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Predictors of Sleep Disorders among HIV Out-Patients in a Tertiary Hospital

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Predictors of Sleep Disorders among HIV Out-Patients in a Tertiary Hospital

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Abstract

Human immunodeficiency virus (HIV)-infected individuals have been shown to have a high prevalence of sleep disturbances. Both the effects of the virus and the antiretroviral drugs may cause sleep disturbances. We sought to determine the prevalence and predictors of sleep disorders among HIV seropositive adult subjects presenting at an outpatient hospital setting. One hundred and fifty six subjects were recruited for the study by using a sleep disorder screening questionnaire. The mean ages of the participants were 38.7 ± 9.23 and 39.5 ± 9.23 for those with and those without sleep disorder, respectively. The prevalence rate of sleep disorders was 46.2%. Elevated systolic blood pressure, lower CD4 count levels, and being on the highly active antiretroviral therapy combination TDF/3TC/ATZ/lpvr were associated with sleep disorders. The high prevalence rate observed necessitates routine screening for sleep disorders among HIV/AIDs patients.

Keywords: HIV; Sleep disorders; Predictors.

1. INTRODUCTION

It has been shown that disturbances in sleep can affect the normal physical, mental, and emotional functioning in human immunodeficiency virus (HIV)-infected individuals [1, 2]. These individuals have been known to have a high prevalence of disturbance ranging from 40% to 70% [3-5]. The combined effects of the virus and the antiretroviral drugs may cause sleep disturbances. There are reports of high rates of neuropsychiatric side effects, including insomnia in patients on efavirenz-based therapies. Efavirenz is associated with decrease in sleep duration which usually resolves within the first week of treatment [6, 7]. Higher rates of neuropsychiatric disorders in patients of African origin have been reported to be linked with the increased serum levels of efavirenz [8, 9]. It is postulated that the defective CYP2B6 G516T variant allele, which is common in African population, impairs the efavirenz metabolism, thus increasing the efavirenz plasma concentrations, thereby leading to toxicity [10, 11].

Moreover, anxiety over the illness, financial concerns, stigmatization, depression, suicidal thoughts, and unemployment are other psychosocial causes of sleep disturbances in the HIV population [12] Sleep disturbances occur throughout the stages of the infection, being more prevalent in the advanced stage [13]. It can be associated with lack of attention, concentration, fatigue, memory/mood swings, and reduction in energy levels [14, 15]. It may also increase the risk of cardiovascular morbidity and mortality, and psychiatric disorders with effects on health care utilization [16]. HIV individuals with sleep problems are less likely to adhere to their antiretroviral therapy regimens as reported in some studies, probably as a result of depression [17, 18]. This nonadherence may result in disease progression, the development of resistant strains, and treatment failure [19]. With increasing life expectancy of people living with HIV because of the use of antiretroviral therapy (ART), sleep disturbances may negatively impact on their quality of life and work performance. Ascertaining the quality of sleep and its effects could help in preventing complications that may arise from HIV disease or the use of ART.

The objective of this study is to determine the prevalence and predictors of sleep disorders among HIV seropositive adult subjects on ART attending the out-patient special treatment clinic (STC) of the University of Calabar Teaching Hospital, Calabar.

2. METHODS

This was a cross-sectional study conducted for 6 months from November 2016 to March 2017 at the Special Treatment Clinic of the University of Calabar Teaching Hospital, Calabar South, South Nigeria. Ethical clearance was obtained from the Health Research Ethical Committee of the University of Calabar Teaching Hospital (UCTH) before commencement of the study. Adult HIV seropositive subjects who provided written consent were recruited into the study. Pregnant subjects three months earlier,

