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Research Article

Adverse Drug Reactions to HAART and Associated Risk Factors among Patients Living with HIV/AIDS in Makurdi, North Central, Nigeria

Itodo Samuel Olusegun[1]*, Paul Okonkwo[2], Asalu Adedayo[3], Anonde Chinedu Mattew[4], Itodo Miracle Chekwube[5], Anyebe Sunday Simeon[6], Emmanuel Olumuyiwa Onifade[7], and Stephen Olaide Aremu[8]

[1]Department of Pharmacology and Therapeutics,College of Health Sciences, Benue State University, Makurdi, Nigeria
[2]Department of Pharmacology and Therapeutics,College of Health Sciences, Benue State University, Makurdi, Nigeria
[3]Department of Clinical Pharmacology and Therapeutics, Nile University of Nigeria, Abuja, Nigeria
[4]Department of Obstetrics and Gynaecology, Enugu State University Teaching Hospital, Parklane, Nigeria
[5]Department of Medicine, Federal Medical Center, Makurdi, Nigeria
[6]Department of Pharmacology and Therapeutics, Federal University of Health Sciences, Otukpo, Nigeria
[7]Department of Microbiology, Federal University of Agriculture, Makurdi, Nigeria
[8]Faculty of General Medicine, Siberian State Medical University, Russian Federation

***Corresponding author**
Samuel Olusegun Itodo, Department of Pharmacology and Therapeutics, College of Health Sciences, Benue State, University, P.M.B. 102119, Makurdi, Benue State, Nigeria, Tel: 2347036760555

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Abstract

Background: Human Immunodeficiency Virus (HIV) infection seems to take a lead in terms of notoriety among other viruses apart from Ebola which gained notoriety due to its epidemic in the year 2014 and the current COVID-19 pandemic. Its treatment using Highly Active Anti-retroviral Therapy (HAART) brought hope to the affected people, reducing mortality and improving the quality of life of People Living with HIV/AIDS (PLWHA). However, has been attributed with development of Adverse Drug Reactions (ADRs), limiting its success. This study analyzed the various types of ADRs associated with HAART and their risk factors in Makurdi.

Method: A retrospective and observational study carried out between October, 2019 and March, 2020 at Federal Medical Centre (FMC), Makurdi. A total of 210 naïve adult HIV positive patients were enrolled, their data and information obtained via personal interview using questionnaires and clinical records.

Result: The majority of the patients were female (68.6%) in the age group between 15-44 years. Most of the respondents had at least secondary school education. 22 patients developed ADRs. More female patients (72.70%) developed ADRs than their male (27.3%) counterparts. Peripheral neuropathy and insomnia were the commonest reported ADRs (18.8% each). The least reported ADRs were CNS and GIT related ADRs such as hallucination and vomiting (4.55% each).Most of the respondents that developed ADRs were those on TDF/3TC/EFV (72.72%) and AZT/3TC/NVP (13.64%) regimen when compared with the number of patients on the various regimens. Prevalence of 10.18% was recorded. Age and type of drug regimen are the major risk factors for ADRs to HAART (p-value<0.05).

Conclusion: ADRs occur in PLWHA on HAART, with Peripheral neuropathy and Insomnia being the commonest. They are more in the older patients and those on Nevirapine and Efavirenz based regimens. The introduction and use of new ARVs such as Dolutegravir should be encouraged since they have decreased the serious adverse effects associated with the older ones.

INTRODUCTION

HIV infection has been described as a leading cause of death in Africa, accounting for over 20% of deaths and the second leader of diseases worldwide [1]. Apart from Ebola which gained notoriety due to its epidemic in the year 2014 and the current COVID-19 pandemic, HIV infection seems to take a lead in terms of notoriety among other viruses. About 38million people were living with HIV/AIDS globally as at 2019and the global burden of HIV/AIDS is still highest in the sub-Saharan Africa [2].The discovery and introduction of anti-retroviral drugs (ARV) in the 1990s marked a breakthrough in the treatment of HIV infection in HIV/AIDS patients, which before then, was a major public health concern. This brought hope to the affected people, reducing mortality and improving the quality of life of PLWHA [3]. AIDS-related mortality declined by more than 55% since the peak of 1.7 mil-

lion in 2004 and 1.4 million in 2010 due to introduction and scale up of antiretroviral treatment (ART) [4].

