNS), to reduce behavioural activity in order to conserve energy for the immune response to infection and limit spread of an infection within a population. One of the earliest cytokines produced in the acute phase response to any infectious disease is interleukin-1 (IL-1), which promotes the onset of fever [18]. Specifically in HIV, IL-1 is implicated in a positive feedback loop of CD4+ T cell programmed cell death in lymphatic tissues [19]. In sleep-wake physiology, IL-1 is one of the most well studied cytokines with sleep regulatory properties. In healthy individuals, IL-1 increases non-rapid eye movement (NREM) sleep, marked by increased electroencephalographic (EEG) delta power, which is indicative of greater sleep intensity [20]. Similar effects have been noted in the study of sleep in other acute infectious diseases. For example, increased levels of IL-1 in influenza are associated with increased NREM sleep duration, but also more fragmented NREM sleep [21]. During NREM sleep, body temperature naturally drops, and therefore the fragmentation of NREM sleep may serve a specific physiological purpose in the form of maintaining a fever state [22]. However, the

primary link between a fever and sleep fragmentation is likely due to the fact that cytokines involved in initiation and maintenance of a fever, such as IL-1, also affect sleep homeostasis when pathologically or artificially elevated. Whilst this response is generally beneficial in the acute stages of disease, chronic maintenance of NREM fragmentation may result in nocturnal awakenings, impaired long-term memory consolidation, and daytime fatigue [23,24].

In addition to IL-1, tumour necrosis factor alpha (TNFα) is a prominent pyrogenic (fever-promoting) inflammatory cytokine produced by macrophages and T cells in response to HIV infection, and remains elevated through all stages of infection [16]. Importantly, TNFα is a key factor mediating HIV entry to the CNS, through increasing permeability of the blood-brain barrier, and by upregulating expression of adhesion molecules, which facilitate migration of infected macrophages and monocytes into the CNS [25]. Like IL-1, TNFα is classed as a sleep regulatory molecule [17]. Animal studies have demonstrated a dose-dependent response to TNFα on sleep, with lower relative levels leading to a quantitative increase in both NREM sleep and slow-wave sleep (SWS) [26,27]. As the dose increases, NREM sleep continues to increase at the expense of rapid eye movement (REM) sleep. Although TNFα and IL-1 are the only cytokines to be classified as sleep regulatory substances [17], several other cytokines are implicated in the modulation of sleep, for example IL-2, which plays a major role in the induction of T cell proliferation [28]. Lower than normal T cell expression of IL-2 has been demonstrated to be one of the first major immunological changes in HIV, with this reduced expression being predictive of loss of CD4+ T cells [29]. IL-2 also has somnogenic effects, with intracerebral administration of IL-2 increasing NREM sleep in a dose dependent manner [30].

Finally, activity of type I interferons (IFNs) may also have an effect on sleep homeostasis. Plasma IFNα increases in the acute stages of an infection such as HIV, stimulating the

expression of restriction factors which limit HIV replication [31]. However, following seroconversion, IFNs may facilitate chronic immune activation due to stimulating T cell activity. Plasma concentrations of IFNs predict impaired recovery of CD4+ T cell populations, in addition to limiting antigen specific T cell responses and induction of CD4+ T cell apoptosis [32]. INFα has also been shown to disrupt sleep in a clinical setting. Side effects of the administration of IFNα, previously used in the treatment of hepatitis C, were significantly increased wake after sleep onset, in addition to a reduction in the efficiency of SWS and increased REM latency. These alterations to sleep architecture were significantly associated with increased daytime fatigue and impaired motor speed [33].

Chronic Untreated HIV – The Bi-directional Relationship between Sleep and Inflammation

Despite the progress in reducing the global burden of HIV, of the estimated 81% of PLWH aware of their status, only 67% have access to treatment [34]. This means that for a significant proportion of PLWH, gradual depletion of CD4+ T cells leads to AIDS. In spite of the rapid progression of AIDS, even delayed treatment can minimise adverse health outcomes. Though sleep disturbances may seem like an insignificant problem when considering the range and significance of co-morbidities associated with untreated HIV, the established bi-directional link between sleep and immune function remains a consideration.

In HIV and progression to AIDS, loss of CD4+ T cells increases vulnerability to opportunistic infection, and therefore increases the risk of an adverse outcome. Disease progression may be accelerated by poor sleep, due to the previously discussed bi-directional relationship between sleep, the acute infection response and pathological immune activation [35]. Additionally, chronic sleep deprivation in rats has been shown to increase commensal bacterial translocation [36,37]. In the context of HIV, such translocation would further fuel innate immune activation.

Moreover, experimental studies in animals and humans have demonstrated that manipulation of sleep, such as sleep deprivation and restriction, modulates a number of immunological parameters, including leukocyte migration and proliferation [38,39]. Specifically, it has been demonstrated that regulatory T cell suppression of CD4+ effector activity was impaired by total sleep deprivation in healthy young adults [38]. Ultimately, this evidence suggests that a chronic inflammatory disease such as HIV would result in a positive feedback loop of inflammation and disturbed sleep. Whilst initiation of ART would allow for recovery of T cell populations and reduce T cell activation, insomnia would increase inflammation in PLWH and lead to higher inappropriate immune activation. Though there is a lack of research on the state of sleep in untreated HIV, one large South African study found an associated two-fold increase between daytime dysfunction and mortality in men, following multivariate adjustment. This may be due to undiagnosed and untreated HIV, due to the high prevalence in the overall population, and the fact that men are more likely to have undiagnosed chronic conditions in a similar setting, compared to women [40].

Chronic Treated HIV, Inflammation and Sleep

It is established that CD4+ T cell depletion, chronic immune activation, and inflammation are the driving forces of HIV pathogenesis, with ART implementation preventing the loss of CD4+ T cells and preserving immune function. However, despite near normal life expectancy with successful treatment, PLWH have an increased risk of multiple diseases in comparison to people without HIV, such as cardiovascular disease and type 2 diabetes [7]. A possible contributor to this is immune activation, which is primarily characterised by increased levels of activation markers HLA-DR, CD25, CD38, in addition to the proliferation marker protein Ki-67, for both CD4+ and CD8+ T cells [16]. Paradoxically, persistent T cell activation

correlates with disease progression and is predictive of a poor prognosis, regardless of treatment status [41]. Though the cause of chronic immune activation is not fully understood, it is thought to be due to both direct and indirect viral effects, initially driven by CD4+ T cell depletion and the cellular and humoral antiviral immune response, and subsequently by rebound of T cell populations following induction of ART [42]. Chronic immune activation is reflected by the persistent altered immunological profile despite treatment. One study found that the plasma cytokine profile of patients on second-line ART, a regimen used in the instance that first-line therapy fails, was comparable to untreated PLWH, even when controlled for viral load and CD4+ T cell count [43]. Of note, serum IL-6 and TNFα were elevated in both groups. Since TNFα is a key sleep regulator, persistently elevated levels potentially alter the proportion of NREM sleep a person experiences, at the expense of REM sleep [44].

