

Insomnia in HIV-infected Patients: Pathophysiologic Implications

Yinghui Low¹, Harold Goforth^{1,2}, Xavier Preud'homme^{1,3}, Jack Edinger^{1,2} and Andrew Krystal¹

¹Insomnia and Sleep Research Program, Department of Psychiatry, Duke University School of Medicine, Durham, NC, USA; ²Durham VA Medical Center, Durham, NC, USA; ³Department of Internal Medicine, Duke University School of Medicine, Durham, NC, USA

Abstract

The prevalence of insomnia in the HIV-seropositive population is estimated to be 29-97%, far greater than the 10% general population prevalence. We carried out a systematic review to assess whether the prevalence of insomnia is indeed higher in HIV-seropositive patients and to better understand the correlates of insomnia in order to attempt to explain the dramatically higher prevalence. Nineteen studies met our search criteria and were included in this review. We found that prior studies estimated the rate of disturbed sleep, but not a single study estimated the prevalence of insomnia using insomnia diagnostic criteria, which require that sleep disturbance occur frequently, persistently, and in association with impairment in quality of life or daytime function. We also found that in addition to correlates of sleep disturbance seen in the general population, there are also correlates specific to the HIV-seropositive population: stage and duration of HIV infection, and cognitive impairment. The most important conclusion of this review is that the prevalence of insomnia which meets diagnostic criteria has yet to be estimated in populations of HIV-seropositive patients and studies are needed to estimate this prevalence rate. The rate of sleep disturbance identified in HIV-infected patients (29-97%) should not be compared against the approximately 10% prevalence of clinically significant insomnia in the general population, which would suggest that HIV infection is associated with an alarming increase in sleep problems. Instead, this rate is best compared with the rate of sleep disturbance in the general population, which is roughly 33%. (AIDS Rev. 2014;16:3-13)

Corresponding author: Yinghui Low, ying.low@duke.edu

Key words

Insomnia. HIV. Prevalence. Correlates.

Introduction

Insomnia is defined as difficulty with sleep onset, maintenance, or restoration that is associated with daytime dysfunction or distress¹. In the only previous review carried out on the frequency of insomnia in

HIV-seropositive patients, Reid and Dwyer reported that the prevalence ranges between 29-97%², which places it well above the 10% estimated prevalence of insomnia in the general population¹.

If correct, this is an important observation for a number of reasons. Firstly, if insomnia is more prevalent in the HIV-seropositive population it suggests that there are specific mechanisms causing insomnia that are unique to this population or to the HIV infection. Secondly, insomnia has been associated with poorer disease outcomes because it adversely affects immune status³, medication adherence^{4,5} and is correlated with increased fatigue and comorbid psychiatric disorders like anxiety/depression, altogether leading to lower overall quality of life⁵⁻⁸. Thirdly, the extremely high prevalence of insomnia suggests that treating insomnia

Correspondence to:

Yinghui Low
Box 3309
Duke University Medical Center
Durham, NC 27710, USA
Email: ying.low@duke.edu

in those with HIV infection may have a substantial impact on at least the quality of life and perhaps the course of the disease. Given this consideration, it is quite concerning that there has yet to be a placebo-controlled trial of the treatment of insomnia in HIV-seropositive patients.

Because of the remarkably high prevalence of insomnia reported in HIV-seropositive patients and the wide range of prevalence estimates reported, we carried out this systematic review to attempt to confirm whether the prevalence of insomnia is indeed higher in HIV-seropositive patients, and to better understand the circumstances associated with insomnia in those with HIV.

Strategy and definitions

We carried out a search of the electronic database MEDLINE using the following search terms: "Human immunodeficiency virus and sleep", "HIV and sleep disturbance", "HIV and insomnia", "HIV and circadian rhythm", "HIV and depression", "HIV and anxiety", "HIV and substance abuse", "AIDS and sleep disturbance", "AIDS and insomnia", "AIDS and circadian rhythm".

We retrieved full texts of relevant articles, including all studies which assessed the prevalence or severity of insomnia or sleep disturbances in HIV patients. We excluded studies that: did not report insomnia as an outcome, only addressed sleep disturbance as a side-effect of therapy (antiretrovirals, antidepressants or anxiolytics) as this association is already well established^{9,10}, studied specific sleep disturbances like obstructive sleep apnea, narcolepsy, or periodic limb movements of sleep, had a sample size < 10, and were not available in English. We also retrieved the full text of relevant articles cited in articles above.

Each article was evaluated with particular attention to the method used to identify insomnia or sleep disturbance, and significant correlates of sleep disturbances or insomnia that were reported by the authors.

Nineteen articles were identified and are summarized in table 1 and in Supplementary Data in order of year of publication. Of these, six were case-control studies comparing sleep disturbances in HIV-seropositive samples to seronegative controls¹¹⁻¹⁶, and the others were cross-sectional; no longitudinal studies have been carried out to date.

Insomnia versus sleep disturbance: measures used to assess sleep

The most commonly used scale to detect insomnia was the Pittsburgh Sleep Quality Index (PSQI) (nine studies), and a variety of other questionnaires were used in other studies. The current gold standard objective measure of sleep physiology is polysomnography (PSG), but few PSG studies have been carried out to date and available studies included small sample sizes. Only one PSG study¹³ met the criteria for inclusion in our review, and although the authors reported significant differences in PSG findings and subjective sleep complaints, they found no difference in the mean PSQI between HIV-seropositive and HIV-negative groups.

Most importantly, none of the studies used instruments or methods which applied clinical diagnostic criteria^{17,18} for insomnia to determine whether insomnia was present (See Supplementary Data). The PSQI which was frequently used in studies of HIV-seropositive groups is a measure of sleep disturbance, but is not validated as an insomnia diagnostic instrument¹⁹.

