Family Support, Clinical Profiles, and Psychiatric Comorbidities among Adult Ambulatory HIV/AIDS Patients In A Tertiary Care Centre: A Cross-sectional Study

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ABSTRACT

Background: People living with Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS), [PLWHA], experience more common psychiatric disorders (CPDs) than the general population, and family support has been reported to influence these disorders. Therefore, this study aimed to determine the relationship between family support, respondents' clinical profiles, and CPDs among PLWHA attending highly active antiretroviral therapy clinics of the University of Ilorin Teaching Hospital Ilorin, Kwara State.

Methods: This was a hospital-based descriptive cross-sectional study, utilizing semi-structured and structured questionnaires to collect data among 363 respondents between March and May 2019. Family support and CPDs were assessed using Perceived Social Support-Family and Mini International Neuropsychiatric Interview respectively. Anthropometric measurements and CD4 cell count test were also performed. Data were analyzed using SPSS version 21. Chi-square tests were used to compare associations between categorical variables; a *p*-value < 0.05 was considered statistically significant.

Results: Family support was strong in 93.7% of respondents, and there were significant associations between family support and CPDs (depression and anxiety disorder {AD}) [*p*-values 0.001 and < 0.001]. AD was found to be significantly associated with CD4 counts and WHO HIV disease staging (*p*-values 0.008 and < 0.001), and Alcohol Use Disorder (AUD) had a significant association with WHO HIV disease staging ($p = 0.001$).

Conclusion: Strong family support was associated with a lower prevalence of CPDs. Family members should be encouraged to offer appropriate and functional social support to PLWHA

Keywords: Common psychiatric disorders, alcohol use disorder; anxiety disorder; depression; family support.

INTRODUCTION

A greater number of comorbid Common Psychiatric Disorders (CPDs) have been reported among people living with Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS), [PLWHA] than other people with long-term illnesses.[1,2] These CPDs especially depression and anxiety disorder (AD) have been described as far more prevalent among PLWHA, and also found to further worsen their immune status, decrease their quality of life, adherence to antiretroviral (ART) drugs, and play a significant role in their premature mortality.[3-5] HIV infection is a deadly incurable communicable disease that exposes infected persons to social difficulties like stigmatisation, and isolation as well as psychopathological issues like anxiety, substance abuse, and depression.[4,5,6] It is one of the world's most concerning public health threats that warranted total global collaboration to halt new infections and ensure PLWHA has better means for its holistic care management.[7] HIV/AIDS has become a long-standing tractable disease due to the emergence of ART, which resulted in improved life expectancy among PLWHA.[8] After this laudable achievement, there exist comorbid illnesses such as CPDs.[8] Psychiatric disorders among PLWHA that remain undetected can have disastrous effects and could further expose them to vulnerable behaviours.[9,10]

Many factors have been established to augment the risk of developing CPDs among PLWHA; these include the gravity of HIV/AIDS, the side effects of ART medications, high levels of viral load, deficient family/social support, and deprived access to health care facilities.[11] Others include impoverished socio-economic status, low educational level, and unemployment.[4] Contrary to these, good family and

social support have been reported to be the most remarkable and dependable factors with a shielding effect on PLWHA.[4,11] Studies have found that inadequate or lack of family support is associated with the occurrence of CPDs among people with long-standing illnesses such as HIV/AIDS.[6,12] Family is frequently considered the foremost source of support in times of illness, whether through tangible instrumental support, such as preparing meals and administering medications, or through emotional support.[4] Thus, uninterrupted family support is an instrument for coping with chronic diseases with a healthier outcome.[4,13] The psychosocial factors aiding these psychiatric co-morbidities remain unexplored. Therefore, this study aimed to unravel the relationship between psychiatric disorders and the associated factors (family support, clinical profiles) among PLWHA, as there is a paucity of data on these aspects in the study region.[4,11]

MATERIALS AND METHODS

The study was conducted between March and May 2019 at the Highly Active Antiretroviral Therapy (HAART) clinic of the University of Ilorin Teaching Hospital (UITH), Ilorin. Ilorin is the capital of Kwara state, located in the North-central geopolitical zone in Nigeria, its inhabitants are mainly Yorubas and majorly practice Islam. This was a hospital-based descriptive cross-sectional study, and the participants were the consenting adult HIV-positive ambulatory patients (≥18 years) who had been on ART medications for at least six months. Patients excluded were those with major chronic medical illnesses, those on treatment for mental disorders, and those who were too sick.

