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Original Research Article

Antiretroviral drug adverse reactions among HIV-positive patients at a tertiary care hospital in North-Eastern Nigeria

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Abstract

Purpose: The objective of this study was to evaluate the prevalence of adverse drug reactions (ADRs) among patients on antiretroviral drugs in a tertiary healthcare facility in Maiduguri, North-Eastern Nigeria.
Methods: The study was conducted among HIV-positive participants using validated questionnaires and personal interviews to obtain information on ADRs. Participants' case notes were used to capture data on socio-demographic characteristics, clinical variables, and treatment profiles. The data collected were analyzed with STATA 10 software using logistic regression and descriptive analyses.
Results: The prevalence rate of ADRs was 26.6% among 134 patients. Gastrointestinal system disorders 40(8.0%), central and peripheral nervous system 38(7.5%), and systemic signs and symptoms 37(7.3%) were the most common clinical ADRs observed. Zidovudine/Lamivudine/Nevirapine combination therapy was mostly implicated for the ADRs. Logistic regression analysis showed that the occurrence of ADRs was associated with marital status, viral load, and Zidovudine/Lamivudine/Nevirapine therapy.
Conclusion: The prevalence of ADRs reported in this study was low. Most of the patients with ADRs had mild effects. Marital status, viral load, and Zidovudine/Lamivudine/Nevirapine contributed to the development of the ADRs. There is a need to closely monitor HIV-infected patients by caregivers to further reduce the prevalence of ADRs and concomitant risks.

Keywords: Antiretrovirals, dolutegravir, gastrointestinal system, human immunodeficiency virus

Indexing: Index Copernicus, African Index Medicus

Introduction

Adverse drug reactions (ADRs) are defined as noxious and unintentional reactions to drugs of prescribed standard dosages through a suitable administration route for the intention of treatment, diagnosis, prophylaxis, or modification of physiological function of the diseases [1]. These reactions are important public health problems, representing the major cause of morbidity and mortality [1]. They are associated with an increase in healthcare costs due to hospital admissions as well as the foremost challenges to the success of antiretroviral therapy (ART) [2]. These may reduce treatment adherence which could eventually lead to poor prognosis, quality of life, and virological failure [3]. The economic burden for individuals with ADRs in the United States in 2010 costs up to 30.1 billion dollars annually with over 1.2 million patients hospitalized [4]. The incidence of ADRs in Brazil in 2020 was 71.1%, making these reactions ranked between the fourth and sixth leading causes of death

globally [5]. In the United Kingdom, the National Health Scheme lost about 466 million pounds annually due to admissions related to ADRs [6]. In Germany, Health care costs related to ADRs amount to 816 million Euros, and 58% of costs resulted from hospitalizations [7].

Earlier studies in Africa include; the study in South Africa with 44.5% ADRs in 2004[8], 18% ADRs were reported in Botswana among the participants in 2007[9] while 65% was reported in Kenya in 2005[10]. Meanwhile, research work in Nigeria reported 54% ADRs among patients on the Zidovudine-based regimen in 2006 [11]. A previous study conducted in the HIV Clinic of the University of Maiduguri Teaching Hospital (UMTH) reported a high prevalence of serious ADRs of 96% among patients initiated on a Zidovudine and Efavirenz-based regimen [12]. Most of these earlier studies conducted in Nigeria and elsewhere had a high prevalence of ADRs. The studies involved the use of stavudine and zidovudine nucleoside backbone as well as Nevirapine and Efavirenz non-nucleoside-based regimen for management of HIV-infected patients.

Thus, reporting of ADRs is considered to be an important step in maintaining and achieving safe drug therapy use [13]. In Nigeria however, the National Agency for Food Drug Administration and Control (NAFDAC) set up a pharmacovigilance medium for reporting ADRs, but this reporting method is currently inefficient nationally and underutilized by Nigerians including the caregivers. In a hospital setting, caregivers who are in contact with the patients are the preferred sources of ADRs information. Every contact of the care providers with the patient provides a good opportunity for reporting any ADRs [14].