To meet the criteria for clinical insomnia using either the Diagnostic and Statistical Manual for Psychiatric Illness IV (DSM-IV), the International Classification of Sleep Disorders Second Edition (ICSD-2), or Research Diagnostic Criteria (RDC)^{17,18}, patients must have difficulty initiating or maintaining sleep, or have non-restorative sleep that: (i) is associated with deficits in daytime function, (ii) persists despite sufficient opportunity to sleep (this distinguishes it from sleep deprivation), and (iii) persists for more than a month.

As a result, the studies carried out so far provide an indication of the rate of "sleep disturbance", rather than clinical insomnia, in the HIV-seropositive population². For this reason, the rest of the paper will deal with sleep disturbance, instead of insomnia.

Prevalence of sleep disturbance

Ten out of 19 studies reported the proportion of their samples that had sleep disturbances, and as Reid and Dwyer² had previously found, the range is wide: 29-97%^{5,7,12,13,20-25}. Five studies reported that sleep disturbances were significant, but did not report the proportion of their sample that was affected^{3,26-29}. Studies which used the PSQI to assess sleep disturbance reported higher prevalence rates (66-97%) than other

Table 1. Sleep disturbance in HIV infection

| Author, year | Sample size | Stage of illness | Insomnia in HIV+ > HIV- ? | Insomnia is associated with |
|--|---------------------|---|---------------------------|-----------------------------|
| Rothenberg, et al., 1990 ²⁰ | 68 | Asymptomatic | No difference | |
| Moeller, et al., 1991 ²⁶ | 50 | All stages | Yes | Stage |
| Brown, et al., 1991 ¹¹ | 155 HIV+ 35 HIV- | All stages | Yes | Stage |
| Darko, et al., 1992 ¹² | 62 HIV+ 50 HIV- | All stages | Yes | AIDS |
| Norman, et al., 1992 ¹³ | 14 HIV+ 10 HIV- | Asymptomatic | Yes | |
| Wheatley, et al., 1994 ¹⁴ | 45 HIV+ 45 HIV- | All stages | Yes | Duration |
| Perkins, et al., 1995 ¹⁵ | 98 HIV+ 71 HIV- | All stages (relatively healthy sample) | No difference | |
| Cohen, et al., 1996 ²¹ | 50 | All stages | Yes | |
| Franck, et al., 1997 ¹⁶ | 18 HIV+ 15 HIV- | All stages | Yes | |
| Rubinstein, et al., 1998 ²² | 115 | CD4 > 200/mm ³ only | Yes | |
| Ammassari, et al., 2001 ⁸³ | 358 | All stages | No difference | |
| Lee, et al., 2001 ²⁷ | 100 | All stages | Yes | |
| Nokes, et al., 2001 ²⁸ | 58 | All stages | Yes | Duration |
| Cruess, et al., 2003 ³ | 57 | CD4 > 200/mm ³ only | No difference | |
| Robbins, et al., 2004 ⁵ | 79 | All stages | Yes | |
| Andersen, et al., 2004 ²³ | 1,821 | All stages | Yes | |
| Vosvick, et al., 2004 ²⁴ | 146 | All stages | Yes | |
| Phillips, et al., 2005 ⁷ | 144 | All stages | Yes | Increased symptoms |
| Hudson, et al., 2008 ²⁹ | 30 | All stages | Yes | |
| Salahuddin, et al., 2008 ²⁵ | 128 | All stages | Yes | Stage |

studies (29-76%). Six case-control studies used age-, gender- or ethnicity-matched HIV-seronegative controls¹¹⁻¹⁶ and of these, four found a difference in sleep quality between HIV-seropositive and HIV-negative groups^{11,12,14,16}.

The prevalence of insomnia in HIV is unknown

The most striking finding which emerged from our systematic review of the literature is that there has yet

to be a study to determine the prevalence of insomnia in the HIV-seropositive population as defined by established diagnostic criteria^{17,18}. As a result, we must conclude that the prevalence of insomnia in this population remains unknown. This finding is somewhat reassuring, for it tempers the alarming conclusions of prior reports that the rate of insomnia is many-fold higher in HIV-seropositive patients than the general population. Instead of the approximately 10% prevalence of insomnia in the general population, the rate of sleep disturbance identified in HIV patients (29-97%) is best compared with the rate of sleep disturbance in the general population, which is roughly 33%³⁰.

At the same time, the absence of any estimates of the prevalence of insomnia based on diagnostic criteria in HIV-seropositive patients is concerning. The key factors in distinguishing insomnia from sleep disturbance are precisely the factors which motivate the treatment of insomnia³¹. Thus, the most important conclusion of this review is that studies are needed to estimate the prevalence rate of HIV-seropositive patients meeting insomnia diagnostic criteria.

Correlates of sleep disturbance

The wide range of sleep disturbance reported likely reflects the presence of a large number of factors which affect sleep, and these may give clues to the pathophysiology of insomnia in these patients. The correlates that were identified in the studies as significant are discussed below.

Age, gender, or race-matched controls were used in four case-control studies. Fatigue was measured in four studies^{5,12,16,25} and stress was measured in five studies^{3,7,14,16,25}, each using different scales. Anxiety and depression were measured using various scales in five studies^{13,15,22,23,28} and two others^{5,25} reported the proportion of their sample who were taking antidepressants and anxiolytics.

There are also correlates which are specific to the HIV population. The first such correlate we identified was the severity of HIV infection, which was measured in most studies using one or more of the following methods: the presence or absence of symptoms, CD4 count, viral load, disease stage, and time from HIV diagnosis. Five of the studies identified in this review imposed restrictions based on the presence of symptomatic HIV conditions (classified in the CDC Stage B or C) or CD4 count, resulting in samples that were in earlier stages of illness^{5,15,20,22,27}.

Cognitive impairment was measured in two studies, again using different tools^{22,28}.