The required minimum sample size (n) was obtained using Leslie Kish's formula.[14] $n = Z^2pq/d^2$, where n = desired sample size (when population > 10,000), z = standard normal deviation, set at 1.96, which corresponds to 95% confidence level. p = proportion of target population based on previous studies; 38.3% proportion previously reported was used.[15] Thus, P = 0.383, q = 1- 0.383 = 0.617, d = Degree of accuracy desired, set at 5% (0.05).

Therefore, $n = \frac{1.96^2 \times 0.383 \times (0.617)}{0.05 \times 0.05} = 363.125$

However, since the study population was less than 10,000 (7,084 was the total number of adult out-patients PLWHA attending HAART clinics), the sample size was adjusted using the formula: $n_f = {}^{n}/_{1+(n/N)}$. n_f = the desired sample size when the population is less than 10,000, n = estimated sample size = 363, N = the estimated population size 7,084,

$n_f = {}^{363}/_{1+(363/7084)} = 345.306$ approximately 345. To take care of missing data; a 95% response rate was assumed, hence the final sample size was determined using the formula: $n_s = n/r$.[17] n_s = adjusted sample size of the response rate, n = calculated sample size = 345, r = response ratio = 0.95. $n_s = 345/0.95 = 363.16$. Thus, an approximate sample size of 363 was recruited using a systematic random sampling technique. Informed consent was obtained from respondents and their confidentiality was maintained. HAART clinics were run four times a week and the average daily attendance of adult out-patients per clinic was about 30, making 120 patients in a week and giving a sample frame of 1,440 over 12 weeks. The number of participants interviewed daily was approximately 8, the sample size/total number of clinic days (363/48) and the sampling interval was approximately 4 (1,440/363). On each clinic day, the participants' folder was assigned a number from 01 to 30 and the first subject was selected by simple balloting, thereafter every 4th consenting participant was chosen. To avoid double sampling, the selected respondents' folders were labelled and when the ballot picked an already interviewed subject or when the respondent declined consent, the next consenting participant was recruited. This procedure was repeated every clinic day until the total sample size was obtained.

A pretested interviewer-administered semi-structured questionnaire was used to obtain information on socio-demographic data while structured questionnaires; Perceived Social Support-Family Scale (PSS-FS) and Mini International Neuropsychiatry Interview (MINI) were used to obtain information on family support and CPDs respectively. Laboratory estimation of CD4 cell counts and anthropometric measurements of the respondents were also done. PSS -FS questionnaire is a twenty-item validated measure of perceived family support developed by Procidano and Heller (1983).[16] Responses to the questions are “yes”, “no”, or “don't know”, with each “yes” answer scoring +1, “no” response scoring 0 and “don't know” -1. Items iii, iv, xvi, xix, and xx are reverse scored (a “no” response will be scored as +1). The scores were added at the end and summated scores were used to arrive at a family support score. Possible ranges of scores are 0 to 20. Scores 10 and below were classified as weak family support, while scores 11 and above were classified as strong family support.

MINI Questionnaire was designed as a brief structured clinician-administered diagnostic interview, used to assess the presence of psychiatric disorders based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and International Classification of Diseases (ICD-10).[17] It has been used in some studies in Nigeria and found to be a reliable screening tool in assessing CPDs.[15,18] It was divided into different diagnostic modules for each psychiatric disorder of interest. At the beginning of each module, the

screening question(s) correspond to the main criteria of the disorder and at the end, diagnostic box(es) permit(s) the clinician to indicate whether the diagnostic criteria are met or not. During the interview, the subjects will respond "yes" or "no" to each question being asked and the rating will be done.[19]

WHO HIV clinical disease stage for each participant was determined and grouped according to their clinical features.[20] Participants' current CD4 cell counts were estimated from their blood samples that were collected into a labelled plain universal bottle and run by an automated flow cytometric machine at the serology laboratory. Based on CD4 cell count results, participants were categorized into 3 sub-groups: C (< 200mm^3/µl), B (between 200 and 500 mm^3/µl), and A (>500mm^3/µl). In conjunction with their clinical stages, the sub-stages were further categorized into 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B, 3C, and 4A, 4B, 4C.[20]
The data collected were analyzed using the Statistical Package for Social Science-21 (SPSS 21) software package. Means and standard deviations were used for continuous variables and categorical variables were expressed in absolute counts and simple percentages. The chi-square test was used to assess the level of significance of association between categorical variables. A *p*-value < 0.05 was considered statistically significant at a confidence interval of 95%.
Ethical approval to conduct the study was received from the Ethical Review Committee of UITH, Ilorin (date: 31st July 2018 and number: UITH/CAT/189/19^{B}/796).

