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Prevalence and Pattern of Adverse Drug Reactions among HIV Infected Patients on Highly Active Antiretroviral Therapy (HAART) in Imo State, Nigeria: A Hospital Based Survey

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ABSTRACT

Introduction: It is a proven fact that almost all drugs carry the potential to produce undesirable effects in addition to the desired ones.

Aim: The aim of this study is to determine the prevalence, pattern and socio-demographic determinants of adverse drug reactions among patients on HAART attending clinics in hospitals in Imo State Nigeria.

Methodology: This was a hospital-based cross-sectional study carried out among HIV patients attending clinics in hospitals in Imo State. The 400 participants were selected using a multistage sampling technique. Data was collected using an interviewer administered, semi-structured questionnaire and analyzed using EPI Info version 3:2:1. Chi-square and regression analysis was used to test association between variables. P-value was set at ≤ 0.05.

Results: The mean age of the participants was 41.7±3.0 years with a male to female ration of 1:2. The adherence level to HIV treatment was 85.0%. The prevalence of ADRs in the last 1 year preceding the study was 13.7% and the common forms of ADR experienced by patients was Hematological symptoms (34%), GIT symptoms (21.8%) and skin manifestation (20.0%). Socio-demographic determinants of the occurrence of ADR among the participants were: age 50 years and above (OR: 9.28), female gender (OR: 2.55) and living in a rural area (OR: 4.47).

Conclusion: Though the prevalence of ADR reported in this study was low, there is need to increase the depth of knowledge among HIV patients in the State, monitor patients closely by care givers and find possible ways to increase adherence to HIV drugs which was not optimal among participants.

Keywords: Prevalence, Pattern, Adverse Drug reactions, HAART, HIV, Patients, Imo State.

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1.0 INTRODUCTION

It is a proven fact that almost all drugs carry the potential to produce undesirable effects, in addition to the desired ones.[1,2] Though most of those taking these drugs gain far more benefits than harm, a sizeable proportion of them still experience undesirable effects from the use of the medicines which occurs at recommended doses and frequencies.[3] These effects, which are known as adverse drug reactions (ADRs) raise concerns to both the clinician and client, adding to the cost of medical treatment and increase morbidity and mortality.[4,5] Adverse drug reaction as defined by World Health Organization (WHO), is any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.[6] It is also defined as an undesirable effect, reasonably associated with the use of the drug that may occur as a part of the pharmacological action of a drug or may be unpredictable in its occurrence.[7]

ADRs are one of the leading causes of morbidity and mortality in health care settings. Furthermore, in many countries ADRs rank among the top ten leading causes of mortality. [8,9,10] Generally it has been found that there is a poor record of reporting ADRs in most hospitals

worldwide.[11,12] American Pharmaceutical System analyzed 39 studies carried out over four decades and found that a total of 106,000 people died as a result of ADRs.[13] Since the discovery of Human Immunodeficiency Virus (HIV) in 1981, there has been an increasing number of patients primarily due to the use of antiretroviral drugs, better diagnostic procedures and widespread awareness about the disease. The introduction of highly active antiretroviral therapy (HAART) in developed countries in the late 90s has been associated with a remarkable decrease in AIDS related mortality. This decrease in mortality has changed the perspective of HIV infection from that of a rapid fatal disease to a chronic manageable infection.[14, 15] Globally 36.9 million people were living with HIV in 2017 with about 21.7 million of them being on Antiretroviral treatment (ART), thereby giving a coverage of 59%. Also 1.8 million new infections were reported in the same year under review.[16] Current reports from National HIV/AIDS Indicator and Impact Survey (NAIIS) showed that HIV prevalence in Nigeria has decreased from previous estimates of 2.8% to 1.4% in March 2019 with about 1.9 million people still living with HIV among whom about one million of them were accessing antiretroviral therapy.[17]