Patient demographics

Of the studies that considered age, sex, or race, none found a difference between different groups¹³⁻¹⁶. However, there are some limitations to these conclusions:

- Except for three studies which were carried out exclusively in females^{7,27,29}, the samples used were either all male or predominantly male. Although the two studies that carried out gender matching found no differences, larger studies may better elucidate any differences present between the male and female HIV-seropositive population, since insomnia is known to be twice as prevalent in females, and the HIV-seropositive population now includes more females³².
- The mean ages reported were between 30-40 years, except for one study of HIV in the pediatric population, where the mean age was 10 years. This leaves a gap in data for the pediatric and elderly population. So although no correlations were found here, the disease demographic has changed and the above studies may not fully represent the current HIV population.

Psychiatric symptoms/comorbidities

Among the studies that qualified for this review, some evaluated the correlation between sleep complaints and psychiatric symptoms. These included depressive symptoms, anxiety symptoms, stress, fatigue, and substance abuse.

A correlation of sleep complaints with depressive symptoms was found in five studies, using various scales including the Hamilton Depression Scale and Hospital Anxiety and Depression Scale^{13,15,16,22,27}. Only one study sought to determine if subjects met clinical criteria for depression using the DSM-III-R, and did not find a correlation of disturbed sleep and a clinical diagnosis of depression¹⁵. A correlation between disturbed sleep and features of anxiety was found in three studies^{11,22,28}, while one which had excluded patients with AIDS did not¹³. Stress was strongly correlated with sleep disturbance^{3,5,14} using different scales, and in one study the score on the Perceived Stress Scale was found to be the best independent predictor⁵. Fatigue, measured using the Revised Piper Fatigue Scale and HIV-related fatigue scale, is also positively correlated

with insomnia^{5,22,25}. The authors of one study also concluded that there is a higher prevalence of insomnia in patients with a history of substance abuse²¹.

The various factors discussed here are well-established correlates of insomnia in the general population. However, there are other factors unique to the HIV-seropositive populations that warrant consideration. These are considered in the following discussion.

Factors specific to HIV

Several factors related to disease severity have been assessed in the studies, and these include HIV stage, duration, CD4 count, and viral load.

Sleep disturbance correlates with HIV stage and duration

Three studies found that advanced disease is significantly associated with higher prevalence and severity of sleep disturbance^{11,12,26}. In other studies, although the stage of disease and disturbed sleep was not formally analyzed using statistical methods, results supported a trend toward greater frequency and severity of sleep disturbance in advanced disease^{2,3,29}. Of four studies which concluded that there was no difference in the prevalence of insomnia, three had used asymptomatic patients²⁰, or selected a relatively healthy sample using strict exclusion criteria^{13,15} (Table 1). A positive correlation with duration of HIV infection was also found in both studies that considered the time from first HIV diagnosis (used as a rough estimate of duration of infection)^{14,28}. Overall, there appears to be a trend toward greater sleep disturbances in advanced stages or greater duration of infection.

Correlation between stage and sleep disturbance

Although PSG findings to date have been conflicting, the study which was included in our review found that disturbance of sleep architecture was most prominent in later stages of HIV infection¹³.

Relationship between the immune markers of CD4 count and viral load

Seven studies^{3,15,16,21,22,24,28} reported that no correlation was found between sleep disturbance and CD4

count, and in the one study which studied the correlation between viral load and insomnia, no correlation was found²⁸.

Antiretroviral therapy and opportunistic infections

Randomized studies, case reports, and reviews have described sleep disturbances with the use of antiretrovirals, in particular the nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz^{9,10,33-35}. Other types of antiretroviral drugs like protease inhibitors and the nucleoside analog zidovudine do not appear as prone to sleep disturbances^{9,26,34,35}.

Four studies were found that reported the rate of sleep disturbances associated with antiretroviral medications (See Supplementary Data). In one study, 291 patients were randomized to a combination of antiretroviral therapy including efavirenz versus antiretroviral therapy including stavudine or amprenavir³⁶. They employed a general symptom questionnaire to assess adverse effects. They found that 8% of the patients randomized to efavirenz had sleep problems compared with 1% in the stavudine/amprenavir group. In another study, 100 patients were randomized to two NNRTI plus efavirenz vs. two NNRTI plus placebo³⁴. They assessed sleep as part of a five-point item adapted from the HIV questionnaire of the Medical Outcomes Study, and found that the sleep disturbing effects of efavirenz appeared to decrease with time. In the efavirenz group, 35% reported sleeping difficulty after four weeks of therapy, 7% reported sleep problems at 24 weeks, and none of the subjects reported problems with their sleep at 48 weeks, whereas in the placebo group, the rate of sleep disturbance was 4% at all time-points studied. An open-label study of 114 patients receiving efavirenz found that 4-6% reported sleep disturbance on a 13-item sleep questionnaire developed at Oviedo University that asks subjects to rate sleep quality, somnolence, insomnia, and nightmares³⁷. Lastly, in another open-label study in 100 patients started on combination antiretroviral therapy, 32% had CNS-related adverse effects which included disturbed sleep³⁸.

Opportunistic infections formed part of the exclusion criteria for nearly all of the studies identified, therefore no correlation was reported.

Cognitive impairment was measured only by one study using the Mini-Mental Status Examination (MMSE) with a cutoff of < 24 for defining impairment²², and the authors reported that cognitive impairment was the

best predictor of disturbed sleep²². This is fairly consistent with the fact that dementias like Alzheimer's, vascular dementia, frontotemporal dementia, and other neurodegenerative disorders are known to cause sleep difficulties³⁹. However, the MMSE was developed as a screening instrument for cortical dementias, and use of this instrument in an HIV population likely would underestimate the presence of cognitive impairment from HIV itself, which is largely a subcortical process. The HIV Dementia Scale, which places greater emphasis on motor speed and concentration, was first designed as a more sensitive screening test for HIV-associated dementia in 1995⁴⁰, but was not used in any of the above studies.

Pathophysiologic implications of correlates of sleep disturbance

The studies identified in this review suggest correlates of sleep disturbance which have implications for potential mechanisms of insomnia in this population.

