

ADHERENCE TO ANTIRETROVIRAL THERAPY: WHO ARE THE DEFAULTERS? A STUDY IN A TREATMENT CENTRE IN NIGERIA

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ABSTRACT

Introduction: Non-adherence to antiretroviral therapy has remained a challenge in achieving desired goals of human immunodeficiency virus (HIV) treatment resulting in progression to acquired immunodeficiency syndrome. The objective of this study is to determine the level of adherence of HIV positive patients to antiretroviral therapy and factors associated with non-adherence.

Methods: This cross-sectional study was conducted among 266 patients receiving antiretroviral therapy in Central Hospital using pretested validated questionnaires consisting of items from the Patient Health Questionnaire-9, Adherence to Refill and Medications scale, and the Visual analog scale. Chi Square and Logistic regression using statistical software SPSS 20 were used for data analysis.

Results: The mean age of those who participated in the study was 39.28±11.05 years. More females participated in the study (76.7%). Fifty-five (19.5%) patients were depressed. Half of the study participants were 100% adherent to antiretroviral therapy. The mean score on the visual analogue scale was 87.78±19.30. None of the socioeconomic factors were associated with adherence to ART, but alcohol (OR 0.477; (CI) 0.282-0.854], and depression (OR 0.416 (CI) 0.238-0.836] were statistically significant factors for non-adherence.

Conclusion: This study reveals poor adherence to antiretroviral therapy among half of the study participants. Only depressed patients and those who use alcohol were found to be defaulters in adhering to therapy. Improvement in the quality of education and counseling offered to patients on a regular basis and programs that help identify alcohol users and those at risk of depression can improve adherence in patients.

Keywords: HIV, Adherence, Antiretroviral therapy, Depression.

Introduction

In Nigeria, an estimated 3.4million (9% of global epidemic) people are living with HIV making the country the second highest Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) burden in the world after South Africa with a prevalence rate of 2.9%. HIV prevalence is highest in Southern Nigeria (South-South Zone) at 5.5% and lowest in the South East at 1.8%¹. The availability of effective antiretroviral drugs now increases the survival rate of patients with HIV infection. The key to successful antiretroviral therapy (ART) lies in the ability and willingness of HIV-positive patients to adhere to regimens. Adherence is a complex, dynamic process that influences outcome of HIV treatment and patient's health status. At least 95% adherence (missing not more than three doses per month) is required to avoid emergence of resistant strains of the virus and for the regimen to be fully effective. Estimates of average rates of adherence ranges from 50-70% and adherence rates of <80% are associated with detected viremia in majority of patients^{2,3}. Yet, it is difficult to attain an adherence of 95%, two systematic reviews show that adherence to antiretroviral therapy is a global issue affecting patients from developed countries. The reviews noted that patients from developed countries reported less than 75% adherence ranging from 20-100% compared to in developing countries where adherence level of more than 75% is reported ranging from 45-100%^{5,6}. Adherence to highly active antiretroviral therapy

(HAART) does not involve only the patients, but also the physician and the public health system^{7,8}. The major determinants of adherence in HIV management in many settings are patient-related factors since drugs are now available unlike in the past when cost of antiretroviral drugs was an issue, in addition, pill burden has reduced as most of the antiretroviral drugs are in fixed dosage form. The patient-related factors affecting adherence to HAART include socio-economic factors such as income, education, unemployment, marital status, and stigmatization^{9,10,11}.

Psychological factors are now considered as major determinant of adherence to antiretroviral therapy and include alcohol and other substance abuse, anxiety and depression. Depression is the most common mental disorder among patients with HIV infection, and these patients are 3-5 times more likely to suffer depression than in the general population¹².

Depression among people living with human immunodeficiency virus (PLHIV) is associated with non-adherence to ART with worse outcome both in morbidity and mortality compared to non-depressed HIV patients^{12,13}. In a Meta-analysis, depression was significantly associated with non-adherence across the ninety five independent samples included in the study, and a 42% decrease in adherence was observed among HIV patients who exhibited depressive symptoms compared to those who did not across low, middle, and high income countries^{14,15}.