Antiretroviral therapy works by providing suppression of a patient's viral load and restoring their Immune system, and about 6.6 million HIV/AIDs related deaths worldwide have been prevented as a result of ART use.[18,19] Despite these benefits, associated with ART, which can only be achieved with high levels of adherence,[10] ART is linked with the occurrence of varying levels of adverse drug reactions and toxicities which is of great public health concern as it constitutes a threat to sustained success of HIV treatment.[19, 20] ADRs due to ART has been reported to occur most commonly during the beginning of treatment as noticed in most chronically administered drug.[22-24] Several studies have shown that ADRs are associated with non-adherence to treatment, discontinuation of ART, treatment failure and disease progression due virologic failure and change in ART regimens.[24-29] Thus understanding the pattern of occurrence and distribution of ADRs among HIV infected patients is imperative to optimally manage their disease, given the significant consequences of ADRs in this patient population.[30] ADRs vary greatly from one individual to another and has been described as single symptoms (e.g. anaemia, headache, nausea, vomiting) or as symptoms involving organs and systems (e.g. dermatological, hematological, gastrointestinal reaction). It can also be classified according to severity or intensity or duration or estimates using scales or absolute numbers.[31,32] ARDs caused by antiretroviral drugs can range from mild presentation e.g. mild gastrointestinal disturbances to serious side effects which includes hematological disorders, hepatotoxicity, neurological disorders, dermatological disorders, musculoskeletal disorders and metabolic disorders among others.[10,20, 30-36.]

Varying prevalence rates of ADRs has been reported from several studies world over, ranging from 6.45% in Nicaragua[30] to as high as 94% in a study from Tehran, Iran.[37] Prevalence rates found in other studies were; 70% in Calabar, Nigeria[20], 89.8% in Gonda, Ethiopia[33], 61.2% in Sikasso, Mali[32], 70.8% in Jush, Ethiopia[36], 19.5% in Duala, Cameroon[14] and 9.4% in Ghana[38]. These wide variations in prevalence rates reported from several studies can be explained by several factors ranging from different methodologies used in the conduct of the studies to the environmental and host factors and type of drug regimen used by the patients.

Thus the aim of this study is to assess the prevalence and pattern of the occurrence of ADRs among HIV patients on HAART and the socio-demographic factors associated with the occurrence of ADRs irrespective of duration of treatment.

2.0 METHODOLOGY

2.1 Study area and population: The study was carried out among HIV positive patients on HAART attending HIV clinics in three selected hospitals from Imo State, South-East, Nigeria. They are; Imo State University Teaching Hospital Orlu, General Hospital Awo-omamma, and Imo State Specialist Hospital Umuguma, Owerri. Two of the hospitals (Imo State University Teaching Hospital Orlu and Imo State Specialist Hospital Umuguma) were located in urban area of the state while General hospital, Awo-omamma was located in a rural area. All of them are government owned hospitals and provide HIV care at all levels.

The study population comprised all adult HIV patients on HAART attending clinics in the selected hospitals in the state.

2.2 Study Design: The study was a hospital-based descriptive cross-sectional type.

2.3 Selection Criteria: All HIV positive patients currently receiving anti-retroviral therapy at the clinics during the study period who consented to participate were enrolled and studied.

Sample Size Estimation: The sample size of 400 patients was used for this study and this was determined using the Cochran sample size formula for cross-sectional studies in populations greater than 10,000 individuals.

$N = Z^2pq/ d^2$

Where n= minimum sample size required, Z = standard normal deviate set at 95% significant level ≈1.96, p = prevalence of adverse reactions in a previous study (70%)[20], q = 1-p, d = degree of precision set at 0.05. Also 10% attrition rate was added in the 400 sample size used.

2.4 Sampling Technique: The respondents used in this study were selected using the multi stage sampling technique.

The first stage involved the selection of the hospitals to be used. This was done by stratifying the hospitals that provide the HIV care in the state into secondary and tertiary health care providers.