those working night shift schedules, and those considerably ill to require hospital admission were excluded from the study. Sleep disorders were evaluated using a sleep disorder screening questionnaire [20], which has 34 items/questions. If a patient scores three or more marks in questions 1-12, the patient shows the symptoms of sleep apnea. Three or more scores in questions 13-19 reflect symptoms of insomnia. In questions 20-29, three or more marks show the symptoms of narcolepsy; whereas, any three or more marks in questions 28-34 show symptoms of restless leg syndrome. A total of 170 subjects were recruited for the study; however, only 156 had complete information that is suitable for the analysis. For all patients, the data on the laboratory tests included the following: serum electrolytes (sodium, potassium), bicarbonate urea, creatinine as well as liver function test, mainly the liver enzymes such as aspartate transaminase (AST), and alanine transaminase (ALT). The Estimated glomerular filtration rate of the patients was calculated using the Cockcroft and Gault equations for males and females, respectively [21]. In addition, the ratio of AST to ALT was calculated to help differentiate between the causes of liver damage or hepatotoxicity [22].

2.1. Data Analysis

The data obtained were analyzed using Statistical Package for Social Sciences (SPSS) version 22. Quantitative data were presented as mean ± SD, and categorical variables were presented as percentages. Statistical comparisons were performed using independent sample *t*-test and Chi-square test as appropriate. In contrast, logistic regression analysis was used to determine the predictors of sleep disorder. Significant levels were fixed at $p < 0.05$

3. RESULTS

Table 1: Socio-demographic characteristics of study participants.

Variable	Frequency (*N* = 156)	Percentage (%)
Gender		
Male	41	26.3
Female	115	73.7
Age category (years)		
20-39	92	59.0
40-59	59	37.8
60 above	5	3.2
BMI category (kg/m²)		
<18.5	4	2.6
18.5-24.9	78	50.0
25.0-29.9	55	35.3
30 above	19	12.2
Religion		
Christians	154	98.7
Muslims	2	1.3
Educational status		
No formal education	4	2.6
Primary	30	19.2
Secondary	56	35.9
Tertiary	66	42.3
Marital status		
Married	87	55.8
Single	41	26.3
Divorced	6	3.8
Widowed/widower	22	14.1
Occupation		
Student	4	2.6
Trader	47	30.1
Farmer	11	7.1
Civil servant	33	21.2
Public servant	21	13.5
Artisan	21	13.5
Unemployed	19	12.2
Alcohol use		
Yes	19	12.2
No	137	87.8
Tobacco use		
Yes	3	1.9
No	153	98.1

Table 1 shows that majority of the participants were females (73.7%), mainly younger patients (20-39 years) constituting 59.0% of the study population. In addition, most of the participants were traders (30.1%) with majority not taking alcohol (87.8%) and tobacco (98.1%).

Table 2 shows that TDF/3TC/ATZ/lpvr combination of ART and lower CD4 count levels were significantly associated with the presence of sleep disorder in HIV patients ($p < 0.05$). All the other parameters are not statistically significant ($p > 0.05$).

In Table 3, SBP was significantly higher in patients with sleep disorder as compared to those without sleep disorder ($p < 0.05$). However, the creatinine levels are higher and the eGFR is lower in patients without sleep disorder. In contrast,

Table 2: Clinical and biochemical parameters of the subjects.

Variable	Sleep disorder present *N* = 72(46.2%), %	Sleep disorder absent *N* = 84(53.8%), %	*p*-value
Gender			
Male	21(51.2)	20(48.8)	0.449
Female	51(44.3)	64(57.3)	
Age category (years)			
20-39	48(52.2)	44(47.8)	0.110
40-59	21(35.6)	38(64.4)	
60 above	3(60.0)	2(40.0)	
BMI category (kg/m²)			
<18.5	1(25.0)	3(75.0)	
18.5-24.9	36(46.2)	42(53.8)	0.335
25.0-29.9	29(52.7)	26(47.3)	
30 above	6(31.6)	13(68.4)	
eGFR (mls/min)			
<90	42(51.2)	40(48.8)	
60-89	27(43.5)	35(56.5)	0.272
30-59	3(27.3)	8(72.7)	
15-29	0(0.0)	1(100.0)	
<15			
HIV- diagnosis (months)			
<3			
3-6	1(100.0)	0(0.0)	0.544
7-12	3(37.5)	5(62.5)	
13-60	26(43.3)	34(56.7)	
>60	42(48.3)	45(51.7)	
ART duration (months)			
<3	1(100.0)	0(0.0)	
3-6	1(100.0)	0(0.0)	0.375
7-12	3(37.5)	5(62.5)	
13-60	27(41.5)	38(58.5)	
>60	40(49.4)	41(50.6)	
Type of ART			
AZT/3TC/NVP	38(43.7)	49(56.3)	
TDF/3TC/EFV	15(39.5)	23(60.5)	
TDF/3TC/EFV	2(66.7)	1(33.3)	0.036
ABC/3TC/NVP	6(40.0)	9(60.0)	
TDF/3TC/ATZ/lpvr	7(100.0)	0(0.0)	
ABC/3TC/ATZ/lpvr	2(66.7)	1(33.3)	
AZT/3TC/ATZ/lpvr	2(66.7)	1(33.3)	
Anemia			
Yes	29(46.8)	33(53.2)	0.515
No	43(45.7)	51(54.3)	
Hypertension			
Yes	9(42.9)	12(57.1)	0.745
No	63(46.7)	72(53.3)	
CD_4 count (µmol/l)			
<200	16(69.6)	7(30.4)	0.015
200 above	56(42.1)	77(57.9)	