The elevated IL-6 noted in second-line treatment for HIV as well as untreated PLWH may be of specific importance in the pathogenesis of sleep disorders. In healthy individuals, the role of IL-6 in sleep-wake maintenance is debated. Some animal studies suggest that whilst IL-6 causes biphasic alterations in REM sleep, antagonising the IL-6 system with IL-6 antibodies does not alter sleep [45]. However, there is clear evidence that several sleep disorders are associated with elevated systemic levels of IL-6, including chronic insomnia and OSA [46–48]. Moreover, sustained elevation of IL-6 has been linked to increased morbidity in several inflammatory diseases, and has been continuously associated with increased mortality and morbidity in HIV despite treatment compliance [49]. This suggests that IL-6 may play a more significant role in sleep when IL-6 expression is elevated in pathological states, which is supported in the literature [50]. Based on this, further exploration of the role of IL-6 in the pathogenesis of sleep disorders in HIV is warranted, due to its known associations with OSA and insomnia.

The chronic immune activation hypothesis of sleep disturbances in HIV is further supported by a study in a sub-Saharan African population. With higher CD4+ counts, as well as a greater rebound in CD4+ counts from a low baseline, sleep quality as measured by the Pittsburgh Sleep Quality Index (PSQI) worsened in participants [13]. The authors hypothesised that this finding is explained by underlying immune activation, and recovery of T cell populations could result in heightened immune activity and inflammation. Importantly, these findings highlight that the effects of ART on sleep quality in HIV are also indirect and paradoxically driven by improved cellular immune function.

The results of this study conflict with the findings of other studies which either report no relationship between CD4+ count and sleep quality [51,52], with other studies noting that with treatment initiation and improving CD4+ counts, reported sleep quality increases [53]. This makes theoretical sense, as one would assume that improving the health status of a person with HIV would reduce associated symptoms such as disturbed sleep. However, sleep disturbances are highly prevalent in HIV regardless of treatment status [13], suggesting that HIV infection and ART may independently and cumulatively contribute to the pathogenesis of sleep disturbances in HIV. The conflicting nature of these studies may also be explained by the varying ancestry of the participants, with studies including participants of African American, Caribbean, Nigerian and South-African descent. In addition to potential socioeconomic factors being a confounder for study comparison, variation in genetic factors, immunogen history and access to healthcare may impact study outcomes. Additionally, there are several infectious diseases endemic in the Southern but not the Northern hemisphere, such as tuberculosis. Co-infection may affect the extent of immune activation in study participants. Viral load and CD4+ count are standard primary markers of HIV progression and treatment response, but may not provide a full picture of an individual's immune health. Including cytokine panels and assessing markers of immune activation may provide a more robust immunological profile.

Summary

The immunological response to both the acute and chronic phases of HIV infection alters sleep physiology. ART attenuates, but does not entirely abolish these responses, and causes sleep problems associated with the rebound of cellular immunity. In the acute phase, these disturbances are likely driven by the pyrexic response to the virus, with increased but fragmented NREM sleep. However, it is the effect of the chronic immunological response which likely has the biggest impact on quality of life. In summary, we can hypothesise that elevated levels of IL-1, TNFα, IL-6 and IFNα due to chronic immune activation contribute to the pathophysiology of insomnia and OSA in PLWH.

HIV and the Central Nervous System

Prior to the implementation of ART, degeneration and diseases of the CNS were highly prevalent in PLWH, and were a major contributor to population mortality [55]. Specifically, HIV facilitated invasive opportunistic infections of the brain leading to meningitis, tumour growth and encephalitis as HIV progresses into AIDS [55]. According to the EuroSIDA cohort study, the incidence of CNS diseases in people with HIV decreased by 40% per calendar year between 1994 and 2002 [55]. This reduction in CNS disease was associated with improved immunological status and suppressed viral replication as a result of ART. For untreated PLWH, these factors remain prominent drivers of morbidity and mortality [56].

Despite the falling incidence of fatal CNS diseases in the era of ART, HIV-associated neurocognitive disorders (HAND), remain a prominent feature of ageing with HIV [57]. HAND is an umbrella term which encompasses diseases of growing severity including

asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD). Whilst the incidence of the most severe forms has fallen, prevalence of milder neurocognitive impairments remains comparable to the pre-ART era [58]. Current studies have consistently placed low CD4+ T cell nadir to be the primary risk factor in the development of HAND during the era of ART, which is linked to poor adherence to ART regimens [59]. This suggests that PLWH who are not receiving treatment, and those who have delayed ART initiation carry the greatest risk of developing HAND.

Pathogenesis of HAND – Implications for Sleep Homeostasis

HIV infects the CNS within the first few weeks of peripheral infection, due to migration of infected monocytes across the blood brain barrier [60]. In the CNS, HIV creates a chronic inflammatory environment due to the secretion of inflammatory mediators from infected monocytes and activated glial cells, such as TNFα, IL-6 and IL-1. Moreover, HIV glycoproteins 120 (gp120), 41 (gp41) and transactivator of transcription (TAT) protein have neurotoxic effects [61]. Inflammatory mediators and HIV associated-proteins contribute to neuronal injury and apoptosis through two main mechanisms: i) a persistent inflammatory response due to activation of infected macrophages and microglia; and ii) glutamate-mediated excitotoxicity [35]. Since extensive neurodegeneration and encephalitis has been minimised due to ART, neurological impairment observed today more likely stems from immune activation in the CNS, altering neuronal function [57]. This persistent inflammatory state in the CNS, coupled with altered neuronal function, could have negative implications for sleep-wake physiology.

Sleep and Cognition – Role of Dopamine

One of the most well documented effects of HIV neurotoxicity in the pathogenesis of HAND is altered dopaminergic signalling due to the propensity of the virus to target the subcortical brain regions [62], specifically the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA). The implementation of ART has decreased the neuropathology and associated clinical manifestations caused by HIV infection. However, notable damage to the subcortical regions of the brain has still been reported despite adherence to ART regimens. This damage manifests as motor dysfunction in older PLWH at greater levels than expected in normal ageing [63]. The physiological significance of these findings is reflected in the report of lower levels of dopamine in the cerebrospinal fluid of PLWH who receive ART [64]. It has been suggested that lower dopamine availability correlates with cognitive impairment in HIV, specifically in the domains of memory, learning and speed of information processing [65]. This would be consistent with the clinical profile of Parkinson's disease (PD), the pathogenesis of which is also associated with degeneration of dopaminergic brain regions. Indeed, a study comparing cognitive and motor deficits in PLWH and adults with PD reported that HIV and PD groups presented with similar deficits in executive function, episodic memory and visual processing, with motor deficits mainly manifesting in PD and not HIV [66].

