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Patterns of adverse drug reactions to approved HAART regimen in an HIV out-patient Clinic in Nigeria.

Ndubuisi I. Ezumezu[1] and Emmanuel Anyika[1]

[1]Department of Clinical Pharmacy and Bio Pharmacy, Faculty of Pharmacy University of Lagos

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* *Corresponding Author:*
ndubuisiezumezu@gmail.com
+234-8063754883

ABSTRACT

Background: Adverse drug reactions have been one of the most important limiting factors to the success of Highly Active Anti-retroviral Therapy because they are responsible for new co-morbidities noticeable by the patients or their families and may result in decreased adherence to treatment which consequently might lead to virological failure and poor prognosis.

Methods: A retrospective cross-sectional study of adverse drug reactions in patients receiving approved HAART regimen in AIDS prevention Initiative in Nigeria Clinic, Nigerian Institute of Medical Research Lagos. The study examined all reported adverse drug reactions in patients who were receiving HAART between January 2005 and December 2013. File maker Pro JAWS® software was utilized to obtain documented ADRs.

Results: 1187 patient folders were reviewed for ADRs. A total of 595 reported ADR cases were analysed in this study. The prevalence of ADRs for the period was 14.7 %. Of the reported ADRs females (64.9%) presented with more ADRs than males (35.1%). The most reported adverse drug reactions were lipodystrophy (17.6%), neuropathy (14.6%), central nervous system effects (12.3%), anaemia (8.7%) and rash (6.7%).

Conclusion: Different types of adverse drug reactions (ADRs) were reported at the Aids Prevention Initiative in Nigeria Clinic (APIN) and occur at different frequencies in patients receiving antiretroviral medication. These reactions were largely representative of the already documented adverse drug reactions of antiretrovirals.

1. Introduction

Human immunodeficiency virus (HIV) infections which causes Acquired immunodeficiency syndrome (AIDS) remains a global public health concern with an estimated 33 million deaths so far recorded due to HIV infection. However, there has been an increased access to diagnosis, treatment and management of HIV along with presenting opportunistic infections [1]. This has improved the longevity of infected patients and made the infection a manageable chronic health condition. By December 2019, an estimate of 38 million people was living with HIV and during this year, 68% of adults and 53% of children living with HIV were on antiretrovirals1. Between the end of 2019 and June 2020, there was a 2.4% increase in the amount of people accessing antiretroviral therapy which was a result of international responses to the HIV infection [1].

In the last decade, considerable reductions in the HIV incidence and mortality has been recorded; a 39% reduction in new cases and a 51% reduction in mortality1. This trend reflected the efforts put in by national HIV programmes, civil society groups and international partners in making HIV testing, treatment and care accessible. Hence, there will continue to be an increase in the utilisation of effective antiretroviral medication by the population.

The use of highly active antiretroviral therapy (HAART) has recorded undoubted clinical efficacy and benefits [2]. There is the risk of development of adverse drug reactions in patients receiving HAART. An ADR as defined by the World Health Organization is a 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

modifications of physiological function [3]. ADRs have been a major culprit in reducing patient adherence to HAART, thereby leading to virological or treatment failure due to insufficient medication use. This in turn, has a ripple effect on treatment costs of the infection and presenting ADR, programmatic constrains (limited treatment options for the patient) etc.

In Nigeria, a public health approach is used in combating HIV infection. A patient is usually treated with fixed dose combinations and generally started up with first line antiretrovirals. Thereafter if treatment failure occurs, a second line regimen is initiated followed by a third line if another failure occurs. Adverse drug reactions are classified into six types (with mnemonics): dose-related (Augmented), non-dose-related (Bizarre), dose-related and time-related (Chronic), time-related (Delayed), withdrawal (End of use), and failure of therapy (Failure) [4].

Another classification based on a three dimensional system of dose relatedness, timing, and patient susceptibility (DoTS) was proposed [5]. Polypharmacy has been defined as the concomitant use of five or more drugs. The use of such amount of drugs has greatly increased the risk of having drug-related problems (DRPs) and a negative health outcome [6]. However, in the definition of polypharmacy it is worthy of note that the value of using a particular number of drugs as a minimum to describe polypharmacy as a risk factor for the occurrence of DRPs has not been validated [6].