The second stage involved the selection of the hospitals to be studied. Two hospitals from the secondary category and one from the tertiary category were selected using simple random sampling by balloting based on number of hospitals in each category.

The third stage involved the selection of the patients to be studied and this was done using the systematic random sampling technique and the clinic register.

2.5 Data collection material: Information was collected from the respondents using a pretested, semi-structured, and interviewer administered questionnaire which comprised four sections. Section A contains questions bordering on socio-demographic characteristics of respondents. Section B; awareness and Knowledge about adverse drug reactions. Section C; drug use and occurrence of adverse drug reactions and section D; factors influencing adverse drug reactions among respondents.

2.5 Data Analysis: Data was analyzed using a computer software (EPI INFO version 3.2:1) Descriptive statistics was presented in tables as frequencies and percentages. Chi

square test statistics was used to test significant associations between variables and logistic regression was used to generate odds ratios where necessary. Basic knowledge questions about adverse drug reactions were asked and scored as follows; 0-49% of the total as poor, 51-79% of the total as fair and >80% of the total as good knowledge.

2. 6 Ethical approval: Ethical approval was gotten from the Ethics Committee of Imo State University Teaching Hospital Orlu before proceeding to study. The research was strictly conducted in line with laid down procedures as stated in Helsinki Declaration of 1964 in studies involving the use of human subjects.

3.0 RESULTS

Table3.1: Socio-demographic characteristics of participants.

Variable	Frequency (%) n=400
Age group (yrs)	
<20	22(5.4)
20-29	81(20.3)
30-39	108(27.0)
40-49	108(28.7)
≥50	81(20.3)
Mean age=41.7±3.0	
Sex	
Male	133(33.2)
Female	267(66.8)
Religion	
Catholics	267(66.8)
Pentecostals	111(27.8)
Orthodox	17(4.2)
Others[1]	5(1.2)
Marital Status	
Ever married	303(75.8)
Never married	97(24.2)
Educational attainment	
None	7(1.7)
Primary	77(19.3)
Secondary	206(51.5)
Tertiary	110(27.5)
Occupational status	
Employed	309(77.3)
Unemployed	91(22.7)
Place of residence	
Rural	142(35.5)
Urban	258(64.5)

Others[1] =Islam, Traditional religion and Paganism

The mean age of the participants was 41.7±3.0 years with majority of them being within the 30-49 years age bracket, (54.0%). There were more females (66.8%) than males (33.2%), with a male to female ratio of 1:2. Majority of them were Catholics (66.8%), ever married (75.8%), had secondary education (51.5%), employed (77.3%) and lives in an urban area (64.5%). Table 3.1

Table 3.2: Awareness and knowledge about adverse drug reactions among participants

Variable	Frequency (%)
Awareness about adverse drug reactions (n=400)	
Yes	374(93.5)
No	26(6.5)
****Sources of information (n=374)**	
Radio	226(60.4)
Health workers	219(58.6)
Television	142(37.8)
Chemist/pharmacy shop	101(27.0)
Friends/neighbors/relatives	67(17.9)
Newspapers/magazines	67(17.9)
School	47(12.6)
Work place	17(4.5)
Billboards/posters	10(2.6)
Seminar/workshops	7(1.8)
Market	6(1.6)
****Adverse drug reactions types mentioned (n=374)**	
Skin manifestations(Rashes & itching)	332(88.8)
GIT manifestations (Nausea, Vomiting and diarrhea)	88(23.5)
Headache	45(12.0)
Drowsiness/Dizziness	19(5.1)
Renal problems	17(4.5)
Cough	15(4.0)
Blurring of vision	14(3.7)
Hearing defects/tinnitus	14(3.7)
Numbness of the extremities	10(2.7)
Yellowness of the eyes	10(2.7)
Anaemia	5(5.3)
Cardiovascular problems	3(0.8)
Insomnia	3(0.8)
Unconsciousness	2(0.3)
Level of knowledge about adverse drug reactions (n= 400)	
Poor (0-49%)	178(44.5)
Fair (50-79%)	146(36.5)
Good (≥80%)	76(19.0)