In Nigeria, adherence rate of 44%-59.9% have been reported with few studies in this regard^{4,16}. Many of the studies that have been conducted in the south-south region of Nigeria did not include the impact of psychological factors such as depression on adherence. The purpose of this study is to determine the level of adherence, and the impact of socio-economic factors, depression on adherence to HAART therapy.

Methods

Study Setting: This study was conducted at the pharmacy unit of Central hospital antiretroviral therapy (CHART) Center, a government-owned secondary healthcare institution and one of the two main centers providing free antiretroviral therapy and care for HIV patients in Benin City, Nigeria.

Study Design and Population

A Cross Sectional questionnaire-based survey was conducted between May-June 2017 among 266 patients from the CHART Centre. Patients were included in the study if they were HIV positive and on HAART therapy for at least 6 months prior to this study, were 18 years and older and gave consent to participate in the study. Exclusion criteria included pregnant HIV positive women, and patients who were mentally unstable. All recruited participants were duly informed verbally about the anonymity and objectives of the study. Convenience sampling was used in recruiting study participants.

Data Collection/Instrument

Data collection tool was an interviewer administered semi-structured questionnaire. The questionnaire consisted of four sections. Socio-demographic characteristics of patients included age, sex, income, employment and education. Other characteristics were duration of HIV diagnosis, alcohol and smoking, associated chronic illness and adverse effects made up section 1. Alcohol and smoking were assessed with the questions "How often do you take alcohol" and "How often do you smoke" with response scale of daily, weekly, sometimes and never, while associated chronic illness and adverse effects were assessed with the questions Do you have other illness apart from HIV that you have been treating for more than a year", and Have you experienced any side effects from the drugs you take for your HIV and reported it to your doctor" with response scale of Yes and No. Section 2 consisted of items from the Patient Health Questionnaire-9 (PHQ-9) used to assess depressive symptoms, while adherence measures using the Adherence to Refills and Medications Scale (ARMS) and the Visual Analog Scale (VAS) formed Sections 3 and 4 respectively. The PHQ-9 has nine questions used to screen for presence of depression. Questions are based on physical symptoms experienced in the past two weeks. The nine questions are rated on a 4-point Likert scale of 0 representing not at all to 3 (nearly every day). The score range is from 0-27, scores of 1-4 represents minimal depression, 5-9 mild depression, 10-14, moderate

depression, 15-19, moderately severe depression, and 20-27 severe depression¹⁷. For screening purpose, a cut-off of 5 has been adopted as recommendations for further screening^{17,18,19}.

The ARMS questionnaire is used to measure adherence in the past 30 days. It consists of a 12-item questionnaire consisting of the following two parts; (1) 8 items related to the medication use as directed (2) 4 items related to the prescription refill. Each item is rated from 1-4 on a 4 point Likert scale. Ranging from 1 (none of the time) to 4 (all of time except for item 12 that is reversely rated). The overall score ranges from 0-48 with lower scores indicating better adherence (≤ 20), and higher score (> 20) indicating poorer adherence. These scoring are in relative terms. This questionnaire has been validated and used in various studies. One advantage of its use is that it was designed for use among patients of low level of education^{20,21}.

The Visual Analog Scale (VAS) is a single item adherence scale that is easy to use. From a scale of 1-10 or 10-100%, an individual is asked to place a circle on self-assessed adherence for the past one month. It has been shown to be well correlated with more complex adherence scale^{20,21}. A cut-off point of 95% is considered appropriate adherence in patients taking antiretroviral drugs.