Highly Active Antiretroviral Therapy (HAART) which involves the use of a combination of anti-retroviral drugs (cARV) of different kinds is now being used and it is highly effective and has proven a remarkable decrease in AIDS-related mortality and changed this rapidly fatal syndrome into manageable infection. The success of HAART in the treatment and prevention of HIV has, however, been limited by the toxicities and adverse drug reactions (ADRs) associated with them [5], in addition to the psychological torture posed by the lifetime dependence on the drugs.

ADR is a response which is noxious and unintended, and which occurs at doses normally used in human for the prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function [6]. ADRs are the single most common reasons for poor adherence to treatment [7,8]. Evidences showed that up to 25% of patients discontinue their HAART regimen because of toxic effects [9]. Studies also show that some patients developed fear for ADRs to HAART which could actually affect their enrolment into HIV/AIDS care services and management of the infection/disease [10-12]. All classes of ARVs have been implicated in ADRs such as Drug Induced Liver Injury (DILI) in HIV-infected patients [13]. Each ARV medication is, however, associated with specific adverse effect, for example, hypersensitivity is associated with the use of neverapine or the medication may cause problem only in specific circumstances [14].

ADRs have the potential to cause significant harm in patients; there is a need to increase awareness of the impacts of ADRs on patient care and public health and its associated risk factors. Only few studies have done on the prevalence or incidence of HAART related ADRs in this part of the world. HIV/AIDS care and treatment is currently being offered in most health facilities in Benue State, North central, Nigeria where this study was done since it has a high HIV/AIDS prevalence. Surprisingly, there are no known studies that provide reliable information on the HAART-related ADRs, its pattern, risk factors and impacts on the management of the infection, hence, the need to undertake such a study in Makurdithat analyzed the various types of ADRs associated with HAART and their risk factors in Makurdi, Benue State, North Central, Nigeria.

METHODOLOGY

Study Area

Benue State lies within the lower river Benue trough in the middle belt region of Nigeria. Its geographic coordinates are longitude 7° 47' and 10° 0' East. Latitude 6° 25' and 8° 8' North; Benue occupies a landmass of 34,059 square kilometres. Makurdi, the state capital is divided by a river called river Benue into north and south banks. In 2007, Makurdi had an estimated population of 500,797[15].

Study Design

It was a hospital based retrospective and, observational study carried out for a period of six months [October, 2019 to March, 2020] in ART clinic, Federal Medical centre (FMC), Makurdi, North Central, Nigeria. We used clinical records and well-structured questionnaires to extract patients' information. The clinic was held three times in a week days; where many HIV positive patients around the state receive anti-retroviral therapy (ART) throughout the year. This center maintains AIDS Prevention Initiatives in Nigeria(APIN) computer database that contains clinical data of all the patients receiving ART which includes anthropometric details, medication history, patient's response to the drugs, duration of therapy, co-morbidities and associated medication etc. collected by the clinicians who were trained to detect and record these information using the pharmacovigilance forms. In addition, the collected data were validated and missing information completed (using structured questionnaire and oral interview) during their clinic visits. The antiretroviral drugs (ARV) are dispensed free of charge, monthly, to over 10,000 registered HIV infected patients including men, pregnant and non-pregnant women, and children from different parts of Benue State.

Study Setting and Participants

Study participants were drawn from the population of adult naive HIV positive patients in Makurdi and its environs. The data of people attending the HIV Counselling and testing clinic anchored by Harvard School of Public Health through Aids Initiative Programme (APIN) in conjunction with FMC, Makurdi as well as those obtained via well-structured questionnaire were captured and analysed. All the audience include adult naive HIV-positive individuals who accepted their HIV status, received post-test counselling and education on the need to enrol for HIV care immediately and were referred to the APIN unit based on their meeting days on the weekly basis. All consecutive treatment subjects of either gender aged 15 years or above, on ART, who were not on any medications that may interact with the ARVs, alcohol, herbals or recreational drugs were included. Subjects having complications, treatment modifications, immunologic failure, pregnant women, lactating mothers and children were excluded from the study.