Despite the extensive studies and attention given to ADRs, they still represent a clinically significant problem and burden with high prevalence. Also, the less toxic new generation drugs introduced into the antiretroviral armamentarium have brought hope of reducing the adverse effects of ART-related ADRs. This prospect remains incredible in the poor resource countries with the topmost global HIV pandemic [15].

In the year 2016, World Health Organization (WHO) introduced a consolidated guideline on antiretroviral drugs in managing HIV-infected patients using Tenofovir or Abacavir/Lamivudine or Emtricitabine/Dolutegravir as a substitute of first-line drugs for the adults that are Dolutegravir eligible [16]. Up to the year 2020, Dolutegravir doses were favorable first-line and second-line ART for patients on Zidovudine/Lamivudine/Nevirapine or Efavirenz fixed-dose combination because of their superior tolerability, efficacy, and less toxicity [17].

In the study area, UMTH, Maiduguri, Nigeria, Tenofovir/Lamivudine/Dolutegravir (TLD) combination therapy was introduced in 2018. There is a dearth of studies on the prevalence of ADRs relating to the use of TLD therapy in this facility. The main objective of this study was to assess the prevalence and severity of ADRs among HIV-positive participants on the new antiretroviral treatment guideline. The specific aim was to identify the correlates of the occurrence of ADRs in the study setting.

Methods

Setting

This study was conducted in the Antiretroviral/Infectious Disease Pharmacy Unit of the UMTH, Maiduguri, located in the North-Eastern part of Nigeria and established in 1974. The setting provides quality tertiary healthcare services in both curative and preventive medicine for people in the North-East and beyond. Currently, the hospital has 630 beds, 23 departments, and several centres including trauma and stroke centres. The Antiretroviral/Infectious Disease Pharmacy Unit is run by seven pharmacists. Since 2013, the unit has been managed by Family Health International 360 through provision of free antiretroviral and opportunistic infectious disease drugs. The daily turnout of patients in the pharmacy Unit is 124.

Study design and population

A prospective and retrospective cross-sectional study was carried out among consenting HIV-infected participants accessing antiretroviral drugs in the Antiretroviral/Infectious Disease Pharmacy Unit of the UMTH. As of 30th January 2020, 5,503 participants were actively on antiretroviral drugs. The study commenced in February, 2020 and continued for three months.

Sample and sampling technique

Based on Yamane's statistical formula, a minimum sample size of 359 was obtained. To increase the statistical power of the study, and the questionnaire's response rates due to attrition, 40% was added to the minimum calculated sample size. Thus, a target sample size of 503 was used to guide participants' enrolment.

Participants' inclusion and exclusion criteria

Those included were: (i) HIV-infected participants on antiretroviral drugs in the UMTH. (ii) Participants aged 18 years and over with any form of adverse drug reactions and (iii) Those willing to participate in the study. The participants excluded were: (i) Patients that were yet to receive antiretroviral drugs. (ii) Those on hospital admission. (iii) Mentally incapacitated patients and (iv) Patients who receive treatment from other health facilities.

Study instruments

i. Personal data Form: The personal data form was used to capture information on the socio-demographic parameters of the participants.
ii. Clinical variable Form: The clinical variable form contained information on CD_4 cell count, viral load, weight, and height of the participants.
iii. Treatment variable Form: This captured information on the type of antiretroviral drugs used by the participants and duration of treatment.
iv. Questionnaire on knowledge and practice of reporting of ADRs: This section consisted of nine questions namely; i). Have you ever experienced any unwanted reactions while taking your medication? ii). Kindly "tick" as appropriate the ADR experienced from the list provided. iii). How long ago is the ADR? iv). Have you taken the medication since your reaction? v). Did you report ADR? vi). To whom? vii). Do you know you should report when you have an ADR? viii). If Yes, how did you get to know and ix).Who are you supposed to report to?

Classification of adverse drug reactions

The common terminology criteria were used to classify the severity of ADRs. The ADRs were categorized as; i. mild when patients did not require an intervention, ii. moderate when patients required an intervention, iii. serious when patients required hospitalization or caused an inability or limited ability to perform daily activities, iv.) life-threatening, when patients required immediate intervention; and v.) fatal if they resulted in the death of the patient directly or indirectly [5]. One on one interview was used to capture data on the severity of the ADRs.
The data abstraction forms used to obtain information from participants' medical folders were personal data, clinical and treatment variable forms.