Data Analysis: Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 20. Frequencies, proportion and means of socio-demographic characteristics were performed

using descriptive statistics. Tests of association between variables in the study and adherence were performed with Chi-square. Multivariate analysis was conducted with binary logistic regression to determine factors affecting adherence after adjusting for confounding variables at 95% confidence interval. The relationship between the ARMS and VAS was done using Spearman's correlation, p-values of less than 0.05 in all analysis were considered significant.

Ethical Consideration

This study was approved by the ethics and review committee of the Faculty of Pharmacy University of Benin, Benin City as part of the "Depression and Anxiety among HIV Patients, their Predictors in Central Hospital Edo" study with reference number EC/FP/018/04.

Results

Two hundred and sixty-six patients took part in this study with an age range of 19-71 years, with mean of 39.28 ± 11.06 . Majority of the participants were females (76.7%), and employed (85.7%). A little less than half (46.2%) of the respondents had attained secondary education, while one-third had less than 12 years of education. More than half (58.3%) of the respondents earned less than the national minimum wage of ₦18000, and 141(53%) of them were married. One hundred and one (38%) of the patients have been on HAART for 1-4 years, and few (9%) for 10 years and greater. One hundred and ninety two (72.2%) of

the participants were on Zidovudine Lamivudine and Nevirapine combination, 40(15%) were on Tenofovir, Emtricitabine and Nevirapine combination, while 34(12.8%) were on Zidovudine, Lamivudine and Enfavirenz combination. Seventy four (27.8%)

of the participants were alcohol users, of which 44(59.4%) were females. Thirteen (4.9%) participants reported that they smoke. Twenty of the participants (7.5%) experienced adverse effects from their medications, while twenty-one (9.9%) had co-morbid

illness. Table 1 shows more details on the frequency distribution of the characteristics of patients used in the study.

Table 1 Socio-demographic Characteristics of Respondents (N=266)

Variable	Frequency (N)	Percentage (%)
Age(years)		
18-29	59	19.5
30-39	98	36.8
40-49	59	22.2
≥50	57	21.4
Sex		
Male	62	23.3
Female	204	76.7
Education		
<12years	83	31.2
Secondary	123	46.2
Post-secondary	60	22.6
Employment		
Employed	228	85.7
Unemployed	38	14.3
Income (₦)		
≤18000	155	58.3
>18000-≤70000	90	23.3
>70000-≥100000	21	7.9
Marital status		
Single	54	20.3
Married	141	53
Divorced/widowed	59	22.1
Partnered but not married	12	4.5
Duration of HIV diagnosis		
<1 year	57	21.4
1-4years	101	38
4-9years	88	16.1
≥10years	20	9
Alcohol		
Yes	74	27.8
No	192	72.2

The mean score of the Patient Health Questionnaire (PHQ- 9) was 3.05 ± 3.98 . Majority (79.3%) of participants did not have any depressive symptoms, 55 (19.5%) of the respondents had depressive symptoms ranging from mild to severe, majority of this group (16.5%) exhibited mild depression, only 1(0.4%) patient had severe depression respectively (Table 2)

Table 2: Frequency Distribution of Depression

Variable	PHQ-9 Score	(N)	(%)
No depression	0	79	29.7
Minimal depression	1 -4	132	49.6
Mild depression	5 -9	44	16.5
Moderate depression	10 -14	10	2.7
Moderately severe depression	15 -19	0	0
Severe depression	20 -27	1	0.4
Total		266	

Two hundred and forty-three (91.35%) of participants were adherent on the ARMs, 133 (50%) patients were 100% adherent, and 36 (13.5%) patients were $\leq 70\%$ adherent on the VAS. The mean score of the ARMs and VAS were 14.50 ± 4.95 , and 87.78 ± 19.31 respectively. Fifty-two (51.5%) of patients who were within 1-4 years on HAART were more than 95% adherent on the VAS, while 9(45%) of those greater than ≥ 10 years on HAART were adherent on the VAS. These differences in adherence between the two measures were not statistically significant. The ARMs adherence tool was found to be of good internal consistency with a high Cronbaach α of 0.909. There was a significant relationship between the ARMs and VAS with correlation coefficient of -0.758 and p-value < 0.001 (Table 3).