AZT – Zidovudine, 3TC – Lamivudine, NVP – Nevirapine, TD – Tenofovir, EFV – Efavirenz, ABC – Abacavir, ATZ – Atazanavir, lpvr – Lopinavir.

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Table 3: Risk factors for sleep disorder among HIV patients.

Variable	Sleep disorder present (*N* = 72)	Sleep disorder absent (*N* = 84)	*p*-value
Age (years)	38.7 ± 9.23	39.5 ± 9.23	0.600
Creatinine (µmol/l)	75.53 ± 19.54	83.50 ± 32.03	0.059
Weight (kg)	65.42 ± 10.25	65.70 ± 12.70	0.875
BMI (kg/m²)	24.75 ± 3.79	25.10 ± 4.15	0.547
eGFR (mls/min)	102.99 ± 35.01	93.89 ± 29.80	0.086
SBP (mmHg)	111.94 ± 15.98	117.25 ± 15.69	0.039
DBP (mmHg)	71.81 ± 11.67	74.70 ± 10.62	0.109
Hb (mg/dl)	12.27 ± 1.54	12.18 ± 1.43	0.710
CD_4 count (µmol/l)	472.85 ± 316.95	510.02 ± 252.99	0.425
AST/ALT ratio	1.0081 ± 0.404	0.9807 ± 0.4400	0.686

Table 4a: Risk factors for sleep disorder pattern among HIV patients.

Variable	Sleep apnea			Insomnia		
	Present (*N* = 34)	Absent (*N* = 38)	*p*-value	Present (*N* = 49)	Absent (*N* = 23)	*p*-value
Age (years)	38.5 ± 9.2	38.9 ± 9.4	0.868	38.9 ± 9.1	38.3 ± 9.7	0.8000
BMI (kg/m²)	24.61 ± 4.09	24.88 ± 3.56	0.767	24.51 ± 3.60	25.26 ± 4.22	0.469
eGFR (mls/min)	105.59 ± 41.31	100.66 ± 28.61	0.563	102.9 ± 30.13	103.17 ± 44.45	0.979
SBP (mmHg)	114.12 ± 16.54	110.0 ± 15.42	0.280	110.82 ± 16.44	114.35 ± 15.02	0.372
DBP (mmHg)	73.24 ± 11.73	70.53 ± 11.61	0.329	70.82 ± 11.34	73.9 ± 12.34	0.314
Hb (mg/dl)	12.32 ± 1.70	12.24 ± 1.41	0.834	12.37 ± 1.44	12.07 ± 1.75	0.470
CD_4 count (µmol/l)	445.35 ± 314.75	497.45 ± 321.07	0.490	467.14 ± 320.59	485.0 ± 315.8	0.825
AST/ALT ratio	1.045 ± 0.412	0.975 ± 0.398	0.468	1.002 ± 0.38	1.020 ± 0.445	0.867

Table 4b: Risk factors for sleep disorder pattern among HIV patients.

