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PATIENT- REPORTED ADVERSE EFFECTS TO ANTI RETROVIRAL DRUGS IN A SPECIALIST HOSPITAL, NORTH WEST NIGERIA

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ABSTRACT: Patients experiencing adverse effects are less likely than those not experiencing it to adhere to treatment. However little is known about the adverse drug reactions to many HIV programme in developing countries, indicating the need for Antiretroviral (ART) safety surveillance. The study is a retrospective analysis of records of adverse reactions by patients initiated on ART. A total of 1870 patients initiated ART between February 2008 and May 2012. 1386 patients had clinical visits during the one year study period. A total of 95 (6.9%) reported 113 suspected Adverse Drug Reactions (ADRs). The incidence rate of ADR in this study was 8/ 100 persons- year and skin rash (21.2%) was the most reported, followed by nausea/ vomiting (16.8%). Skin rash was associated with Zidovudine/Lamivudine/Nevirapine combination OR= 5.35 (1.55-20.24) and P value of 0.0045. Over 70% of reported ADRs occurred within 6 months after commencement of ARV. Gender was not associated with ADR occurrence OR= 1.09(0.7-1.69),P value= 0.77. ADRs were higher in Zidovudine/Lamivudine/Nevirapine combination. There is need for active pharmaceutical care in therapeutic drug monitoring of antiretroviral to improve tolerability.

INTRODUCTION: The HIV/AIDS has created an enormous challenge worldwide since recognition of the disease and more than 25million people have died of AIDS since 1981[1]. However, antiretroviral therapy has significantly reduced rates of morbidity in HIV infected persons [2].

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In spite of this antiretroviral therapy benefits, adverse reactions to these drugs have been pointed to as one of the main reasons for discontinuation, switch and non-adherence to antiretroviral therapy [3]. These ADRs have been one of the most important limiting factors to the success of HAART [4] because they are responsible for new co-morbidities noticeable by the patient or their families and may result in decreased adherence to treatment which consequently might lead to virological failure and poor prognosis [4]. Up to 84% of HIV patients discontinue their initial HAART regimen within the first 8months of therapy due to ADRs [5].

In one trial, patients experiencing adverse events were 13times less likely than those not experiencing adverse events to have highest levels (95-100%) of adherence [6].

Studies are therefore required to determine these adverse effects, the trend in which they occur, the factors which are related to their occurrence and identification of subgroups requiring different monitoring intensities. A better understanding of these is of interest in optimizing therapy, hence the need for this study.

MATERIALS AND METHODS: This study was a retrospective analysis of patient's reports of adverse reactions to ARVs available at the point of drug collection (Pharmacy Department) of the study site. Ethical clearance for this study was obtained from the Hospital's Ethics Committee.

Study Site: The study was conducted at a secondary health institution (Specialist Hospital Sokoto). At the time of this study, it serves over 1800 HIV/AIDS patients with supports from the Global HIV/AIDS Initiative, Nigeria (GHAIN), a USAID funded program managed by Family Health International (FHI).

Study Population and Sample: The study included all patients who were initiated on ART and had at least one follow up visit during the study period. They were screened for complaints of onset of adverse drug reaction after initiation of ART.

Data Collection: Active ADR screening commenced in May, 2009 under the GHAIN project. GHAIN developed a structured ADR screening form modified from World Health Organization and closely related to the ADR form used by the National Agency for Food, Drug Administration and Control (NAFDAC). Clinicians and Pharmacists were trained on the content and use of the form by the Medical Services Department of FHI and they were required to use the form on all patients on ART at any clinical visit. Each visit screened for ADR is captured as a yes/no (*i.e.* yes if an ADR is reported).

Statistical Analysis: Descriptive analysis was performed to characterize the number and type of adverse reactions. Data were analysed using chi-square test.

All statistical calculations were performed using Epi Info Version 6. Incidence rate was calculated by considering the ratio of ADRs and the exposure patients. Level of significance was set at $P< 0.05$.

