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Original Article

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Adverse Drug Reactions to Antiretroviral Therapy in Federal Medical Centre, Makurdi, Nigeria

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Abstract

***Background & Aims*:** Human immunodeficiency virus (HIV) is a retrovirus belonging to the family of lentiviruses. It is the causative organism of Acquired Immune Deficiency Syndrome (AIDS), which has become one of the greatest public health challenges faced by mankind. Highly Active Antiretroviral Therapy (HAART) has remarkably improved survival and the quality of life of the people living with HIV, but the occurrence of adverse reactions is a serious challenge. This study assessed adverse drug reactions (ADRs) in the people living with HIV on first line HAART attending Federal Medical Centre (FMC), Makurdi, Benue State, Nigeria.

***Materials & Methods*:** In this descriptive-retrospective study, the data of 350 people on HAART attending FMC, Makurdi, Nigeria from 2010 to 2012 were collected, using a structured questionnaire. Data was analyzed using Chi-square with the aid of SPSS v.20 software. A p-value <0.05 was considered significant.

***Results*:** HIV infection was more in females (66%) than in males (34%). Adverse Drug Reactions (ADRs) were more in females (60%) than in males (40%). The most prescribed HAART regimens were zidovudine/lamivudine/nevirapine (44.3%), and tenofovir/emtricitabine/nevirapine (31.7%). ADRs were observed in 195 (55.7 %) of the people living with HIV on first line HAART. The observed ADRs were abdominal pain (28.7%), diarrhea (10.8%), vomiting (3.6%), hepatitis (17%), mild skin rash (22%), severe skin rash (4%), anemia (0.4%), peripheral neuropathy (5.4%), insomnia (4.0%), and dizziness (3.6%). Most ADRs were observed in nevirapine based HAART; zidovudine/lamivudine/nevirapine (46.6%) and tenofovir/emtricitabine/nevirapine (32.6%). The nature of the observed ADRs was mild (71.6%), moderate (27.1%) and severe (1.30%).

***Conclusion*:** The use of first line HAART seems safe, because observed ADRs were not severe, but the patients should be routinely monitored for ADRs.

***Keywords*:** Adverse Drug Reactions, Antiretrovirals, Human Immunodeficiency Virus

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Introduction

Human Immunodeficiency Virus (HIV), which causes acquired immune deficiency syndrome (AIDS) is one of the serious public health challenges experienced by mankind. HIV infection causes chronic and progressive destruction of neurologic and immune

systems (1). When it is not managed, it leads to the possible establishment of opportunistic infections, malignancy, and consequently death (2, 3). In 2016, it was estimated that the world had 36.7 million people living with HIV and 1.8 million new infections (4). The sub-Saharan Africa accounts for about 69.5% of HIV infections in the world, with only 54.1% having access to Highly Active Antiretroviral Therapy (HAART) (5, 6). The availability and the use of HAART as an essential strategy to have an AIDS-free generation has reduced new HIV infection by 14%, from 2.1 million in 2013 to 1.8 million in 2016 (7).

Despite the remarkable improvement in the survival and quality of life of people living with HIV on HAART, recent studies showed that HAART is associated with adverse drug reactions (ADRs), independent of HIV status (8). In most cases, ADRs of HAART may be observed within the first few days, weeks, or months after the commencement of therapy (9).

The severity and spectrum of ADRs vary among HIV-infected persons as a result of host genetic factor, comorbidity, and malnutrition. Also, drug-drug interaction lading to ADRs may occur when HAART is co-administered with other conventional medicines or with herbal medications. Other important factors that can contribute to ADRs due to HAART include poor patient counseling, illiteracy, and diagnostic delays attributed to inadequate laboratory monitoring for some the patients (10). ADRs caused by HAART can compromise the quality of life and interfere with adherence to HAART (11). Poor adherence could result in the development of early resistance, affect medication review, refill, and consequently drug supply to health care centers (12). Based on safety and efficacy, most HAARTs were validated in developed countries (primarily in white populations), but are now being widely used in developing countries especially in Africa where the vast majority of HIV-infected people live (10). Thus, continual safety evaluation of HAART is imperative for the population of African descent. This study evaluated ADRs caused by first line HAART in the people living with HIV attending Federal Medical Centre (FMC) Makurdi, Benue State, Nigeria.

Materials & Methods

Study area: The study was conducted at APIN/PLUS Clinic, FMC, Makurdi, Benue State, Nigeria. This clinic provides comprehensive care for the people living with HIV.

Study population: They are people living with HIV on first line HAART attending APIN/PLUS clinic at FMC Makurdi, Benue State, Nigeria. The prescribed first line HAART include zidovudine / lamivudine / efavirenz (ZDV/3TC/EFV), zidovudine / lamivudine / nevirapine (ZDV/3TC/NVP), tenofovir / emtricitabine / efavirenz (TDF/FTC/EFV), and tenofovir / emtricitabine / nevirapine (TDF/FTC/NVP).