First, psychiatric symptoms, including depressive symptoms, anxiety, stress and fatigue, and substance use and abuse were correlated with sleep disturbance among HIV-seropositive patients and are also known correlates of sleep disturbance in the general population. However, we also found correlates of sleep disturbance which are specific to the HIV population, including advanced stage or longer duration of infection, and cognitive impairment. These represent important indicators of the possible mechanisms of sleep disturbance that are specific to this population.

The correlation of sleep disturbance with disease severity may appear contradictory at first glance: while sleep disturbances are especially significant in later stages or longer duration of infection, they are not correlated with CD4 count or viral load. This apparently conflicting result may be explained by the fact that although CD4 count serves as a point marker of current immune function and often correlates with peripheral viral load, it may not reflect the viral burden in the CNS⁴¹⁻⁴⁴. On the other hand, most staging criteria take into account a person's history of the disease, which means that previous insults, like a low CD4 nadir or previous opportunistic infections, will be reflected as a more advanced stage^{45,46}. Because many popular HAART regimens do not reach the CNS efficiently, the CNS disease burden accumulates from the time of onset of infection, and this accumulation may be accelerated when viral

load and replication is not well-controlled⁴². Sleep disturbance could therefore reflect the cumulative effects of HIV in the CNS. The mechanisms by which the CNS neurotoxic effects of HIV might predispose affected individuals to experience disturbed sleep remain unknown. Here we review the CNS neurotoxic mechanisms of HIV in order to explore factors that might explain the relationship of insomnia with disease severity and greater time since infection and whether there is evidence that HIV causes alterations in CNS systems that are known to be associated with disturbed sleep.

HIV neurotoxic mechanisms in the central nervous system

The key characteristics of HIV infection in the CNS are: (i) it is cumulative, and (ii) its pathology at the molecular and cellular level involves damage caused by both direct effects of viral products collectively known as HIV neurotoxins, and the inflammatory response to viral infection^{41-44,47,48}.

Cumulative effect of the HIV virus in the central nervous system

The virus gains access to the CNS when infected peripheral macrophages migrate across the blood-brain barrier⁴³. However, the HIV virus does not appear to infect neurons directly; instead infection and viral replication occur mainly in the macrophages and microglia, and to a limited extent in astrocytes^{43,49}. These become viral reservoirs because many current HAART regimens do not reach the CNS efficiently^{41-43,49,50}. Occurring in conjunction with cellular infection or damage are inflammation, and an increased CNS inflammatory cytokine level⁴². This in turn attracts greater macrophage migration across the blood-brain barrier, and over time leads to an accumulated CNS viral load. This process of gradual accumulation of CNS viral load might explain the increased likelihood of sleep disturbance with longer time since infection.

Neurotoxic and inflammatory mechanisms (Table 2)

In broad terms, the neurotoxic effects of the virus involves: (i) the release or secretion of viral products (neurotoxins) from infected cells into the extracellular space where they can interact with neurons

Table 2. Neurotoxic mechanisms in HIV

| Viral neurotoxin or inflammatory mediator | Molecular and cellular effects | Target neurons/regions of CNS |
|---|--|---|
| <p>Tat protein (<i>Trans-activator of transcription</i> protein)</p> <ul style="list-style-type: none"> • A regulatory protein needed to activate full HIV virus replication | <p>Neurons:</p> <ul style="list-style-type: none"> • Tat enhances NMDAR-mediated glutamate transmission and apoptosis <p>Astrocytes:</p> <ul style="list-style-type: none"> • Tat induces production of chemokines like CCL2 → chemotaxis of macrophages and microglia • Upregulates iNOS and impairs astrocyte's glutamate-buffering ability | <ul style="list-style-type: none"> • Dopaminergic neurons • Tat transported via axons across different regions of the brain, notably from the striatum to the substantia nigra, and also associated with destruction of neurons in CA3 region of hippocampus • <i>In vitro</i> (rat PC12 cell cultures) injection of Tat → decreased TH and DA gene expression |
| <p>Glycoproteins 120 and 41</p> <ul style="list-style-type: none"> • Mediate entry into host cell: • Gp120 is a viral coat protein which engages CD4 receptors • This induces conformational change to allow Gp41 to bind CCR5/ CXCR4 and enter host cell | <ul style="list-style-type: none"> • Microglia and macrophages the only CNS cells that have both CD4 and CCR5 receptors • Activated microglia and macrophages release inflammatory mediators and have decreased buffering ability for excitatory amino acids • Eventually results in apoptotic cascades | <p>In HAD patients, HIV neurotoxic proteins Tat and gp120 both found in basal ganglia</p> |

CNS: central nervous system; NMDAR: N-methyl-D-aspartate receptor; iNOS: inducible nitric oxide synthase; HAD: HIV-associated dementia.

and synapses, (ii) recruitment of inflammatory mediators – cytokines, chemokines and more macrophages, and (iii) the viral neurotoxins and inflammatory mediators feeding forward in cycles that result in escalating neuronal damage, particularly in dopaminergic and glutamatergic neurons.

The HIV neurotoxins that have been identified to date are the transactivator of transcription (tat) protein and glycoproteins 120 (Gp120) and 41 (Gp41).

Tat is a regulatory protein needed to activate the full HIV virus replication⁵¹. Tat has been detected in the brain of HIV-associated dementia (HAD) patients, and is the only HIV protein that is actively secreted by infected microglia into the extracellular space and cerebrospinal fluid^{51,52}. In neurons, Tat enhances N-methyl-D-aspartate receptor (NMDAR)-mediated glutamate transmission, causing an increase in intracellular calcium, whose downstream effects are neuronal nitric oxide synthase (nNOS) activation and mitochondrial damage, both of which induce neuronal apoptosis⁵². In astrocytes, Tat induces the production of chemokines like CCL2, which in turn induces chemotaxis of macrophages and microglia to and within the CNS. It also upregulates inducible nitric oxide

synthase (iNOS) production of nitric oxide and impairs the astrocyte's glutamate-buffering ability, thus further contributing to oxidative stress and increased extracellular glutamate⁵³.