The impact of HIV on dopaminergic signalling, independent of ART, has potential consequences for sleep homeostasis. Dopamine rich brain regions targeted by HIV are also implicated in initiating and maintaining wakefulness through the sleep regulatory network [57]. Dopaminergic signalling enhances wakefulness and suppresses SWS, as thalamocortical arousal state is modulated by both mesostriatal and mesothalamic dopaminergic pathways [67]. At a receptor level, it has been determined that D1 receptor agonists increase behavioural arousal, translating into increased wakefulness and reduction in the amount of SWS and REM sleep [67]. Additionally, D2 receptor agonists have biphasic effects. At low doses, targeting D2 receptors reduces wake and increases SWS and REM sleep, whereas high doses confer the

opposite effect. Though limited, there is evidence for impaired dopaminergic modulation of wakefulness in HIV, with a study demonstrating that lower urinary dopamine levels directly correlated with self-reported poor sleep quality [68]. This would make sense in the context of the common clinical profile in HIV, which describes insomnia and unrefreshing sleep, resulting in daytime fatigue. Furthermore, reduced behavioural arousal associated with depleted dopamine could also provide a biological basis for the persistent fatigue often experienced in this population.

Though the literature implies a cause and effect relationship between cognitive impairment and sleep disturbances in HIV, it is important to also note the well-established impact of insomnia or sleep loss on cognition in otherwise healthy people, with sleep loss being consistently linked to impaired cognition, in a dose dependent manner [69]. Since sleep disturbances facilitate a persistent inflammatory environment in the CNS, any sleep disturbance could also exacerbate cognitive impairment experienced by people with HAND and contribute to associated disruption of dopaminergic neural pathways. Based on this bi-directional relationship, sleep disturbances such as insomnia should not be treated only as a symptom, but also a risk factor in the progression of HAND.

Glutamate and Sleep

HIV is also associated with altered brain glutamate metabolism, attributed to glutamate-mediated excitotoxicity due to the action of pro-inflammatory cytokines and HIV associated proteins on neurones [70]. Despite being one of the most prominent alterations to CNS metabolism, the clinical consequences of dysregulated glutaminergic signalling in the context of sleep and HIV are largely unexplored. The consequences of disrupted glutamate homeostasis include neuronal injury and lower intracellular glutamate availability, the clinical

consequences of which are reflected by the association between cognitive impairments in HIV and lower brain glutamate availability [71]. Glutaminergic signalling is also implicated in a number of sleep-wake regulatory mechanisms. Whilst wakefulness is primarily driven by dopaminergic signalling in the ascending reticular activation system, the onset of NREM is mediated by increased glutaminergic activity in the ventrolateral preoptic nucleus (VLPO) and median preoptic nucleus (MnPO), which in turn have inhibitory projections to the brainstem and arousal centres in the hypothalamus [72]. The interaction between these brain regions to allow rapid transition between the sleep and waking states is referred to as the hypothalamic sleep switch, designed to ensure behavioural state stability. However, damage to these systems can impair the inhibitory feedback required to maintain bistability. For example, VLPO degeneration attributed to ageing is associated with sleep fragmentation and increased frequency of daytime naps [73]. Based on this limited evidence, further studies should aim to confirm whether lower glutamate availability is also associated with insomnia, poor sleep quality and daytime sleepiness in HIV.

Summary

The risk of developing HAND has been reduced due to the wide implementation of ART. However, asymptomatic and mild cognitive impairments are still prevalent in PLWH, suggesting that CNS damage may begin prior to the initiation of ART. As described in Figure 1, the pathogenesis of neurocognitive disorders in HIV is linked to disrupted dopaminergic signalling due to the propensity of the virus to target the subcortical brain regions. The disrupted dopaminergic signalling also has implications for sleep homeostasis and arousal, due to reduced signalling in the ascending reticular activation system, manifesting as persistent fatigue and disturbed sleep. Additionally, disrupted glutaminergic signalling may impair signalling associated with the hypothalamic sleep switch. Due to the bi-directional relationship

between sleep and inflammation, poor sleep may also exacerbate cognitive dysfunction in people living with HIV and facilitate the pathogenesis of HAND. The local sleep dysregulation model proposed by Buysse and colleagues could describe the occurrence and heterogeneity of sleep disturbances in people with HIV [74]. The model proposes that insomnia occurs as a result of competing region-specific wake-like and sleep-like neuronal activity patterns, due to altered signalling in arousal and sleep promoting systems.

Figure 1: **Theoretical basis for sleep disturbances in HIV.** The disease progresses in parallel in the periphery and the central nervous system (CNS), with blue boxes denoting mechanisms and pink boxes denoting sleep disturbances. The acute peripheral response to the virus results in expression of inflammatory cytokines such as interleukin 1 (IL-1) and tumour necrosis factor alpha ($TNF\alpha$), which are also sleep regulatory substances. As the inflammation becomes chronic, the severity of sleep disturbances increases, and also facilitates the onset of obstructive sleep apnoea (OSA). In the CNS, the initial immune response to HIV would mirror the acute immune response in the periphery; however, as the CNS infection progresses, chronic inflammation would result in dysregulation of glutamate (GLU) metabolism and dopaminergic transmission, in turn resulting in reduced behavioural arousal and impacting the bistability of the sleep switch. Without antiretroviral therapy, chronic neurotoxicity eventually causes neurodegeneration and heavily impaired dopaminergic activity (DA). This will impact the sleep regulatory properties of the ascending reticular activation system, manifesting as impaired rapid eye movement (REM) and slow wave sleep (SWS) quality, and reduced behavioural arousal (Created using biorender.com).

Sleep and Anti-Retroviral Treatments

In addition to the immunopathological effects of HIV on sleep, we must also consider the pharmacological effects of ART. Treatment regimens typically combine two nucleoside

reverse transcriptase inhibitors with a third drug which is either an integrase inhibitor, non-nucleoside reverse transcriptase inhibitor, or a protease inhibitor [75]. Regimens are amended based on tolerability and drug efficacy, as reflected by viral load and changes in CD4+ cell count. Sleep disturbances are a well-established adverse effect of ART initiation [76] — specifically, abnormal dreams, night terrors, insomnia and daytime sleepiness. Of the drugs used as part of the first-line treatment regimen [77], efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor, is the one most commonly associated with disturbed sleep [78,79]. Genetic factors may also influence the severity of side effects. For example, a polymorphism of the liver enzyme CYP2B6 affects the metabolism of efavirenz, increasing the likelihood of poor sleep quality and insomnia [54].