Variable	Narcolepsy			Restless leg syndrome		
	Present (*N* = 17)	Absent (*N* = 55)	*p*-value	Present (*N* = 11)	Absent (*N* = 61)	*p*-value
Age (years)	35.4 ± 7.9	39.8 ± 9.4	0.064	40.1 ± 9.1	38.5 ± 9.3	0.597
BMI (kg/m²)	25.28 ± 2.93	24.59 ± 4.03	0.445	21.98 ± 3.04	25.25 ± 3.72	0.006
eGFR (mls/min)	112.12 ± 32.16	100.16 ± 35.65	0.202	105.45 ± 41.12	102.54 ± 34.17	0.828
SBP (mmHg)	107.65 ± 18.55	113.27 ± 15.04	0.266	115.45 ± 16.95	111.31 ± 15.86	0.464
DBP (mmHg)	67.65 ± 9.70	73.09 ± 11.99	0.065	74.55 ± 10.36	71.31 ± 11.90	0.367
Hb (mg/dl)	11.83 ± 1.24	12.41 ± 1.61	0.127	12.37 ± 1.03	12.26 ± 1.62	0.757
CD_4 count (µmol/l)	627.76 ± 408.68	424.96 ± 269.63	0.069	282.82 ± 191.46	507.12 ± 323.96	0.005
AST/ALT ratio	0.992 ± 0.328	1.013 ± 0.427	0.830	0.992 ± 0.243	1.011 ± 0.428	0.886

patients with sleep disorder have a lower CD4 count and higher AST/ALT ratio. However, these differences are not statistically significant ($p > 0.05$).

In Tables 4a and 4b, among the various sleep disorder patterns, lower BMI and CD4 count levels were risk factors for the presence of restless leg syndrome ($p < 0.05$). The other variables did not show any significant association with sleep apnea, insomnia, and narcolepsy.

In this logistic regression model in table 5, SBP is the only parameter that is closely a likely predictor of sleep disorder ($p = 0.051$). All other variables are not predictors of sleep disorder in this model.

Table 5: Predictors of sleep disorder among HIV patients.

Variable	Odds Ratio	95%CI	*p*-value
Gender (1)	0.849	0.231-3.113	0.804
Age (years)	0.998	0.945-1.054	0.939
BMI (kg/m²)	1.170	0.921-1.486	0.198
eGFR (mls/min)	0.991	0.961-1.022	0.558
Duration of ART exposure (months)			
ART D	-	-	0.989
ART D (1)		0.000	1.000
ART D (2)		0-0.000	1.000
ART D (3)		0.132-7.328	0.988
ART D (4)		0.534-2.927	0.607
Type of ART combination			
Type ART	-	-	0.820
Type ART (1)	2.315	0.170-31.454	0.528
Type ART (2)	3.388	0.280-49.832	0.374
Type ART (3)	0.559	0.013-23.176	0.760
Type ART (4)	3.492	0.210-58.015	0.383
Type ART (5)	0.000	0.000	0.999
Type ART (6)	1.429	0.036-57.444	0.850
SBP (mmHg)	1.042	1.000-1.086	0.051
DBP (mmHg)	0.995	0.940-1.053	0.855
Hb (g/dl)	0.823	0.545-1.244	0.356
CD_4 count (µmol/l)	1.000	0.999-1.002	0.625
AST/ALT ratio	0.894	0.218-3.665	0.876