Instruments validation

The validity of the content of the questionnaire was evaluated by distributing the questionnaires to fifty HIV-infected patients recruited from the Antiretroviral/infectious Disease Pharmacy Unit, UMTH, as a pilot study for the validation process. After the pilot study, the responses from the questionnaires were analyzed with STATA 10 software package. Cronbach's alpha coefficient reliability test was used to assess the reliability and internal consistency of the items in the questionnaire. The mean of the internal consistency of the questionnaire was 0.83. The result of the Cronbach alpha obtained shows that the questionnaire is valid. The validated questionnaire was employed to obtain data on the participants' adverse reactions to antiretroviral drugs. The questionnaire was adapted from earlier studies and the NAFDAC's yellow form for reporting of ADRs. The questionnaire yielded information on the types of ADRs experienced by the participants based on affected body organs, the frequency of reporting ADRs, to whom the ADRs were reported (pharmacists, physicians, and case managers) and awareness of participants to report ADRs.

Data collection

The objectives of the study were explained to each participant on enrolment. The structured validated questionnaires were administered to the participants after assuring them of the confidentiality of their responses. Information on the socio-demographic variables and adverse reactions to antiretroviral drugs of the participants were collected by one-on one interviews. Hausa, Kanuri, English, and Pidgin were used in communicating with participants when and where appropriate.

Data processing and statistical analysis

The data collected were analyzed using STATA 10 software (Stata Corporation, College Station,

Texas). Descriptive statistics were used to represent the socio-demographic characteristics of the participants. Logistic regression analysis of the dependent variable (adverse drug reactions) and the independent variables (socio-demographic, clinical, and treatment variables) was used to assess the relationship between patient factors and the prevalence of antiretroviral adverse drug reactions.

Consent and ethical clearance

Appropriate approvals were sought from the Hospital's Ethics Committee of UMTH (Protocol Number: UMTH/REC/605). Informed consent forms were endorsed by the participants that agreed to participate in the study.

Results

Of the 503 participants evaluated during this study (Table 1), almost half of the participants 224 (44.5%) were within the age range of 41-60 years. The average age was 40.42 ± 9.158 years and 356 (70.8%) of them were females. Most of them were married 322 (64.0%), and the predominant cases were those in their third and fourth decades of life.

Table 1: Demographic variables of the participants (N=503)

Demographic variables	Frequency	Percentage
Age (years)		
18 – 20	5	1.0
21 – 30	70	13.9
31 – 40	194	38.6
41 – 50	170	33.8
51 – 60	54	10.7
> 60	10	2.0
Gender		
Female	356	70.8
Male	147	29.2
Marital status		
Single	67	13.3
Married	322	64.0
Divorced	41	8.2
Widowed	73	14.5

Many participants 413 (82.1%) had CD_4 counts greater than 500 cells/µL with an average value of 683.36 ± 311.45 (Table 2). More than one-fifth of 101 (20.1%) of the participants had an undetectable viral load (< 20 copies/mL) and 402 (79.9%) had suppressed viral load between 20-1000 copies/mL. None of the participants had a viral load greater than 1000 copies/mL. The mean of viral load recorded was 51.90 ± 89.39 copies/mL. Almost half, 244 (48.5%) had normal weight and 181 (36.0%) were overweight. Few, 17 and 1 of the participants were underweight (3.4%) and morbidly obese (0.2%) respectively. The mean of the body mass index was 25.00 ± 3.885 Kg/m^2.

Table 2: Distribution of participants by clinical variables (N=503)

Clinical variables	Frequency	Percentage
Body Mass Index(Kg/m^2)		
Underweight (<18.5)	17	3.4
Normal (18.5 – 24.9)	244	48.5
Overweight (25.0 – 29.9)	181	36.0
Obese (30.0 – 40.0)	60	11.9
Morbidly Obese (≥40.0)	1	0.2
CD_4 counts (cells/µL)		
<50	0	0.0
50-199	9	1.8
200-349	19	3.8
350-499	62	12.3
≥500	413	82.1
Viral Load (VL) (RNA copies/mL)		
<20 (undetectable VL)	101	20.1
20 - 1000 (suppressed VL)	402	79.9
>1000 (non-suppressed VL)	0	0.0

