OCCURRENCE AND REPORTING OF ADVERSE DRUG REACTIONS AMONG PATIENTS ON HIGHLY ACTIVE ANTIRETROVIRAL THERAPY IN A NIGERIAN UNIVERSITY TEACHING HOSPITAL

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ABSTRACT:

Background: Adverse drug reactions (ADRs) have reduced the benefits of Highly Active Antiretroviral Therapy (HAART). There is a dearth of data of adverse drug reactions due to HAART in Nigeria. The objective of this study is to determine the pattern of ADR reporting; and evaluate the prevalence, types and severity of ADRs due to HAART in a Nigerian university teaching hospital.

Methods: Key Informant Interview (KII) was conducted for healthcare providers for HIV/AIDS patients. Data was also collected using a pre-tested questionnaire administered to consenting patients above the age of 18 using accidental sampling technique. Data was collected for 5 consecutive weeks between August and September, 2013, and was analysed for descriptive and inferential statistics. Interviews were transcribed and analysed using Atlas.ti software for qualitative analysis.

Results: Analysis of KII revealed that yellow forms are not being used in ADR reporting. Out of 179 patients evaluated, 72.6% were female. Most of the patients (96.6%) were on first line HAART regimen. Ninety patients (50.3%) reported at least an ADRs and 5% of the ADRs were life threatening reactions. Only 7 (3.9%) of the patients reported a previous medication change due to ADR and the commonly reported ADRs were; dizziness (18.4%), skin rash (8.4%), hallucination (6.1%), somnolence (5.6%), and tingling/numbness (4.5%).

Conclusion: The prevalence of ADR among patients on HAART in the study centre was 50.3% and majority of the reported ADRs were mild. Healthcare team members at the study site observed ADR among patients on HAART, but yellow forms were not used in reporting the observed ADRs. Some commonly reported adverse drug reactions reported by the patients include; dizziness, skin rash, hallucination, somnolence and tingling/ numbness.

KEYWORDS: Adverse Drug Reactions, Highly Active Antiretroviral Therapy, HIV, Nigeria, Pharmacovigilance.

INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) has greatly reduced morbidity and mortality rates associated with HIV/AIDS pandemic.[1,2] However, reports of morbidity and mortality from adverse drug reactions (ADRs) associated with the HAART tend to reduce the benefits derived from antiretroviral therapy[3]; adverse drug reactions also reduce patients' adherence to therapy.[4] Adverse drug reaction has been defined as an unintended response to a medicine which is appreciably harmful or unpleasant and which occurs at normal dose administered for the prevention, diagnosis or treatment of diseases, or for the modification of physiological function.[5,6]

It has been reported that the spontaneous reporting system, which is the reporting system widely used in Nigeria, is characterized by low reporting rates.[7] As at 2016, there were 3,200,000 living with HIV in Nigeria[8] and over 415,000 patients were on antiretroviral therapy (ART);[9] however, information regarding the incidence of ADRs is very scarce as a result of deficiencies in ADR surveillance in clinical practice. For instance, according to the Pharmacovigilance Newsletter of National Agency for Food and Drug Administration and Control (NAFDAC), only 17% of individually reported ADRs are due to antiretroviral medicines.[10] The effectiveness of treatment in low and middle-income countries such as Nigeria has been limited by adverse drug reactions.[10] ADRs pose serious problem in chronic conditions where medicines are taken over a long period, particularly those requiring the use of drug combinations such as tuberculosis, malaria, hypertension, diabetes, among others.[9] However, majority (72%) of ADRs experienced are avoidable.[11]

Antiretroviral therapy can have a wide range of adverse effects on the users. Commonly reported adverse effects in early antiretroviral regimens include gastrointestinal effects such as bloating, nausea and diarrhoea, which may be transient or may persist throughout treatment. Other common adverse effects are fatigue and headache which is common with zidovudine (AZT) while nightmares are common with efavirenz (EFV).[12] There are several uncommon but sometimes serious adverse effects associated with antiretroviral therapy. These include; AZT-associated anaemia, stavudine (d4T)-associated peripheral neuropathy, protease inhibitors (PI)-associated retinoid toxicity (exemplified by pruritus and ingrown toe nails) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)-associated hypersensitivity reactions. Some other serious adverse effects are; lactic acidosis, hepatic steatosis, hyperlactatemia, hepatotoxicity, hyperglycemia, fat maldistribution, hyperlipidemia, bleeding disorders, osteoporosis and skin rash.[12]

