Poor Adherence Predictors and Factors Associated with Antiretroviral Treatment Failure among HIV Seropositive Patients in Western Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SOU, OTO, GPO, AJA, O. Abodunde, GBA and O. Adeola designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors SOU, OTO, GPO, O. Abodunde, TA, O. Adeola, MO and AJA managed the analyses of the study. Authors SOU, OTO, GPO, TA, GBA and MO managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: The efficiency and success of antiretroviral therapy (ART) depends on a good level of patient's adherence to a life-long regimen of antiretroviral (ARV) which is beneficial in reducing the risk of emergence of HIV resistant strains. This adherence is however influenced by several

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factors related mainly to patient and medication. This study is therefore carried out to determine the adherence rate of adult patients infected with HIV and identify the factors associated with antiretroviral therapy (ART) interruption or poor adherence.

Methods: This cross sectional study was carried out in Ondo & Ekiti States, South Western Nigeria. The target population was adult patients living with HIV and already initiated on ART. Data was collected by trained volunteers and supervised by appointed supervisors, by a face-to-face interview. All data were statistically analysed, using statistical package for the social sciences (SPSS) and statistical test of significance was performed with Chi-Square test.

Results: A total of 412 consenting respondents participated in the study with a mean age ± SD is 37.93 ± 9.30 years. 116 (40.8%) of them are males while 244 (59.2%) are females. ART adherence level was 79.6%. The main factor associated with ART adherence was educational status (χ^2 = 16.18, df = 3, P = 0.001). Drug reminder strategy have lower association with missing ART drug (OR: 0.51, 95% CI: 0.28 – 0.92) while patients experiencing ART drug side effect have higher association with missing ART drug (OR: 1.82, 95% CI: 1.01 – 3.28).

Conclusion: ART adherence is sub-optimal, with barriers largely patient-dependent thus it is imperative to intensify medication adherence counselling in an holistic behavioural educational improvement strategy aimed at improving the ability to fit therapy into own lifestyle, avoid drug exhaustion, achieve optimal adherence and remarkable patient outcome.

1. INTRODUCTION

Human Immunodeficiency Virus (HIV) epidemic has seen more than 70 million people already infected with the virus and about 35 million people have died of HIV, thus, this epidemic continues to be a major global public health challenge. In 2015, an estimated 36.7 million people were living with HIV (including 1.8 million children), a global HIV prevalence of 0.8% of adults aged 15-49 years worldwide living with HIV [1,2]. Majority of these people live in Low and Middle Income Countries (LMICs) with sub Saharan Africa being the most severely affected, where nearly 1 in every 25 adults (14.4%) live with HIV and account for nearly 70% of people living with HIV worldwide. Nigeria ranks among the top three countries with the highest number of the infections [1,2].

The efficiency and success of antiretroviral therapy (ART) depends on a near-perfect level of patient's adherence to a life-long regimen of antiretroviral (ARV). Interrupting ART for any reason whatsoever is an indication of a compromised adherence to ARV therapy. Cultural, behavioural, clinical and socio-economic factors have all been reported in various studies to be associated with poor ART adherence, including pill burden from other drugs used in treating co-infections with HIV. A research study conducted by Suleiman et al., 2016 in Bayelsa, Southern Nigeria, revealed that 73.4% of the patients had ≥95% adherence level, with some of the most important reasons given for missing doses including simply forgetting, 24.5% and avoiding side effects was reported to be 5.5% [3]. A research study conducted in Brazil in 2015 showed that there was 25% non-adherence prevalence among ART patients in Salvador, with variables such as adverse drug reaction, illicit drug use, age under 34 years and less than 8 years of school education, all associated with non-adherence [4]. In Nairobi Kenya, 18% of patients were said to be non-adherent and main reason (38%) for missing therapy were being busy and forgetting [5]. A study on factors influencing adherence to antiretroviral therapy in Port Harcourt, South South Nigeria, showed 76.1% patients had adherence rates of ≥ 95%, with 59.2% reported to be 100% adherent. The common caregiver-related factors for missing doses were forgetfulness (55.2%), travelling (25.3%) and drugs finishing (18.4%) while child-related factors were refused drugs (11.5%), sleep (9.2%) and vomiting episode (9.2%). 31.9% caregivers reported missing clinic visit due to travel (26.5%), illness (17.6%) and family problems (13.2%). Co-morbidity was identified as a predictor of poor adherence while socio-economic status, education, type of ART and duration of ART were reported not to significantly affect adherence [6].