The geriatric population are at risk for polypharmacy, which is associated with major outcomes such as adverse effects, medication nonadherence, drug-drug and drug-disease interactions, and increased risk of geriatric syndromes. Providers should evaluate all existing medications at each patient visit for appropriateness and weigh the risks and benefits of starting new medications to minimize polypharmacy [7]. Polypharmacy is a common occurrence in elderly patients due to reasons like multiple co-morbidities and multiple prescribing physicians [8]. The frequencies of sex related ADRs could be attributed to pharmacokinetic or pharmacodynamic factors, polypharmacy, or differences in reporting patterns [9]. The anatomic and physiologic differences in men and women; ranging from hormonal levels, fat distributions, bone density etc. could affect pharmacokinetic and pharmacodynamics of ingested drugs. This study hence seeks to document patterns of adverse drug reactions to approved HAART regimen in a selected HIV out-patient Clinic in western Nigeria.

2. Methods

This was a retrospective study of reported adverse drug reactions in patients receiving HAART at a tertiary research institute using a computerized database.

2.1 Study Site and Design

The study was carried out using documented adverse drug reactions at the AIDS Prevention Initiative in Nigeria (APIN) Clinic, Nigerian Institute of Medical Research (NIMR), Lagos, Nigeria. Ethical approval was obtained from NIMR, a research Institute with a HIV treatment centre which is under the Clinical Sciences Division. The APIN clinic provides outpatient services to about 400 patients daily and is one of the United States Presidential Emergency Plan for AIDS Relief (PEPFAR) funded centres for HIV relief. The study included all documented adverse drug reactions in patients who were receiving HAART between January 2005 and December 2013.

A total of 595 ADRs were analysed in this study. Patients who develop an adverse drug reaction or who have reacted to a drug before, have such reactions/toxicity, documented. The toxicity forms were filled by doctors and then are uploaded into the computer database by data officers who confirm the entry, make corrections, or refer back for clarifications.

Data contained in the toxicity form includes: Patient's clinic number, sex, description of ADR, Suspected drug details, severity of reaction, concomitant medicines, treatment of reaction, treatment plan for the reaction, outcome of reaction, source of report.

The reports are adverse drug reaction documentations are printed, scanned and then sent to the National Agency for Food Drug Administration and Control (NAFDAC). The data for this study was obtained from the Clinic's software – File maker Pro. 1187 unique files were assessed and a total of 595 reported cases of adverse drug reactions were analysed since a lot of data were readily available.

2.2 Method of data collection

Data on reported ADRS between Jan 2005 and December 2013 was obtained from the database. Each of the years under study, had the following data extracted: sex of the patient; description of the ADR; suspected drug and date reported. Adverse drug reactions were described differently by reporting doctors. Hence, such were analysed and grouped under several broad categories including Neuropathy, Lipodystrophy, Atrophy, Liver disorders, Pigmentation, CNS effects, Sleep disorders etc.

2.3 Method of data analysis

There were no questionnaires utilized during this study. Data exported from the clinic's software were organized in Microsoft excel. Descriptive statistics was mainly used to explain the data. Simple bar chart and tables were used. Data were entered into Statistical Package for Social Sciences (SPSS) 17.0 and statistically analysed. Chi-square was used to compare the frequency of adverse drug reactions between both sexes. P-value was set at 0.05; a p-value less than 0.05 was

statistically significant.