Several studies have investigated the effects of EFV on sleep architecture, as measured by polysomnography (PSG). One study identified a subgroup of EFV treated HIV patients who did not have a history of a sleep disorder [76]. After psychometric evaluation, 13 of the 18 patients were diagnosed with insomnia. Exploration of sleep architecture in these individuals revealed that they had decreased sleep efficiency compared to HIV negative individuals and EFV treated individuals without clinical insomnia. However, EFV-treated participants showed a decrease in both REM and N3 sleep, regardless of whether they reported having insomnia. This finding supports the hypothesis that the hepatic cytochrome P450 2B6 polymorphism which results in slower metabolism and elimination of EFV [78], may also be associated with variation in EFV-related insomnia symptoms. A later study examined the effects of EFV on sleep in HIV negative participants, to remove the confounding factor of HIV infection [80]. The study design consisted of a 3-day placebo period, followed by either seven days of EFV or continuation of the placebo. Interestingly, the results revealed an increase in NREM without sacrificing REM duration in the EFV group, which is the opposite result of studies in HIV positive participants. To investigate this result further, spectral analyses were performed and

revealed that EFV reduced sigma power during NREM sleep, as well as sleep spindles. These observations correlated with daytime sleepiness and impairments in attentional performance. However, major side effects of ART, including insomnia, generally resolve within three months of treatment initiation [78]. Though switching from EFV to rilpivirine has been shown to improve self-reported sleep quality [81], a further study noted that despite switching regimens, sleep abnormalities persist in PLWH who have cognitive impairment [82]. This suggests that ART may not play a major role in long-term sleep disturbances in PLWH, with the effects more likely indirectly attributed to the inflammation associated with ART, and the infection itself altering sleep independent of treatment.

HIV and Sleep Disordered Breathing

Of the several noted sleep disorders associated with HIV infection, one that has particular significance is obstructive sleep apnoea (OSA)[83], the downstream pathophysiology of which makes it one of the most clinically relevant sleep disorders in PLWH. OSA arises due to obstruction or collapsing of the upper airway during sleep, resulting in recurrent hypoxemia and frequent awakenings. HIV infection and older ART regimens have both been independently associated with an increased risk of OSA due to metabolic changes such as lipodystrophy, insulin resistance and hyperlipidaemia, in addition to systemic immune activation [84]. Metabolic changes are linked to increased adiposity in the upper abdomen and neck, which can impact upper airway integrity during sleep [84]. Metabolic dysfunction directly attributed to HIV is associated with a persistent inflammatory environment in adipose tissue due to chemotaxis of activated macrophages, resulting in adipose dysfunction. In HIV negative individuals, secretion and increased circulation of inflammatory markers from adipose tissue, such as TNFα and IL-1, has been associated with impaired upper airway neuromuscular control [85]. This effect also appears to occur independently of metabolic dysfunction. A study

involving untreated HIV positive men demonstrated that the typical sleep disordered breathing metrics of body mass index (BMI), waist and neck circumference were predictive of OSA in HIV negative men and treated HIV positive men. However, they did not accurately predict OSA in untreated individuals with HIV [86], suggesting that whilst dyslipidaemia does occur in untreated HIV, systemic immune activation is most likely driving OSA pathogenesis (as opposed to metabolic dysfunction). Additionally, this suggests that the standard diagnostic criteria for OSA may result in missed diagnosis of OSA in PLWH. The role of immune activation in OSA pathogenesis was further supported by a later study, which reported that elevated circulating levels of TNFα was associated with moderate to severe OSA, only in untreated HIV positive men compared to treated people with HIV [87].

The day-to-day consequences of OSA include poor sleep quality and daytime fatigue, which can significantly impact quality of life. Long term, OSA is a substantial risk factor for the development of cardiovascular disease, often multiplied by the same underlying risk factors [88]. Despite this, OSA remains largely undiagnosed and untreated in PLWH [83]. Since PLWH already have an increased incidence of cardiovascular disease and cardiac events [89], identifying and treating OSA could reduce the risk of developing cardiovascular disease . Clinicians should be aware that traditional risk factors for OSA such as obesity, may not be present in PLWH, suggesting the need to modify screening criteria in order to accurately diagnose OSA in PLWH. Importantly, treatment of OSA with continuous positive airway pressure is one of the few sleep medicine interventions which directly targets the underlying cause of the disorder. Based on this, monitoring for OSA should be routine in HIV primary care, as it could significantly reduce population morbidity and mortality.

Conclusions

In summary, HIV can disrupt sleep homeostasis through two main mechanisms: the direct effects of the immunological response to the virus, and the indirect neurotoxic effects as a consequence of the immunopathological response in the CNS. In the early stages of infection, sleep disturbances are likely driven by the acute immunological response to the virus, resulting in longer sleep duration, but with more fragmented sleep and daytime fatigue. Following seroconversion, persistent expression of sleep regulatory and modulatory cytokines due to immune activation may interfere with homeostatic sleep regulation. This may result in the onset of a range of sleep disturbances, including insomnia, OSA and poor sleep quality. Whilst ART has been successful in attenuating these and other effects of HIV infection, the rebound of CD4+ counts with successful implementation of ART may also contribute to the persistent immune activation observed in PLWH. This immunological environment appears to facilitate the development of OSA, which in turn multiplies risk for further comorbidities. Additionally, sustained immune activity in the CNS may result in dysfunction of dopaminergic neurones, and impede glutamate metabolism. This may manifest as reduced behavioural arousal, in conjunction with impaired sleep due to altered glutamate activity in the hypothalamic sleep switch. Poorly controlled and untreated HIV can ultimately lead to significant neurodegeneration. Neurodegeneration of areas involved in the homeostatic regulation of sleep could result in disruption of sleep-wake physiology, with evidence to suggest that disturbed sleep precedes cognitive symptoms of HAND. Based on this, clinical sleep medicine should play a more integral role in the management of HIV. For PLWH on ART, pharmacological management of insomnia and associated sleep disorders should be approached cautiously due to potential drug interactions and risk of dependence [78]. Non-pharmacological approaches such as implementing sleep hygiene routines may be of benefit to patients. Moreover, simply communicating the importance of sleep health to PLWH may encourage patients to discuss sleep disturbances with their primary care providers, and in turn improve the diagnosis and treatment of sleep disorders in PLWH.

Sleep disturbances in HIV can be debilitating and can significantly affect quality of life. Whilst this review examines possible aetiology, it remains largely theoretical. Due to the public health significance outlined and the increased life expectancy of HIV patients, further research on the effects of chronic immune activation on sleep-wake physiology in PLWH is imperative.

Practice Points

1. The successful treatment of HIV has resulted in an increased number of people living with HIV with a potentially normal life expectancy, but also presenting with more ageing-related co-morbidities.
2. Sleep disturbances are a significant source of morbidity in PLWH, with the ability to impact daytime functioning and quality of life.
3. Successful ART, particularly in patients with low pre-treatment CD4 counts, may paradoxically worsen sleep disturbances through cellular immune activation, which may warrant symptomatic treatment
4. Interventions to reduce co-morbid systemic inflammation in people living with HIV, such as screening and treatment of OSA, may significantly improve quality of life and reduce population morbidity and mortality, and minimise neurological impairment.

Research Agenda

1. Longitudinal collection of immunological markers, in conjunction with longitudinal sleep measures.

2. Longitudinal magnetic resonance imaging studies, to understand precise neural networks impacted by HIV-associated neurodegeneration, in conjunction with collection of immunological markers and longitudinal sleep data.
3. Intervention studies aiming to reduce sleep disturbances, including insomnia and OSA. This may include behavioural and pharmacological approaches.
4. Assess the effects of intervention studies on HIV disease progression and immune activation, as measured by immunological markers such as IL-1ß, TNFα, and IL-6. This should also be a priority area for discovery of immunological and other biomarkers.