RESULTS

The mean age of respondents was 44.87 ± 10.05 years while the mean household size of respondents was 4.90 ± 2.22. Respondents were mostly married in a monogamous setting and the majority were self-employed. Table 1 shows the level of family support among the respondents to be as high as 93.7%.

TABLE I: THE LEVEL OF PERCEIVED FAMILY SUPPORT AMONG RESPONDENTS, N = 363

FAMILY SUPPORT	FREQUENCY (N)	PERCENTAGE (%)
WEAK SUPPORT	23	6.3
STRONG SUPPORT	340	93.7
TOTAL	363	100.0

number of respondents in the various groups
% = the proportion of respondents in the various groups.

Table 2 below shows the current clinical profiles of the respondents, the majority of the respondents 343 (94.5%), were in non-AIDS stages. Over half 215 (59.2%), of the respondents had normal BMI while 58 (16.0%) respondents had CD4 cell counts < 200 cells/ul.

TABLE II: CURRENT CLINICAL PROFILES OF RESPONDENTS N=363

CLINICAL INFORMATION FACTORS	CLINICAL	FREQUENCY	PERCENTAGE(%)
WHO Staging	AIDS (3&4)	20	5.5
	Non-AIDS	343	94.5
(1&2)			
BMI	**(kg/m²)**	18	5.0
	Underweight	18	5.0
	Normal weight	215	59.2
	Overweight	74	20.4
	Obese	56	15.4
CD4 Count (cells/ul)	< 200	58	16.0
	200- 500	163	44.9
	> 500	142	39.1

NB: AIDS = HIV Clinical stages 3 and 4, 1C, 2C, 3A, 3B, 3C, 4A, 4B, 4C. **non-AIDS =** HIV Clinical stages 1 and 2, 1A, 1B, 2A, 2B

Table 3 shows the relationship between family support and the occurrence of CPDs among the respondents. The prevalence of depression and AD were higher among respondents with weak family support, 52.2% and 47.8% respectively, and the association was statistically significant (*p*- values 0.001 and < 0.001). Among those with strong family support, the prevalence of AUD was 0.6%.

TABLE III: ASSOCIATION BETWEEN FAMILY SUPPORT AND CPDS AMONG RESPONDENTS N = 363

Variables	Depression		X^2	P
	No	Yes n_1		
Family Support (PSS-Fa)				
Weak (%)	11 (47.8)	12 (52.2)	10.282	**0.001**
Strong (%)	263 (77.4)	77 (22.6)		
	Anxiety Disorder			
	No	Yes n_2		
Weak (%)	12 (52.2)	11 (47.8)	16.734	**< 0.001**
Strong (%)	290 (85.3)	50 (14.7)		
	Alcohol Use Disorder			
	No	Yes n_3		
Weak (%)	23 (100)	0 (0.00)	0.129	0.719
Strong (%)	338 (99.4)	2 (0.6)		

χ2: Chi-square test, ***p*-**value <0.05 (Statistically Significant) **N:** Total number of respondents, $\mathbf{n}_{1:}$ number of respondents with depression, $\mathbf{n}_{2:}$ number of respondents with AD, $\mathbf{n}_{3:}$ number of respondents with AUD

Table 4 shows the association between depression and the respondents' current clinical parameters. About two-thirds of 215 of the respondents had normal BMI, out of which 58 (27.5%) had depression. There were 163 respondents with CD4 cell counts between 200 and 500, and 38 (23.3%) had depression. The majority of the respondents 313 were in WHO HIV clinical stage 1 and those with depression were 73 (23.3%). There were no significant associations.