Inclusion criteria: The people living with HIV on first line HAART with adherence of 99% attending APIN/PLUS clinic at FMC Makurdi between 2010-2012.

Exclusion criteria: The people living with HIV on first line HAART with co-morbid conditions and using other medications.

Sample size determination: Population size was obtained from the database of the people living with HIV on first line HAART attending the APIN clinic between 2010 and 2012. The database has 2892 patients where the sample size was determined mathematically using Yaro Yamane, as shown below.

$n = N/[1+Ne^2]$

Where

n=Sample size required for the study

N = Population size 2892

e= Level of significance (precision) = (0.05%)

$$N = \frac{2892}{1+2892 \times 0.05^2}$$

The sample size (n) =350

Method of data collection: Structured questionnaire was used to collect secondary data from the patient's case file using available review records.

Data analysis: Data was analyzed using Chi-square with the aid of Statistical Package for Social Science

(SPSS) version 20. A p-value <0.05 was considered significant.

Results

Among the 350 people 119 (34%) were males while a larger proportion of 231 (66%) were female. The age group (31-40 yrs) had the largest number of people (125) on first line HAART, which represents 35.7%, while the age group ≥61 had the least number of people (13) on HAART, which represent just 3.7% (Table 1). ZDV/3TC/NVP (44.3%) and TDF/ETC/NVP (31.7%) were the most frequently prescribed HAART, whereas the least prescribed were TDF/FTC/EFV (19.4%) and ZDV/3TC/EFV (4.6%) (Table 2). Out of the 350 people assessed for ADRs, 195 (55.7%) had ADRs, while the number of ADRS observed was 223. The observed ADRs were more in females 115 (60%) than in males 80 (40%) (Table 3). ADRs distribution based on HAART regimens showed that most of the ADRs occurred in the patients on NVP containing regimens ZDV/3TC/NVP (46.6%) and TDF/ETC/NVP (32.3%). On the other hand, ADRs was fewer in the patients on TDF/FTC/EFV (19.7%) and was least in the patients on ZDV/3TC/EFV (5.98%) (Table 4). Abdominal pain (27.8%) (p=0.03) is the most gastrointestinal ADRs observed in this study followed by diarrhea (10.8%) (p=0.73), while the least is vomiting (3.6%) (p=0.95). Central nervous system ADRs observed in this study were peripheral neuropathy (12%) (p=0.88), insomnia (4.0%) (p=0.90), and dizziness (3.6%) (p=0.98). Insomnia occurred primarily in the patients on ZDV/3TC/EFV and TDF/FTC/EFV (Tables 4 and 5). It was observed that hepatitis occurred in 39 people representing 17.5% (p=0.05), while anemia occurred in one person representing 0.4% (p=1.33). Hepatitis primarily occurred in the people on ZDV/3TC/NVP, TDF/FTC/NVP and TDF/FTC/EFV. Hypersensitivity reactions characterized by mild and severe rash occurred in 49 (22%) and 9 (4.0%), respectively. The observed hypersensitivity reactions occurred primarily in the patients on ZDV/3TC/NVP and TDF/FTC/NVP (Tables 4 and 5).

Table 1. Demographic data of the patients

Gender	Frequency (%)
Male	119 (34)
Female	231 (66)
Total	350 (100)
Age group	Frequency (%)
18-30	99 (28.3)
31-40	125 (35.7)
41-50	75 (21.4)
51-60	38 (10.9)
≥61	13 (3.7)

Table 2. Antiretroviral regimens taken by the patients

Regimen	Frequency (%)
ZDV/3TC/EFV	16 (4.6)
ZDV/3TC/NVP	155 (44.3)
TDF/FTC/EFV	68 (19.3)
TDF/FTC/NVP	111(31.9)

ZDV: Zidovudine, 3TC: Lamivudine, NVP: Nevirapine, EFV: Efavirenz, TDF: Tenofovir, FTC: Emtricitabine.

Table 3. Adverse effect of antiretroviral regimens in males and females

Gender	Frequency (%)
Male	80 (40)
Female	115 (60)
Total	195 (100)

Table 4. Distribution of adverse drug reactions according to antiretroviral regimens

ADRs	ZDV/3TC/EFV	ZDV/3TC/NVP	TDF/FTC/EFV	TDF/FTC/NVP
Hypersensitivity				
Mild skin rash	0	29	0	20
Severe Skin rash	0	5	0	4
Central Nervous System				
Peripheral neuropathy	4	4	2	2
Insomnia	1		8	
Dizziness	1	0	7	0
Gastrointestinal				
Vomiting	2	4	6	0
Diarrhea	1	13	3	7
Abdominal pain	4	26	12	24
Hepatitis	0	18	6	15
Hematologic				
Anemia	0	1	0	0
Total (%) (n=223)	21 (5.82%)	104 (46.6%)	44 (19.7%)	(72) 32.3%
P values	0.72	0.02	0.05	0.04

ADRs: Adverse Drug Reactions, CNS: Central Nervous System, ZDV: Zidovudine, 3TC: Lamivudine, EFV: Efavirenz, NVP: Nevirapine, TDF: Tenofovir, FTC: Emtricitabine.