Studies have shown a wide range manifestation of ADRs in HAART. In an intensively monitored ART patients in India, 43.8% incidence and 39.7% prevalence of ADRs was reported;[13] Another report cited the incidence of ADR among patients taking ARV to range between 11 and 35.9%.[14] The presence of opportunistic infection can increase incidence of ADR to as high as 54%.[15]

In Uganda, ADRs incidence rate was 4.47/100 person-months; and the commonly reported ADRs were peripheral neuropathy (36%), rash (6%), and hypersensitivity reaction (2%).[3] Eluwaet al. (2012) reported ADR incidence rate of 4.6/100 person-years among people living with HIV/AIDS in Nigeria; and commonest ADRs were pain (30%) and skin rash (18%).[16] Olowookere et al. (2008) reported nausea/vomiting (19.5%), skin rash (15.7%), diarrhoea (23.9%), dizziness (13.8%), paraesthesia (11.9%) and bad dreams (14.5%) in patients on ART some of which affected adherence to medication.[17]

Patients on longer duration of antiretroviral treatment has been found to have decreased odds of developing an ADR compared to patients whose commencement of treatment was less than one year.[16] However, fingernail discoloration and proximal muscle weakness/pain have been reported as significant late ADRs of AZT, which occur in patients who have received the drug for more than 6 months.[18] Obiakoet al. (2012) studied patients with varying onset of ADR from 10 to 1090 days, bad dreams were observed with a median interval as short as 16 days while facial lipodystrophy was as long as 254 days. However, majority of the ADRs occurred between 31 to 91 days with median interval being significantly earlier in females (32 days) than males (36 days).[19]

The objectives of this study were to determine the prevalence of adverse drug reactions among patients on HAART, types and severity of ADR due to HAART, and the practice of pharmacovigilance among healthcare team managing people living with HIV/AIDS (PLWHA), in a Nigerian University Teaching

Hospital.

METHODS:

Setting

This study was carried out at the Institute of Human Virology of Nigeria (IHVN), Obafemi Awolowo University Teaching Hospital Complex (OAUTHC) branch. The IHVN in OAUTHC serves people from Osun State and beyond. Services available to patients free of charge include: tests for HIV, medical consultations, counselling and treatment. There are physicians, pharmacists, nurses, laboratory scientists and adherence counsellors that provide medical care for people living with HIV/AIDS (PLWHA) attending clinic at the institute and the official working hours is 8am – 4pm, Mondays to Fridays. The physical location of the building is within the hospital environment.

Study Design

The study was a cross-sectional survey that utilized questionnaire guided interview to obtain data from patients and Key Informant Interview (KII) was conducted for professionals involved in the management of HIV/AIDS patients.

Population and Sample Size

Two sets of population were involved in this study; healthcare professionals and patients on HAART attending clinic at the centre. KII was conducted for the head of pharmacy unit, chief resident physician, senior nursing staff, and the head of adherence counselling unit while questionnaires were administered to the patients.
Based on the prevalence of HIV/AIDS in Nigeria (4.6%), the calculated sample for the patients was 68 using the Cochran formula for calculating sample size however, 179 questionnaires were administered to increase its statistical power.[20]

Sampling and Data Collection

The two adult clinic days of the week (Mondays and Wednesdays) were chosen to recruit participants and an average of 25 patients were recruited by accidental sampling technique on both clinic days. The demographic information of the patients including age and weights were copied from the patients' prescriptions and case notes while the questions relating to ADR, duration and HAART regimen were asked and answered directly by the patient.