4. DISCUSSION

The prevalence rate of sleep disorders in our study subjects was 46.2%. Similar studies had rates of 46.7% and 59.3%, respectively [12, 23]. The different prevalence rates may be attributed to different screening tools used to assess sleep disorders in those studies. In addition, environmental, sociocultural, state of health among other factors may influence sleep disorders evaluation and assessment. The highly active antiretroviral therapy (HAART) combination of tenofovir, lamivudine, Atazanavir, and lopinavir was significantly associated with sleep disorders in our study. Moreover, the use of lamivudine and lopinavir has been shown to be associated with insomnia [24]. However, efavirenz-based therapies have been associated with sleep disorders among these groups of patients in similar studies [8, 9, 12, 25]. In conformity with similar studies [12, 25, 26], lower CD4 count levels were associated with the presence of sleep disorders. Lower CD4 count is associated with disease progression in HIV/AIDS subjects. The subjects become prone to opportunistic infections, as their immune status decline. With decline in health, the productivity becomes less. Moreover, they become dependent on others for support with fear accompanying worry and depression, which may contribute to the subjects becoming victims of sleep disorders. Studies have documented hypertension as being a correlate of sleep disorders in HIV seropositive subjects [25]. Systolic blood pressure elevation was high among subjects with sleep disorders in our study. Studies have reported sleep disorders such as obstructive sleep apnea-hypopnea syndrome (OSAS) as being strongly associated with elevated liver enzymes and fatty liver [27]. Higher AST/ALT ratio was associated with sleep disorders in our study. Even though this was not statistically significant, it is possible that there is a subtle progressive injury to the liver from the use of ART. Gao *et al*. observed in a study that both overall and abdominal adiposity are associated with increased likelihood of having restless leg syndrome [28]. This was at variance with our findings, where lower BMI values were a risk factor for developing restless leg syndrome. The difference in the findings may be because of the subjects that were studied. Gao looked at normal adults that were without HIV, while we studied HIV patients who tend to have weight loss as part or progression of the disease.

5. CONCLUSION

Elevated systolic blood pressure, lower CD4 count levels, and being on the HAART combination of TDF/3TC/ATZ/lpvr were associated with sleep disorders in our study. We observed a high rate of sleep disorders (46.2%) in this study. We, therefore, recommend routine screening for sleep disorders among HIV positive patients, particularly those on HAART and administer appropriate therapeutic measures to those who show symptoms. These measures could improve upon their quality of life and overall wellbeing.

Author Contributions
E.M.B was involved in the concept, design and acquisition of data. U.E.W and O.E.E. drafted the article and revised it critically for important intellectual content. H.O.O and E.M. were involved in the analysis and interpretation of data. All authors were involved in reviewing the final approval of the version to be published.

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Conflict of Interest
None.

