

# Poor Sleep Quality in Persons Living with HIV: a Systematic Review and Meta-Analysis

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## Review Article

### ABSTRACT

**Aim:** To review and meta-analyze poor sleep quality in persons living with HIV.

**Method:** Using the Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) guidelines, we extracted information from studies about poor sleep quality in persons with HIV. Most studies adopted a cross-sectional design. Data were extracted on study details, eligibility, and results.

**Results:** We identified seventeen papers from five of which we calculated effect sizes. There was evidence of a relationship between HIV and occurrence of poor sleep quality. However, further studies are needed on variables that affect sleep quality to clearly explain the differences between good and bad sleepers.

**Conclusion:** This review has shown that people with HIV are vulnerable to poor sleep quality. The main factors related to this phenomenon are use of antiretroviral medications and psychological problems such as anxiety, depression and stress.

**KEYWORDS** Sleep; HIV, Sleep disorders, Anti-retroviral agents

### INTRODUCTION

HIV and AIDS are a major public health problem in many countries [1-2]. In the last 30 years, AIDS has become an epidemic disease with devastating consequences for families, communities and society. UNAIDS estimates that more than 7,000 people acquire HIV infection by day, and one person dies every 20 seconds of an AIDS-related disease throughout the world [3].

Persons living with HIV are more likely to experience health disorders than other groups, including problems that are not necessarily related to the immune system. For example, about 70% of adults with HIV experience sleep disturbances, such as insomnia, excessive daytime sleepiness and fragmented sleep. It is still unclear whether poor sleep quality is associated with CD4 cell count, HIV viral load, social problems, or antiretroviral therapy [4].

Some studies have been developed to identify which factors negatively affects sleep and rest in people with HIV. Sleep quality and daily sleep are related to fatigue, as well as anxiety and depression, which are problems that are frequent in persons living with HIV [5]. A four-year cohort study has shown that manifestations such as pain, depression, daytime sleepiness, and CD4<sup>+</sup> T-cell increase were frequent in people with HIV who also had a very low CD4<sup>+</sup> T-cell count and poor sleep quality [6].

Another study has shown that people with HIV have twice the chances of developing sleep disorders than those without the virus [7]. The use of specific drugs, such as non-nucleoside reverse transcriptase inhibitors may be involved [8]. This is accentuated in people with advanced infection. In this case, the relationship between CD4<sup>+</sup> T-cell count and sleep quality seems to be inverse due to signs and symptoms such as pain, diarrhea, incontinence, fever, cough and dyspnea [7].

It is well known that sleep disorders can affect a people's quality of life significantly. Poor sleep quality can cause insomnia, respiratory, cardiac and metabolic disorders, depression, and nocturnal movement disorders. Lastly, a poor night's sleep may affect daily activities and work performance, as well as mood and physiological parameters [8].

People with HIV represent a vulnerable group, as they suffer from the social stigma of the disease. Besides that, HIV treatment includes medications that have unpleasant side effects and increase the risk for metabolic syndrome. Thus, poor sleep quality in these individuals may be a clinical predictor of subsequent problems that needs to be investigated.

Before this study, we conducted an extensive bibliographic review in Pubmed and Google Scholar databases and no previous studies have been found on our subject. We also noticed a scarcity of data by searching gray literature and by hand searching.

We believe that society needs solid scientific evidences regarding the living habits and health indicators of persons living with HIV that goes beyond the study of socioeconomic, cultural, and political factors [9]. Bibliographic review studies are important tools to support the practice since they bring practicality to the decision-making process and can be used to update health care workers. This study aims to review systematically the available evidence from studies on sleep quality in persons with HIV infection.

## **MATERIALS AND METHODS**

A systematic review and meta-analysis of studies that reported the prevalence of sleep disorders in persons with HIV infection was undertaken using the PRISMA protocol [10]. The analysis included descriptive and statistical data from the selected studies.

### **Eligibility Criteria**

Eligible studies included published articles that investigated sleep disorders in persons with HIV, categorized as original research, published from 2007 to 2018, and written in English, Spanish or Portuguese. We excluded reviews, case reports, book chapters, monographs, dissertations or theses, newspaper articles, and editorials.

### **Search Strategy and Study Selection**

A systematic search of Pubmed, Science Direct, BDNF, and LILACS was performed from December 2017 to January 2018. Medical Subject Headings (MeSH) and text terms were used in the search, including the following: 'sleep', 'human immunodeficiency virus', and 'acquired immunodeficiency syndrome'.

One author screened the titles of retrieved studies and chose those of potential relevance. Then, two authors, using a form, examined eligibility of the abstracts. Disagreements were resolved by discussion.