Only patients 18 years and above were included in this study. Also, the heads of department, or a senior member of the department were sampled among the healthcare professionals.

The interviews conducted for healthcare providers were transcribed and analysed using the Atlas.ti software for qualitative analysis.
The data collected was analysed for descriptive and inferential statistics using SPSS version 16.

Research Instrument

The research instrument was an adapted adverse drug reactions yellow card used by the Nigerian National Pharmacovigilance Centre. The adapted form which was used for the questionnaire had five sections; Demographic information/Patient details, Antiretroviral medicine(s) in use, Adverse drug reaction(s), WHO severity grading of ADRs[21]. Interview schedules were used for the semi-structured interviews conducted for the healthcare professionals. The questions centred on the occurrence of ADR among their patients, severity of such ADR, documentation and reporting of such ADRs using yellow form.

Ethical Approval

Ethical approval for this study was obtained from Health Research and Ethics Committee of Institute of Public Health, Obafemi Awolowo University, Ile-Ife, Nigeria.

RESULTS:

Result of the Key Informant interview with the physician, pharmacist, nurse and Adherence Counsellor is presented in table 1.

Table 1. Health Professional's Observations and practices of Pharmacovigilance

Characteristics	Responses
	Physician
Occurrence of ADR	"Some report ADR when we start them on HAART, especially at the initial period. Some times when we start them on the drugs, they sometimes develop skin rashes, renal problem, etc."
Severity of ADR	"Less than one month ago, we managed a patient in the surgical ward due to reactions to Nevirapine."
Pattern of observed ADR	"The pattern I can see is that sometimes they are drug specific; I will say it is more common to Nevirapine than Efavirenz."
ADR Documentation	"We have records, the donors who fund this program takes all of this and they have records. As matter of fact, if you change any drug, it has to be documented. We report ADR, but that is being mostly handled by the pharmacy section of the IHVN"
Knowledge and Use of Yellow Form for ADR Reporting	"We have records, the donors who fund this program takes all of this and they have records. As matter of fact, if you change any drug, it has to be documented. We report ADR, but that is being mostly handled by the pharmacy section of the IHVN"
	Pharmacist
Occurrence of ADR Severity of ADR	"Occasionally we have seen some ADR, not too often""I think the only one we have seen here is a pregnant woman that reacted to Nevirapine."
Pattern of observed ADRADR DocumentationKnowledge and Use of Yellow Form for ADR Reporting	"I think the observed pattern is due to the type of drugs and not gender.""In this facility generally we have not really seen the effect of that report""In this facility generally we have not really seen the effect of that report."
	Nurse
Occurrence of ADR	"We cannot give specific numbers of patients per month. It is observed from time to time."
Severity of ADR	"We had one especially on Nevirapine. She was pregnant in her second trimester. She had something like Stephen-Johnsons Syndrome. It was so bad. But she is okay now. She delivered the baby safely. She's back in the ward now."
Pattern of observed ADR	"Usually we have a lot of them manifesting the side effects of Efavirenz. They come back complaining wanting to stop the drug but we keep encouraging them that within a short time the side effect will wear off. And with time they adjust giving good responses."
ADR Documentation	Nil
Knowledge and Use of Yellow Form for ADR Reporting	"Yellow card? Is it drug tag? I've never used it here."
	Adherence Counsellor
Occurrence of ADR	"It usually occurs when they are just placed on the drugs"
Severity of ADR	Nil
Pattern of observed ADR	"It depends on individual's body system."
ADR Documentation	Nil
Knowledge and Use of Yellow Form for ADR Reporting	"We don't have it here. I think yellow card is used by people that want to travel out of the country."

Out of179 patients recruited, 130 (72.6%) were female and 49 (27.4%) were male. Specific age was written for 109 (60.9%) prescriptions while the remaining was written as 'Ad' (adult). For the 109 that had their ages written, the mean age was 42.3 ±9.5 (20-71). The weight of 157 patients was recorded on the prescription forms and the mean weight was 59.6±11.4 (32-99). The Chi-square test for independence indicated no significant association between adverse drug reaction and sex of patients. More than half (65.6%) respondents had been commenced on HAART for more than one year as shown in table 2.