References

[1] ***Wu J, Wu H, Lu C, Guo L, Li P. Self-reported sleep disturbances in HIV-infected people: A meta-analysis of prevalence and moderators. Sleep Med 2015;16:901–7. https://doi.org/10.1016/j.sleep.2015.03.027.**

[2] Lee KA, Gay C, Portillo CJ, Coggins T, Davis H, Pullinger CR, et al. Types of sleep problems in adults living with HIV/AIDS. J Clin Sleep Med 2012;8:67–75. https://doi.org/10.5664/jcsm.1666.

[3] Cukrowicz KC, Otamendi A, Pinto JY, Bernert RA, Krakow B, Joiner TE. The impact of insomnia and sleep disturbances on depression and suicidality. Dreaming 2006;16:1–10. https://doi.org/10.1037/1053-0797.16.1.1.

[4] Fortier-Brochu É, Morin CM. Cognitive Impairment in Individuals with Insomnia: Clinical Significance and Correlates. Sleep 2014;37:1787–98. https://doi.org/10.5665/sleep.4172.

[5] Rogers BG, Lee JS, Bainter SA, Bedoya CA, Pinkston M, Safren SA. A multilevel examination of sleep, depression, and quality of life in people living with HIV/AIDS. J Health Psychol 2020;25:1556–66. https://doi.org/10.1177/1359105318765632.

[6] James SM, Honn KA, Gaddameedhi S, Van Dongen HPA. Shift Work: Disrupted Circadian Rhythms and Sleep—Implications for Health and Well-being. Curr Sleep Med Reports 2017;3:104–12. https://doi.org/10.1007/s40675-017-0071-6.

[7] Lucassen EA, Rother KI, Cizza G. Interacting epidemics? Sleep curtailment, insulin resistance, and obesity. Ann N Y Acad Sci 2012;1264:110–34. https://doi.org/10.1111/j.1749-6632.2012.06655.x.

[8] Cappuccio FP, Miller MA. Sleep and Cardio-Metabolic Disease. Curr Cardiol Rep 2017;19:1–9. https://doi.org/10.1007/s11886-017-0916-0.

[9] Opp MR, Baracchi F. Sleep and immune function. Curr Adv Sleep Biol 2009;32:15–

39.

[10] Woldu M, Minzi O, Engidawork E. Prevalence of cardiometabolic syndrome in HIV-infected persons: a systematic review. J Diabetes Metab Disord 2020;19:1671–83. https://doi.org/10.1007/s40200-020-00552-x.

[11] Galescu O, Bhangoo A, Ten S. Insulin resistance, lipodystrophy and cardiometabolic syndrome in HIV/AIDS. Rev Endocr Metab Disord 2013;14:133–40. https://doi.org/10.1007/s11154-013-9247-7.

[12] Esteve E, Ricart W, Fernández-Real JM. Dyslipidemia and inflammation: An evolutionary conserved mechanism. Clin Nutr 2005. https://doi.org/10.1016/j.clnu.2004.08.004.

[13] ***Redman KN, Karstaedt AS, Scheuermaier K. Increased CD4 counts, pain and depression are correlates of lower sleep quality in treated HIV positive patients with low baseline CD4 counts. Brain Behav Immun 2018;69:548–55. https://doi.org/10.1016/j.bbi.2018.02.002.**

[14] Irwin MR. Sleep and inflammation: partners in sickness and in health. Nat Rev Immunol 2019;19:702–15. https://doi.org/10.1038/s41577-019-0190-z.

[15] Simon V, Ho DD, Abdool Karim Q. HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. Lancet 2006;368:489–504. https://doi.org/10.1016/S0140-6736(06)69157-5.

[16] Paiardini M, Müller-Trutwin M. HIV-associated chronic immune activation. Immunol Rev 2013;254:78–101. https://doi.org/10.1111/imr.12079.

[17] Krueger J. The Role of Cytokines in Sleep Regulation. Curr Pharm Des 2008;14:3408–16. https://doi.org/10.2174/138161208786549281.

[18] Opp MR, Krueger JM. Interleukin 1-receptor antagonist blocks interleukin 1-induced sleep and fever. Am J Physiol - Regul Integr Comp Physiol 1991;260:453–7. https://doi.org/10.1152/ajpregu.1991.260.2.r453.

[19] Doitsh G, Galloway NLK, Geng X, Yang Z, Monroe KM, Zepeda O, et al. Cell death by pyroptosis drives CD4 T-cell depletion in HIV-1 infection. Nature 2014;505:509–14. https://doi.org/10.1038/nature12940.

[20] Majde JA, Krueger JM. Links between the innate immune system and sleep. J Allergy Clin Immunol 2005;116:1188–98. https://doi.org/10.1016/j.jaci.2005.08.005.

[21] Fang J, Sanborn CK, Renegar KB, Krueger JM, Majde JA. Influenza Viral Infections Enhance Sleep in Mice. Proc Soc Exp Biol Med 1995;210:242–52. https://doi.org/10.3181/00379727-210-43945.

[22] ***Ibarra-Coronado EG, Pantaleón-Martínez AM, Velazquéz-Moctezuma J, Prospéro-García O, Méndez-Díaz M, Pérez-Tapia M, et al. The Bidirectional Relationship between Sleep and Immunity against Infections. J Immunol Res 2015;2015. https://doi.org/10.1155/2015/678164.**

[23] Stepanski EJ. The effect of sleep fragmentation on daytime function. Sleep 2002;25:268–76. https://doi.org/10.1093/sleep/25.3.268.

[24] Lee ML, Katsuyama AM, Duge LS, Sriram C, Krushelnytskyy M, Kim JJ, et al. Fragmentation of rapid eye movement and nonrapid eye movement sleep without total sleep loss impairs hippocampus-dependent fear memory consolidation. Sleep 2016;39:2021–31. https://doi.org/10.5665/sleep.6236.

[25] Fiala M, Looney DJ, Stins M, Way DD, Zhang L, Gan X, et al. TNF-α Opens a Paracellular Route for HIV-1 Invasion across the Blood-Brain Barrier. Mol Med 1997;3:553–64. https://doi.org/10.1007/bf03401701.

[26] Fang J, Wang Y, Krueger JM. Mice lacking the TNF 55 kDa receptor fail to sleep more after TNFα treatment. J Neurosci 1997;17:5949–55. https://doi.org/10.1523/jneurosci.17-15-05949.1997.

[27] Dickstein JB, Moldofsky H, Lue FA, Hay JB. Intracerebroventricular injection of TNF-α promotes sleep and is recovered in cervical lymph. Am J Physiol - Regul Integr

Comp Physiol 1999;276:1018–22. https://doi.org/10.1152/ajpregu.1999.276.4.r1018.

[28] Ross SH, Cantrell DA. Signaling and Function of Interleukin-2 in T Lymphocytes. Annu Rev Immunol 2018;26:411–33. https://doi.org/10.1146/annurev-immunol-042617-053352.