The duration of therapy with the highest frequency of 400 (79.5%) was four years and above (Table 3). The participants were on different first-line combination therapies, of which Tenofovir/Lamivudine/Dolutegravir 331(61.7%) were mostly prescribed followed by Tenofovir/Lamivudine/Efavirenz 98(19.5%) and the least of 1(0.2%) was Zidovudine/Lamivudine/Nevirapine. The most frequently used second-line antiretroviral drug combination was Tenofovir/Lamivudine/Atazanavir/ritonavir 44(8.8%).

Out of the 503 participants studied, the prevalence of ADRs found was 26.6% in 134 participants (Table 4). Of all the 134 participants with ADRs, 86 (64.2%) were mild, 38 (28.3%) were moderate and a few 10 (7.5%) were severe ADR reactions. More than one half 327(65.0%) of the participants were knowledgeable on the report of ADRs though only 222(44.1%)

expressed their feelings on ADRs to either a physician and/or a pharmacist.

Table 3: Treatment profiles of participants on antiretroviral drug combinations (N=503)

Variables	Frequency	Percentage
Duration of antiretroviral drugs (Years)		
1-2	52	10.3
3-4	51	10.2
>4	400	79.5
Types of antiretroviral drugs		
First line drugs		
Z/L/N	1	0.2
Z/L/E	2	0.4
ABC/L/E	5	1.0
T/L/E	98	19.5
T/L/D	331	65.7
Second line drugs		
ABC/L/ATV/r	2	0.4
Z/L/LPV/r	2	0.4
T/L/LPV/r	7	1.4
Z/L/LPV/r	11	2.2
T/L/ATV/r	44	8.8

ABC=Abacavir; L=Lamivudine; ATV/r=Atazanavir/ritonavir; E=Efavirenz; T=Tenofovir; LPV/r=Lopinavir/ritonavir; D=Dolutegravir; Z=Zidovudine; N=Nevirapine

In the participants ADRs mostly affected the gastrointestinal/hepatobiliary/renal systems. (40; 8.0%). Other body systems affected are as shown in Table 5.

Among the first-line antiretroviral drug combination, the occurrence of ADRs was high with Zidovudine/Lamivudine/Nevirapine and least with Tenofovir/Lamivudine/Dolutegravir. Also, the ADRs experienced by the patients on Zidovudine/Lamivudine/Lopinavir/ritonavir as second-line drugs were minimal. ADRs occurring in Tenofovir/Lamivudine/Lopinavir/ritonavir and Abacavir/Lamivudine/Atazanavir/ritonavir were in equal proportion (Table 6).

Table 4: Reporting of Adverse Drug Reactions among the participants

Variables	Frequency	Percentage
Ever experienced ADRs	134	26.6
The severity of the ADRs		
Mild	86	64.2
Moderate	38	28.3
Severe	10	7.5
Awareness to report ADRs	327	65.0
To whom do you report ADRs?		
Physician	184	82.9
Pharmacist	38	17.1

Table 5: Types of ADRs among HIV-infected participants on antiretroviral drugs

System/Organ affected	Frequency	Percentage	ADRs
Skin and appendages	7	1.4	Skin rash
Gastrointestinal /hepato-biliary/renal system	40	8.0	Abdominal pain, constipation, nausea, vomiting, diarrhea hepatomegaly, increase in appetite, loss of appetite, weight gain, weight loss, dyspepsia, jaundice, and edema,
Metabolic/endocrine system	1	0.2	Excessive urination
Systemic signs and symptoms (General)	37	7.3	Fever, malaise, anemia, fatigue, body weakness, and heavy menstrual bleeding
Central and peripheral Nervous System	38	7.5	Insomnia, headache, nightmares, body pain, anorexia, and dizziness.
Cardiovascular/respiratory system	2	0.4	Palpitation and dyspnea
Musculoskeletal system	9	1.8	Arthralgia, myalgia, and myopathy
Total	**134**	**26.6**	