### **Data Extraction**

Two reviewers extracted relevant data from each study and completed the data extraction form. Data extracted included: (1) study details (authors, year of publication, country of publication, publication type); (2) study eligibility (type of study, participants, outcome measures); and (3) results (comparison, outcome, subgroup analyses).

### **Data Analysis**

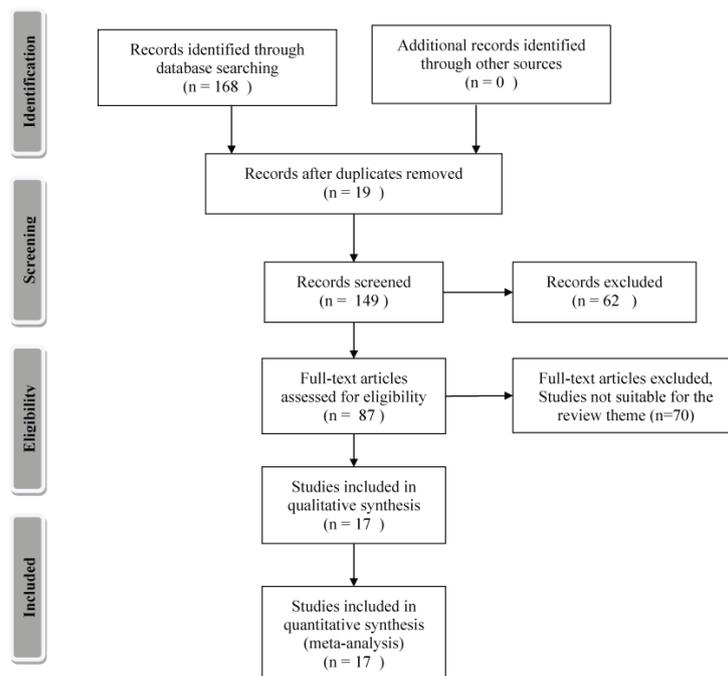
Meta-analyses were undertaken using Stata® version 14. Because of the predominance of cross-sectional research, we conducted a meta-analysis of proportions. In case of significant test for heterogeneity, a random effects method was applied, and a 95% confidence interval (CI) was constructed.

All relevant data such as bibliographical data, study aims, design, scenario, participants, year of publication, and other were entered in an Excel spreadsheet.

## **RESULTS**

### **Description of Studies**

The search yielded 168 records. Seventeen studies were included (Figure 1).



**Figure 1.** Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

Most studies were cross-sectional, developed in the last five years, authored by physicians, and published in Brazil, China or the United States. The frequency of poor sleep quality based on the Pittsburgh Sleep Quality Index (PSQI) scores ranged from 46.7% to 80%. None of the studies employed polysomnography (PSG) to assess sleep quality. The most frequent symptoms related to bad sleep quality in the studies were daytime somnolence and depression (Table 1).

**Table 1.** Main characteristics of the seventeen included studies.

Year	Title	Authors	Objectives	Main findings
2008	Women living with HIV/AIDS: Sleep impairment, anxiety and depression symptoms	Junqueira et al. [11]	To evaluate sleep impairment, symptoms of anxiety and depression, and associations with sleep characteristics of sleep in female HIV/AIDS patients.	Sleep quality was more impaired in those with HIV/AIDS than in control subjects.
2009	Daytime sleepiness, nighttime sleep quality, stressful life events, and HIV-related fatigue	Salahuddin et al. [12]	To describe the relationships between daytime sleepiness, nighttime sleep quality, stressful life events, and HIV-related fatigue.	Poor nighttime sleep was significantly correlated with fatigue intensity ( $r = .46, p < .05$ ), as was daytime sleepiness ( $r = .20, p < .05$ ).
2012	Sleep quality in HIV-positive outpatients	Ferreira et al. [13]	To characterize the sleep quality of HIV seropositive outpatients with or without AIDS symptoms.	Sixty-five patients (53.3%) reported good quality sleep, while 57 (46.7%) had poor sleep quality, according to the Pittsburgh Sleep Quality Index (PSQI).
2012	Sleepiness and sleep quality in patients with HIV infection	Wibbeler et al. [14]	To evaluate the sleep quality of HIV patients referred to internal and neurological HIV clinics.	All scores of the Epworth Sleepiness Scale, PSQI, and the Beck's Depression Inventory were significantly increased in the HIV infected patients as compared to the control group.
2012	Prevalence and factors associated with sleep disturbances among early-treated HIV-infected persons	Cianflone et al. [15]	To assess the prevalence of sleep disorders in patients with HIV.	Forty-six percent of HIV-infected persons had insomnia (PSQI >5), and 30% reported daytime drowsiness (ESS ≥10).
2013	Prevalence and associated factors to insomnia and poor sleep in patients with HIV/AIDS at Seville, Spain	Corpas et al. [16]	To determine the prevalence and associated factors of poor sleep quality and insomnia in HIV+ patients in Spain.	Mean Insomnia Severity Index score was 7.3 (SD = 9.1); 40.9% of the poor sleepers showed moderate or severe insomnia. In patients classified as good sleepers the mean Insomnia Severity