3. Results

The nine year study review period showed occurrences of ADRs for each year reviewed consisting of classical documented ADRs. Lipodystrophy had the highest reported ADR frequency of 17.6% followed closely by neuropathy 14.6%. Headaches recorded the least reported ADR (Table 1)

Table 1 Overall pattern and distribution of adverse drug reactions

Adverse Drug reaction	Frequency	Percentage (%)
Anaemia	52	8.7
Atrophy	23	3.9
CNS effects	73	12.3
Dyslipidemia	1	0.2
Elevated serum creatinine	7	1.2
GI upset	29	4.9
Gynaecomastia	23	3.9
Headache	1	0.2
Lipodystrophy	105	17.6
Liver disorder	11	1.8
Muco - cutaneous ulceration	3	0.5
Musculoskeletal disorders	2	0.3
Neuropathy	87	14.6
Oedema	9	1.5
Pain	12	2.0
Pigmentation	22	3.7

Table 2 Yearly pattern and distribution of adverse drug reactions

Lipodystrophy had the highest frequency of documented cases next to neuropathy. The least reported ADR was dyslipidaemias and headaches.

ADR	Ye ar									Total
	2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	
Anaemia	0	5	2	5	7	7	7	15	4	**52**
Atrophy	1	0	0	13	6	0	1	2	0	**23**
CNS effects	4	9	8	7	14	4	16	5	6	**73**
Dyslipidemias	0	0	1	0	0	0	0	0	0	**1**
Elevated serum creatinine	0	0	1	1	1	1	2	1	0	**7**
GI upset	1	2	3	2	4	0	7	9	1	**29**

Gynaecomastia	1	2	0	1	6	1	4	6	2	**23**
Headache	0	0	0	0	0	0	0	0	1	**1**
Lipodystrophy	7	32	25	24	11	3	0	1	2	**105**
Liver disorders	1	0	1	2	2	0	0	5	0	**11**
Muco - cutaneous ulcerations	0	1	0	0	0	0	0	1	1	**3**
Musculoskeletal disorders	0	1	0	0	0	0	0	1	0	**2**
Neuropathy	8	19	22	32	6	0	0	0	0	**87**
Oedema	0	0	0	2	2	0	2	3	0	**9**
Pain	0	4	3	0	1	2	1	0	1	**12**
Pigmentation	1	2	5	1	1	1	4	4	3	**22**

The overall gender distribution of documented adverse drug reactions was higher in the female gender. 64.9% reported cases were reported in females while 35.1% were reported in males.

Table 3 Gender distribution of individual adverse drug reactions (* p < 0.05)

ADR	Gender				Total
	Female		**Male**		
ADR	**Frequency**	**%**	**Frequency**	**%**	
Anaemia	38	9.8	14	6.7	52
Atrophy	17	4.4	6	2.9	23
CNS ef fects	37	9.6	36	17.2	73
Dyslipidemia	1	0.3	0	0.0	1
Elevated serum creatinine*	5	1.3	2	1.0	7
GI upset	22	5.7	7	3.3	29
Gynaecomastia	6	1.6	17	8.1	23
Headache	1	0.3	0	0.0	1
Lipodystrophy	83	21.5	22	10.5	105
Liver disorder*	8	2.1	3	1.4	11
Muco -cutaneou s ulceration*	2	0.5	1	0.5	3
Musculoskeletal disorders	2	0.5	0	0.0	2
Neuropathy*	47	12.2	40	19.1	87
Oedema*	8	2.1	1	0.5	9
Others	25	6.5	20	9.6	45
Pain*	8	2.1	4	1.9	12

Pigmentation	14	3.6	8	3.8	22
Rash	30	7.8	10	4.8	40
Skin manifestations	19	4.9	5	2. 4	24
Sleep disorders	7	1.8	12	5.7	19
Stevens Johnson Syndrome*	6	1.6	1	0.5	7
Total	386	100	209	100	595

Table 4 Adverse drug reactions (ADR) showing implicated drugs and frequency of occurrence.