**= multiple response

Majority of the participants (93.5%), were aware about adverse drug reactions and the common sources of information were from; radio (60.4%), health workers (58.6%) and television (37.8%). The commonest adverse drug reaction mentioned were skin manifestations (88.8%), with more of them having poor (44.5%) or fair (36.5%) knowledge about adverse drug reactions. Table 3.2

Table 3.3: Adherence to anti-retroviral drugs and combination with other drugs

Variable	Frequency (%)
HIV treatment Regimen currently used (n=400)	
AZT+3TC+NVP	368(92.0)
D4T+3TC+EFV	20(5.0)
AZT+3TC+EFV	8(2.0)
TDF+FTC+EFV	4(1.0)
Adherence to HIV drugs (n=400)	
Yes	340(85.0)
No	60(15.0)
Frequency of non-adherence (n=60)	
2 or more times a week	50(83.3)
Once weekly	8(13.3)
At least once monthly	2(3.4)
Main reason for missing dose (n=60)	
Forgot	40(66.7)
Travelled	7(11.7)
Tired of drug	5(8.3)
Sick	3(5.0)
Due to side effect	3(5.0)
No reason	2(3.3)
Combination with herbal drugs (n=400)	
Yes	22(5.5)
No	378(94.5)
Herbs commonly used (n=22)	
Aloe vera	6(27.3)
Herbal concoction (Agbo)	6(27.3)
Moringa (Drum stick leaf)	4(18.2)
Dogoyaro (neem leaf)	4(18.2)
Garlic	1(4.6)
Ginger	1(4.6)
Combination with other orthodox drugs (n=400)	
Yes	151(37.6)
No	249(62.3)
Combination with TB drugs (n=400)	
Yes	24(6.0)
No	376(94.0)

AZT: Zidovudine; 3TC: Lamivudine; NVP: Nevirapine; D4T: Stavudine; EFV: Evavirenz; TDF: Tenofovir; FTC: Emtricitabine.

Majority of the participants (92.0%) were on AZT+3TC+NVP treatment regimen and adherence level among them was 85.0%. Majority of those that were non-adherent to their drugs claim that they missed it more than once a week, (83.3%) and their main reason for not taking their drugs was that they forgot it (66.7%). A small proportion of the respondents (5.5%) combine their drug intake with herbs and common herbs used were; aloe vera, (27.3%), and herbal concoctions (27.3%). About 37.6% and 6.0% of the participants combine their drugs with other orthodox drugs and TB drugs respectively. Table 3.3

Table 3.4: Occurrence and reporting of Adverse Drug Reactions (ADRs) among Participants

Variable	Frequency (%)
Ever experienced adverse drug reaction in your life time (n=400)	
Yes	146(36.5)
No	254(63.5)
Experience of ADRs while on HIV drug treatment in the last 1 year (N=400)	
Yes	55(13.7)
No	345(86.2)
****Forms of ADRs currently experienced (n=55)**	
Anaemia	19(34.6)
Nausea & Vomiting	11(20.0)
Itching/ Rashes	11(20.0)
Joint pain/Muscle weakness	10(18.2)
Hallucinations	5(9.1)
Peripheral Neuropathy/numbness	5(9.1)
Renal impairment	4(7.3)
Depression/ Insomnia	3(5.5)
Confusion/ Prostration	2(3.6)
Hearing impairment	1(1.8)
Abdominal pain	1(1.8)
Reported the reaction (n=55)	
Yes	53(96.4)
No	2(3.6)
Persons reported to (n=53)	
Doctor	42(79.3)
Pharmacist	6(11.3)
Nurse	5(9.4)
****Actions taken by those reported to (n=53)**	
Counseled me about the drug and its actions	27(50.9)
Asked me to continue the drug	19(35.9)
Changed the drug regimen	15(28.3)
Treated the reaction	4(7.6)
Were you given the ADR form to fill (n=55)	
Yes	8(14.6)
No	47(85.4)
What was the fate of the ADR (n=55)	
Resolved spontaneously	43(78.2)
Resolved over a long time	6(10.9)
Resolved with some complications	3(5.5)
Never resolved	3(5.5)