				Index score was 1.3 (DE = 2.3), whereas in patients classified as bad sleepers mean Insomnia Severity Index score was 12.0 (DE = 9.7) (p < 0.001). 40.9% of poor sleepers had moderate severity or severe insomnia.
2013	Improving Sleep Hygiene Behavior in Adults Living with HIV/AIDS: a randomized control pilot study of the SystemCHANGE™-HIV Intervention	Webel et al. [17]	To evaluate the feasibility and estimate the magnitude of the effect of a novel, evidence-based behavioral intervention, SystemCHANGE™-HIV on sleep outcomes and quality of life in people living with HIV compared with a usual care control group.	At the end of the intervention, participants in the intervention group experienced a 10 minute/night increase in sleep time (p=0.71), a 2.3% increase in sleep efficiency (p=0.33), a 2% decrease in sleep fragmentation (p=0.57), a 0.7% decrease in sleep disturbances (p=0.79), and a 0.5% increase in sleep-related impairments (p=0.88) relative to the control group. Participants in the intervention group experienced a 2.1 point increase in life satisfaction (p=0.79) and 3.0 increase in overall functioning (p=0.57).
2013	A Pilot study of sleep quality and rest-activity patterns in persons living with HIV	Taibi et al. [18]	To explore sleep quality and rest-activity patterns in persons living with HIV.	Compared to accepted norms for "good sleepers," sleep diaries described moderate sleep disturbance, and actigraphy revealed severe sleep disturbance. Results of the study suggest that sleep disturbance remains problematic in persons living with HIV.
2014	Sleep quality in Efavirenz-treated Chinese HIV patients – comparing between GT and GG genotype of CYP2B6-516 G/T polymorphisms	Lee et al. [19]	To evaluate prospectively the associations between CYP2B6 516 G/T polymorphisms and sleep quality following treatment with an efavirenz-based regimen.	Using generalized estimating equations analysis to track the variance over time, there was poorer PSQI in GT compared to GG genotype, while GT genotype was associated with a higher efavirenz level of >4 mg/L.
2014	HIV Tat protein affects circadian rhythmicity by interfering with the circadian system	Wang et al. [20]	To test the hypothesis that the sleep quality of patients with HIV/AIDS affected by an altered circadian rhythm correlates with cerebrospinal HIV Tat protein concentration.	The circadian amplitude of systolic blood pressure and the PSQI score were negatively related with HIV Tat protein concentration, while the melatonin value was positively related with Tat protein concentration.
2014	Quality of sleep in an HIV population on antiretroviral therapy at an urban tertiary centre in Lagos	Oshinaike et al. [21]	To determine the prevalence of sleep disturbance and its associated characteristics in HIV-positive outpatients on HAART using the PSQI.	The mean PSQI score of those with poor quality sleep was comparable to that of those with good quality sleep. On multivariate analyses, the independent associations with sleep quality were the duration since HIV diagnosis (p=0.29), efavirenz based regimen (p<0.001), and lower CD4 cell count (p<0.001).
2015	Prevalence and risk factors of sleep disturbance in a large HIV-infected adult population	Allavena et al. [22]	To evaluate the prevalence and factors associated with sleep disturbances in French adult HIV-infected outpatients.	Poor sleep quality was observed in 47 % of the patients, and moderate to serious depressive symptoms in 19.7 %. Factors significantly associated with sleep disturbances were depression, male gender, active employment, living single, tobacco-smoking, duration of HIV infection, nevirapine or efavirenz-including regimen.
2015	La mala calidad de sueño se asocia a una menor adherencia al tratamiento antirretroviral de gran actividad en pacientes peruanos con infección por VIH/SIDA	Tello-Velásquez et al. [23]	To analyze the association between poor quality of sleep and adherence to highly active antiretroviral therapy (HAART) in 389 Peruvian patients with HIV/AIDS.	Poor sleep quality was observed in 47 % of the patients, and moderate to serious depressive symptoms in 19.7 %. Factors significantly associated with sleep disturbances were depression, male gender, active employment, living single, tobacco-smoking, duration of HIV infection, nevirapine or efavirenz-