RESULTS: A total of 1870 patients initiated ART between Feb 2008 and May 2012. A total of 494 patients were excluded from the analysis because they had no clinical visits during the study period. During the one year period of this study, 1386 patients had 8693 clinical visits, an average of 6 visits per patient. There were more females 814 (58.7%) than males 572 (41.3%). A total of 95 (6.9%) of these 1386 patients reported adverse effects to antiretroviral.

Gender was not associated with reported ADRs as there was no significant difference between male and female OR= 1.09(0.7-1.69), P value= 0.77.

Regarding onset of ADR, 72.6%, 10.5% and 16.8% of reported ADRs occurred at 0-6months, 6-12months and above 12months respectively, after commencement of ARV. All of the reported ADR occurred in those above the age 15years, with none reported in those below 15 years of age. These patient characteristics and ADR distribution are shown in **Table 1**.

TABLE 1: PATIENT'S CHARACTERISTICS AND DISTRIBUTION OF ADR

Variable	Total Number of Patient (%)	Number of Patients Reporting ADRs (%)
Sex		
Male	572(41.3)	41(43.2)
Female	814(58.7)	54(56.8)
Age (Years)		
<15	37(2.7)	Nil (0)
>15	1349(97.3)	Nil (0)
Onset of ADR		
0-6months		69 (72.6)
6-12months		10 (10.5)
>12 months		16 (16.8)

A total of 284 drugs were prescribed for the patients who reported adverse drug reaction with Lamivudine been the most prescribed 88 (30.9%), followed by Nevirapine 70 (24.6) and Zidovudine 61 (21.5%). This is shown in **Table 2**.

TABLE 2: DRUG COUNTS OF ANTIRETROVIRALS PRESCRIBED

Antiretroviral drug	Frequency (%)
Lamivudine	88 (30.9)
Nevirapine	70 (24.6)
Zidovudine	61 (21.5)
Tenofovir	32 (11.2)
Efervirenz	21 (7.4)
Emtricitabine	5 (1.8)
Ritonavir	3(1.1)
Lopinavir	3 (1.1)
Kaletra	1 (0.4)

All the antiretroviral drugs were prescribed in fixed dose combination with Zidovudine/ Lamivudine/ Nevirapine (AZT/3TC/NVP) combination been the most prescribed (60%) followed by Tenofovir/ Lamivudine/ Efervirenz (TDF/3TC/EFZ) (14.7%). This is shown in **Table 3**.

TABLE 3: PERCENTAGE DISTRIBUTION OF ANTIRETROVIRAL COMBINATION REGIMEN

Antiretroviral drug combination	Frequency (%)
Zidovudine/Lamivudine/Nevirapine	57 (60)
Tenofovir/Lamivudine/Efervirenz	14 (14.7)
Tenofovir/Lamivudine/Nevirapine	12 (12.6)
Tenofovir/Emtricitabine/Efervirenz	4 (4.2)
Zidovudine/Lamivudine/Efervirenz	3 (3.2)
Alluvia (Lopinavir/ Ritonavir)	3 (2.1)
Zidovudine/Lamivudine/ Alluvia	1 (1.1)
Lamivudine/ Tenofovir/ Kaletra	1 (1.1)
Tenofovir/Emtricitabine/Nevirapine	1 (1.1)

A wide range of adverse drug reactions were reported in this study. 113 suspected ADRs were reported by 95 patients. Of these ADRs, 61.1%, 29.2% and 8% respectively occurred in patients on Zidovudine/Lamivudine based, Tenofovir/ Lamivudine based and Tenofovir/ Emtricitabine based NRTI backbone regimen. The incidence rate of adverse drug reaction was 8/100 person year. Skin rash 24(21.2%) was the most reported adverse drug reaction, followed by nausea & vomiting (16.8%), then dizziness (15.9%) while the least reported effects were dyspepsia, mouth ulcer, edema and night mare with 0.9% each. This is shown in **Table 4**.