[29] De Medeiros RM, Valverde-Villegas JM, Junqueira DM, Gräf T, Lindenau JD, De Mello MG, et al. Rapid and slow progressors show increased IL-6 and IL-10 levels in the Pre-AIDS stage of HIV infection. PLoS One 2016;11:1–12. https://doi.org/10.1371/journal.pone.0156163.

[30] Kubota T, Brown RA, Fang J, Krueger JM. Interleukin-15 and interleukin-2 enhance non-REM sleep in rabbits. Am J Physiol - Regul Integr Comp Physiol 2001;281:1004–12. https://doi.org/10.1152/ajpregu.2001.281.3.r1004.

[31] Utay NS, Douek DC. Interferons and HIV Infection: The Good, the Bad, and the Ugly. Pathog Immun 2016;1:107–16. https://doi.org/10.20411/pai.v1i1.125.

[32] Fernandez S, Tanaskovic S, Helbig K, Rajasuriar R, Kramski M, Murray JM, et al. CD4 + T-cell deficiency in HIV patients responding to antiretroviral therapy is associated with increased expression of interferon-stimulated genes in CD4 + T cells. J Infect Dis 2011;204:1927–35. https://doi.org/10.1093/infdis/jir659.

[33] Raison CL, Rye DB, Woolwine BJ, Vogt GJ, Bautista BM, Spivey JR, et al. Chronic interferon-alpha administration disrupts sleep continuity and depth in patients with hepatitis C: Association with fatigue, motor slowing, and increased evening cortisol. Biol Psychiatry 2010;65:942–9. https://doi.org/10.1016/j.biopsych.2010.04.019.

[34] WHO. Global Health Sector Strategy on HIV 2016-2021. 2016.

[35] Besedovsky L, Lange T, Haack M. The sleep-immune crosstalk in health and disease. Physiol Rev 2019;99:1325–80. https://doi.org/10.1152/physrev.00010.2018.

[36] Bergmann BM, Gilliland MA, Feng PF, Russell DR, Shaw P, Wright M, et al. Are physiological effects of sleep deprivation in the rat mediated by bacterial invasion?

Sleep 1996;19:554–62. https://doi.org/10.1093/sleep/19.7.554.

[37] Everson CA, Toth LA. Systemic bacterial invasion induced by sleep deprivation. Am J Physiol - Regul Integr Comp Physiol 2000;278:905–16. https://doi.org/10.1152/ajpregu.2000.278.4.r905.

[38] ***Bollinger T, Bollinger A, Skrum L, Dimitrov S, Lange T, Solbach W. Sleep-dependent activity of T cells and regulatory T cells. Clin Exp Immunol 2009;155:231–8. https://doi.org/10.1111/j.1365-2249.2008.03822.x.**

[39] Wilder-Smith A, Mustafa FB, Earnest A, Gen L, MacAry PA. Impact of partial sleep deprivation on immune markers. Sleep Med 2013;14:1031–4. https://doi.org/10.1016/j.sleep.2013.07.001.

[40] ***Gómez-Olivé FX, Thorogood M, Kandala NB, Tigbe W, Kahn K, Tollman S, et al. Sleep problems and mortality in rural South Africa: Novel evidence from a low-resource setting. Sleep Med 2014;15:56–63. https://doi.org/10.1016/j.sleep.2013.10.003.**

[41] Liovat AS, Rey-Cuillé MA, Lécuroux C, Jacquelin B, Girault I, Petitjean G, et al. Acute Plasma Biomarkers of T Cell Activation Set-Point Levels and of Disease Progression in HIV-1 Infection. PLoS One 2012;7:e46143. https://doi.org/10.1371/journal.pone.0046143.

[42] ***Appay V, Sauce D. Immune activation and inflammation in HIV-1 infection: Causes and consequences. J Pathol 2008;214:231–41. https://doi.org/10.1002/path.2276.**

[43] Espíndola MS, Lima LJG, Soares LS, Cacemiro MC, Zambuzi FA, De Souza Gomes M, et al. Dysregulated immune activation in second-line HAART HIV+ Patients Is similar to that of untreated patients. PLoS One 2015;10:1–17. https://doi.org/10.1371/journal.pone.0145261.

[44] Kapsimalis F, Basta M, Varouchakis G, Gourgoulianis K, Vgontzas A, Kryger M.

Cytokines and pathological sleep. Sleep Med 2008;9:603–14. https://doi.org/10.1016/j.sleep.2007.08.019.

[45] Hogan D, Morrow JD, Smith EM, Opp MR. Interleukin-6 alters sleep of rats. J Neuroimmunol 2003;137:59–66. https://doi.org/10.1016/S0165-5728(03)00038-9.

[46] Vgontzas AN, Zoumakis M, Papanicolaou DA, Bixler EO, Prolo P, Lin HM, et al. Chronic insomnia is associated with a shift of interleukin-6 and tumor necrosis factor secretion from nighttime to daytime. Metabolism 2002;51:887–92. https://doi.org/10.1053/meta.2002.33357.

[47] Mills PJ, Dimsdale JE. Sleep apnea: A model for studying cytokines, sleep, and sleep disruption. Brain Behav Immun 2004;18:298–303. https://doi.org/10.1016/j.bbi.2003.10.004.

[48] Okun ML, Giese S, Lin L, Einen M, Mignot E, Coussons-Read ME. Exploring the cytokine and endocrine involvement in narcolepsy. Brain Behav Immun 2004;18:326–32. https://doi.org/10.1016/j.bbi.2003.11.002.

[49] Boulware DR, Hullsiek KH, Puronen CE, Rupert A, Baker J V., French MA, et al. Higher levels of CRP, D-dimer, IL-6, and hyaluronic acid before initiation of antiretroviral therapy (ART) are associated with increased risk of AIDS or death. J Infect Dis 2011;203:1637–46. https://doi.org/10.1093/infdis/jir134.

[50] Rohleder N, Aringer M, Boentert M. Role of interleukin-6 in stress, sleep, and fatigue. Ann N Y Acad Sci 2012;1261:88–96. https://doi.org/10.1111/j.1749-6632.2012.06634.x.

[51] Nokes KM, Kendrew J. Correlates of sleep quality in persons with HIV disease. J Assoc Nurses AIDS Care 2001;12:17–22. https://doi.org/10.1016/S1055-3290(06)60167-2.

[52] Shi Y, Yang C, Xu L, He Y, Wang H, Cao J, et al. CD4+ T Cell Count, Sleep, Depression, and Anxiety in People Living With HIV: A Growth Curve Mixture

Modeling. J Assoc Nurses AIDS Care 2020;31:535–43. https://doi.org/10.1097/JNC.0000000000000112.

[53] Oshinaike O, Akinbami A, Ojelabi O, Dada A, Dosunmu A, John Olabode S. Quality of sleep in an HIV population on antiretroviral therapy at an urban tertiary centre in Lagos, Nigeria. Neurol Res Int 2014;2014. https://doi.org/10.1155/2014/298703.