				including regimen. Prevalence of poor sleepers was high in this HIV adult outpatient population.
2016	Engagement in care, psychological distress, and resilience are associated with sleep quality among HIV-positive gay, bisexual, and other men who have sex with men	Downing et al. [24]	To investigate risk and protective factors associated with sleep quality among a national sample of HIV-positive gay, bisexual, and other men who have sex with men (GBMSM).	Moderate/severe poor quality of sleep remained associated with inadequate treatment adherence in both a crude and an adjusted model.
2016	Sleep, Fatigue, and Problems With Cognitive Function in Adults Living With HIV	Byun et al. [25]	To examine associations of sleep and fatigue with self-reported cognitive problems in 268 adults living with HIV.	Poorer self-reported sleep quality ( $p < .001$ ), short or long total sleep time ( $<7$ or $>8$ vs. 7-8 hours, $p = .015$ ), and greater fatigue ( $p < .001$ ) were associated with lower self-reported cognitive function scores after controlling for demographic and clinical characteristics.
2017	The impact of daily and trait loneliness on diurnal cortisol and sleep among children affected by parental HIV/AIDS	Zilioli et al. [26]	To investigate the impact of trait loneliness and daily loneliness on diurnal cortisol and daily reports of sleep in a large sample of children aged 8 to 15 years affected by parental HIV/AIDS in rural China.	High levels of trait loneliness were found to predict lower morning cortisol levels, longer time in bed, lower sleep quality, and a higher number of night awakenings. Daily loneliness was associated with a flatter diurnal cortisol slope and shorter time in bed.
2018	Increased CD4 counts, pain and depression are correlates of lower sleep quality in treated HIV positive patients with low baseline CD4 counts	Redman et al. [27]	To investigate whether subjective sleep quality was associated with CD4+ T lymphocyte reconstitution in treated South African HIV+ patients.	Patients had overall poor sleep quality (average PSQI = 7.7). 61% reporting PSQI $> 5$ , 41% had clinical depression (average BDI = 17) and 55% reported pain. In two separate multivariate analyses, both the overall CD4 count increase from baseline ( $p = 0.0006$ ) and higher current CD4 counts ( $p = 0.0007$ ) were associated with worse sleep quality.

None of the manuscripts mentioned the existence of any health policy or protocol aimed at improving sleep quality of persons living with HIV. The main categories covered by the studies were use of medications and psychological problems related to HIV. However, characteristics related to the treatment of sleep problems, quality of life, social interaction or prejudice are little explored. Preventive and sleep hygiene measures were not further proposed in the reviewed studies. From the studies, we can summarize that poor sleep quality in persons living with HIV is related to the use of specific medications and to the presence of psychological manifestations like anxiety, depression and stress.

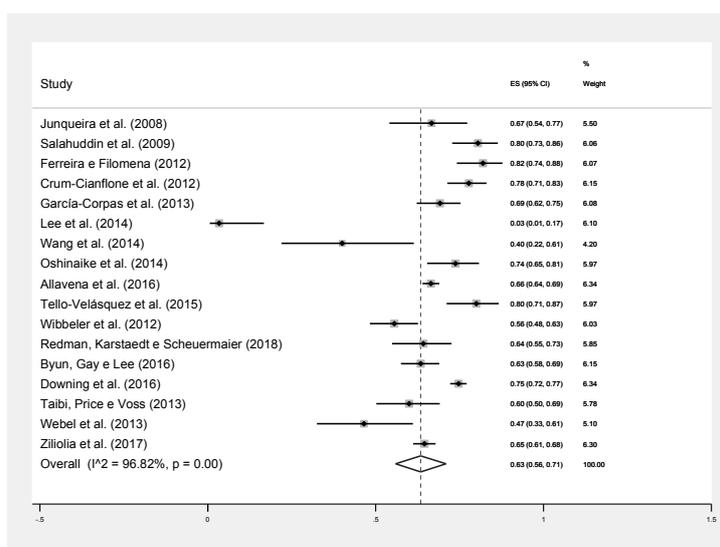


Figure 2. Forest plot: proportion subjects living with HIV who had sleep disorders.

The meta-analysis showed an association between living with HIV and poor sleep quality ( $p < 0.001$ ) and yielded a positive overall effect (SMD [95% confidence interval] = 0.63 [0.56-0.71]), with probability of superiority of 66.4% (Figure 2).

