

Antiretroviral Therapy-related Problems among Human Immunodeficiency Virus-infected Patients: A Focus on Medication Adherence and Pill Burden

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Abstract

Background: There are problems associated with antiretroviral therapy despite its achievement. Poor medication adherence and inability to tolerate large pill burden are major problems facing patients with chronic illnesses. These drug therapy problems are under-studied among people living with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) in Nigeria. We evaluated adherence and pill burden among this set of patients in a tertiary hospital in Lagos. **Methods:** Data for eligible HIV-infected adults were documented from case notes and through interviews using a well-structured questionnaire. Important details extracted were sociodemographics, pills information, and CD4 counts. The main outcome measures were drug adherence, as assessed by the four-item Morisky Medication Adherence Scale and pill burden, as measured by daily pill >5. **Results:** Of the 296 patients, 219 (74%) were females. Median age (interquartile range) was 40 (35.0–47.7) years. Majority (262; 88.5%) were married, had at least a secondary education (142:48.0%), and CD4 count >500 cells/ml (215; 72.6%). Pill burden >5 pills/day was observed in 12.2% of the patients, while adherence was documented for 83.4% of the patients. Majority (259; 87.5%) were receiving fixed-dose combination of antiretroviral drugs. Forgetfulness (16.5%) and being too busy to take pills (10.5%) were the most common reasons for nonadherence. Pill burden in those who were not receiving fixed-dose combination was significantly associated with medication nonadherence. However, only pill burden was found to be an independent prognosticator of non-adherence. (Odd ratio = 0.67, confidence interval = 0.03–1.66, $P < 0.00$). **Conclusion:** Medication nonadherence and pill burden were observed in more than one-tenth of patients. These were the two major antiretroviral therapy-related problems reported in this study.

Keywords: Adherence, antiretroviral therapy, human immunodeficiency virus, people living with human immunodeficiency virus/acquired immunodeficiency syndrome, pill burden

INTRODUCTION

The human immunodeficiency virus (HIV) infection is a major community health concern with significant morbidity and mortality.^[1] The prevalence of HIV infection is reported to be high in Africa in 2017. It was estimated to be 25.7 million, constituting 70.0% of the 36.9 million people infected with HIV/acquired immunodeficiency syndrome (AIDS) globally.^[2] Nigeria is ranked second among countries with the leading HIV epidemics worldwide due to its large population size. It had a national prevalence of 1.5% and estimated population of 1.9 million individuals living with HIV/AIDS in 2018.^[3,4]

There is a substantial reduction in the disease and death of People Living with HIV/AIDS (PLWHA) in the past decade following the initiation and implementation of combined antiretroviral therapy (cART).^[5] The ultimate aim of cART is to achieve the utmost and lasting repression of viral replication,

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which manifests as improved quality of life and prolonged life expectancy.^[6]

Notwithstanding these achievements, there are problems associated with the use of cART, which include poor drug adherence, high pill burden, adverse drug reactions, and risks of renal and hepatic impairments.^[7,8] Pill burden is the number of pills in the form of tablets, capsules, or other dosage forms that are regularly taken by a patient.^[9] A high pill burden is known to be associated with poor drug adherence, particularly among individuals with chronic diseases.^[10,11] The World Health Organization, defined medication adherence as the degree that a person's conduct toward medication utilization, effecting lifestyle changes, and complying with a diet agrees with approved instruction from a health-care provider.^[12] Several methods are used to assess medication adherence, which include refill rates, therapeutic drug monitoring, self-report survey form, and electronic devices. A combination of various methods has been recommended as a modern approach for assessing adherence.^[13] Adherence to cART is essential to achieve durable clinical outcomes in PLWHA. Cohen *et al.* recorded an elevated risk of incomplete viral suppression in patients having poor adherence to cART. This can lead to viremia and potentially increase the risk for disease progression and untimely death.^[10]

Despite the enormous challenges posed by poor adherence and pill burden to individuals with chronic illnesses, little is known about the magnitude of these drug therapy problems among PLWHA in Nigeria. We, therefore, evaluated cART-related problems among PLWHA and focused on their medication adherence and pill burden.