References

1. Norman SE, Resnick L, Cohn MA, Duara R, Herbst J, *et al*. Sleep disturbances in HIV seropositive patients. J Am Med Assoc. 1988; 260(7):992.
2. Wiegand M, Moller AA, Schreiber W, Krieg JC, Holsboer J. Alterations of nocturnal sleep in patients with HIV infection. Acta Neurol Scand. 1999; 83(2):141-42.
3. Taibi DM. Sleep disturbances in persons living with HIV. J Assoc Nurses AIDS Care. 2013; 24(1):872-85.
4. Reid S, Dwyer J. Insomnia in HIV infection: a systematic review of prevalence, correlates and management. Psychosom Med. 2005; 67(2):260-69.
5. Rubinstein ML, Selwyn PA. High prevalence of insomnia in an out-patient population with HIV infection. J Acquir Immune Defic Syndr Hum Retrovirol. 1998; 19(3):260-65.
6. Rosekind MR. The epidemiology and occurrence of insomnia. J Clin Psychiatry. 1992; 53(6):4-6.
7. Gray J, Young B. Acute onset insomnia associated with the initiation of raltegravir: a report of two cases and literature review. AIDS Patient Care STDs. 2009; 25(9):689-90.
8. Brennan-Benson P, Lyus R, Harrison T, Pakianathan M, Macallan D. Pharmakonitec interactions between Efavirenz and Rifampicin in the treatment of HIV and tuberculosis; one size does not fit all. AIDS. 2005; 19(14):1541-43.
9. Burger D, Van Der Heiden I, La Porte C, Groeneveld P, Richter C, *et al*. Inter-patient variability in the pharmakokinetics of the HIV non-nucleoside reverse transcriptase inhibitor Efavirenz: the effect of gender, race, and CYP_2B6 polymorphism. Br J Clin Pharmacol. 2006; 61(2):148-54.
10. Xu C, Quinney SK, Guo Y, Hall SD, Li L, *et al*. "CYP_2B6 pharmacogenetics-based in vitro – in vivo extra-population of Efavirenz clearance by phisiologically based pharmacokinetic modelling. Drug Metab Dispos. 2013; 41(12):2004-11.
11. Wyen C, Hendra H, Siccardi M, Platten M, Jaeger H, *et al*. Cytochrome P4502B6 (CYP_2B6) and constitutive and resistant receptor (CAR) polimorphisms are associated with early discontinuation of Efavirenz containing regimens. J Antimicrob Chemother. 2011; 66(9):2092-98.
12. Oshinaike O, Akinbami A, Ojelabi O, Dada A, Dosumie A, *et al*. Quality of sleep in all HIV population on antiretroviral therapy at an urban tertiary centre in Lagos, Nigeria. Neurol Res Int. 2014; 2014:Article ID 298703, 6 pages 2014. doi:10.1155/2014/298703
13. Junqueira P, Belluci S, Rossini S, Reimalo R. Women living with HIV/AIDS: sleep impairment, anxiety and depression symptoms. Arq Neuro-Psiquiatr. 2008; 66(4):817-20.
14. Low Y, Preud Homme X, Goforth HW, Omonuwa T, Krystal AD. The association of fatigue with depression and insomnia in HIV-seropositive patients: a pilot study. Sleep. 2011; 34(1):1726-33.
15. Ustinov Y, Lichstein KI, Wal GSV, Taylor DJ, Riedel BW, *et al*. Association between report of insomnia and daytime functioning. Sleep Med. 2010; 11(2):63-68.
16. Gamaldo CE, Gamaldo A, Creighton J, Salas RE, Selnes OA, *et al*. Evaluating sleep and cognition in HIV. J Acquir Immune Defic Syndr. 2013; 63(5):609-16.
17. Saberi P, Netlands TB, Johnson MO. Quality of sleep associations with antiretroviral non-adherence. AIDS Patient Care STDs. 2011; 25(9):517-24.
18. Babson KA, Heinz AJ, Bonn-Miller MO. HIV medication adherence and HIV symptom severity: the roles of sleep quality and memory. AIDS Patient Care STDs. 2013; 27(10):544-52.
19. Little SJ, Holte S, Routy JP, Daar ES, Markowitz M, *et al*. Antiretroviral – drug resistance among patients recently Infected with HIV. N Engl J Med. 2002; 347(2):385-94.
20. Sleepmed of Central Georgia, available at http://sleepcenters.org/ga/selftesthtml.html, accessed May 1, 2017.
21. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16(1):31-41.
22. Nybilom H, Berggren U, Balldin J, Olsson R. High AST/ALT ratio may indicate advanced alcoholic liver disease rather than heavy drinking. Alcohol. 2004; 39(4):336-39.
23. Ferreira LTK, Ceolin MF. Sleep quality in HIV-positive outpatients. Rev Esc Enfem USP [interact]. 2012; 46(4):892-99.
24. Side effect of HIV and AIDS, drug, available at www.webmd.com/HIV-AIDS/AIDS-HIV-medication-side-effect, accessed May 22, 2017.
25. Shittu RO, Odeigah LO, Moradeyo AK, Sanni MA, Aderibigbe SA, *et al*. Short sleep duration and correlates among SSO positive HIV patients in Nigeria, West Africa. Br J Med Med Res. 2015; 10(7):1-10.

26. Seay JS, Mclutosh R, Fekete EM, Fletcher MA, Kumar M, *et al*. Self-reported sleep disturbance is associated with laws CD4 count and 24-hours urinary dopamine levels in ethnic minority women living with HIV. Psychoneuroedoerinology. 2013; 38(11):2647-53.
27. Byrne TJ, Parish JM, Somers V, Aquel BA, Rakela J. Evidence for liver injury in the setting of obstructive sleep apnea. Ann Hepatol. 2012; 11(2):228-31.
28. Gao X, Schwarzschild MA, Wang H, Ascherio A. Obesity and restless legs syndrome in men and women. Neurology. 2009; 72(14):1255-61.

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