## DISCUSSION

This study showed that only a few studies contribute to the understanding of the relationship between poor sleep quality and living with HIV. Most studies assessed sleep quality using the PSQI, a self-rated questionnaire or global sleep quality and specific aspects of sleep disturbance. From the analysis of the manuscripts, we observed that the prevalence of poor sleep quality, according to the PSQI values, ranged from 46.7% to 80% [11-25].

We found no studies developed in high-HIV countries such as India, despite the worrisome scenario and socioeconomic disadvantage of such regions [15]. The danger is that, if there is a concentration of investments/efforts on studies about other phenomena (e.g. adherence to drug treatment, prevention and treatment of co-infections), poor sleep quality is not given the importance that it deserves.

The results of the meta-analysis corroborate the effect of HIV infection on sleep quality and reinforces that these individuals are vulnerable to sleep disorders. Factors such as treatment program, social stigma, illness-related complications and psychological stress were pointed out in the studies as possible causes of the problem.

Drug therapy, for example, is an important factor that should be closer examined. HIV therapy adherence is critical for the minimization of infection-related complications and, despite of its contraindications and adverse events, must be prioritized. However, it is well-known that most antiretroviral drugs alter the sleep and rest patterns, and that aspect even affects treatment adherence [16]. Considering this, why sleep quality is still not recognized as a major factor for the institution of appropriate therapy?

Another issue to be emphasized is the need to expand the number of studies coordinated by non-doctor healthcare professionals, such as nurses, occupational therapists, physical educators, psychologists, dentists, nutritionists, etc. Persons living with HIV should be cared using a holistic approach that stresses the multiplicity of factors that affect sleep hygiene (including economic, gender, social and religious issues). It is a fact that quality of life and its components may contribute to the sleep quality. In this way, a multidisciplinary approach can throw new light on sleep disorders.

In this review, we found no significant associations involving variables such as gender, occupation, form of contamination, disease stage or number of anti-retrovirals taken and sleep quality. However, one study showed significant differences between good and bad sleepers regarding sleep latency, duration and efficiency [11]. In this sense, the review was useful to clarify how to classify patients with sleep disturbances, but further studies are needed on variables that affect sleep quality to clearly explain the differences between good and bad sleepers.

Authors investigated the relationship between sleep disorders, depressive symptoms and medication adherence in women. The authors found a greater frequency of sleep disorders, depressive symptoms and poor medication adherence in women with HIV [8].

Other authors agree that people with HIV are more vulnerable to poor sleep quality, depression and anxiety than other groups of patients. A multivariate analysis showed that smokers, singles and unemployed are more likely to present the above-mentioned problems. There seems to be a directly proportional relationship between PSQI scores and anxiety cases in this group of patients [16,21,23].

Sleep complaints of people with HIV includes waking up in the middle of the night or early in the morning, getting up to go to the restroom during the night, and others that are all common to non-HIV persons [11]. What these people may overlook is the relationship of such complaints to the prescribed pharmacological treatment. Some antiretroviral drugs, especially efavirenz can trigger psychiatric and psychological complaints such as agitation, hallucinations, amnesia, anxiety, mental confusion, convulsions, depression, difficulty concentrating, irritability, insomnia, nightmares and vivid dreams. Furthermore, it is important to keep in mind that poor sleep quality is a depressant phenomenon for the immune system (which is already weakened in HIV patients).

Two studies indicate that changes in sleep patterns occur in higher proportions in HIV patients (80% to 100%) and they are attributed to the infection itself and to other factors directly related to it [7,9]. It is also known that the HIV virus can cross the blood-brain barrier and cause neurological changes, such as meningitis, polyneuropathy, myelopathy and even dementia. However, there is a discourse that anxiety, depression and socioeconomic problems would be the main disruptors of sleep quality [27].

By gathering evidences from the reviewed studies, we concluded that use of medications, anxiety, depression, and stress are the main factors that influence sleep quality in persons with HIV infection. Besides that, daytime somnolence was reported in many studies, which is a relevant finding since this symptom usually compromise the quality of life.

The analyzed studies have limited levels of evidence, so it is not possible to clarify many questions regarding sleep quality in people with HIV based on their findings. We believe that further studies with higher evidence levels are needed for definite conclusions to be reached about sleep quality in people with HIV.

## CONCLUSION

This review has emphasized the fact that HIV patients are vulnerable to poor sleep quality. The main factors possibly related to this phenomenon are use of antiretrovirals (coupled with side effects), and psychological problems such as anxiety, depression and stress. Experimental research must be conducted in order to clarify cause-effect relationships. For example, it is important to examine whether the effect of anti-retroviral drugs, HIV viral load, and CD4 cell count are affected by brain waves during sleep. We also suggest that further studies should be based on accurate objective measures, such as actigraphy and PSG.

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