ADR	DRUGS																			TOTAL (%)
	3TC	**ABC**	**ATV**	**AZT**	**AZT/3TC**	**AZT/3TC/NVP**	**D4T**	**D4T/3TC**	**DDI**	**EFV**	**IND**	**LPV**	**LPV/r**	**NVP**	**TDF**	**TDF/3TC**	**TDF/3TC/EFV**	**TDF/FTC**	**TDF/FTC/EFV**	
Anaemia	1	0	0	40	2	8	0	0	0	0	0	0	0	1	0	0	0	0	0	8.7
Atrophy	0	0	0	0	1	2	20	0	0	0	0	0	0	0	0	0	0	0	0	3.8
CNS Effects	0	0	0	7	0	1	2	0	0	54	0	0	0	1	0	0	2	0	6	12.2
Dyslipidemia	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0.1
Elevated serum creatinine	1	0	0	0	0	0	0	0	0	0	0	0	0	0	5	1	0	0	0	1.1
GI upset	0	5	3	3	1	1	0	0	1	1	0	0	8	0	2	2	0	1	1	4.8
Gynaecomastia	0	0	0	1	0	1	4	0	0	14	0	0	0	0	0	0	1	0	2	3.8
Lipodystrophy	0	0	0	8	0	2	89	1	1	0	0	0	1	1	0	1	0	1	0	17.6
Liver disorders	0	0	4	0	0	0	0	0	0	0	0	0	0	7	0	0	0	0	0	1.8
Muco-cutaneous ulceration	0	0	0	1	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0.5
Musculoskeletal disorders	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0.3
Neuropathy	0	1	0	4	0	0	81	0	1	0	0	0	0	0	0	0	0	0	0	14.6

4. Discussion

The prevalence of reported adverse drug reactions in APIN-NIMR out-patient clinic from 2005 to 2013 was 14.7%. 1187 patient folders were reviewed for ADRs. A total of 595 reported ADR cases were analysed in this study. A Cross-sectional retrospective study in Ghana from 2003 to 2007 reported that the period prevalence of ADRs as 9.4% [11]. Anaemia is a condition in which the number of red blood cells or their oxygen-carrying capacity is insufficient to meet physiologic needs, which vary by age, sex, altitude, smoking, and pregnancy status [12]. Zidovudine (ZDV) is known to be associated with life threatening toxicity like anaemia [13]. From this study, anaemia accounted for 8.7% of adverse drug reactions. Of this, 96% was as associated with zidovudine and zidovudine containing regimen. A Nigerian study reported 4.3% cases of anaemia of which 94.5% were reported in patients who received zidovudine-based regimens which is similar to the result of this study in which zidovudine and zidovudine containing regimens accounted for 96% [14].

Another study in north central Nigeria reported a frequency of anaemia of 23.4% as opposed to 8.7% in this study. The variances with the result of this study may arise from co-morbidities and nutritional status of patients [15-17]. A southern Indian study found anaemia in 5.4% of patients. Variances in the frequency of anaemia may have been due to different nutritional status of patients. Central Nervous System effects accounted for 12.3% of the adverse drug reactions of which 73% was associated with efavirenz [15-17]. A study on adverse drug reactions in HIV infected patients at an ART centre of tertiary care hospital in Guwahati, India reported CNS adverse drug reaction as being 16.2% of adverse drug reactions. The difference may have been due to the classification of some ADRs as CNS effects (e.g. numbness, headaches etc.) which this study placed under another category or as a single category. In this study, 73% of CNS adverse effects were reported with efavirenz use. This finding was consistent with the work done by Shubber *et al.,* [18] which revealed increased risk of severe CNS effects in patients receiving efavirenz compared to those receiving nevirapine.

High rates were identified of neuropsychiatric side effects including vivid dreams, insomnia and mood changes in approximately 50% of patients who initiate Efavirenz. These effects occur rapidly usually within 14 days of commencing use [19]. Gynecomastia accounted for 60.8% of reported adverse drug reactions in this study. A study on efavirenz directly modulating the oestrogen receptor and inducing breast cancer cell growth [20]demonstrated that efavirenz directly binds and activates the oestrogen receptor. This seems to be a probable mechanism behind efavirenz-induced gynaecomastia in HIV-infected patients. Dyslipidaemia had only a 1% frequency of all adverse drug reactions and only stavudine was linked to this. A 2006 study [21] concluded that the substitution of tenofovir for stavudine causes a sustained improvement of dyslipidaemia and that switch strategy is safe and improves lipid profiles, especially triglycerides, in HAART-treated patients. In Nigeria, stavudine is no longer being used in patient management. Elevated serum creatinine was observed to occur in tenofovir (TDF) and TDF containing regimen both accounting for 85% of cases while lamivudine (3TC) only accounted for the remainder. 1.2% of the reported adverse drug reactions accounted for elevated serum creatinine. The low frequency of elevated serum creatinine agrees with the findings from another study [22] study which reported that baseline risk factors for the development of increased serum creatinine on-study were elevated serum creatinine, concomitant nephrotoxic medications, low body weight, advanced age, and lower CD4 cell count. The study concluded in favour of a safety profile of tenofovir.