Table 6: Frequency of ADRs among antiretroviral drug combinations

Antiretroviral combinations	Frequency used	ADR produced	ADR to users percentage (%)	User: ADRs ratio
ABC/L/E	5	2	40.0	1:0.40
ABC/L/ATV/r	2	2	100.0	1:10
T/L/ATV/r	44	10	22.7	1:0.23
T/L/LPV/r	7	7	100.0	1:10
T/L/E	98	41	41.8	1:0.42
T/L/D	331	58	17.5	1:0.17
Z/L/ATV/r	11	2	18.2	1:0.18
Z/L/E	2	1	50.0	1:0.50
Z/L/LPV/r	2	0	0	0
Z/L/N	1	11	1100.0	1:11
TOTAL	503	134		

Risk factors for ADRs considered among the participants were gender, marital status, alcohol consumption, cigarette smoking, antiretroviral drugs, body mass index, age, viral load, and CD_4 counts (Table 7). Of all these factors, only marital status [OR 1.559; 95% Confidence Interval 0.995-2.995; $p < 0.043$], viral load [OR 0.775; 95% Confidence Interval 0.584-1.028; $p < 0.027$], and Z/L/N [OR 11.334; 95% Confidence Interval 0.105-3.712; $p < 0.049$] were found to be statistically significant. The married were 1.59 times more likely to develop ADRs than those that were single while those that had higher viral load had a lower risk of developing ADRs than those with lower viral load. Patients on Z/L/N combination therapy were 1.33 times more likely to develop ADRs than those on other antiretroviral drug combination therapies.

Table 7: Logistic regression analysis for factors associated with the development of ADRs in HIV-infected participants on antiretroviral drugs

Factors	95% confidence interval	Odds ratio	P-value
Gender (Male)	0.627-1.601	1.002	0.993
Marital status (Married)	0.995-2.572	1.599	0.043*
Body Mass Index (Kg/m2)	0.276-3.731	1.012	0.984
Age (Years)	0.231-1.306	0.549	0.175
Viral load (copies of RNA)	0.584-1.028	0.775	0.027*
CD_4 counts (cells/µL)	0.623-1.849	1.073	0.798
Antiretroviral drugs (Z/L/N)	0.105-3.712	1.334	0.049*

*Statistically significant at $P < 0.05$; Z; Zidovudine, L; Lamivudine, N; Nevirapine

Discussion

In this study, the prevalence of ADRs was 26.6% which is directly related to marital status, viral load, and Zidovudine/Lamivudine/Nevirapine combination therapy. Most of the ADRs experienced were mild. However, Tenofovir/Lamivudine/Dolutegravir was the least first-line regimen associated with ADRs while the least second-line regimen was Zidovudine/Lamivudine/Lopinavir/ritonavir combination. The duration of therapy with the highest frequency was four years and above. There is a need to closely monitor the HIV-infected patients by caregivers in our studied hospital to further reduce the prevalence of ADRs and the concomitant risks.

The ADRs among HIV-infected participants on ART are the foremost health challenges to antiretroviral drug delivery, particularly in poor resource countries. In this study, most of the participants were in the age range of 50 years and over. The reason for the majority of the participants being older was due to the availability of free antiretroviral medicines, thereby prolonging survival among patients infected with HIV. Also, globally, there is an upsurge in the number of persons with HIV at an older age. These patients are staying healthy into old age due to the utilization of antiretroviral therapy [18].

Furthermore, HIV infection was found to be predominant among women because of

biological and socioeconomic factors. Besides, restrictions in accessing treatment, care services, and economic constraints are key drivers of the HIV epidemic in women [19, 20]. A low number of our participants had an undetectable viral load of fewer than 20 copies/ml and many were with suppressed viral load copies/ml [17]. This could be attributed to the effective combination therapy used in the management of the patients in this setting. Of all the combination therapy used in our study, Tenofovir/Lamivudine/Dolutegravir was mostly prescribed and dispensed to the participants.

This could be that Dolutegravir-based treatment was better than protease inhibitor-based treatment and Efavirenz with better rapid viral load suppression as well as enhanced tolerability. The Dolutegravir-based treatment efficacy was observed in our study as most of the participants had their viral load suppressed with a higher CD4 count. Similarly, there was a report in Europe that Dolutegravir/Abacavir/Lamivudine used for the treatment of HIV infection suppressed viral load at the end of 48 weeks [21].