Data Management and Analysis

Completed questionnaires were examined for any inconsistencies in data recording. Data obtained from the patients' medical records, computer database and completed questionnaires were entered, sorted and coded using Microsoft excel sheet. It was analyzed using descriptive statistics, Chi-square test of independence and binary logistic regression. The analysis was done with the help of Statistical Package for Social Sciences (SPSS) 2020 version software. Findings were presented inform of piecharts, bargraphs, frequency tables and percentages. For statistical test, a p-value <0.05was considered significant.

Ethical Consideration

The approval for this study was obtained from the Health

research and Ethical Review committee of the FMC, Makurdi where the study was carried out (ethical reference no: FMH/FMC/MED.108/VOL.I/X). All information obtained from regarding the patients was kept confidential.

RESULTS

A total of 210 naïve HIV patients, who met the study criteria were enrolled, their data was retrieved from the hospital records and personal interview. The socio demographic data showed that majority were female with 68.6%, in the age group between 15-44 years. Most of the respondents had at least secondary school education as shown in Table 1.

Most of the respondents that developed ADRs were on TDF/3TC/EFV and AZT/3TC/NVP regimen. Association between type of regimen used and the presentation of ADRs among the respondents is statistically significant (p-value <0.05, refer to Table 4 & 5).

Majority of the ADRs encountered among patients were therefore mild. Most of the patients that developed ADRs were female, 16(72.7%). 15(68.18%) were between 15-44years while 10 (45.5%) of them were married. Of all the demographic features of the respondents, only age (p-value<0.05) of the patients has a statistically significant association with the presentation of ADRs.

DISCUSSION

Twenty-two (22) respondents out of the total two hundred and ten (210) patients used in the study developed ADRs to HAART. This represents an overall prevalence of 10.48%, which

Table 1: Gender, Age, Marital Status and Occupation of Adult HIV Patients on HAART at FMC, Makurdi

Variables	Frequency	Percentage (%)
Gender		
Male	66	31.4
Female	144	68.6
Total	210	31.4
Age		
≤44years	175	83.3
45-64years	18	8.6
≥ 65years	17	8.1
Total	210	100
Marital Status		
Single	90	42.9
Married	85	40.5
Widowed	20	9.5
Separated	15	7.1
Total	210	100
Occupation		
Salaried (Employed)	53	25.3
Waged Labour (Casual)	37	17.6
Petty trade (Hawker)	38	18.1
Merchant/Trader	27	12.9
Peasant farmer	12	5.7
Housewife	3	1.4
Unemployed	40	19
Total	210	100

Table 2: Religion, Education and Weight of Patients on HAART at FMC, Makurdi

Variables	Frequency	Percentage (%)
Religion		
Christianity	200	95.2
Muslim	6	2.9
Not Indicated	4	1.9
Total	**210**	**100**
Education		
Primary	33	15.7
Secondary	77	36.7
Post-Secondary	63	30
Never Been to School	27	12.9
Not Indicated	10	4.8
Total	**210**	**100**
Weight		
≤ 50	17	8.9
51- 80	174	82.9
≥ 81	16	7.6
Not Indicated	3	1.4
Total	**210**	**100**

Table 3: Types of HAART Regimen and Prevalence of ADRs among Adult HIV positive patients at FMC, Makurdi

ADRs	AZT/3TC/NVP	TDF/3TC/EFV	TDF/3TC/DTG
P. Neuropathy	-	4(18.18%)	-
Insomnia	-	1(4.55%)	3(13.64%)
Anemia	3(13.64%)	-	-
Palpitation	-	3(13.64%)	-
Depression	-	1(4.55%)	-
Hallucination	-	1(4.55%)	-
Heartburn	-	1(4.55%)	-
Skin rash	-	1(4.55%)	-
Drowsiness	-	1(4.55%)	-
Vomiting	-	1(4.55%)	-
Diarrhea	-	2(9.09%)	-
Total	**3(13.64%)**	**16(72.72%)**	**3(13.64%)**

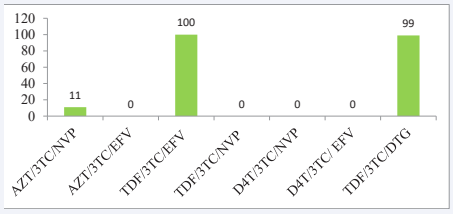

Figure 1 HAART regimen among Adult HIV Patients during the Study Period at FMC, Makurdi.