An 86% adherence level was reported in a study carried out on 212 paediatric patients in Nigeria, with drug exhaustion, child sleep and caregiver unavailability being the most common

reasons for those that missed one or more ARV doses [7]. A 2014 study carried out in Sokodé Togo on the predictors to adherence to antiretroviral therapy revealed that 67.0% of the respondents were living with their partners, 72.2% had formal education, adherence level was 78.4% and factors associated with ART adherence include level of education and HIV status disclosure to sexual partner [8]. The aim of the study was to determine the level of adherence and identify the factors or predictors associated with antiretroviral therapy (ART) interruption or poor adherence among adult patients initiated on ART.

2. RESEARCH HYPOTHESIS

1) Educational status does not significantly affect ART adherence.
2) Duration of ART does not significantly affect ART adherence.
3) Disclosure of HIV status does not significantly affect ART adherence.

3. METHODS

This study is a cross sectional study carried out at the randomly selected primary, secondary and tertiary level hospitals across Ekiti State & Ondo State, South-Western Nigeria. The sampling frame was 66 healthcare facilities. They were randomly selected using a simple random technique. The target population was adult patients living with HIV (PLHIV) and already initiated on ART. A pre-tested questionnaire was administered to the respondents. The total number of respondents was 412. Demographic and socio-economic information was collected. Data was collected by trained volunteers and supervised by appointed supervisors and investigators, by a face-to-face interview using a pre-tested structured questionnaire on the HIV status & disclosure, adherence level, predictors of ART adherence, factors associated with poor ART adherence, among others. Ethical approval was obtained from the Ethical Review Board of the Federal Teaching Hospital Ido Ekiti Nigeria.

3.1 Sample Size

Sample size calculation was done using 95% confidence interval, 0.05 precision and prevalence rate. The report of the 2013 study revealed 59.2% of patients had 100% ART adherence in Southern Nigeria [6]. Using Leslie Fischer's formula for population >10,000, the formula for sample size calculation is: $n = Z^2PQ/d^2$ [9].

$$n = Z^2PQ/d^2$$

Where,

n = minimum sample size, d = degree of precision (taken as 0.05),
Z = standard normal deviation at 95% confidence interval which is 1.96,
P = proportion of the target population (estimated at 50.9% which is 59.2/100 = 0.592),
Q = alternate proportion (1-P) which is 1-0.592 = 0.408

$$n = \frac{(1.96)^2 \, (0.592)(0.408)}{(0.05)^2} = 371$$

Also, adding a 5% non-response rate, the minimum sample size (n) will be 5/100 X 371 = 19.
Thus, it will be 19 + 371 = 390 = n

3.2 Statistical Analysis

Data was statistically analysed using Statistical Package for the Social Sciences (SPSS) for windows version 23.0 software (SPSS Inc., Chicago, IL, USA). All data were expressed as Mean ± Standard Deviation (SD). Frequency counts were generated for all variables and statistical test of significance was performed with Chi-Square test. Significance was fixed $P < 0.05$ and highly significance is $P < 0.01$.

4. RESULTS

4.1 Socio-demographic Data

A total of 412 consenting respondents participated in the study. The mean age ± SD is 37.93 ± 9.30 years. One hundred and sixty (40.8%) of them are males while two hundred and fourty four (59.2%) are females. Most of them are married, 356 (86.4%), with tertiary education being the highest level of education attained by most, 150 (36.4%) while trading/business is the major vocation, 132 (32.0).

Most of the respondents are in the age range 25 - 30 years, mainly female, married and attained tertiary education. About 57.3% of the respondents have disclosed their HIV status to

their partner. The fear of divorce was the main reason why HIV status is not disclosed to partner. The HIV status of 85.4% respondents is not known to their friends while 60.2% of the respondents' partners have tested for HIV, with 11.7% of them tested positive. The ART regimen type mostly taken by the respondents is Zidovudine/Lamivudine/Nevirapine (78.1%). Meanwhile, 20.4% of them have missed their ART regimen dose schedule in the past one month largely due to travels thus forgetting to take their regimen.

Table 1. Socio-demographic data of respondents

Variables	Frequency (%)
Age group (years)	
< 25 years	16 (3.9)
25 - 30 years	92 (22.3)
31 - 35 years	84 (20.4)
36 - 40 years	80 (19.4)
41 - 45 years	68 (16.5)
46 - 50 years	32 (7.8)
51 - 55 years	24 (5.8)
56 - 60 years	12 (2.9)
> 60 years	4 (1.0)
Gender	
Male	168 (40.8)
Female	244 (59.2)
Marital status	
Single	28 (6.8)
Married	356 (86.4)
Separated	4 (1.0)
Divorced	16 (3.9)
Widowed	8 (1.9)
Level of education	
No formal education	38 (9.2)
Primary education	100 (24.3)
Secondary education	124 (30.1)
Tertiary education	150 (36.4)
Occupation	
Artisan	110 (26.7)
Trading/Business	132 (32.0)
Public servant	36 (8.7)
Farmer	5 (1.2)
Teacher	36 (8.7)
Unemployed	28 (6.8)
Self employed	41 (10.0)
Private sector worker	24 (5.8)