[54] Mukonzo JK, Okwera A, Nakasujja N, Luzze H, Sebuwufu D, Ogwal-Okeng J, et al. Influence of efavirenz pharmacokinetics and pharmacogenetics on neuropsychological disorders in Ugandan HIV-positive patients with or without tuberculosis: A prospective cohort study. BMC Infect Dis 2013;13. https://doi.org/10.1186/1471-2334-13-261.

[55] D'Arminio Monforte A, Cinque P, Mocroft A, Goebel FD, Antunes F, Katlama C, et al. Changing Incidence of Central Nervous System Diseases in the EuroSIDA Cohort. Ann Neurol 2004;55:320–8. https://doi.org/10.1002/ana.10827.

[56] Barbier F, Mer M, Szychowiak P, Miller RF, Mariotte É, Galicier L, et al. Management of HIV-infected patients in the intensive care unit. Intensive Care Med 2020;46:329–42. https://doi.org/10.1007/s00134-020-05945-3.

[57] Saylor D, Dickens AM, Sacktor N, Haughey N, Slusher B, Pletnikov M, et al. HIV-associated neurocognitive disorder - Pathogenesis and prospects for treatment. Nat Rev Neurol 2016;12:234–48. https://doi.org/10.1038/nrneurol.2016.27.

[58] Aung HL, Bloch M, Vincent T, Quan D, Jayewardene A, Liu Z, et al. Cognitive ageing is premature among a community sample of optimally treated people living with HIV. HIV Med 2020:1–14. https://doi.org/10.1111/hiv.12980.

[59] Wang Y, Liu M, Lu Q, Farrell M, Lappin JM, Shi J, et al. Global prevalence and burden of HIV-associated neurocognitive disorder: A meta-analysis. Neurology 2020;95:e2610–21. https://doi.org/10.1212/WNL.0000000000010752.

[60] Ho DD, Rota TR, Schooley RT, Kaplan JC, Allan JD, Groopman JE, et al. Isolation of

HTLV-III from Cerebrospinal Fluid and Neural Tissues of Patients with Neurologic Syndromes Related to the Acquired Immunodeficiency Syndrome. N Engl J Med 1985;12:1493–7. https://doi.org/10.1056/nejm198512123132401.

[61] ***Nath A, Geiger J. Neurobiological aspects of human immunodeficiency virus infection: Neurotoxic mechanisms. Prog Neurobiol 1998;54:19–33. https://doi.org/10.1016/S0301-0082(97)00053-1.**

[62] Nickoloff-Bybel EA, Calderon TM, Gaskill PJ, Berman JW. HIV Neuropathogenesis in the Presence of a Disrupted Dopamine System. J Neuroimmune Pharmacol 2020;15:729–42. https://doi.org/10.1007/s11481-020-09927-6.

[63] Valcour V, Sithinamsuwan P, Letendre S, Ances B. Pathogenesis of HIV in the central nervous system. Curr HIV/AIDS Rep 2011;8:54–61. https://doi.org/10.1007/s11904-010-0070-4.

[64] Obermann M, Küper M, Kastrup O, Yaldizli O, Esser S, Thiermann J, et al. Substantia nigra hyperechogenicity and CSF dopamine depletion in HIV. J Neurol 2009;256:948–53. https://doi.org/10.1007/s00415-009-5052-3.

[65] Kumar AM, Ownby RL, Waldrop-Valverde D, Fernandez B, Kumar M. Human immunodeficiency virus infection in the CNS and decreased dopamine availability: Relationship with neuropsychological performance. J Neurovirol 2011;17:26–40. https://doi.org/10.1007/s13365-010-0003-4.

[66] Müller-Oehring EM, Fama R, Levine TF, Hardcastle C, Goodcase R, Martin T, et al. Cognitive and motor deficits in older adults with HIV infection: Comparison with normal ageing and Parkinson's disease. J Neuropsychol 2020. https://doi.org/10.1111/jnp.12227.

[67] Monti JM, Monti D. The involvement of dopamine in the modulation of sleep and waking. Sleep Med Rev 2007;11:113–33. https://doi.org/10.1016/j.smrv.2006.08.003.

[68] ***Seay JS, McIntosh R, Fekete EM, Fletcher MA, Kumar M, Schneiderman N, et**

al. Self-reported sleep disturbance is associated with lower CD4 count and 24-h urinary dopamine levels in ethnic minority women living with HIV. Psychoneuroendocrinology 2013;38:2647–53. https://doi.org/10.1016/j.psyneuen.2013.06.022.

[69] Van Dongen HPA, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 2003;26:117–26. https://doi.org/10.1093/sleep/26.2.117.

[70] Vázquez-Santiago FJ, Noel RJ, Porter JT, Rivera-Amill V. Glutamate metabolism and HIV-associated neurocognitive disorders. J Neurovirol 2014;20:315–31. https://doi.org/10.1007/s13365-014-0258-2.

[71] Ernst T, Jiang CS, Nakama H, Buchthal S, Chang L. Lower brain glutamate is associated with cognitive deficits in HIV patients: A new mechanism for HIV-associated neurocognitive disorder. J Magn Reson Imaging 2010;32:1045–53. https://doi.org/10.1002/jmri.22366.

[72] Schwartz MD, Kilduff TS. The Neurobiology of Sleep and Wakefulness. Psychiatr Clin North Am 2015;38:615–44. https://doi.org/10.1016/j.psc.2015.07.002.

[73] Fuller PM, Gooley JJ, Saper CB. Neurobiology of the sleep-wake cycle: Sleep architecture, circadian regulation, and regulatory feedback. J Biol Rhythms 2006;21:482–93. https://doi.org/10.1177/0748730406294627.

[74] Buysse DJ, Germain A, Hall M, Monk TH, Nofzinger EA. A neurobiological model of insomnia. Drug Discov Today Dis Model 2011;8:129–37. https://doi.org/10.1016/j.ddmod.2011.07.002.

[75] Saag MS, Gandhi RT, Hoy JF, Landovitz RJ, Thompson MA, Sax PE, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2020 Recommendations of the International Antiviral Society-USA Panel. JAMA - J Am

Med Assoc 2020;324:1651–69. https://doi.org/10.1001/jama.2020.17025.

[76] Gallego L, Barreiro P, Rio R del, Gonzalez de Requena D, Rodriguez-Albarino A, Gonzalez-Lahoz J, et al. Analyzing Sleep Abnormalities in HIV-Infected Patients Treated with Efavirenz. Clin Infect Dis 2004;38:430–2. https://doi.org/10.1086/380791.

[77] WHO. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines. Supplement to the 2016 consolidated guidelines on the use of antiretrovir. World Heal Organ 2018:1–79.

[78] Omonuwa TS, Goforth HW, Preud'homme X, Krystal AD. The pharmacologic management of insomnia in patients with HIV. J Clin Sleep Med 2009;5:251–62. https://doi.org/10.5664/jcsm.27496.

[79] Adkins JC, Noble S. Efavirenz. Drugs 1998;56:1055–64. https://doi.org/10.2165/00003495-199856060-00014.