Table 2: Duration of use of antiretroviral medicine

Duration	Frequency (N=125)	Percentage (%)
Less than 2 weeks	2	1.6
2 weeks – 1 month	6	4.8
1 month – 3 months	11	8.8
3 months – 6 months	14	11.2
6 months – 1 year	10	8.0
More than 1 year	82	65.6

There was significant association between adverse drug reaction and duration of ART use (x^2= 15.860, p= 0.007, phi= 0.356).

About 58.3% had CD4 count of less than 500 as shown in table 3.

Table 3: CD4 counts of patients

CD4 Count	Frequency (N=60)	Percentage (%)
Less than 100	4	6.7
101-350	20	33.3
351-500	11	18.3
501-750	13	21.7
751-1000	7	11.7
More than 1001	5	8.3

There was no significant association between adverse drug reaction and CD4 Count (x^2= 4.405, p= 0.493, phi=0.271).

Majority of the patients (96.6%) were on first line drugs such as Lamivudine + Zidovudine + Nevirapine while about 3.4% were on second line drugs using Lopinavir/Ritonavir in combination with either Abacavir + Lamivudine or Zidovudine (or Lamivudine) + Tenofovir.

Majority of the medicines (99.4%) were in fixed dose combinations with 66 (36.9%) patients receiving fixed dose combination of three medicines combined in one formulation (Zidovudine+Lamivudine+Nevirapine or Tenofovir+Lamivudine+Efavirenz) as shown in table 4.

Table 4: Frequency of antiretroviral regimen with reported adverse drug reactions

Antiretroviral regimen (ARVs) in use	Patients on Regimen		Adverse Drug Reactions	
	Frequency (N=179)	Percent (%)	Frequency (N=179)	Percent (%)
***(AZT+3TC+NVP)	64	35.8	26	14.5
***(TDF+3TC+EFV)	2	1.1	1	0.6
**(TDF+FTC) + EFV	6	3.4	2	1.1
**(TDF+FTC) + NVP	1	0.6	7	3.9
**(TDF+3TC) + NVP	17	9.5	7	0.6
**(3TC+AZT) + EFV	36	20.1	25	14.0
**(3TC+AZT) + NVP	35	19.6	11	6.1
**(3TC+TDF)+(Alluvia)	2	1.1	1	0.6
**(3TC+TDF) + EFV	11	6.1	5	2.8
**(Alluvia) + ABC	1	0.6	1	0.6
**(3TC+AZT)+(Alluvia)	3	1.7	3	1.7
*(TDF)+(NVP)+(ABC)	1	0.6	1	0.6

Key:

****Fixed dose combination with three components*

***Fixed dose combination with two components*

**Medicines not in fixed dose combination.*

3TC-Lamivudine

ABC-Abacavir

Alluvia-

AZT-Zidovudine

EFV-Efavirenz

FTC-Emtricitabine

NVP-Nevirapine

TDF-Tenofovir

Out of 179 patients studied, 90 (50.3%) reported adverse drug reactions to antiretroviral therapy. Majority (91.2%) of the patients that reported adverse drug reactions admitted that the reaction was mild, causing no limitation in activity or need for medical intervention. However, about 5% of the patients had severe adverse reactions that required hospitalization and significant medical intervention/therapy. Only 7 (3.9%) of the patients reported a previous change in antiretroviral medicine due to adverse drug reactions. Dizziness (18.4%) and skin rash (8.4%) were the most reported ADR as shown in table 5.