METHODS

Study design

This study is a cross-sectional observational study involving PLWHA receiving cART at the AIDS Prevention Initiative in Nigeria (APIN) clinic, Lagos University Teaching Hospital (LUTH). PLWHA who presented consecutively to the clinic were recruited over a four-month period, between September 1, 2017, and December 31, 2017. LUTH is an 800-bedded capacity tertiary health facility situated in Lagos, Nigeria. The hospital provides tertiary care for over 20 million residents of Lagos and its environs.

Study population and sampling technique

We recruited 296 PLWHA on cART who were attending the APIN clinic using a convenient sampling method. Patients were enrolled in the study if ≥ 18 years old, were HIV infected, on cART for ≥ 3 months, and willing to give informed consents. Patients who were non-consenting, critically ill, pregnant, or < 18 years old were excluded.

Sample size

We calculated sample size using Raosoft® online calculator (with a power of 95% confidence level, response distribution set at 50%, error margin of 6%, and a population size of

18,100 registered patients as of 2017). A sample size of 263 was obtained through the calculation which was increased to 296 to make up for 10% attrition.

Data collection and study instrument

Eligible patients were interviewed with the aid of a well-structured questionnaire. The questionnaire was self-designed and adapted from the various studies evaluating adherence and pill burdens among adults with chronic illnesses,^[7,8] and other studies evaluating drug therapy problems in PLWHA.^[10,11] The instrument was validated by experts in the fields of clinical pharmacology and pharmacoepidemiology. It was pretested at the HIV Clinic, General Hospital Ikorodu, among PLWHA receiving treatment at the center. Any ambiguity and questions that were difficult for the participants to understand were simplified and modified before the questionnaire was used in the study proper. The questionnaire was interviewer administered in which a trained interviewer asked questions from each eligible patient in English Language or Pidgin English. Information sought included sociodemographics (age, sex, level of education, marriage status, employment standing, and once-a-month income). Clinical information about the patients was extracted from the case notes and included confirmation of HIV infection, presence of comorbidities, type of cART regimen used by the patients, concomitant medications used to treat the comorbidities, number of pills taken per day, and baseline CD4 count. Medication adherence was evaluated with the four-item Morisky Medication Adherence Scale (MMAS). The following were the questions asked: (1) Do you forget to take your medications? (2) Are you careless about time of taking your medications? (3) Do you stop taking your medications when you feel better? and (4) Do you stop taking your medications when you feel worse? These questions were asked if they occurred over the last six months. The answers were scored by giving each "yes" reply a score of 1 and each "no" reply was given a score of 0. The good adherent group had 0 mark and poor adherent group had 1–4 marks. The main outcome measures were (a) the adherence level over six month's period as defined by complete negative answers to all MMAS questions and (b) the level of pill burden as defined by the number of pills > 5 /day among PLWHA.

Ethical approval

The LUTH Health Research Ethics Committee (HREC) gave approval for the study with a reference No. ADM/DCST/HREC/APP/1046. Consent of all people who took part in the study was obtained.

Statistical analysis

We analyzed data obtained using the Statistical Package for the Social Sciences (SPSS®), version 20, Chicago, Illinois, United States. The categorical data were reported as percentage and proportion, while continuous variables were presented as median (interquartile range [IQR]). The sociodemographic features for adherence categories were compared using simple descriptive statistics. The categorical variables for patients with

good and poor adherence were compared using Fisher’s exact tests or Chi-square, while the Mann–Whitney test was used for continuous variables since they were not normally distributed. Multivariate analysis was done to determine the independent risk factors for poor adherence. Any $P \leq 0.05$ was regarded to be statistically significant.