Table 2. HIV status & disclosure

Variables	Frequency (%)
Number of years since respondent has been living with HIV	
< 2 years	94 (22.8)
2 – 3 years	131 (31.8)
4 – 5 years	105 (25.5)
6 – 10 years	70 (17.0)
> 10 years	12 (2.9)
HIV status known by partner	
Yes	236 (57.3)
No	176 (42.7)
Reason why partner is not aware of HIV status	
Fear of divorce	60 (14.6)
Fear of stigma/discrimination	52 (12.6)
Fear of physical abuse	37 (9.0)
Fear of accusation of infidelity	27 (6.6)
HIV status known by family member	
Yes	256 (62.1)
No	156 (37.9)
Family member aware of HIV status	
Father Only	131 (31.8)
Mother Only	72 (17.5)
Sister Only	20 (4.9)
Child/Children Only	16 (3.9)
Both Parents Only	4 (1.0)
Father, Mother & Brother Only	4 (1.0)
All family members	4 (1.0)
HIV status known by friend (s)	
Yes	60 (14.6)
No	352 (85.4)
Partner has tested for HIV	
Yes	248 (60.2)
No	164 (39.8)
Result of Partner HIV test	
Positive	48 (11.7)
Negative	164 (39.8)
Not willing to disclose	16 (3.9)
Unknown	20 (4.9)

5. DISCUSSION

This research outcome has shown that 79.6% of the respondents are adherent to their ART drug regimen especially in the past month. This is largely in agreement with some previous studies reported in Brazil, Kenya, South South Nigeria & Togo [3,4,5,6,7,8]. The adherence level is lower than the standard of ≥ 95% required to avoid virologic failure. This is

because Antiretroviral Therapy (ART) success mainly centres on adherence defined as the extent to which a client's behaviour matches the prescribed healthcare professional regimen in terms of care including correct date and time for clinic appointment and treatment involving correct drug, timing, dosing, compliance to food restrictions and no missed doses. Unlike drugs for other chronic illnesses where adherence levels of 70 - 80% are considered adequate to achieve treatment goals, in the case of antiretroviral therapy, adherence levels greater than 95% is required to obtain a successful treatment outcome [10,11]. The challenges faced by the patients in achieving ≥ 95% adherence level include adverse drug reaction & busy work schedule as reported by 1.9% of the respondents. Also, hiding the drug from someone who is not aware of the status, as reported by 2.2% of them; forgetting to carry the drugs along during travels, reported by 6.6%,

drug fatigue as reported by 3.2% while some simply forgot taking the drug as reported by 2.9% of them. This is slightly similar to what was reported in other studies across the world, where the patients either simply forgot taking the drug, busy schedules, travels, finished drugs or even in an effort to avoid certain side effects or adverse drug reactions [3,4,5,6,7]. This may be due to the fact that some of the patients have not even disclosed their status thus are not bold taking drugs easily as would be the case is status is well disclosed, as 42.7% did not disclose their status to their partners, 37.9% did not disclose to their family members and a whopping 85.4% did not inform their friends, especially in the situation where the patient is hiding the drug from someone. Moreover, since a massive 70.9% do not have any drug reminder strategy, this may likely also contribute to forgetfulness and drug finishing.

Table 3. ART adherence

Number of years ART has been taken	
1 year	80 (19.4)
2 years	45 (10.9)
3 years	92 (22.3)
4 years	92 (22.3)
5 years	55 (13.3)
6 years	17 (4.1)
7 years	11 (2.7)
8 years	10 (2.4)
9 years	2 (0.5)
10 years	4 (1.0)
12 years	4 (1.0)
ART regimen type taken by respondent	
Tenofovir/Lamivudine/Efavirenz	86 (20.9)
Zidovudine/Lamivudine/Nevirapine	322 (78.1)
Tenofovir/Lamivudine/Lopinavir-Ritonavir	4 (1.0)
ART drug side effect mostly experienced	
Nausea	24 (5.8)
Vomiting	4 (1.0)
Itching	12 (2.9)
Rashes	8 (1.9)
Neuropathy	20 (4.9)
No serious side effect	344 (83.5)
Number of time ART clinic appointment missed in last one year	
Nil	233 (56.6)
Once	68 (16.5)
Twice	56 (13.6)
Thrice	23 (5.6)
Four Times	16 (3.9)
Five Times	12 (2.9)