[80] Simen AA, Ma J, Svetnik V, Mayleben D, Maynard J, Roth A, et al. Efavirenz modulation of sleep spindles and sleep spectral profile. J Sleep Res 2015;24:66–73. https://doi.org/10.1111/jsr.12196.

[81] Lapadula G, Bernasconi DP, Bai F, Focà E, Di Biagio A, Bonora S, et al. Switching from efavirenz to rilpivirine improves sleep quality and self-perceived cognition but has no impact on neurocognitive performances. Aids 2020;34:53–61. https://doi.org/10.1097/QAD.0000000000002377.

[82] Shikuma CM, Kohorn L, Paul R, Chow DC, Kallianpur KJ, Walker M, et al. Sleep and neuropsychological performance in HIV+ subjects on efavirenz-based therapy and response to switch in therapy. HIV Clin Trials 2018;19:139–47. https://doi.org/10.1080/15284336.2018.1511348.

[83] ***Owens RL, Hicks CB. A wake-up call for Human Immunodeficiency Virus**

(HIV) providers: Obstructive sleep apnea in people living with HIV. Clin Infect Dis 2018;67:472–6. https://doi.org/10.1093/cid/ciy217.

[84] Masenga SK, Elijovich F, Koethe JR, Hamooya BM, Heimburger DC, Munsaka SM, et al. Hypertension and Metabolic Syndrome in Persons with HIV. Curr Hypertens Rep 2020;22:78. https://doi.org/10.1007/s11906-020-01089-3.

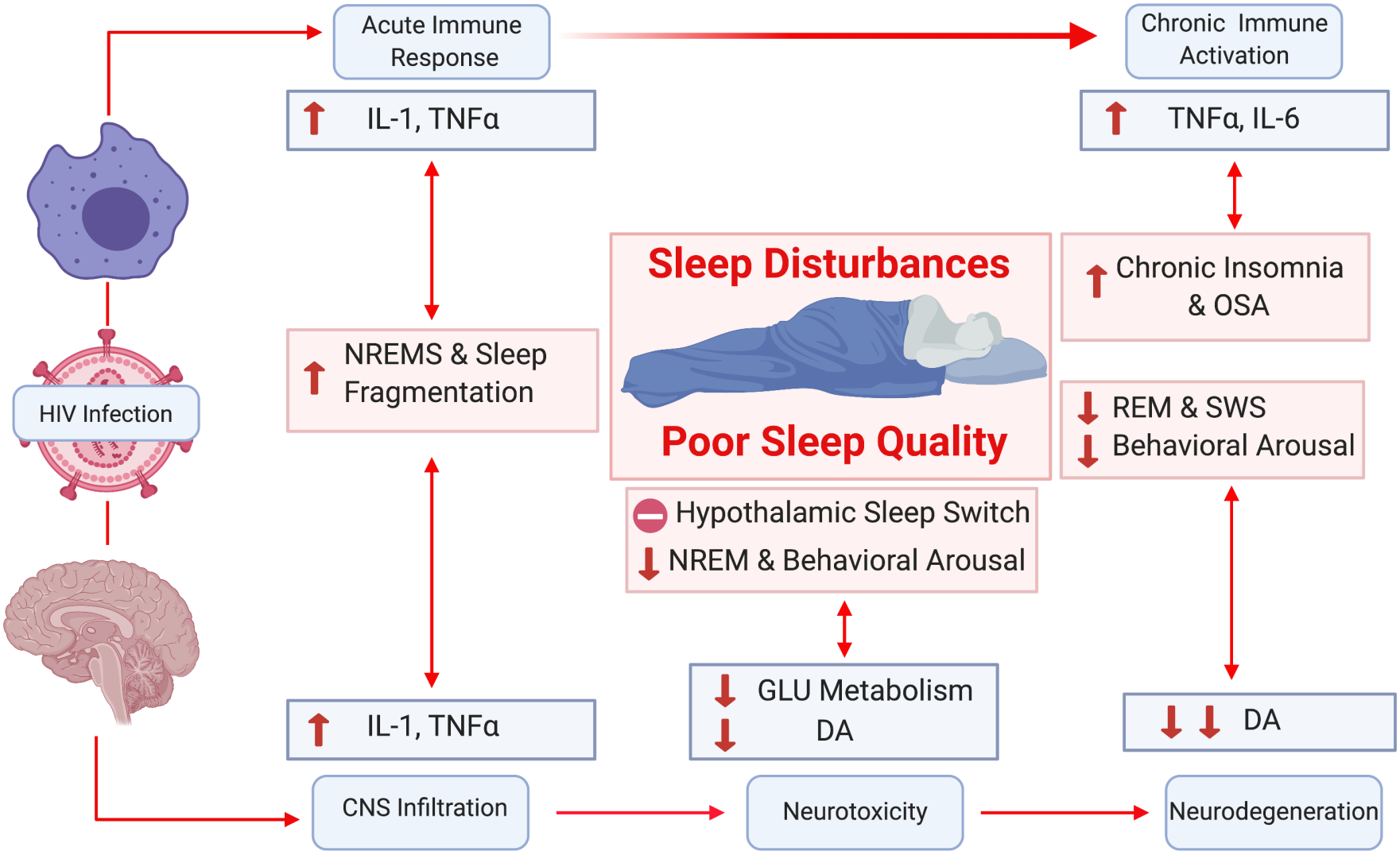
[85] Schwartz AR, Patil SP, Squier S, Schneider H, Kirkness JP, Smith PL. Obesity and upper airway control during sleep. J Appl Physiol 2010;108:430–5. https://doi.org/10.1152/japplphysiol.00919.2009.

[86] Brown TT, Patil SP, Jacobson LP, Margolick JB, Laffan AM, Godfrey RJ, et al. Anthropometry in the prediction of sleep disordered breathing in HIV-positive and HIV-negative men. Antivir Ther 2010;15:651–9. https://doi.org/10.3851/IMP1572.

[87] Brigham EP, Patil SP, Jacobson LP, Margolick JB, Godfrey R, Johnson J, et al. Association between systemic inflammation and obstructive sleep apnea in men with or at risk for HIV infection. Antivir Ther 2014;19:725–33. https://doi.org/10.3851/IMP2745.

[88] Tasali E, Ip MSM. Obstructive sleep apnea and metabolic syndrome: Alterations in glucose metabolism and inflammation. Proc Am Thorac Soc 2008;5:207–17. https://doi.org/10.1513/pats.200708-139MG.

[89] Triant VA. Cardiovascular disease and HIV infection. Curr HIV/AIDS Rep 2013;10:199–206. https://doi.org/10.1007/s11904-013-0168-6.


Acute Immune Response
Chronic Immune Activation
IL-1, TNFα
TNFα, IL-6
HIV Infection
NREMS & Sleep Fragmentation
Sleep Disturbances
Poor Sleep Quality
Chronic Insomnia & OSA
REM & SWS
Behavioral Arousal
Hypothalamic Sleep Switch
NREM & Behavioral Arousal
GLU Metabolism
DA
DA
IL-1, TNFα
CNS Infiltration
Neurotoxicity
Neurodegeneration