Table 5. Distribution of adverse drug reactions according to antiretroviral regimens

Class of ADRs	ADRs	Frequency %
Hypersensitivity	Severe body reaction	9 (4.0)
	Mild body reaction	49(22.0)
Central Nervous System	Peripheral neuropathy	12(5.4)
	Insomnia	9(4.0)
	Dizziness	8(3.6)
Hematology	Anemia	1(0.4)
Hepatitis	Hepatitis	39 (17.5)
Gastrointestinal	Vomiting	8(3.6)
	Diarrhea	24(10.8)
	Abdominal pain	64(28.7)

ADRs: Adverse Drug Reactions

Discussion

ADRs are known to occur with the use of HAART, which affects therapy. HAART associated ADRs has impacted negatively on the management of HIV through a number of factors which include decrease adherence, treatment discontinuation, switching of regimens, and death (14). Thus, the assessment of ADRs in the patients on HAART is highly imperative. This study assessed the data of 350 people living with HIV on first line HAART for ADRs, attending APIN/PLUS Clinic, Federal Medical Centre (FMC), Makurdi, Benue State, Nigeria. This study observed more HIV infection in females (66%) than males (34%). This is consistent with observations that suggest that HIV infection occurs more in females (15,16). Based on age distribution, HIV infection was found to be most in the people within the age range of 31-40. This observation is consistent with previous reports (11). This may be due to higher and non-protective sexual activity among the people in the aforementioned age bracket. On the other hand, HIV infection was least in the people ≥ 61 which may be attributed to reduction in sexual activity. The prescription of HAART is usually tailored according to the health need of the patients. Finding in this study showed that NVP containing regimens were frequently prescribed with ZDV/3TC/NVP been the most prescribed. This observation is consistent with the earlier reports (17). The prevalence of ADRs was 55.7% in this study, which is similar to the rate reported in a study done by Eluwa et al. in 2012 in Nigeria (54%) (18). However, it is lower than the rate reported in the study of Sharma et al. in 2008 in India (71.1%) (19), but higher than the rate reported in the study of Menezez de Pádua et al. in 2006 in Brazil (34.5%) (20) and Keiser et al. in 2007 in Switzerland (45%) (21). The variations in ADRs reported in different studies showed that the spectrum of ADRs differs from country to country, primarily between developed and developing countries. The variations may be attributed a number of factors including genetics, economic, HAART regimens prescribed, and study protocol. The current study observed some of gastrointestinal effects including abdominal pain (28.7%), vomiting (3.6%), and diarrhea (10.8%) as the most common ADRs. Similarly, studies have reported the occurrence of the aforementioned gastrointestinal effects with the use of HAART (9). Hypersensitivity reactions are common ADRs associated with the use of NVP (22). Hypersensitivity reactions observed in this study were severe skin rash (4%), and mild skin rash (22%). This observation occurred in NVP containing HAART. The rate of skin rash observed in this study is less than the rate reported in the study of Obiako et al. in 2012 in Nigeria (65.5%) (23), but higher than the rate reported in the study of Verweel et al. in 2003 in United Kingdom (20%) (24). CNS ADRs may occur with the clinical use of HAART; the CNS ADRs observed in this study were peripheral neuropathy (5.4%), insomnia (4.0%), and dizziness (3.6%), which occurred in ZDV/3TC/EFV and TDF/FTC/EFV regimens. This is at variance with the studies that reported lower incidence of peripheral neuropathy (2.7%) (16), and higher incidence of insomnia (17.6%) and dizziness (32.9%) (25). Most antiretroviral drugs have been associated with varying degrees of liver injuries including hepatitis (26). In this study, the incidence of hepatitis was 17.5% which is higher than the rates reported by Sharma et al. in 2008 (1.5%) (19) and Sulkowski et al. in 2002 (5.5%) (27). Hepatitis observed in this study occurred most in NVP containing HAART, which is in agreement with previous reports (27). Anemia is a common ADR associated with zidovudine containing HAART (28). In this study, the incidence of anemia was 0.4%, which is lower than the rate between 12 to 16% reported in the studies in Jamaica (28) and India (29).

Conclusion

This study discovered that first-line HAART may be safe and well tolerated due to low levels of ADRs. Most of the ADRs observed in this study were not severe, but the patients should be regularly monitored for ADRs.

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Ethical statement

Ethical approval (FMH/FMC/ HREC/108/VOL1) was obtained on 13-06-2014 from the Health Research Ethics Committee (HREC) of FMC, Makurdi, Benue State, Nigeria. The procedures adhered to the ethical guidelines of the Declaration of Helsinki.

Data availability

The raw data supporting the conclusions of this article are available from the authors upon reasonable request.

Conflict of interest

None declared

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