The low prevalence rate of ADRs observed in this study was in line with the findings in a study in Ibadan[22] Nigeria but lower as compared to the results obtained in other studies conducted in Nigeria and elsewhere [19, 23, 24]. Our study revealed that most of the patients were on a first-line Dolutegravir-based regimen. Dolutegravir combination therapy is a well-tolerated antiretroviral drug regimen, with a lower prevalence of ADRs as compared with EFV-based regimen [25]. Also, the few ADRs associated with the Dolutegravir regimen (body weakness, anorexia, fever, insomnia, and nightmare) were mild and self-limiting.

The previous studies conducted in Nigeria [12,26] showed dissimilarities to the findings of this study. However, the earlier studies [12, 19, 23, and 24] showed high prevalence rates of ADRs because the patients were mostly on first-line Zidovudine-Efavirenz-based, Zidovudine-based Nevirapine, and Stavudine-based Nevirapine regimens which were associated with frequent and severe adverse effects as compared with the Dolutegravir-containing regimen. Furthermore, ADRs prevalence reports lower than our studies were obtained by Paul and Egwu (2020) in Port-Harcourt, and Adisa and Omitogun (2019) in Ibadan [17, 22]. Several factors that may contribute to differences in the ADRs prevalence rate include; inadequate pharmaceutical care counseling offered to the participants due to time constraint on part of the pharmacists, insufficient monitoring for ADRs in participants without formal education, those with comorbid diseases, antiretroviral drug combination therapy types used, gender differentials (This refers to sex differences whereby one gender is regarded as inferior to the other), older participants recruited, different pharmacovigilance practices in the different settings, the population of participants in the studies, under-report of ADRs by healthcare practitioners in different regions and the duration of participants follow-up on ADRs.

The existing first-line regimen of Zidovudine backbone and second-line regimen of Tenofovir-based regimen may have been responsible for the ADRs found in this study. Also, the correlates for the development of ADRs in our participants were marital status, viral load, and Zidovudine/Lamivudine/Nevirapine combination therapy. The majority of our respondents were also female and married [19]. Women generally account for a large proportion of the world's HIV population. [27].

The odds ratio for the occurrence of ADR was almost four times higher among the Tenofovir/Lamivudine/Efavirenz therapy compared to the Tenofovir/Lamivudine/Dolutegravir therapy suggesting a safer profile of Tenofovir/Lamivudine/Dolutegravir combinations over Tenofovir/Lamivudine/Efavirenz. These findings appeared to have some clinical relevance in the studied region, as it may serve as a guide in the choice of therapy between the two combinations and signal to pharmacists involved in pharmaceutical care the need to keenly monitor ADR among HIV participants since any little modification in therapy could result to wide occurrence of ADRs.

The knowledge gained from this research was that HIV-infected patients on antiretroviral drugs may not develop severe adverse drug reactions while on Tenofovir Lamivudine Dolutegravir combination therapy. Conversely, the small number of patients involved in this study may be a limitation to the application of these data.

Conclusion

The prevalence of ADRs in our study was low and Zidovudine/Lamivudine/Nevirapine drug combination therapy was mostly responsible for the ADRs observed. Marital status, viral load, and Zidovudine/Lamivudine/Nevirapine were modifiable risk factors for the ADRs. There is a need to sustain the use of a safer profile of Tenofovir/Lamivudine/Dolutegravir combination for effective treatment. These findings have shown clinical relevance in the studied region, as they may serve as a guide in the choice of therapy between different ART combinations. Furthermore, close monitoring of HIV-infected participants by caregivers in our studied hospital to further reduce the prevalence of ADRs and the concomitant risks are of the essence.

Conflict of Interest

No conflict of interest is associated with this work.

Contribution of Authors

The authors stated that this research was conducted by all authors mentioned in this manuscript and all liabilities applying to the manuscript content will be accepted by them. However, SIB, NYI, and IMK conceived and designed the research; SIB collected the data; while SIB and JDO analyzed the data and wrote the manuscript. All the authors read and approved the manuscript before submission for publication.

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