Gp120 is a viral coat protein whose function is to engage CD4 receptors, inducing a conformational change which allows Gp41 to bind the chemokine receptors CCR5 or CXCR4 and enter the host cell⁵⁴. In the CNS, the microglia and macrophages are the only cells that have both CD4 and CCR5 receptors, which explains why these cells bear the heaviest burden of viral infection⁴². Both Gp120 and Gp41 have also been studied extensively in relation to neurotoxicity, and like Tat, exert damage by inducing apoptotic cascades through NMDA-mediated enhanced glutamate transmission, leading to increased intracellular calcium, and microglial and astrocyte activation⁵¹.

Activated microglia and macrophages also release inflammatory mediators, in particular the cytokines interleukin-1 β , tumor necrosis factor- α and interferon- γ , and also excitatory amino acids like glutamate and quinolinate^{42,53,55}. These aggravate the production of nitric oxide, and free radicals like peroxynitrite and

superoxide anion, which further contribute to a molecular and cellular milieu for neuronal damage and death^{42,43,49}.

There is reason to believe that these neurotoxic mechanisms have the most deleterious effect on glutamatergic and dopaminergic (DA) neurons, both of which affect sleep/wake function and could mediate sleep disturbance in HIV-seropositive patients⁵⁶⁻⁶¹.

Dopamine

Of the various modulatory neurotransmitters, changes in the dopaminergic system are perhaps also the best documented in HIV dementia. The earliest evidence for this came from postmortem studies, which found the highest concentration of pathological cells (multinucleated giant cells, microglial nodules, and infected macrophages) in the basal ganglia, particularly in the caudate and putamen^{62,63}, and neuronal death in the substantia nigra⁶⁴. As newer molecular laboratory methods became available, it was observed that the basal ganglia, and particularly the caudate and putamen, contained higher viral DNA loads⁶⁵, and that dopamine levels were decreased in the striatum and substantia nigra, nucleus accumbens, and amygdala^{66,67}. One study also found significantly lower dopamine transporter levels in the putamen and striatum, which was correlated with higher viral loads⁶⁸. Cerebrospinal fluid dopamine levels have also been found to be diminished in AIDS patients, especially those with HAD^{69,70}. Radiological and metabolic studies have detected abnormalities in the basal ganglia, which is consistent with the motor symptoms in HAD. There is a correlation between HAD and caudate atrophy, smaller basal ganglia volumes, and in children, symmetrical bilateral basal ganglia calcifications^{69,70}. These changes in dopamine have been found to correlate with a clinical picture of cognitive and motor changes, both of which are associated with sleep disturbance in HIV-seropositive patients.

Dopaminergic transmission appears to be involved in mediating sleep processes, but in ways that are not yet well defined; these are described below. Our hypothesis is that in HIV infection, neuronal damage in DA pathways and a state of relative DA deficiency could therefore lead to sleep disturbances.

The earliest evidence for this came from observations that there are often associations between sleep disorders and movement disorders like Parkinson's disease and Huntington's disease^{71,72}, and the

wake- and sleep-promoting effects of various dopaminergic agents⁷³. Of the movement disorders, Parkinson's disease has received the most attention: sleep disturbances are now accepted as common phenomena in the disease, and attempts at manipulating dopaminergic transmission to treat the disease, both with pharmacological methods (dopamine agonists) and surgical methods (targeted stimulation of dopaminergic neurons, or ablation of downstream neurons), can also produce new sleep disturbances^{71,74-78}.

Studies of dopaminergic pharmacotherapy using D1/D2 specific agents have yielded conflicting results, but it appears that in general high doses of agonists, which stimulate post-synaptic (D1) activity, have wake-promoting effects, while low doses which stimulate pre-synaptic activity (D2), promote slow-wave and REM sleep⁷³.

Further evidence comes from the anatomical mapping of DA neurons in the brain using retrograde axonal tracers or electrolytic lesions, which show that DA neurons receive inputs and send outputs to the basal forebrain, dorsal raphe nucleus, lateral hypothalamus, and thalamus, which place them at signaling crossroads where they have the potential to modulate sleep^{71,73}. The firing patterns of DA neurons have also been studied, and DA burst firing activity has been hypothesized to promote both REM sleep and wakefulness⁷³.

Glutamate

Neuronal degeneration and brain atrophy in HAD is most severe in frontal lobe and hippocampus, where glutamate is the primary excitatory neurotransmitter⁶¹. Glutamate neurotransmission is excitatory and is responsible for cortical activation and activity in the thalamus and ascending reticular activating system, which maintain a waking state⁷⁹.

Our hypothesis is that the increase in extracellular glutamate, caused or promoted by the multiple mechanisms described above, predisposes to neuronal damage or impaired astrocyte buffering activity, thereby potentially disturbing sleep, particularly if this damage occurs in the cortex, thalamus, and brainstem reticular formation.

In summary, neuronal damage in the glutamatergic and dopaminergic pathways caused by viral neurotoxic and inflammatory mechanisms could potentially lead to sleep disturbance in HIV-seropositive patients. Sleep disturbances could thus be an early sign

of CNS damage in HIV, and could be a marker for HAD. Based on our review of the literature, study of these systems would be promising for better understanding the mechanisms of sleep disturbance in HIV-seropositive individuals and are of interest as targets for treatment of sleep disturbance in this population.

Clinical implications

Sleep disturbance is very common in HIV-seropositive individuals. It may be more common in some subgroups of patients than others, such as those with longer time since diagnosis, later stages of the disease, and those with HAD. As a result, it might be particularly important to be vigilant for sleep disturbance in these groups and to administer appropriate treatments.

Given that an increased glutamatergic excitotoxicity could be responsible for sleep disturbances and neurocognitive deficits, the use of a benzodiazepine or non-benzodiazepine gamma-aminobutyric acid (GABA) modulating agent may yield the benefit of not just sedation, but reduced neuronal damage because of diminished excitatory transmission in the CNS. However, long-acting agents may exacerbate the daytime fatigue or contribute to daytime sedation, which is already a common complaint in this population^{80,81}.