AZT/3TC/NVP combination was found to be significantly associated with skin rash when compared with all other combinations OR= 5.35 (1.55- 20.24) and P value of 0.0045. Unlike skin rash, Nausea and vomiting was not found to be associated with AZT/3TC/NVP when compared with all other combinations, OR= 2.56 (0.78-8.96), P value = 0.14. We observed that AZT/3TC/NVP combination had the highest proportion of adverse drug reactions while TDF/FTC/NVP had the least proportion of adverse effects as in **Table 5**.

TABLE 4: DISTRIBUTION OF ADVERSE DRUG REACTIONS REPORTED

Adverse drug reaction	Frequency (%)
Skin rash	24 (21.2)
Nausea/vomiting	19 (16.8)
Dizziness	18 (15.9)
Anaemia	8 (7.1)
Fatigue/weakness	7 (6.2)
Abdominal pain	6 (5.3)
Diarrhea	6 (5.3)
Pruritis	5 (4.4)
Hyperpigmentation	4 (3.5)
Excessive hunger	3 (2.7)
Anorexia	3 (2.7)
Headache	2 (1.8)
Insomnia	2 (1.8)
Excessive appetite	1 (0.9)
Pain/tingling/numbness	1 (0.9)
Dyspepsia	1 (0.9)
Mouth ulcer	1 (0.9)
Edema	1 (0.9)
Night mares	1 (0.9)
Total	113(100)

TABLE 5: ANTIRETROVIRAL DRUGS AND REPORTED ADVERSE EFFECTS

Antiretroviral drug combination	Adverse drug reaction (number of patient who reported adverse reaction)
Zidovudine/Lamivudine/Nevirapine	Skin rash (20), nausea/vomiting (14), fatigue/weakness (5), Dizziness (4), excessive hunger (3), pruritis (3) hyperpigmentation (3), anaemia (3), abdominal pain (3), headache (2), excessive appetite (1) mouth ulcer (1) pain/tingling/numbness (1).
Tenofovir/Lamivudine/Eferverenz	Dizziness (5), skin rash (2), anaemia (1), pruritis (1), abdominal pain (1), diarrhea (2), night mares (1), nausea/vomiting (1).
Tenofovir/Lamivudine/Nevirapine	Anaemia (4), nausea/ vomiting (3), anorexia (3), fatigue/weakness (2), skin rash (1), abdominal pain (1), dyspepsia (1), dizziness (1), diarrhea (1), insomnia (1).
Tenofovir/Emtricitabine/Efervirenz	Dizziness (5), insomnia (1), diarrhea (1), edema (1).
Zidovudine/Lamivudine/Efervirenz	Dizziness (3), skin rash (1)
Alluvia	Diarrhea (1), abdominal pain (1).
Zidovudine/Lamivudine/ Alluvia	Nausea/vomiting (1), diarrhea (1).
Lamivudine/ Tenofovir/ Kaletra	Hyperpigmentation (1).
Tenofovir/Emtricitabine/Nevirapine	Pruritis (1).

DISCUSSION: Our study showed that there is no significant difference in reported ADR between male and female. This is similar to the observation of Eluwa [7] and Agu and Oparah [2]. Other earlier studies suggest that sex differences may exist in several aspects of HIV infection and its management, including differences in the tolerability of some antiretroviral drugs [8, 9]. Our study also showed that there was no case of reported ADR in those below the age of 15years. This is similar to the reports of Eluwa [7]. However, in a similar study in India, 2.15% of the reported ADR to ARVs occurred in the age group 1-20years [9]. Akuse and Garnett [10] in a study on spontaneous general ADR reporting in ABUTH Zaria, Nigeria observed that there is a gross underreporting of ADR generally in pediatrics patients. Hence, there is need for special attention in surveillance of ADRs to ARVs in these age group as this may go unreported.