Table IV: Association between respondents' current clinical parameters and depression N=363

Variables	Depression		χ^2	*P*value
	No n_1= 274 (%)	Yes n_2 = 89(%)		
Current BMI				
Underweight	12 (66.7)	6 (33.3)	4.255	0.235
Normal	157 (72.6)	58 (27.4)		
Overweight	60 (82.4)	14 (17.6)		
Obese	45 (80.4)	11 (19.6)		
Current CD4				
Cell Count				
< 200	46 (79.3)	12 (20.7)	1.324	0.516
200 – 500	125 (76.7)	38 (23.3)		
> 500	130 (91.5)	12 (8.5)		
Current WHO				
Clinical Stage				
1	240 (76.7)	73 (23.3)	0.327	0.849[y]
2	18 (60.0)	12 (40.0)		
3	10 (71.4)	4 (28.6)		
4	4 (66.7)	2 (33.3)		

χ2: Chi-square test, *P: p*-value (> 0.05) not statistically significant, **N:** Total number of respondents, $\mathbf{n}_{1:}$ number of respondents without depression, $\mathbf{n}_{2:}$ number of respondents with depression, **y**= Yates corrected value. **BMI:** Body Mass Index

Table 5 shows the association between respondents' current clinical parameters and AD. More than two-thirds of the respondents 215 had normal weight out of which 17.7% had AD. The respondents with CD4 cell count between 200 and 500 were 163 and 25 (15.3%) among them had AD. The majority of the

TABLE V: ASSOCIATION BETWEEN RESPONDENTS' CURRENT CLINICAL PARAMETERS AND ANXIETY DISORDER (AD) N=363

Variables	Anxiety Disorder		χ^2	*P*value
	No n_1= 302 (%)	Yes n_2 = 61(%)		
Current BMI				
Underweight	14 (77.8)	4 (22.2)	2.205	0.531
Normal	177 (82.3)	38 (17.7)		
Overweight	61 (82.4)	13 (17.6)		
Obese	50 (89.3)	6 (10.7)		
Current CD4				
Cell Count				
< 200	51 (87.9)	7 (12.1)	9.607	**0.008**
200 – 500	138 (84.7)	25 (15.3)		
> 500	113 (79.6)	29(20.4)		
Current WHO				
Clinical Stage				
1	266 (85.0)	47(15.0)	19.070	**< 0.001**
2	22 (73.3)	8 (26.7)		
3	10 (71.4)	4 (28.6)		
4	4 (66.7)	2 (33.3)		

χ2: Chi-square test, *P: p*-value (> 0.05) not statistically significant, **N:** Total number of respondents, $\mathbf{n}_{1:}$ number of respondents without anxiety disorder, $\mathbf{n}_{2:}$ number of respondents with anxiety disorder, **y**: Yates corrected value. **BMI:** Body Mass Index

Table 6 shows the association between respondents' current clinical parameters and AUD. 215 respondents were found to have normal weight out of which only 2 (27.4%) had AUD. Slightly less than half (163) of the respondents had CD4 cell counts between 200 and 500 cells/ul and none had associated AUD. Almost all the respondents 343 were in WHO HIV clinical stage 1, out of which only 1 respondent (0.3%) had associated AUD. A statistically significant association exists between AUD and the current WHO HIV disease clinical staging (*P* < 0.011).

TABLE VI: ASSOCIATION BETWEEN RESPONDENTS' CLINICAL PARAMETERS AND AUD N = 363

Variables	Alcohol Use Disorder		χ^2	*P* value
	No n_1= 361 (%)	Yes n_2 = 2 (%)		
Current BMI				
Underweight	18 (100)	0 (0.0)	1.869	0.600^y
Normal	213 (72.6)	2 (27.4)		
Overweight	74 (100)	0 (0.0)		
Obese	56 (100)	0 (0.0)		
Current CD4 Cell Count				
< 200	57 (98.3)	1 (1.7)	0.387	0.824^y
200 – 500	163 (100)	0 (0.0)		
> 500	141 (99.3)	1 (0.7)		
Current WHO HIV Clinical Stage				
1	342(99.7)	1 (0.3)	9.103	**0.011^y**
2	0(0.0)	0 (0.0)		
3	5 (83.3)	1 (16.7)		
4	14 (100)	0 (0.0)		