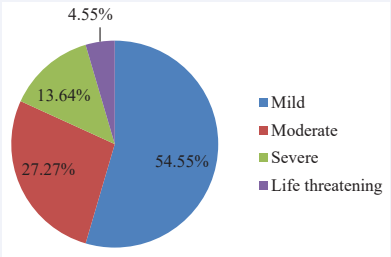

Figure 2 Severity of ADRs Associated with HAART Developed among adult HIV Patients at FMC, Makurdi.

Table 4: Risk Factors of Adult HIV Patients with ADRs to HAART at FMC, Makurdi (n=22)

Variables	Frequency	Percentage (%)	p-value
Gender			
Male	6	27.3	
Female	16	72.7	0.638
Total	**22**	**100**	
Age			
≤44years	15	68.18	
45-64years	6	27.27	0.043
≥ 65years	1	4.55	
Total	**22**	**100**	
Marital Status			
Single	5	22.7	
Married	10	45.5	0.374
Widowed	5	22.7	
Separated	2	9.1	
Total	**22**	**100**	
Occupation			
Salaried (Employed)	5	22.72	
Waged Labour (Casual)	2	9.09	0.434
Petty Trade (Hawker)	3	13.64	
Merchant/Trader	4	18.18	
Peasant Farmer	1	4.55	
Housewife	1	4.55	
Unemployed	6	27.27	
Total	**22**	**100**	
Education Status			
Primary	5	22.7	
Secondary	9	40.9	
Post-Secondary	7	31.8	0.205
Never Been to School	1	4.5	
Not Indicated	0	0	
Drug Type			
TDF/3TC/DTG	3	13.6	
TDF/3TC/EFV	16	72.7	0.032
AZT/3TC/NVP	3	13.6	
Total	**22**	**100**	

Table 5: Treatment Outcome of the ADRs among Adult HIV positive Patients at FMC, Makurdi

Outcome	Frequency	Percentage (%)
Full recovery	21	95.5
Physical residual Disability	Nil	Nil
Death	1	4.5
Total	**22**	**100**

agrees with previous studies done by Kindie, Alamrew and Work [16], and Obiako *et al.*[17], which reported 10.0% and 10.4% respectively. This, however, is lower than 53.4% reported in Maiduguri (North-East, Nigeria)[13]and 75.4% in India [14]. Thus, Sherfa *et al.* [18], reported that the incidence of HAART-associatedd ADRs has reduced when compared with previous studies. It was high in early years of ART initiation. The observed difference in the current study and the study done in Maiduguri may also be due to the fact that the study in Maiduguri was a retrospective study involving higher number of patients (7,260) that were followed up for longer duration (four years).

Similarly, the study done in India involved a longer duration of follow up of the patients (18 months) and was carried out at two different centres unlike this study which was done in a single centre. The commonest ADRs reported in this study were peripheral neuropathy and insomnia, (18.18%) each, followed by anaemia and palpitation, 13.64% each while the least were depression, hallucination and drowsiness, 4.55% each. Weldegebreal, Mitiku and Teklemariam [19], and Florence [20], in their studies reported that peripheral neuropathy was the commonest ADR documented. The finding in this study, however, contradicts the observation of Ogwuche *et al.*[21], where anaemia was reported as the commonest ADR (23.8%) and Abdela, Assefa, Shamele [22], who reported 34.8% for anaemia. This discrepancy might be explained by possible variation in regimen type. Majority of the patients in their studies were on Zidovudine (AZT) containing regimen which was also mostly responsible for the reported ADRs unlike in this study, most of the patients were on Dolutegravir (DTG) and Efiverenz (EFV) containing regimen (Figure 1). Zidovudine is more associated with anaemia than DTG and EFV [23].