One of the antidepressants that can be used for sleep-promoting effects is the 5HT_{2A}-, 5HT₃-, and α_2 -adrenergic receptor antagonist mirtazapine, and in HIV patients, this provides an additional benefit of prophylaxis or treatment against one of the CNS opportunistic infections by the human polyomavirus John Cunningham virus (JCV), which causes progressive multifocal leukoencephalopathy (PML).

Given the association of sleep disturbance with the development of HAD and the possible commonality of a role of increased glutamatergic activity in HAD and sleep disturbance, the onset of sleep disturbance may be useful as a marker for excitotoxic CNS damage. Also, NMDA-R antagonists like acamprosate or memantine, which have been shown in animal models⁸² but not clinical trials to protect against HIV dementia, may have a therapeutic effect on sleep disturbance that does not respond to traditional therapy.

Since HAD may reflect a relative state of dopamine deficiency similar to that in movement disorders like Parkinson's disease, D2-specific agonists should be used with caution because they may predispose to

sleep attacks and REM sleep disorders. Agents which block DA transmission, like antipsychotics or certain anti-emetics, may not only have sedating effects but also precipitate extrapyramidal motor deficits from the decrease in DA activity.

This review mainly reflects limitations in the available studies that have been carried out assessing the prevalence and correlates of insomnia in HIV-seropositive individuals. Most notably, variation in methodology across studies precluded our carrying out a formal meta-analysis. The available studies used a variety of different measures to assess sleep, only one study employed PSG, the gold standard measure of sleep physiology, and no studies employed insomnia diagnostic criteria to establish the presence of insomnia. The studies also did not provide sufficient data to definitively determine the relationship whether there are differences in the nature of sleep disturbance in earlier and later stages of disease, and as a function of severity of disease or CD4 counts/viral loads. Such information would be valuable as it may provide insight into unique neurophysiologic processes that lead to sleep disturbances, which could improve the treatment of sleep disturbance in this population.

Conclusions

In this review we found that prior studies estimated the rate of disturbed sleep, but not a single study estimated the prevalence of insomnia using insomnia diagnostic criteria, which require that sleep disturbance occur frequently, persistently, and in association with impairment in quality of life or daytime function. We also found that, in addition to correlates of sleep disturbance seen in the general population, there are also correlates specific to the HIV-seropositive population: stage and duration of HIV infection, and cognitive impairment. The most important conclusion of this review is that studies are needed to estimate the prevalence rate of insomnia in HIV-infected patients using insomnia diagnostic criteria. The rate of sleep disturbance identified in HIV-infected patients (29-97%) should not be compared against the approximately 10% prevalence of clinically significant insomnia in the general population, which would suggest that HIV infection is associated with an alarming increase in sleep problems. Instead, this rate is best compared with the rate of sleep disturbance in the general population, which is roughly 33%.

Our review also suggests that large-scale longitudinal studies are needed to confirm the correlates of insomnia or sleep disturbances in HIV. These correlates may be different in early vs. late-stage disease, and may reflect different underlying mechanisms. The HIV infection is a factor that could potentially predispose to or precipitate sleep disturbances due to psychosocial stress or anxiety with having to cope with a new disease, or it could precipitate and perpetuate these disturbances through a pathological process of neuronal injury. Another implication of this review is that studies of sleep disturbance or insomnia in HIV should take into account not just CD4 count and viral load, but also duration and stage of disease.