χ2: Chi-square test, *P: p*-value (< 0.05) statistically significant, **N:** Total number of respondents $\mathbf{n_{1.}}$number of respondents without AUD, $\mathbf{n_{2.}}$number of respondents with AUD, **y**= Yates corrected value. **BMI:** Body Mass Index

DISCUSSION

In this study, a higher prevalence of 93.7% of strong family support was found among the respondents. This, however, was not surprising because it had been reported that family still maintains the tradition and relationship of caring for their members whenever the need arises.[21] Omosanya et al in Ido-Ekiti, South West Nigeria reported a high prevalence (85%) of strong family support among PLWHA.[22] Similarly, Chinweokwu et al in Delta State Nigeria also reported an 84.5% prevalence of strong family support in their study.[21] The reasons for this could be because a larger proportion of the respondents were married, and studies have shown that spouses offer the most significant support during periods of illness.[4,23] This can be explored in the routine management of HIV infection and could further reduce stigmatization and isolation of infected individuals.

In comparison to the respondents with weak family support, those with strong family support had a lower prevalence of depression and AD, and the association was statistically significant ($p < 0.001$). This was in tandem with the findings from the previous studies.[4,6,21] Zewdu et al in Ethiopia reported a significant relationship between perceived family support and CPDs among PLWHA.[11] Respondents in this study were found to experience social support from their family members in a positive way and this gives some insight into the reason for the lower prevalence of CPDs among those with strong family support. Sule et al in Jos, Nigeria reported that respondents with weak family support were twice more likely to have depression than subjects with good family support.[24] The reasons for the higher prevalence of CPDs among respondents with weak family support could be attributed to their inability to cope with the psychological and physical effects of living with incurable debilitating diseases. Also, financial hardship, lack of tangible family members and absence of spousal support among the widows could be among the reasons. Therefore, family support may be an important tool that could be used to improve the quality of life and mental well-being of PLWHA.

According to this study, no statistically significant association was found between depression and the respondents' current clinical parameters (BMI, CD4 cell counts and WHO HIV disease clinical staging). However, the proportion of respondents with depression was highest among those who had normal BMI and lowest among the underweights. In contrast to this, Jenkins et al, reported that depression was higher among respondents with high BMI.[25] The reasons for the higher prevalence of depression among respondents with normal BMI in this study could be attributed to the fact that PLWHA in the study area has considered HIV infection as a chronic manageable disease condition, coupled with the strong family support found among them. CD4 cell counts and depression were also found not to have a significant association with depression, and this was in tandem with a study carried out in Jamaica by Clarke and colleagues.[26] In contrast, some studies had reported a high prevalence of depression among respondents with CD4 cell counts < 200 cells/ul.[5,27] The reasons could be that respondents with lower CD4 cell count had pronounced symptoms of HIV infection with more social, emotional and psychological instability in their study areas, whereas the index study found strong family support among the respondents that subsequently buffers the psychopathological effects of HIV disease.

WHO clinical staging of HIV/AIDS was found to not

have a significant association with depression in this study. The majority of the respondents were in the WHO HIV clinical stage one. Similarly, Clarke et al in Jamaica reported no significant association.[26] On the contrary, Motumma et al in Eastern Ethiopia and Bhatia in India found significant associations between HIV/AIDS disease stage one and depression in their studies.[28,29] The difference in the findings could be attributed to the predominant age group among the various study populations, as it had been reported that depression is more common among the older age group.[28] Majority of respondents in the index study were in their middle age group.

The association between respondents' current clinical parameters (CD4 Cell Counts and WHO HIV stages) and AD in this study were found to be statistically significant (*p* values 0.008 and < 0.001) but no significant association exists between AD and respondents' BMI. This was in consonant with previous studies.[6,27] The reasons for this could be that there was a high level of compliance and adherence to the HAART regimen and less stigmatization among PLWHA in the various study locations. In tandem with the index study, Bhatia et al in India reported no significant association between AD and respondents.[29] The respondents with extremes of BMI, low CD4 cell count (< 200cell/ul) and those in WHO HIV stages 3 and 4 had been reported to have comorbid AD.[6,27,29] Bauer et al reported that the synergistic effects of HIV and an overweight or obese could lead to impairment in brain function and motor behaviour among PLWHA with poorer outcome.[30] The reason could be attributed to the difference in the study population and the locality where the various studies were carried out. In the index study, there was high literacy and the majority of the respondents were in the middle age group which could account for better self-care awareness on health-related challenges associated with being underweight, overweight or obese. It is pertinent to further explore if the extremes of BMI could have a significant association with the occurrence of AD among PLWHA.