Lipodystrophy was the most reported adverse drug reaction. It had an occurrence of 17.6%. D4T accounted for 84% of lipodystrophy cases. In a study on adverse drug reactions [23], Lipodystrophy accounted for 5.3% of all ADRs and was the main reason for treatment change in 25% of patients. Lipodystrophy had its highest frequency in year 2006; thereafter reported cases declined. This appears to be due to the phasing out of stavudine - after which, cases of lipodystrophy declined. Atrophy was observed in only 3.9% of reported adverse drug reactions. 86% of such cases were suspected to be caused by stavudine (D4T) while the other cases were linked to AZT/3TC and AZT/3TC/NVP. Neuropathy was the second highest reported adverse drug reaction with a 14.6% frequency of occurrence. A cross sectional study in Cameroon [23], had the most commonly reported ADR to be peripheral neuropathy (21.2%) whilean Indian study had reported cases of peripheral neuropathy to be 14.1% [25] which was very close to that reported in this study. In this study, 93% of neuropathy was implicated with D4T use.

Rash was observed to occur in 6.7% of the reported adverse drug reactions. Rather *et al.,* reported 18.2% of rash [25]. The wide variance with respect to this study may be as a result of pharmacogenetic variations, HIV disease progression or the nutrition status of patients involved. Of the reported case of rash, NVP accounted for 67.5%, EFV-10% while ABC- 7.5%. Stevens - Johnson syndrome was observed to have an occurrence of 1.2%; with NVP being the only drug implicated in all the cases. This result agrees with the United states Department of Health and Human Services (2015) [26] guidelines which points to the fact that nevirapine is the NNRTI having the most likelihood of causing Stevens Johnson Syndrome. In a multicentric retrospective study study [27], nevirapine was responsible for 50% of Stevens Johnson reactions; zidovudine was responsible for 8.3% while stavudine reported no reaction. Peripheral neuropathy (PN) is common among patients receiving antiretroviral therapy in resource-limited settings [28-29]. In this study, neuropathy was the second highest reported adverse drug reaction of which a higher frequency was found to be among females. In a study on sex differences in the incidence of peripheral neuropathy among Kenyans initiating antiretroviral therapy [31], Kenyan women were almost 10 times more likely than men to develop peripheral neuropathy in the first year of ART. Several studies have described differences in pharmacokinetics in drug response toxicity between males and females, but it is difficult to link differences in sexual constitution to simple distinct mechanisms. Differences in drug levels or in drug response depend on different factors like body size, genetics, sociocultural activities, behavioural factors, molecular or biochemical factors, and hormonal/reproductive influences [32].

The use of herbal medicines concomitantly with HAART by HIV positive patients could pose beneficial or otherwise harmful effects in such patients [33]. The combination of such remedies which may cause an enzyme induction or inhibition in-vivo could cause beneficial or harmful effects. Generally, and in the interest of patient safety, the use of herbal remedies together with HAART should be discouraged [33] in order to prevent potential exacerbation of ADRs unless in established cases of beneficial concomitant use.

5. Conclusion

Different types of adverse drug reactions (ADRs) were reported at the APIN clinic. HAART related ADRs occur at different frequencies in patients receiving antiretroviral medication. These reactions were largely representative of the already documented adverse drug reactions of antiretrovirals. The most frequently reported ADRs were Lipodystrophy, neuropathy, central nervous system effects, anaemia, and rash. The prevalence of the reported adverse drug reactions is an indicator for the need for a more active ADR monitoring which should involve not only the pharmacists but the entire health team so that untoward antiretroviral effects could be appropriately identified, monitored, and better explained to

patients.

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