Peripheral neuropathy is prevalent among HIV patients on HAART, hence, the need to screen these patients to establish their medical, physiotherapy and rehabilitation needs [24]. Whereas, insomnia accounted for 18.18% of the ADRs observed in the study which is higher than the finding by Obiako *et al.*[16], where insomnia contributed only 2.6% of the overall ADRs. The difference in the drug type used by the patients in the two different studies could explain the variation. In the study done by Obiako*et al.*[16], majority of the patients (55.5%) were on AZT/3TC/NVP while only 2.1% were on AZT/3TC+EFV and none was on DGT containing regimen. Conversely, majority of the patients in this study were on TDF/3TC/EFV (47.6%) and TDF/3TC/DTG (47.1%). Insomia has been attributed mainly with EFV and DTG [22].

Furthermore, anaemia contributed to 13.64% of the overall ADRs, making it the second commonest ADRs observed in the study. A similar study done by Lidya, Siyo and Indermeet [25], reported a prevalence of 16% for anaemia. These finding was lower than what was reported by Ogwuche *et al.*[20], in his study where anaemia 23.4% was the most common ADR and Abdela, Assefa, Shamele [17], who also reported anaemia as most common ADR with a prevalence of 34.8%. This difference is because about thirty-two percent (31.6%) of study subjects of Ogwuche *et al.* [20], were on zidovudine containing regimen, AZT/3TC/NVP as against 5.2% of our patients on AZT/3TC/NVP while AZT/3TC/NVP was the second most prescribed HAART in the study conducted by Abdela, Assefa, and Shamele [21]. Anaemia is mainly caused by zidovudine [22].

With regards to skin rashes which accounted for 1(4.55%) of the total ADRs. A similar study by Ramanjireddy and Yitagesu [26], reported 3.4% for skin rashes. The value was lower than 15.9% that Ogwuche *et al.* [20], reported in his study. More of his respondents (31.6%) were on nevirapine containing regimen (AZT/3TC/NVP) as against 5.5% of our respondents who were on (AZT/3TC/NVP). Nevirapine is the major cause skin rash [22].

Moreover, symptoms such as diarrhea, vomiting and heartburn depict just 2(9.09%) of all patients who developed ADRs presented with diarrhoea as adverse effect of their medications. A similar study by Florence [20], and Sumit, Himanshu and Sharma [27], reported 9.88% and 7.7% respectively for diarrhoea.

Vomiting was reported by only one, 1(4.55%) of the patients. This is similar to 3.61% reported by Eluwa, Badrus and Akpoigbe [28], but lower than 15% found in a study by Ramanjireddy and Yitagesu [25].The difference is due to attitudinal difference in reporting ADRs. Some patients in this study attribute vomiting to disease or things other than the medications.

Heartburn contributed to 4.55% of the ADRs reported in this study. A similar study by Florence [20] reported 6.8% for heartburn. Also, other CNS Symptoms like depression, hallucination and drowsiness accounted for 1(4.55%) each. This finding agrees with the value (4.3%) reported by Lidya, Siyoma and Indermeet [24] in their study. It was however lower than 0.64% reported by Abah *et al.,*[29]. The reporting attitude of the patients in the study by Abah*et al.* [29], was poor compared with patients in this study. In their study, only 7.9% of 12,115 patients, followed up for four years developed ADRs unlike this study where 10.48% of 210 patients, followed up for 6 months developed ADRs.

Palpitation (Emerging Adverse Effect) in this study showed that three (3) of the respondents that developed ADRs, representing 13.64%, presented palpitation as ADR. However, there were little or no previous studies done to show palpitation as ADR of ARV, hence, this may be an emerging side effect that requires further investigations.

With respect to severity and outcome of ADRs to HAART in this study which showed that majority of the respondents had mild (Grade 1) ADRs (54.55%) while only 4.55% had a life threatening (Grade 4) ADR based on the WHO grading system shown in Table 2. This is shown in figure 4.3. Similar finding was reported by Eluwa, Badru and Akpoigbe [27], where most of the reported ADRs were mild [Grade1] (39%), followed by moderate [Grade 2] (32%), severe [Grade 3] (28%) and life threatening [Grade 4] (1%). Therefore, the treatment outcome of ADRs in this study as shown in Table 3 was generally good with 21 (95.45%) of them recovering fully and only 1(4.54%) recorded death case. None of the patients developed any physical residual disability. This agrees with what Obiako *et al.* [16], observed in his study where majority of his patients, 338(88.9%), recovered fully with treatment. The fact that most of the observed and reported ADRs were mild with general good treatment outcome should allay the fear of HIV/AIDS patients who are afraid of enrollment or taking their medications. Hence, this set of patients should be properly educated.

