Adverse reactions to antiretroviral drugs in patients receiving therapy in a Federal teaching hospital Southwest Nigeria

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ABSTRACT

Background: Antiretroviral drugs have proven efficacy in reducing viral load to undetectable plasma levels. Although, adverse reactions to antiretroviral drugs may cause death, prolongation of hospitalization, non-adherence and treatment failure in HIV infected persons; they are not fully documented in Nigeria. It is therefore necessary to evaluate adverse reactions of patients to antiretroviral drugs in Nigeria.

Objectives: This study aimed to document the adverse reactions to antiretroviral drugs (ARVs) in HIV-positive patients, assess their severity causality and identify the risk factors for the development of the ADRs.

Methods: With the aid of data capture form and interview, information about ADR was obtained prospectively from 51 new patients eligible to commence ARV for a period of 3 months. The retrospective arm made use of information extracted from the case notes of 137 ARV-experienced patients selected using a web-based random method from June 2009 – July 2010).

Results: Dizziness (17.40%) was the most frequently reported adverse event in both arms of the study followed by body weakness (11.85%), anemia (11.11%), rash (9.63%), pruritus (9.63%), nausea and vomiting (7.41%) and fatigue (7.41%). Majority of suspected ADRs were mild (76.5%) while only few were severe (3.9%). Female gender (p=0.0010), $CD4^+$ cells count below 200 cells/mm^3 (p=0.0005) and antiretroviral drug combination of Zidovudine + lamivudine + nevirapine (p=0.0099) were significantly associated with the development of ADRs to ARVs.

Conclusion: The most common adverse event to antiretroviral drugs in this study was dizziness followed by body weakness, anaemia, skin rash, body itching, lipodystrophy, nausea and vomiting. Most of the ADRs were mild and their development was significantly associated with female gender, $CD4^+$ cells count below 200 cells/mm^3 and antiretroviral drug combination of Zidovudine + lamivudine + nevirapine.

Keywords: Adverse Drug Reactions, Antiretroviral therapy, HIV Patients

Effets Indésirables Aux Médicaments Antirétroviraux Chez Les Patients Traités À Une Élection Fédérale Chu Sud-Ouest Nigeria

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RÉSUMÉ

Contexte: les médicaments antirétroviraux ont prouvé leur efficacité dans la réduction de la charge virale à des niveaux indétectables de plasma. Bien que, les réactions indésirables aux médicaments antirétroviraux peuvent causer la mort, prolongation de l'hospitalisation, le non-respect et l'échec du traitement chez les personnes infectées par le VIH; ils ne sont pas entièrement documentés au Nigeria. Il est donc nécessaire d'évaluer les effets indésirables des patients à des médicaments antirétroviraux au Nigeria.

Objectifs: Cette étude visait à documenter les effets indésirables des médicaments antirétroviraux (ARV) chez les patients VIH-positifs, d'évaluer leur gravité et la causalité identifier les facteurs de risque pour le développement des ADR.

Méthodes: Avec l'aide du formulaire de saisie de données et entretien, des informations sur les ADR ont été obtenus de manière prospective à partir de 51 nouveaux patients admissibles à commencer ARV pour une période de 3 mois. Le bras fait usage rétrospective des informations extraites des notes de cas de 137 patients sous ARV expérimenté sélectionné à l'aide d'une méthode aléatoire basé sur le Web à partir de Juin 2009 - Juillet 2010).

Résultats: Vertiges (17,40%) a été l'événement le plus fréquemment rapporté défavorable dans les deux bras de l'étude, suivi par la faiblesse du corps (11,85%), l'anémie (11,11%), éruption cutanée (9,63%), prurit (9,63%), nausées et vomissements (7,41%) et la fatigue (7,41%). Majorité des effets indésirables étaient d'intensité légère suspects (76,5%) alors que seulement quelques-uns ont été sévères (3,9%). Le sexe féminin (p = 0,0010), les cellules CD4 + comptent moins de 200 cellules / mm3 (p = 0,0005) et la combinaison de médicaments antirétroviraux de zidovudine + lamivudine + névirapine (p = 0,0099) étaient significativement associés avec le développement des ADR aux ARV.