RESULTS

We evaluated 296 patients who completed the study. There were more females (219; 74.0%) than males (77; 26.0%) in this study with a female:male ratio of 2.8:1. Table 1 shows the sociodemographic and clinical characteristics of PLWHA receiving cART. The median (IQR) age of the patients was 40 (35.0–47.7) years. Majority were married (262; 88.5%), in employment (267; 90.2%) and had at least a secondary school education (142; 48.0%). Majority (256; 86.5%) had no comorbidities, but among the few with comorbidities, hypertension was the most common (13; 4.4%). Majority (247; 83.4%) of the patients had good adherence to cART resulting in a poor adherence rate of 16.6%. Pill burden exceeding 5 pills/day was observed in 36 (12.2%) patients. Majority (215; 72.6%) of the patients had a CD4 count >500 cells/mL.

Pattern of adherence to combined antiretroviral therapy in people living with human immunodeficiency virus/acquired immunodeficiency syndrome

Table 2 shows the comparison of clinical characteristics of PLWHA that had good and poor adherence to cART and their socio-demographics. Poor adherence was statistically significantly associated with a higher frequency of pill burden ($P < 0.001$) but not with the use of fixed-dose combinations ($P < 0.001$). There was, however, no statistically significant difference in age, gender, marital status, employment status, level of education, commodity pattern, and CD4 count. Figure 1 shows the reasons for poor adherence among PLWHA. Forgetting to take pills (44; 16.5%) was the most common reason for poor adherence

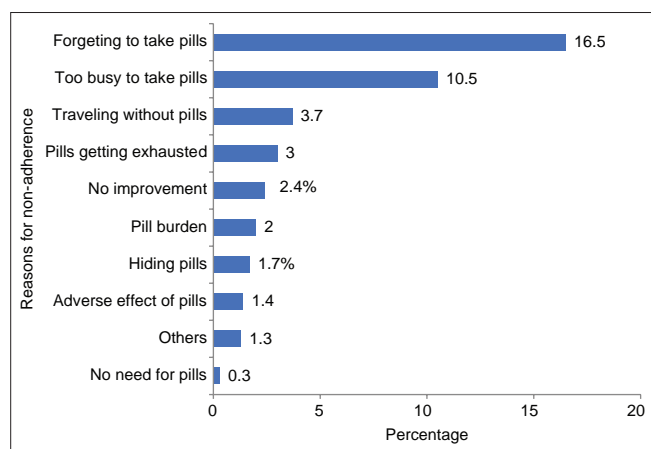


Figure 1: Reasons for nonadherence among human immunodeficiency virus-infected patients

followed by being too busy to take pills (10.5%) and traveling without pills (3.7%).

Prescription pattern of combined antiretroviral therapy for people living with human immunodeficiency virus/acquired immunodeficiency syndrome

Majority (259; 86.5%) of the patients were using fixed-dose combination. Table 3 shows the pattern of cART regimen combinations used by PLWHA.

Independent predictor of nonadherence

Being female, presence of comorbidity, not receiving fixed-dose combination, and CD4 count level were not independent

Table 1: Sociodemographic and clinical characteristics of human immunodeficiency virus-infected patients receiving antiretroviral drugs

Variable	Frequency (%)
Median age (IQR) years	40 (35.0-47.7)
Gender	
Male	77 (26.00)
Female	219 (74.00)
Marital status	
Single	22 (7.40)
Married	262 (88.50)
Divorced	3 (1.00)
Widowed	9 (3.00)
Employment status	
Employed	267 (90.20)
Unemployed	29 (9.80)
Educational level	
None	11 (3.70)
Primary	49 (16.60)
Secondary	142 (48.00)
Tertiary	94 (31.80)
Comorbidity	
Yes	256 (86.50)
No	40 (13.50)
Comorbidity pattern	
None	256 (86.50)
Hypertension	13 (4.40)
Diabetes	5 (1.70)
Others	22 (7.50)
Pill burden*	
Yes	36 (12.20)
No	260 (87.80)
Adherence*	
Yes	247 (83.40)
No	49 (16.50)
Fixed-dose combination	
Yes	259 (87.50)
No	37 (12.50)
CD4 count (cells/ml)	
<500	81 (27.40)
>500	215 (72.60)