Table 5: Common types of adverse drug reactions reported and their outcomes

ADR			Outcomes		
	Frequency	Percentage	Recovered	Resolving	Continuing
Dizziness	33	18.4	25	7	1
Skin rash	15	8.4	13	2	-
Hallucination	11	6.1	6	3	2
Somnolence	10	5.6	8	1	1
Tingling/Numbness	8	4.5	7	1	-
Pruritus	7	3.9	6	1	-
Nausea	7	3.9	6	-	1
Fatigue	6	3.4	5	1	-

DISCUSSION:

All the healthcare professionals interviewed said they observed ADR among patients who were on HAART. Both the physician and the adherence counsellor also noted that it was common when patients were newly placed on it. The response of the pharmacist to the occurrence: "Occasionally we have seen some ADR, not too often" showed that the pharmacist don't see ADR often among the patients. With the nurse saying that "...It is observed from time to time", it is probably an indication that the pharmacists need to improve on their interactions with their patients. The observation of the physician and the adherence counsellor is in alignment with previous studies that reported that ADRs are common at the onset of therapy.[16] The physician, pharmacist and the nurse attributed the observed ADR to the type of medicine the patient is taking rather than demographics (such as age and gender) of the patients. Similar patterns have been reported in literature.[9,22,23]

In answering the question on ADR documentation, the physician said "we have records, the donors who fund this program take all of this and they have records. As matter of fact, if you change any drug, it has to be documented" and use of yellow form for reporting, he said "Yes, I know of yellow card but we've not been using it. But our records will still achieve what yellow card would have achieved". This shows that there were various forms for documentation of ADR, change of medicines etc. However, it is obvious that yellow forms are not used in this facility. It is however not clear whether the ADR forms filled for the sponsors ever get reported to regulatory authority such as the National Pharmacovigilance Centre (NPC) of National Agency for Food and Drug Administration and Control (NAFDAC) of Nigeria. The physician and the pharmacist were aware of the yellow form for ADR reporting but the adherence chancellor and the nurse did not demonstrate adequate knowledge of the form.

Most of the patients that participated

in this study were females and it is consistent with what was observed in previous studies among HIV/AIDS patients.[9,16,19] Having more females in HIV related studies could possibly be because more females get aware of their status earlier than their male counterparts especially due to the fact that HIV screening, according to WHO directives is now compulsory at antenatal clinics.[24] Furthermore, the findings of this survey is similar to that of Agu et al (2013), that reported that there was no significant association between the sex of patients and adverse drug reactions among patients on antiretroviral therapy (ART).[9] In contrast however, Singh et al, in an earlier cohort study reported a significant association between sex and ADR.[25] This study did not detect any association between ADR and age of respondents. The patients assessed for CD4 count had less than 350 cells/mm^3. This study did not find any significant relationship between ADR and CD4 count. On the contrary, a recent cross-sectional retrospective study done at a tertiary hospital in Ghana, reported that high CD4 count (250 cells/mm^3 or more) predisposed to ADR while low CD4 count (less than 250 cells/mm^3) was protective.[23]

While there is need for more prospective research on the chronic effects of HAART, this survey observed a statistically significant association between duration of use of HAART and prevalence of ADR, with about half of patients that reported adverse reactions being initiated on ART in less than one year, this is consistent with previous studies.[18,19] High rate of patients experiencing skin rash with Nevirapine based regimen (AZT+3TC+NVP) observed in this study is consistent with previous studies in which Nevirapine based regimen was significantly associated with ADR such as skin rash.[9,17,25]

Reports have also shown association between Efavirenz based regimen and central nervous system (CNS) adverse effects such as nightmares, hallucination, drowsiness and depression.[9,16,23] Findings from this study also corroborate the previous studies on Efavirenz as majority of the patients that reported dizziness and hallucination were on Efavirenz.[9]

CONCLUSION:

The prevalence of ADR among patients on HAART in the study centre was 50.3% and majority of the reported ADRs were mild. Healthcare team members at the study site observed ADR among patients on HAART, but yellow forms were not used in reporting the observed ADRs.

Some commonly reported adverse drug reactions reported by the patients include; dizziness, skin rash, hallucination, somnolence and tingling/ numbness.

LIMITATIONS OF RESEARCH

The sampling procedure was a non-probability sampling which could introduce some element of bias into the research findings.

ACKNOWLEDGEMENT:

We acknowledge members of staff of Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC) branch of Institute of Human Virology, Nigeria.

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