**=Multiple response

Table 3.4 showed the occurrence and reporting of ADRs among participants. The prevalence of ever experiencing ADRs among them was 36.5% and the current experience of ADRs while on anti-retroviral drugs was 13.7%. The common forms of ADRs experienced by respondents were; anaemia (34.6%), nausea and vomiting (20.0%), itching/rashes (20.0%). Most of the respondents (96.4%) claimed to have reported the ADR to a caregiver, with majority of them (79.3%) reporting it to their physicians. Common actions taken by those reported to were; counselling about the drug (50.9%) and encouraging them to continue with the drugs (35.9%). Most of those that had adverse reaction did not fill the ADR forms, (85.4%) and majority of them (78.2%), claiming that the reactions resolved spontaneously.

Table 3.5: Socio-demographic Determinants of the occurrence of ADRs among participants

Variable	Occurrence of adverse drug reaction			Statistics (X^2) P-value	OR (95% CI)
	Yes (%)	No (%)	Total (%)		
Age group (yrs)					
< 50	22(6.9)	297(93.1)	319(100)	**62.235**	1.00
>50	33(40.7)	48(59.3)	81(100)	**P<0.0001***	**9.28* (4.99-17.25)**
Total	**55(13.7)**	**345(86.3)**	**400(100)**		
Sex					
Male	9(6.8)	124(93.2)	133(100)	**8.192**	1.00
Female	46(17.2)	221(82.8)	267(100)	**p=004***	**2.55* (1.28-5.04)**
Total	**55(13.7)**	**345(86.3)**	**400(100)**		
Marital status					
Ever married	38(12.5	265(87.5)	303(100)	1.539	1.00
Never married	17(17.5)	80(82.5)	97(100)	p=0.215	1.40 (0.83-2.36)
Total	**55(13.7)**	**345(86.3)**	**400(100)**		
Educational level					
≤ secondary	40(13.8)	250(86.2)	290(100)	0.002	1.00
Tertiary	15(13.6)	95(86.4)	110(100)	p=0.968	0.99 (0.52-1.87)
Total	**55(13.7)**	**345(86.3)**	**400(100)**		
Occupational status					
Employed	47(17.9)	262(82.1)	309(100)	2.443	1.73 (0.85-3.53)
Unemployed	8(8.8)	83(91.2)	91(100)	p=0.118	1.00
Total	**55(13.7)**	**345(86.3)**	**400(100)**		
Place of residence					
Urban	19(7.4)	239(92.6)	258(100)	**24.999**	1.00
Rural	36(25.4)	106(74.7)	142(100)	**P<0.0001***	**4.27* (2.34-7.79)**
Total	**55(13.7)**	**345(86.3)**	**400(100)**		

*=significant

Socio-demographic factors found to be associated with the occurrence of adverse drug reactions as reported by the participants were; age (X^2=62.235, p<0.0001), sex (X^2=8.192, p=0.004), and place of residence (X^2=24.999, p<0.0001). The likely predictors of the occurrence of an adverse drug reaction as reported by the patients were; being at age ≥ 50 years (OR: 9.28), a female (OR: 2.55), and living in a rural area, (OR: 4.77).

4.0 DISCUSSION

Despite great success recorded in the management of HIV/AIDS globally with the introduction of HAART, adverse drug reactions associated with the drugs has been an impediment in the overall care of HIV/AIDs patients. This is worrisome in that it leads to reduced adherence to HIV/AIDs treatment with its attendant problems. Thus our study sought to determine the prevalence of ADRs and associated socio-demographic factors among patients on antiretroviral therapy irrespective of the time initiation of treatment.