Table 3 Adherence pattern of participants in relation to duration of HIV treatment (N=266)

Variable	<1year N (%)	1-4years N (%)	>4-9years N (%)	>10years N (%)	Total N (%)	p-value
ARMs Score						
Adherence	53(92.9)	91(90.9)	80(90.9)	19(95)	243(91.3)	0.950
Non-adherence	4(7.1)	10(9.9)	8(9.9)	1(5)	23(8.7)	
Total (N)	57	101	88	20	266	
VAS (%)						
0-70	9(15.7)	13(12.9)	11(12.5)	2(10.0)	36(13.5)	0.861
80-90	19(33.3)	35(34.6)	34(38.5)	9(45.0)	97(36.5)	
100	29(50.8)	52(51.5)	43(48.9)	9(45.0)	133(50)	

Results of bivariate and multivariate analysis are shown in Table 4. Participants aged 18-29 years were less adherent than those older, but adjusting for other cofounding variables, age was not a predictor for adherence. Sex, education, income, marital status, adverse effects and length of duration of HIV were not statistically significant predictors for adherence both in the bivariate and multivariate analysis, whereas, alcohol use and depression were independent determinants of adherence to ART ($p < 0.05$). After adjusting for confounding factors, alcohol users were 52.3% [(OR) 0.477; (CI) 0.282-0.854] less adherent than non-alcohol users. Seventy four participants were alcohol users in this study, 46 of them had adherence below 90 on the VAS, thus accounting for 17.7% non-adherence in the general sample of study and 34.6% of those who were non-adherent alcohol users. Similarly, non-depressed patients were 2.4 times more adherent than depressed patients (OR 0.416 (CI) 0.238-0.836). Of the fifty-five depressed patients in this study, thirty-four were less than 95% adherent on the VAS thereby accounting for 12.8% of non-adherence in the study population and 62% non-adherence among depressed population compared to 47% non-adherence among non-depressed patients in the study. Alcohol use was a statistically significant factor for depression [(OR) 1.611; (CI) 1.138-2.282, p -value=0.01].

Table 4 Factors associated with non-adherence to ART (N=266)

Variable	Adherent N (%)	Non Adherent N (%)	Odds Ratio (OR) (Confidence Interval)	Adjusted OR (Confidence Interval)
Age (years)				
18-29	19(14.3)	33(2.8)	0.343(0.157 -0.751)	0.498(0.184 -1.349)
30-39	47(35.3)	51(38.3)	0.567(0.291 -1.103)	0.731(0.312 -1.714)
40-49	32(24.1)	27(20.3)	0.745(0.356 -1.560)	1.027(0.437 -2.415)
≥50	35(26.3)	22(16.5)	1	1
Sex				
Male	33(24.8)	29(22)	1.159(0.65 -2.056)	1.531(0.758 -3.091)
female	100(75.2)	104(78)	1	1
Education				
≤12 years	44(33.1)	39(29.3)	1.053(0.538 -2.061)	0.646(0.287 -1.457)
Secondary	57(42.8)	66(49.6)	0.806(0.431 -1.506)	0.697(0.343 -1.417)
Post-secondary	32(24.1)	28(21.1)	1	1
Marital status				
Married	74(55.6)	67(50.3)	1	1
Single	18(13.5)	36(27)	0.875(0.226 -3.384)	1.123(0.262 -4.802)
Divorced/widowed	36(27.1)	23(17.3)	2.663(0.700 -10.134)	2.70(0.633 -11.545)
Partnered but unmarried	5(3.8)	7(5.3)	1.933(0.542 -6.897)	2.063(0.547 -7.783)
Employment				
Employed	114(85.7)	114(85.7)	1.046(0.522 -2.097)	0.933(0.425 -2.049)
Unemployed	19(14.3)	19(14.3)	1	1
Income (Naira)				
≤18000	76(57.1)	79(59.4)	0.576(0.226 -1.470)	0.709(0.241 -2.086)
>18000-70000	44(33.1)	46(34.5)	0.589(0.222 -1.557)	0.614(0.210 -1.791)
>70000->100000	13(9.8)	8(6.1)	1	1
Alcohol				
Yes	28(21)	46(34.5)	0.491(0.282 -0.854)	0.477(0.256 -0.889)
No	105(79)	87(66.5)	1	1
Smoking				
Yes	3(2.2)	10(13.3)	0.288(0.077 -1.072)	0.353(0.081 -1.528)
No	131(97.8)	123(86.7)	1	1
Depression				
Yes	21(15.8)	34(25.6)	0.456(0.238 -0.836)	0.413(0.243 -0.821)
No	112(84.2)	99(74.4)	1	1
Co-morbidity				
Yes	11(8.2)	10(13.3)	1.127(0.62 -2.753)	0.805(0.280 -2.312)
No	122(17.3)	123(86.7)	1	1
Adverse effects				
Yes	7(5.3)	13(9.8)	0.521(0.201 -1.351)	1.296(0.470 -3.579)
No	126(94.7)	120(90.2)	1	1