**Adherence: MMAS score of 0, *Pill burden: >5 pill/day, Others: Hepatitis B 12 (4.1), Hepatitis C 5 (1.7), Tuberculosis 5 (1.7). IQR: Interquartile range, MMS: Morisky medication adherence scale

Table 2: Comparison of sociodemographic and clinical characteristics of human immunodeficiency virus-infected patients receiving antiretroviral therapy stratified by adherence category

Variable	Adherence (n=247), n (%)	Nonadherence (n=49), n (%)	P
Median age (IQR) years	40 (35-48)	40 (35-47)	0.60
Gender			
Male	63 (25.50)	14 (28.60)	0.72
Female	184 (74.50)	35 (71.40)	
Marital status			
Single	17 (6.90)	5 (10.20)	0.69
Married	220 (89.10)	42 (85.70)	
Divorced	2 (0.80)	1 (2.00)	
Widowed	8 (3.20)	1 (2.00)	
Employment status			
Employed	222 (89.90)	45 (91.80)	0.79
Unemployed	25 (10.10)	4 (8.20)	
Educational level			
None	11 (4.50)	0 (0.00)	0.33
Primary	39 (15.80)	10 (20.40)	
Secondary	121 (49.00)	21 (42.90)	
Tertiary	76 (30.80)	18 (36.70)	
Comorbidity pattern			
None	213 (86.20)	43 (87.80)	0.70
Hypertension	10 (4.00)	3 (6.10)	
Diabetes	5 (2.00)	0	
Others	19 (7.70)	3 (0)	
Comorbidity			
Yes	34 (13.77)	6 (12.24)	<0.00*
No	213 (86.23)	43 (87.75)	
Pill burden			
Yes	2 (0.81)	34 (69.38)	<0.00*
No	245 (99.19)	15 (30.61)	
Fixed-dose combination			
Yes	243 (98.38)	16 (32.65)	0.22
No	4 (1.61)	33 (67.34)	
CD4 count (cells/ml)			
<500	65 (26.30)	16 (32.70)	0.36
>500	182 (73.70)	33 (67.30)	

*Significant. IQR: Interquartile range

predictors of poor adherence to cART. Table 4 shows a multivariate analysis of the predictors of poor adherence to cART. Only pill burden >5/day was found to be independently associated with poor adherence (odd ratio = 0.67, confidence interval = 0.03–1.66, $P < 0.001$).

DISCUSSION

Studies have shown that treatments with cART are limited by drugs-related problems such as poor adherence, pill burden, adverse drug reactions, impairment of renal function, and hepatotoxicity.^[11] In this study, we reported good adherence to cART which was observed in 83.4% of the patients. On the contrary, we observed a high proportion of pill burden >5 pills/day in 12.2% of the patients. Medication adherence is a strong-willed behavior. It is influenced by

Table 3: Pattern of antiretroviral regimen combinations among human immunodeficiency virus-infected patients

Variable	Frequency (%)
ART drug class	
NRTI	296 (100.00)
NNRTI	266 (89.86)
PI	19 (6.41)
Boosted PI	3 (1.01)
Combination regimen	
Fixed-dose combo 3	257 (86.82)
Fixed-dose combo 2	27 (9.12)
Individual drugs	37 (12.50)
Tenofovir-based therapy	
Yes	143 (48.31)
No	153 (51.68)
Abacavir-based therapy	
Yes	8 (2.70)
No	288 (97.29)