Considering risk factors for ADRs to HAART, Chi-square test and logistic regression were used to test the association between some variables and ADRs to HAART among our respondents. The association between the age of the patients and the types of HAART regimen taken by the patients with ADRs were statistically significant with p-value <0.05for age and drug type. Other variable such as education, gender did not show any significant association with the presentation of ADRs since their p-value is >0.05. This implies that for an additional year in age the odds of experiencing adverse drug reaction is higher by a factor 3.032. Alternatively, we say that the probability of experiencing ADR increases with age all other things being equal. Increase in age is therefore considered as risk factor for ADRs from this study.

Similar study by Florence agrees with the finding in this study. She observed that age was a significant factor in the occurrence of ADRs and those above the 25 years were at a higher risk of developing ADRs. Physiologic changes that accompany aging may be responsible for the very old people being prone to ADRs [30].

Considering the drug type with p- value < 0.05, we see that type of drug administered is significant since p-value is less than 0.05. The contribution of drug type to the model is equally significant. The prevalence of ADRs among those patients with ADRs was highest with TDF/3TC/EFV regimen when compared with others that were used in the study.

When compared with the total number of patients on AZT/3TC/NVP combination regimen as shown in Figure 2, the prevalence of ADRs is higher in patients on AZT/3TC/NVP regimen (27.27%) than TDF/3TC/DTG combination regimen (3.03%). Consequently, patients at this centre are now being switched over to DTG combination. Similarly, Obiako *et al.* [16], noted that type of drug regimen is a significant risk factor for ADRs among HIV/AIDS patients on HAART. He observed that patients on TDF/3TC/EFV combination regimen presented with more ADRs than those on other types of drug combination regimen. Also, the likelihood of developing ADRs with AZT/3TC/NVP regimen has been reported to be significant [21]. Nevirapine and Efavirenz were the most common type of ARVs that were implicated in DILI [13]. Of the ARVs used by HIV patients in a study, Efavirenz was implicated in hepatocellular DILI contributing 30.8% of ADRs developed by these patients [31]. This could also explain why Nevirapine and Efavirenz based regimens were more associated with ADRs in this study.

CONCLUSION

The study showed that there is low prevalence of ADRs to HAART among HIV/AIDS patients on HAART in Benue State. The most reported ADRs to HAART were neuropathy and insomnia. The occurrence of these ADRs were only significantly affected by age and type of drug regimen (risk factors) taken by the patients. Nevirapine and Efavirenz based regimens were more associated with ADRs than Dolutegavir based regimen. Advancement in age increases the development of ADRs associated with HAART. Majority of the ADRs encountered in the study were mild with good management outcomes. Palpitation is a new emerging ADR reported in this study, hence, the need to monitor these patients for further new ADRs especially those related to cardiovascular system.

Since the development and introduction of new ARVs such as DTG has contributed to decrease in the serious adverse effects associated with the older ones with improved tolerability of the patients to this ARV and increased effectiveness against HIV, the study strongly recommends the use of Dolutegavir based combination regimen among HIV/AIDS patients. There should be constant monitoring of the HIV positive patients for new ADRs especially the older patients and those on Nevirapine and Efavirenz based regimens.

The study also recommends that patient centered health education programs should be incorporated into all the medical facilities in Benue State. The programs should put emphasis on pharmacovigilance especially of ARVs. Reporting of all symptoms either related to the disease or the medications should be encouraged among the patients.

What is Already Known about on this Topic

PLWHA on HAART have demonstrated high prevalence of ADRs to these drugs before now with the commonest ADRs being peripheral neuropathy and anaemia. Risk factors such as gender, age, occupation, education of the patients have been reported to have association with development of ADR in these patients.

What this Study Adds

The study has shown that prevalence of ADRs to HAART among PLWHA has reduced with the use newer ARV. While peripheral neuropathy still takes the lead as ADR, insomnia is also common ADR now among PLWHA. Emerging ADR like palpitation has also been reported among these patients. Age and the type of drug regimen used by the patients are the most significant risk factors for the development of ADRs.

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