Discussion

This study aims to determine the adherence pattern to antiretroviral medications in the past thirty days. A near perfect ($\geq 95\%$) adherence is recommended for all HIV patients on HAART. In this study half of the participants met this requirement for adherence using the visual analog scale. Although both adherence tools adopted in this study are well correlated which means that they both measured adherence in our respondents, the VAS gave a better assessment and accuracy of adherence pattern among HIV positive patients than the ARMs since it meets the requirement of grading adherence with ease of interpretation. In the management of other chronic diseases, generally acceptable adherence rate is $\geq 80\%$ ¹⁵, higher adherence ($\geq 95\%$) is desired in HIV disease management for sustained viral suppression and prevention of progression of infection. The VAS has been reported to accurately measure adherence compared to the Medication Event Monitoring System (MEMS) which is the “most sensitive method” for detecting non-adherence^{22,23}.

Adherence rate from this finding is lower than the 62% reported globally and also lower than in studies done previously in Southern Nigeria where adherence of 59.9%, and 54.5% were reported^{4,16,24}. The figure from this study is comparable to that reported in Eastern Nigeria, where only 49.3% of the patients were adherent, however, the Eastern Nigeria study was conducted at the time when subsidized HIV medication had not

reached a wider coverage^[25]. Studies conducted in Nigeria have reported lower adherence compared to those done in other African countries where HIV prevalence is high. In South Africa 68% and 77% of patients were $\geq 95\%$ adherent to antiretroviral therapy using pill count method and self-report respectively, 62.2% has been reported in Ghana using self-reported method, while in Uganda 86.4% with pill count was measured, and 87% in Ethiopia with self-report adherence measure, these adherence reports varied with adherence time-frame ranging from days to months^{11,26,27,28,29}.

Socio-economic factors and adherence

None of the socio-economic factors were associated with adherence in this study as have been reported. Unemployed and low income earners among HIV positive patients are said to be less adherent than their counterparts. Although more than half of the participants in this study earned less than the minimum wage, and 85% were employed, these factors did not impact on adherence. These factors are said to improve psychosocial well-being and material wealth thereby promoting adherence^{9,11,24}. Agu et al¹⁰ in their study concluded that employment status was associated with poor adherence as patients might be busy and tend to forget to take their medication.