The findings from the index study showed that there was a statistically significant association (*p = 0.001*) between AUD and WHO HIV clinical stages, but none was found between AUD, BMI and CD4 cell counts. Despite this significant association, lower percentages of respondents (0.6%) were found to abuse alcohol. This could be a result of the larger number of female respondents (72.1%) among the study population who are less likely to take alcohol due to their socio-cultural background and religious prohibition, as more than half (54.2%) of the respondents were practising Islam which prohibits alcohol ingestion. This was similar to what was reported by Egbe et al in Abuja, where the prevalence of AUD was found to be 7%.[9] Sokoba and colleagues in Ethiopia, also found a lower prevalence rate of 2.8% using AUDIT as a screening tool.[31] BMI and AUD in this study were found not to have a statistically significant association. There is a paucity of studies on the association between BMI and AUD among PLWHA, though there exist on the effects of alcohol abuse on nutritional status among infected individuals.[32,33] AUD among PLWHA has been reported to cause malnutrition which further leads to poor ART adherence with increased morbidity and mortality.[34] Any intervention to reduce alcohol misuse among PLWHA would be beneficial to the overall treatment outcome of HIV infection.[21] Furthermore, AUD and CD4 cell counts had no statistically significant association. This was contrary to the findings reported by Vagenas et al in the USA and Kader et al in South Africa.[34,35] Gebre et al in Ethiopia found a significant association and stated that PLWHA having a CD4 count < 200 cell/ul were 19 times more likely to abuse alcohol than those with CD4 counts > 500 cell/ul.[32] The possible explanation for various dissimilar findings might be due to contextual differences, sample size variation and instruments used to assess AUD in addition to socio-cultural background. Further studies need to be done to ascertain the findings from this study.

CONCLUSION

The current CD4 cell counts and WHO HIV disease staging were determinants of the occurrence of AD while only WHO HIV disease staging was a determinant of AUD and they were found to be statistically significant. One important predictor of CPDs found in this study was family support and there was a significant association between family support and CPDs (depression and AD). Respondents with strong family support had a lower prevalence of CPDs.

LIMITATIONS OF THE STUDY

This study was a hospital-based cross-sectional descriptive study, and the results may not be generalized for the entire population of PLWHA in Ilorin, Kwara State. The various statistically significant observations between the variables tested in this study were not necessarily causal. The research instruments used for assessing the presence of CPDs were based on self-report and observations which are prone to self-report bias.

RECOMMENDATIONS;

FOR POLICYMAKERS

1. Stakeholders and policymakers should enact policies that would incorporate mental health

care services into HIV/AIDS management programs at various levels of health care delivery services.
2. They should ensure periodic or continuous and adequate training and re-training of the involved health care providers.
3. The Instruments (MINI) used in this study to screen for CPDs could be included in the patient's care assessment form which will allow easy screening, early diagnosis, and prompt provision of holistic care to PLWHA with comorbid psychiatric disorders.

FOR CLINICAL PRACTICE

1. Primary care physicians, who offer comprehensive, coordinated, and holistic care to all patients including PLWHA should be engaged in the proper evaluation, health education, and counselling of HIV/AIDS clients during the clinic visits.
2. Routine screening for CPDs should be done for all clients with HIV infection to identify those at risk.
3. Referral to a specialist for further evaluation and management should be done as may be required.

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Authors' Contributions

Ibraheem AS: Conceptualization & study design, literature review, data collection, data analysis & interpretation manuscript writing and manuscript revision. **Odeigah LO:** Conceptualization & design of the study, manuscript revision and final approval. **Kuranga IS** the Conceptualization & design of the study, manuscript revision and final approval. **Omowumi RK:** Data collection, Data analysis & interpretation and manuscript revision. **Maiyegun AA:** Conceptualization & design of the study, manuscript revision and final approval. **Ayodapo AO:** Literature review, manuscript revision and final approval.

All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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