The prevalence of ADRs as revealed in our study was 13.7%. This was higher than figures report from Nicaragua (6.45%)[30] and Ghana (9.4%)[38] but lower than reports from several other studies. [14,20,32,33,36,37] This low prevalence reported from our work could be associated to a lot of factors ranging from method of data collection and materials used, to host and environmental factors. The prevalence was calculated for the year preceding the survey and by that time, some of the old patients may have been stable on treatment and may not be having ADRs or might also have forgotten if it actually occurred. It could be connected to low level of knowledge about ADR's that was found among the participants. Common ADR's reported in this study were; hematological manifestations GIT manifestations, Dermatological manifestations and CNS manifestations. This pattern of manifestation was similar to findings reported from several studies.[10,11,20,33,34,36] It is also worthy to note that this pattern of ADRs reported was similar to the common side effects associated with major HAART regimen used by most of the patients (zudovudine + Lanuvudine +Nevirapine). There is a likelihood that some mild ADRs may not have been reported by the patients nor found by the researchers due to their similarity with the symptoms and signs of HIV infection which further supports the low prevalence rate reported from the study.

Socio-demographic factors that were formed to be associated with the occurrence of ADRs among the participants were: age of patient, sex of patient and place of

residence. Patients 50 years and above had a higher likelihood of developing ADR than those below 50 years of age. This pattern of association with age has been reported in previous studies.[19,22] Nevertheless, many other studies reported no association with age.[14,33,38,39,40] Age has been noted to be a very important factor which affects the occurrence of ADRs generally and older people have been reported to be more than twice at risk of developing an ADR than the younger people.[8,41] It has been reported that as people get older, the liver loses the ability to metabolize drugs. Aging also affects other organs that help in drug metabolism and excretion thus leaving higher concentrations in the body fluid which could dispose them to having ADR. This can be supported by the fact that many older people are likely to have many health problems and thus take several prescriptions which could lead to drug interactions and adverse effects.

Our study revealed that females were more than twice likely to develop an ADR than their male counterparts. Sex difference in ADRs occurrence to antiretroviral drugs has been reported from other studies.[8,10,19,38,43] This could be accounted for by the biological differences between males and females which affects the action of many drugs. There are differences in body weight, body composition, gastrointestinal tract functions, liver metabolism and renal function etc. Women when compared to men, have lower body weight and organ size, more body fat, different gastric motility, lower glomerular filtration rate and more active hepatic enzyme CY3A4 which may lead to different effects on drug metabolism.[8, 44.]

Place of residence of the patients was associated with the occurrence of ADRs with those living in the rural areas being more likely to have an ADR to antiretroviral therapy than their urban counterparts. Though no study was seen to report an association with residency of people, some studies found a relationship between employment status and occupation with the occurrence of ADR.[33,39] One of the studies further showed that the unemployed, students and petty traders to be more likely to develop ADR than others. This association could be linked to psychosocial problems caused by poverty and other related problems not necessarily due to a direct link with antiretroviral drug intake.

It is worthy to note that there was no significant association found in this study between religion, marital status, educational attainment and employment status of participants with the occurrence of ADRs. This corroborates with finding from previous studies.[14,33,38,39]

Study limitation

This study finding was a self-reported type and the prevalence of ADRs could have been under or over reported. Furthermore no laboratory investigations or other diagnostic test for ruling out other causes were implored. The reporting could also be influenced by the patient's ability to memorize events related to ADRs. Thus caution should be taken in generalizing the findings of this research.

CONCLUSION

Our study showed a low knowledge about ADRs and also a low prevalence of the occurrence of ADRs among the patients on HAART in the studied facilities in the State. We also observed a low level of adherence when compared to the general cut off of 95% adherence and predictors of occurrence of ADRs found in this study were female gender, older age group and living in the rural areas of the state. There is therefore need to create awareness about ADRs among patients of HAART in the state by making patient education a key part of HIV/AIDS treatment.

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