References

- Roth T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med.* 2007;3:S7-10.
- Reid S, Dwyer J. Insomnia in HIV infection: a systematic review of prevalence, correlates, and management. *Psychosom Med.* 2005; 67:260-9.
- Cruess D, Antoni M, Gonzalez J, et al. Sleep disturbance mediates the association between psychological distress and immune status among HIV-positive men and women on combination antiretroviral therapy. *J Psychosom Res.* 2003;54:185-9.
- Kremer H, Sonnenberg-Schwan U, Arendt G, et al. HIV or HIV-therapy? Causal attributions of symptoms and their impact on treatment decisions among women and men with HIV. *Eur J Med Res.* 2009; 14:139-46.
- Robbins J, Phillips K, Dudgeon W, et al. Physiological and psychological correlates of sleep in HIV infection. *Clin Nurs Res.* 2004;13:33-52.
- Corless I, Kirksey K, Kempainen J, et al. Lipodystrophy-associated symptoms and medication adherence in HIV/AIDS. *AIDS Patient Care STDS.* 2005;19:577-86.
- Phillips K, Sowell R, Boyd M, et al. Sleep quality and health-related quality of life in HIV-infected African-American women of childbearing age. *Qual Life Res.* 2005;14:959-70.
- Anis A, Nosyk B, Sun H, et al. Quality of life of patients with advanced HIV/AIDS: measuring the impact of both AIDS-defining events and non-AIDS serious adverse events. *J Acquir Immune Defic Syndr.* 2009;51:631-9.
- Omonuwa T, Goforth H, Preud'homme X, et al. The pharmacologic management of insomnia in patients with HIV. *J Clin Sleep Med.* 2009;5:251-62.
- Rihs T, Begley K, Smith D, et al. Efavirenz and chronic neuropsychiatric symptoms: a cross-sectional case control study. *HIV Med.* 2006; 7:544-8.
- Brown S, Atkinson H. Correlation of subjective sleep complaints, absolute T-4 cell number and anxiety in HIV illness. *Sleep Res.* 1991; 20:363.
- Darko D, McCutchan J, Kripke D, et al. Fatigue, sleep disturbance, disability, and indices of progression of HIV infection. *Am J Psychiatry.* 1992;149:514-20.
- Norman S, Chediak A, Freeman C, et al. Sleep disturbances in men with asymptomatic human immunodeficiency (HIV) infection. *Sleep.* 1992;15:150-5.
- Wheatley D, Smith K. Clinical sleep patterns in human immune virus infection. *Human Psychopharmacology.* 1994;9:111-15.
- Perkins D, Leserman J, Stern R, et al. Somatic symptoms and HIV infection: relationship to depressive symptoms and indicators of HIV disease. *Am J Psychiatry.* 1995;152:1776-81.
- Franck L, Johnson L, Lee K, et al. Sleep disturbances in children with human immunodeficiency virus infection. *Pediatrics.* 1999;104:e62.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th Text Revision (DSM-IV-TR)* (Washington, DC, 2000).
- American Academy of Sleep Medicine. *International Classification of Sleep Disorders, Revised: Diagnostic and Coding Manual (2nd ed)* (Westchester, Illinois, 2005).
- Buysse D, Reynolds C, Monk T, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28:193-213.
- Rothenberg S, Zozula R, Funesti J, McAuliffe V. Sleep habits in asymptomatic HIV-seropositive individuals. *Sleep Res.* 1990;19:342.
- Cohen F, Ferrans C, Vizgirda V, et al. Sleep in men and women infected with human immunodeficiency virus. *Holist Nurs Pract.* 1996; 10:33-43.
- Rubinstein M, Selwyn P. High prevalence of insomnia in an outpatient population with HIV infection. *J Acquir Immune Defic Syndr Hum Retroviro.* 1998;19:260-5.
- Anderson W, Weatherburn P. The needs of people with HIV in the UK: findings from a national survey. *Int J STD AIDS.* 2004;15:793-6.
- Vosvick M, Gore-Felton C, Ashton E, et al. Sleep disturbances among HIV-positive adults: the role of pain, stress, and social support. *J Psychosom Res.* 2004;57:459-63.
- Salahuddin N, Barroso J, Leserman J, et al. Daytime sleepiness, nighttime sleep quality, stressful life events, and HIV-related fatigue. *J Assoc Nurses AIDS Care.* 2009;20:6-13.
- Moeller A, Oechsner M, Backmund H, et al. Self-reported sleep quality in HIV infection: correlation to the stage of infection and zidovudine therapy. *J Acquir Immune Defic Syndr.* 1991;4:1000-3.
- Lee K, Portillo C, Miramontes H. The influence of sleep and activity patterns on fatigue in women with HIV/AIDS. *J Assoc Nurses AIDS Care.* 2001;12:19-27.
- Nokes K, Kendrew J. Correlates of sleep quality in persons with HIV disease. *J Assoc Nurses AIDS Care.* 2001;12:17-22.
- Hudson A, Portillo C, Lee K. Sleep disturbances in women with HIV or AIDS: efficacy of a tailored sleep promotion intervention. *Nurs Res.* 2008;57:360-6.
- Silva J, Sartorius M, Roth T. Special Report from a symposium held by the World Health Organization and the World Federation of Sleep Research Societies: An Overview of insomnias and related disorders - recognition, epidemiology, and rational management. *Sleep.* 1996; 19:523-25.
- Krystal A. Treating the health, quality of life, and functional impairments in insomnia. *J Clin Sleep Med.* 2007;3:63-72.
- Fowler M, Melnick S, Mathieson B. Women and HIV. *Epidemiology and global overview.* *Obstet Gynecol Clin North Am.* 1997;24:705-29.
- Nunez M, Gonzalez de Requena D, Gallego L, et al. Higher efavirenz plasma levels correlate with development of insomnia. *J Acquir Immune Defic Syndr.* 2001;28:399-400.
- Fumaz C, Tuldra A, Ferrer M, et al. Quality of life, emotional status, and adherence of HIV-1-infected patients treated with efavirenz versus protease inhibitor-containing regimens. *J Acquir Immune Defic Syndr.* 2002;29:244-53.
- Kenedi C, Goforth H. A systematic review of the psychiatric side-effects of efavirenz. *AIDS Behav.* 2011;15:1803-18.
- Bartlett J, Johnson J, Herrera G. Long-term results of initial therapy with abacavir and lamivudine combined with efavirenz, amprenavir/ritonavir or stavudine. *J Acquir Immune Defic Syndr.* 2006;43:284-92.
- Gutierrez-Valencia A, Viciano P, Palacios R. Stepped-dose vs full-dose efavirenz for HIV infection and Neuropsychiatric adverse events: a randomized trial. *Ann Intern Med.* 2009;151:149-56.
- Jena A, Sachdeva R, Sharma A, et al. Adverse drug reactions to non-nucleoside reverse transcriptase inhibitor-based antiretroviral regimen: a 24-week prospective study. *J Int Assoc Physicians AIDS Care (Chic Ill).* 2009;8:318-22.
- Petit D, Montplaisir J, Boeve Bradley F. *Alzheimer's Disease and Other Dementias. Principles and Practice of Sleep Medicine.* 2005; 71:853-62.
- Power C, Selnes O, Grim J, et al. HIV Dementia Scale: a rapid screening test. *J Acquir Immune Defic Syndr Hum Retroviro.* 1995;8:273-8.
- Brew B, Crowe S, Landay A, et al. Neurodegeneration and ageing in the HAART era. *J Neuroimmune Pharmacol.* 2009;4:163-74.
- Bell J. An update on the neuropathology of HIV in the HAART era. *Histopathology.* 2004;45:549-59.
- Kaul M, Garden G, Lipton S. Pathways to neuronal injury and apoptosis in HIV-associated dementia. *Nature.* 2001;410:988-94.
- Langford T, Letendre S, Larrea G, et al. Changing patterns in the neuropathogenesis of HIV during the HAART era. *Brain Pathol.* 2003; 13:195-210.
- World Health Organization. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children.* 2007.
- Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep.* 1992; 41:1-19.
- Ozdener H. Molecular mechanisms of HIV-1 associated neurodegeneration. *J Biosci.* 2005;30:391-405.
- Power C, Boisse L, Rourke S, et al. NeuroAIDS: an evolving epidemic. *Can J Neurol Sci.* 2009;36:285-95.