The percentage of patients that reported an adverse drug reaction was highest in the first six months of commencing ARV. This is similar to previous studies [7]. Duval [11] proffered an explanation that early occurrence of ADRs is an expression of a mechanism of intrinsic intolerance than a time – dependent toxic accumulation process. Close monitoring of patients within this time frame is thus imperative to prevent the occurrence of severe ADRs. However, 16% of reported ADR occurred after 12 months of commencing ARVs. There is therefore need to intensify long term ADR monitoring in patients on ARV.

Our study also revealed that Lamivudine was the most prescribed anti-retroviral drugs; this could be because it is safer with little or no side effect [12]. Of all the fixed dose combination, AZT/3TC/NVP was the most prescribed. This combination with 2 nucleoside reverse transcriptase inhibitor is one of the World Health Organization pre-qualified fixed dose combination widely promoted as Highly Active Anti-retroviral Therapy (HAART) scale-up programme [13]. TDF/FTC/NVP was the least prescribed.

Skin rash was the most reported adverse drug reaction in this study. This is in agreement with a similar study in Nigeria [14]. However, some other studies showed otherwise where a low incidence of skin rash were reported [15, 16].

Furthermore, AZT/3TC/NVP combination was found to be significantly associated with skin rash when compared with all other combinations. Nevirapine-associated rash rate reported in this study was consistent with previous study [17]. In a similar study, Akshaya [18] reported that skin rash and aneamia were the most commonly observed ADR to ARV. They also reported that ADRs were higher with AZT/3TC/NVP combination. The use Zidovudine/ Lamivudine with Nevirapine or Efervirenz was one of the risk factors for ADR observed in a study in India [19].

Nausea/vomiting and other gastrointestinal (GI) distress were also common in this study. However, unlike skin rash, it was not found to be associated with AZT/3TC/NVP, OR=2.557 (0.78-8.96), P value = 0.14. Anemia was also reported and was observed in patients on both Tenofovir and Zidovudine based regimen.

The least reported adverse effects were edema, mouth ulcer, night mares and dyspepsia. Night mare particularly was observed with patient on efervirenz. This was also reported in a similar study [12]. AZT/3TC/NVP was associated with more adverse effects, this could be as a result of the fact that most of the patients who attended the clinic were placed on this regimen, while TDF based combination reported least adverse effect and were least in terms of number of patient placed on it. However, this is not the case in a similar study where despite the high number of patients who were on AZT/3TC/NVP, less number reported adverse effect compared to the small number of patient placed TDF based combination [7].

Most cases of dizziness was revealed to occur in patient on efervirenz, this is same with a study which revealed that efervirenz causes dizziness and other central nervous system effects as part of its adverse effect[12].

Our findings also showed that 8% reported at least one ADR. This is lower than what was reported in an Indian study of 400 patients on HAART in 2010 where the prevalence of ADRs was 17.5%[19].

CONCLUSION: In conclusion, the incidence of ADRs to ARV was 8/100 persons-year. Skin rash was the most commonly reported ADR to ARV and AZT/3TC/NVP was associated with its occurrence.

The role of therapeutic drug monitoring of antiretroviral drugs needs to be further clarified. Individualized dose regimens based on drug plasma levels may reduce the frequency and severity of some of these adverse reactions and thus improve tolerability.

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REFERENCES:

1. Chelkeba L and Abdissa G: Assessment of ART adverse reactions and determinants at a primary hospital in Ethiopia. International Journal of Basic and Clinical Pharmacology 2013; 1:208-215.
2. Agu KA, Ochei UM, Oparah CA and Onoh O: Treatment outcomes in patients receiving combination antiretroviral therapy in Central Hospital Benin, Nigeria. Tropical Journal of Pharmaceutical Research 2010; 9:1–10.
3. McNicholl I: Adverse Effects of Antiretroviral Drugs. University of California San Francisco, Available at http://hivinsite.ucsf.edu/InSite. 2012. Accessed on 8th Jan 2014.
4. Domingo P and Lozano F: Management of antiretroviral drug toxicity. Enfermedades Infecciosas Microbiologia Clinica. 2011; 29:535–44.
5. Rajesh R, Vidyasagar S, Naren P, Manju V: Safety aspects of antiretroviral therapy for management of HIV Infection. Journal of Basic Clinical Pharmacy 2010; 1:47-53.
6. Kirsten B: Adverse reactions to HIV medications. Guide for HIV/AIDS clinical care, HRSA HIV/AIDS Bureau. The AIDS Education & Training Center National Resource Center June 2012.
7. Eluwa GI, Badru T, Akpoigbe KJ: Adverse drug reaction to anti-retroviral drugs: incidence, type and risk factors in Nigeria; BMC Clinical Pharmacology 2012; 12:7.
8. Rajesh R, Vidyasagar S, Nandakumar K. Highly active antiretroviral therapy induced adverse drug reactions in Indian human immunodeficiency virus positive patients. Pharmacy Practice (Internet) 2011; 9:4855.
9. Reddy A, Lihite RJ, Lahkar M, Choudhury U and Baruah SK: A study on adverse drug reactions in HIV infected patients at a ART center of tertiary care hospital in Guwahati, India. Asian Journal of Pharmaceutical and Clinical Research 2013; 6: 102-104.
10. Akuse RM and Garnet FF: Spontaneous reporting of peadiatric adverse drug reactions in a Nigerian tertiary health center- any relationship to severity? International Journal of Pharmaceutical Science Invention 2013; 2: 05-11.
11. Duval X, Journot V, Leport C, Chene G, Dupon M, Cuzin L, May T, Morlat P, Waldner A, Salamon R, Raffi F: Antiprotease Cohort (APROCO) study group. Incidence of and risk factors for adverse drug reactions in a prospective cohort of HIV infected adults initiating protease inhibitor containing therapy. Clinical infectious diseases 2004; 39: 248-255.
12. Mc Nicholi IR: Adverse effect of anti-retroviral drugs AETC Natural Resource Center and UCSF Center for HIV information. July 2011.
13. Mudzviti T, Maponga CC, Khoza S, Ma Q and Morse GD: The impact of herbal drug use on adverse drug reaction profiles of patients on antiretroviral therapy in Zimbabwe. AIDS Research and Treatment. Article ID 434171, doi: 10.1155/2012/434171.
14. Ighovwerha O and Clair P. Sex difference in adverse reaction to anti-retroviral drug. Top HIV Med 2003; 11: 55-59.
15. Lauret C, Boureois A, Mpoudi-Ngole E, Claffi L, Kouanfack C, Mougnutou R, Nkoue N, Calmy A, Koulla-shiro S and Delaporte E: Tolerability and effectiveness of first line regimens combining nevirapine and lamivudine plus zidovudine or stavudine in Cameroon AIDS Res Human Retrovirus 2008; 24: 393 -399.
16. Forna F, Liechty CA, Solberg P, Asiimwe F, Were W, Mermi J, Behumbilize P, Tong T, Brooks JT and Weidle PJ: Clinical toxicity of highly active anti-retroviral therapy in a home-based… Journal of acquired immune deficiency syndromes. J. AIDS 2007; 44: 456 – 462.
17. Van Ooosterhout JJ, Bodasing N, Kumwenda JJ, Nyirenda C, Mallewa J, Cleary PR, Debar MP, Schuurman R, Burger OM and Zijlstra EE: Evaluation of antiretroviral therapy results in a resource poor setting in Blantyre, Malawi. Tropical Medicine and International Health 2005; 10: 464-470.
18. Akshaya SB, Chandra BS, Harlokesh NY and Sunil KJ: Incidence of adverse drug reactions in human immune deficiency virus- positive patient using highly active antiretroviral therapy. Journal of Advanced Pharmaceutical Technology & Research. 2012; 3: 62-67.
19. Modayil RR, Hurugeri A, Parthasarathi G, Ramesh M, Prasad R, Naik V and Giriyapura V: Adverse drug reactions to antiretroviral therapy (ART): an experience of spontaneous reporting and intensive monitoring from ART center in India. Pharmacoepidemiology and drug safety 2010; 19: 247-55.

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