Social habits as predictors of non-adherence

Alcohol use and smoking are patient-related factors that have been shown to contribute to non-

adherence^{3,30,31}. Smoking did not affect adherence in this study, the reason for our finding may be due to the few smokers in the study. Alcohol use was a determinant of non-adherence as patients who took alcohol were 52.3% less adherent than non-users. Alcohol use is a known predictor for non-adherence to ART, in a combined review, alcohol drinkers were approximately 50-60% less adherent compared to abstainers³¹, although alcohol use in this study was not classified as either casual, heavy or drinkers with alcohol use disorder, other studies have linked both current alcohol consumption and hazardous drinking with non-adherence with females being more at risk^{33,34,35}. Alcohol use also increases depressive symptoms in patients^{30,36}. Suggested reasons for this relationship includes that patient may forget to take their medication as a consequence of alcohol consumption, and alcohol use may help patients live in denial on HIV sero-positivity. It is also likely that alcohol users may be aware of possible adverse drug reaction when used with medications thus promoting non-adherence³⁷.

Depression and non-adherence

One-fifth of the patients in this study had depressive symptoms. Depression accounted for non-adherence in 12.8% of all patients from this study, among those depressed, 62% were non-adherence compared with 47% of non-adherence among those not depressed. This trend was observed in a study conducted in Zaria, Nigeria, where 63.6% of study participants with depressive

disorder had poor adherence to HAART compared to 21.1% of participants without depressive disorder³⁷. In Cameroun, 75% of depressed patients were non-adherent compared to 35% of non-depressed patients^[38]. Depressive symptoms are more in HIV patients than in the general population, it is linked to the inevitable reaction observed in the initial diagnosis of the infection, and is associated stigma. Depression affects an individual's self-care behavior which impacts negatively on adherence to ART^{39,40}.

Other factors relating to non-adherence

Duration of therapy, gender, adverse effects, marital status, education and co-morbid diseases did not affect adherence in this study. There are conflicting reports on the effect of these factors on adherence. Higher education, being married, older age, and long duration of therapy have been reported as promoters of adherence^{25,37,41}. In a Meta-analysis, among 19 studies, adherence was significantly lower in patients who experienced adverse drug reactions to ART than in those who did not⁴². One-fifth of study participants do not adhere to refill of their medications while about one-fourth reported non-adherence with more than once daily regimen.

The implications of non-adherence primarily results in deterioration of the immunological benefit of ART and increased AIDS-related morbidity, mortality and hospitalizations, and increased cost of care. The risk of emerging drug

resistant strains of the virus is a threat to ART drug utilization as there are few options of drugs in managing HIV/AIDS²³. Evidence-based approach in promoting adherence now includes identifying patients with mental illness and substance use/abuse. Alcohol focused intervention programs are currently implemented in some treatment centers⁴³. The fact that two outcome measures for adherence were employed in this study adds to the strength of the study, yet this study has some limitations. This study was done in one treatment center and among a cohort of patients at a specific period, thus the results should be interpreted with caution in relation to the general HIV positive population. Subjective data from self-reported tool was used in the analysis, the tendency of recall bias as common in operational research cannot be over emphasized. Only an aspect of adherence was studied (some patient-related factors), health system and relationship with health care providers were not assessed in this study. The extent of alcohol use, type and frequency of substance that was smoked and type and severity of adverse/side effects experienced by participants were not elaborately studied. However, alcohol use and smoking are generally frowned at in the region where this study was done, thus the results presented gives a measure of accuracy with regards to participants who reported those habits.

Conclusions

This study reveals that adherence to HAART among HIV patients in Central Hospital Benin was far

below optimal ($\geq 95\%$). Although many of the socio-demographic factors were not determinants of adherence in this study, alcohol use and depression were observed as major determinants of non-adherence. There's need for more effective education and counseling of HIV patients on a regular basis to emphasize the importance of adherence, especially at the point of collection of these medications. Early screening for depression and providing psychosocial support for those at risk can improve adherence indices. Screening and counseling for alcohol use should be incorporated into HIV programs in order to curtail non-adherence from alcohol use.

Conflict of interest

The authors declare no financial nor non-financial competing interest.

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