49. Kaul M, Lipton S. Mechanisms of neuronal injury and death in HIV-1 associated dementia. *Curr HIV Res.* 2006;4:307-18.
50. Cespedes M, Aberg J. Neuropsychiatric complications of antiretroviral therapy. *Drug Saf.* 2006;29:865-74.
51. Nath A, Geiger J. Neurobiological aspects of human immunodeficiency virus infection: neurotoxic mechanisms. *Prog Neurobiol.* 1998;54:19-33.
52. King J, Eugenin E, Buckner C, et al. HIV tat and neurotoxicity. *Microbes Infect.* 2006;8:1347-57.
53. Brabers N, Nottet H. Role of the pro-inflammatory cytokines TNF-alpha and IL-1beta in HIV-associated dementia. *Eur J Clin Invest.* 2006;36:447-58.
54. Clapham P, McKnight A. HIV-1 receptors and cell tropism. *Br Med Bull.* 2001;58:43-59.
55. Bansal A, Mactutus C, Nath A, et al. Neurotoxicity of HIV-1 proteins gp120 and Tat in the rat striatum. *Brain Res.* 2000;879:42-9.
56. Berger J, Nath A. HIV dementia and the basal ganglia. *Intervirol.* 1997;40:122-31.
57. Kure K, Weidenheim K, Lyman W, et al. Morphology and distribution of HIV-1 gp41-positive microglia in subacute AIDS encephalitis. Pattern of involvement resembling a multisystem degeneration. *Acta Neuropathol.* 1990;80:393-400.
58. Hofmann B, Nishanian P, Fan J, et al. HIV Gag p17 protein impairs proliferation of normal lymphocytes in vitro. *AIDS.* 1994;8:1016-17.
59. Kruman I, Nath A, Maragos W, et al. Evidence that Par-4 participates in the pathogenesis of HIV encephalitis. *Am J Pathol.* 1999;155:39-46.
60. Bennett B, Rusyniak D, Hollingsworth C. HIV-1 gp120-induced neurotoxicity to midbrain dopamine cultures. *Brain Res.* 1995;705:168-76.
61. Ferris M, Mactutus C, Booze R. Neurotoxic profiles of HIV, psychostimulant drugs of abuse, and their concerted effect on the brain: current status of dopamine system vulnerability in NeuroAIDS. *Neurosci Biobehav Rev.* 2008;32:883-909.
62. Navia B, Cho E, Petito C, et al. The AIDS dementia complex: II. Neuropathology. *Ann Neurol.* 1986;19:525-35.
63. Brew B, Rosenblum M, Cronin K, et al. AIDS dementia complex and HIV-1 brain infection: clinical-virological correlations. *Ann Neurol.* 1995;38:563-70.
64. Reyes M, Faraldi F, Senseng C, et al. Nigral degeneration in acquired immune deficiency syndrome (AIDS). *Acta Neuropathol.* 1991;82:39-44.
65. Fujimura R, Goodkin K, Petito C, et al. HIV-1 proviral DNA load across neuroanatomic regions of individuals with evidence for HIV-1-associated dementia. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;16:146-52.
66. Reynolds G, Sardar A. 5-Hydroxytryptamine deficits in the caudate nucleus in AIDS. *AIDS.* 1996;10:1303-4.
67. Sardar A, Czudek C, Reynolds G. Dopamine deficits in the brain: the neurochemical basis of parkinsonian symptoms in AIDS. *Neuroreport.* 1996;7:910-12.
68. Wang G, Chang L, Volkow N, et al. Decreased brain dopaminergic transporters in HIV-associated dementia patients. *Brain.* 2004;127:2452-8.
69. Berger J, Kumar M, Kumar A, et al. Cerebrospinal fluid dopamine in HIV-1 infection. *AIDS.* 1994;8:67-71.
70. Nath A, Anderson C, Jones M, et al. Neurotoxicity and dysfunction of dopaminergic systems associated with AIDS dementia. *J Psychopharmacol.* 2000;14:222-7.
71. Rye D. The two faces of Eve: dopamine's modulation of wakefulness and sleep. *Neurology.* 2004;63:S2-7.
72. Arnulf I, Nielsen J, Lohmann E, et al. Rapid eye movement sleep disturbances in Huntington disease. *Arch Neurol.* 2008;65:482-8.
73. Monti J, Monti D. The involvement of dopamine in the modulation of sleep and waking. *Sleep Med Rev.* 2007;11:113-33.
74. Jankel W, Niedermeyer E, Graf M, et al. Case report: polysomnographic effects of thalamotomy for torsion dystonia. *Neurosurgery.* 1984;14:495-8.
75. Bricolo A. Insomnia after bilateral stereotactic thalamotomy in man. *J Neurol Neurosurg Psychiatry.* 1967;30:154-8.
76. Bricolo A. [Clinical and electroencephalographic considerations on a case of insomnia appearing after bilateral stereotaxic thalamotomy]. *Riv Neurobiol.* 1966;12:622-38.
77. De Cock V, Vidailhet M, Arnulf I. Sleep disturbances in patients with parkinsonism. *Nat Clin Pract Neurol.* 2008;4:254-66.
78. Lima M, Andersen M, Reksidler A, et al. The role of the substantia nigra pars compacta in regulating sleep patterns in rats. *PLoS One.* 2007;2:e513.
79. Jones B. (Ed). *Basic Mechanisms of Sleep-Wake States* (Elsevier, Philadelphia, 2005).
80. Breitbart W, McDonald M, Rosenfeld B, et al. Fatigue in ambulatory AIDS patients. *J Pain Symptom Manage.* 1998;15:159-67.
81. Sullivan P, Dworkin M. Prevalence and correlates of fatigue among persons with HIV infection. *J Pain Symptom Manage.* 2003;25:329-33.
82. Anderson E, Gendelman H, Xiong H. Memantine protects hippocampal neuronal function in murine human immunodeficiency virus type 1 encephalitis. *J Neurosci.* 2004;24:7194-8.
83. Ammassari A, Murri R, Pezzotti P, et al. Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. *J Acquir Immune Defic Syndr.* 2001;15:28:445-9.