NRTI: Nucleoside or nucleotide reverse transcriptase inhibitor, NNRTI: Non-NRTI, PI: Protease inhibitor, ART: Antiretroviral therapy

factors that are associated with quality of health-care delivery, patient-related variables, patient–health-care provider interconnection, and treatment regimen complexity.^[14] Good adherence to cART ranges between 63% and 93% worldwide, which was based on the assessment methods used. The rate is higher in developed than in developing countries.^[15,16]

We observed 83.4% adherence in our study. This is similar to those reported in two separate studies from Ethiopia.^[17,18] By contrast, our finding was slightly higher than the 75.5%–78.0% reported in a smaller population of PLWHA attending a teaching hospital in Kano, Northern Nigeria,^[8] and another public hospital in India.^[19] These varied adherence rates may be attributed to the methodological differences in assessing adherence. Other factors that may explain the diverse adherence rates include socioeconomic levels of the patients, location of the study, and level of adherence counseling received by the patients.

Poor adherence to cART in our study was associated with forgetfulness to take pills, being too busy to take pills, traveling without pills, exhaustion of pills without refill, and adverse effects of the pills. Similar factors had been reported to promote poor adherence to cART in other studies.^[8,20] Cohen *et al.* reported that a high pill burden, characterized by the use of multiple cART, was associated with lower rates of complete adherence in the United States, consequently, resulting in a higher overall health-care cost for PLWHA.^[10] Despite cART being considered to be very convenient for PLWHA, the regimen remains a lifelong treatment for this population group. Therefore, PLWHA are expected to be prescribed different medications that are related to HIV infection or other comorbid conditions thereby increasing the medication pill for this group of patients.

A comparatively high burden of medication among PLWHA compared to their uninfected counterparts was reported in

Table 4: Multivariate analysis of predictors of nonadherence

Variable	OR	95% CI	P
Gender (female)	0.71	0.26-13.44	0.69
Comorbidity (yes)	2.32	1.21-5.82	0.44
Pill burden >5/day	0.67	0.03-1.66	<0.00*
Fixed dose combination (no)	1.19	0.01-3.87	0.83
CD4 count (cells/ml) <500	0.37	0.04-0.79	0.57

*Significant. OR: Odd ratio, CI: Confidence interval

studies conducted in Canada and Switzerland.^[21] We reported a pill burden of over five pills a day in more than one-tenth of our patients. A study by Zhou *et al.* that assessed PLWHA total daily pill burden in the Southern United States reported eight pills (IQR: 6–11) as the median number of medications per patient.^[22] The Zhou study observed that a significantly huge pill burden of over 10 pills/day was associated with the presence of more than three comorbidities in PLWHA. The high number of comorbidities among PLWHA in the Zhou study may account for the high pill burden compared to ours. Nonetheless, we observed that a pill burden of >5 pills/day was a predictor of poor adherence to cART similarly reported by Cohen *et al.*^[11] and Zhou *et al.*^[22]

We found no direct association between sociodemographic characteristics of PLWHA and medication adherence compared to previous studies that reported an association.^[8,10,22] Our study is characterized by some limitations such as being a single-center study, which makes it impossible to generalize our findings among the entire population of PLWHA in Nigeria. Furthermore, we used a self-reporting adherence evaluation method (MMAS) compared to an observational pill counting method that genuinely assessed adherence. Therefore, we may have overestimated or underestimated adherence in our study. Notwithstanding these limitations, our study has provided some important clinical findings that are helpful to clinicians in exploring measures to improve adherence to ARV drugs and to lessen the pill burden.

CONCLUSION

Drug adherence and pill burden are important cART-related problems observed among PLWHA. Although a good adherence level to cART was observed in this study, the proportion of patients exhibiting poor adherence is concerning and needs to be improved. Pill burden was a predictor of poor adherence; therefore, measures to reduce this problem and to improve the level of adherence to cART are hereby advocated.

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Conflicts of interest

There are no conflicts of interest.

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