Reason for missing clinic appointment	
Family problems	38 (9.2)
Busy Schedule	39 (9.5)
Travelled	32 (7.8)
Forgot	14 (3.4)
Illness	21 (5.1)
Transport fare issues	17 (4.1)
Hospital Strike Action	18 (4.4)
ART regimen dose schedule missed in the past one month	
Yes	84 (20.4)
No	328 (79.6)
Number of times ART regimen missed in the past one month	
Once	41 (10.0)
Twice	32 (7.8)
Thrice	3 (0.7)
Four Times	8 (1.9)
Reason for missing ART regimen	
Busy Schedule	8 (1.9)
Travelled & forgot to carry it along	27 (6.6)
Tired of taking the drugs	13 (3.2)
Hiding the drug from someone	9 (2.2)
Adverse drug reaction	8 (1.9)
Forgot	12 (2.9)
Drug Finished	7 (1.7)
Action taken after missing ART regimen dose	
Took double dose	4 (1.0)
Continued normal dose	80 (19.4)
ART Drug Reminder Strategy	
Yes	120 (29.1)
No	292 (70.9)
ART Drug Reminder Strategy Choice (Choice of reminder on taking drug)	
Father	4 (1.0)
Mother	26 (6.3)
Child/Children	13 (3.2)
Alarm	60 (14.6)
Wife	9 (2.2)
Husband	8 (1.9)

Table 4. Chi square result showing factors influencing ART Adherence

Variables (hypotheses)	χ^2	df	Critical value	Decision	P-value
Educational status does not have significant effect on ART adherence	16.18	3	7.82	Rejected	0.001
Duration of ART does not have significant effect on ART adherence	9.79	10	18.31	Accepted	0.459
Disclosure of HIV status does not have significant effect on ART adherence	3.80	1	3.84	Accepted	0.063

The null hypothesis is rejected when the test statistic is greater than the tabled value or critical value.

Table 5. Odd's ratio (OR) table

Variables	OR	95% CI
Estimated odds that patient that doesn't have a drug reminder strategy will miss ART drug	0.51	0.28 – 0.92
Estimated odds that patient having ART drug side effect will miss their ART drug	1.82	1.01 – 3.28

Only 56.6% of the patients have kept to their clinic appointment schedules in the past one year, with reasons for missing clinic appointment mainly being family problems, transport fare issues, busy work schedules, illness, travelling, among others. This is similar to the 2013 report in South South Nigeria where clinic visits were missed due to family problems, illness and travel [6]. This finding shows that a lot of work still needs to be done in the area of intensive adherence counselling, which regular clinic visits form a part. This will encourage positive living and ensure regular drug refills thus improving adherence to antiretroviral therapy (ART) in the process.

The Chi Square analysis in table 4 shows that educational status have significant effect on antiretroviral therapy (ART) adherence (χ^2 = 16.18, df = 3, P = 0.001) as observed by the rejection of the null hypothesis, which may be a result of enhanced knowledge of the implications of poor adherence among the more educated patients translating to improved adherence rates. This is also in agreement with the outcome of a Togolese study that showed level of education as one of the factors associated with ART adherence [8]. The acceptance of the second hypothesis on the duration of ART having significant effect on ART adherence (χ^2 = 9.79, df = 10, P = 0.459) as in table 4 shows that the period during which a patient has been on these drugs does not determine how adherent the patient will be. The acceptance of the third hypothesis on the disclosure of HIV status to partner having significant effect on ART adherence (χ^2 = 3.80, df = 1, P = 0.063) as in table 4 shows that the disclosure of HIV status does not also determine how adherent the patient will be. This however differs from the outcome of a Togolese study that showed HIV status disclosure to sexual partner as one of the factors associated with ART adherence [8]. The odd's ratio (OR) table in table 5 shows that drug reminder strategy has lower association with missing ART drug (OR: 0.51, 95% CI: 0.28 – 0.92). This shows that drug reminder strategy is a good strategy but does not necessarily or seriously

have impact on a patient missing ART drug as he or she plans to take the drugs based on other more crucial factors such as side effects of the ART drug as evident in the measure of association (odd's ratio) showing that patients experiencing ART drug side effect have higher association with missing ART drug (OR: 1.82, 95% CI: 1.01 – 3.28).

6. CONCLUSION

The implication of our findings is that ART adherence is sub-optimal, with barriers largely patient-dependent thus it is imperative to intensify medication adherence counselling, especially regarding the implications of poor adherence, early disclosure of status and keeping regular clinic appointments in an holistic behavioural educational improvement strategy aimed at improving the ability to fit therapy into own lifestyle, avoid drug exhaustion, achieve optimal adherence and tremendous patient outcome.

CONSENT

All authors declare that 'written informed consent was obtained from the subjects and other approved parties for publication of this paper and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee (the ethical review committee of the Federal Teaching Hospital, Ido Ekiti, Nigeria) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki." ethical standards laid down in the 1964 Declaration of Helsinki."

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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