Conclusion L'événement indésirable le plus fréquent aux médicaments antirétroviraux dans cette étude a été suivie par des vertiges faiblesse du corps, de l'anémie, éruption cutanée, démangeaisons du corps, la lipodystrophie, des nausées et des vomissements. La plupart des effets indésirables étaient d'intensité légère et leur développement a été significativement associés au sexe féminin, les cellules CD4 + comptent dessous de 200 cellules / mm3 combinaison de médicaments antirétroviraux et de la zidovudine + lamivudine + névirapine.

Mots-clés: Effets indésirables, le traitement antirétroviral, les patients VIH

INTRODUCTION

HIV infection affects over 34 million people worldwide.[1] Sub-Saharan Africa has over two thirds of all people infected with HIV globally.[2] Nigeria is in the second position worldwide behind South Africa with estimated population of 3.3 million of people infected with HIV and overall national prevalence of 3.6%.[1]

The use of a combination of three or more antiretroviral drugs known as highly active antiretroviral therapy (HAART) can reduce the viral load to undetectable level, dramatically reduce the morbidity and mortality and prevent the development of opportunistic infections.[3] However, HAART is associated with problems of non-adherence, drug toxicity and treatment failure. It has been discovered that about a quarter of the patients on antiretroviral therapy (ART) discontinued the treatment within the first eight months due to, adverse drug reaction or inability to adhere to treatment.[4]

The beneficial effects of drugs are coupled with the inescapable risk of untoward effects, and antiretroviral drugs are not left out. Post marketing survey and studies are important in the detection of the occurrence of new adverse effects, delayed adverse effects, drug interactions and the associated risk factors.

In developed countries, clinical trials and post marketing studies have documented adverse drug reactions from ART. For the nucleoside reverse transcriptase inhibitors (NRTI's) a notable class-wide adverse effect is mitochondrial toxicity, which is responsible for the clinical syndromes of lactic acidosis with hepatic steatosis, peripheral neuropathy, and lipoatrophy. Although this toxicity is classwide, the deoxynucleoside analog reverse transcriptase inhibitors namely stavudine (d4T), didanosine (ddI), and zalcitabine (ddC) are the drugs most frequently associated with it[5] while lamivudine (3TC), abacavir (ABC), tenofovir (TDF), and emtricitabine (FTC) are the NRTIs with low mitochondrial toxicity potential.[5] Hypersensitivity reactions have been reported in approximately 5% of patients receiving abacavir.

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) approved for the treatment of HIV include nevirapine, delavirdine, efavirenz and etravirine. The most common adverse effect associated with all NNRTIs is rash. Rash usually occurs within the first 6 weeks of initiation of therapy and has been noted in up to 35% of patients receiving nevirapine.[6] Nevirapine is also associated with hepatotoxicity[7], particularly in women with CD4 counts higher than 250 cells/mm^3 and men with CD4 counts above 400 cells/mm^3. The risk of hepatotoxicity is greatest in the first 6 weeks of therapy. However, it may occur at any time during treatment and in some cases may not be reversible with discontinuation of therapy. Rash was observed in approximately half of the patients with symptomatic hepatotoxicity.[7] Efavirenz, on the other hand, has been commonly associated with central nervous system (CNS) adverse effects, ranging from dizziness to hallucinations, insomnia, nightmares, and worsening of psychiatric illnesses.[8] These CNS adverse effects are more common during the first 2 weeks of therapy. Efavirenz also causes fetal malformations in pregnant monkeys and neuraltube defects in children of pregnant women who received it.[9] The risk of hepatotoxicity appears to be less with efavirenz as compared to nevirapine.[10]

The documented adverse effects of the protease inhibitors include nausea, vomiting, diarrhea, abdominal pain, rash and fatigue. Darunavir and tipranavir cause hypercholesterolemia and hypertrigliceridemia. Indinavir causes kidney stones and darunavir also causes hyperglycemia while ritonavir causes stone disturbance.[11]

The HIV fusion inhibitor (enfuvirtide) and the remaining classes of antiretroviral drugs are seldom used and have not been associated with severe adverse drug reactions. Injection site reactions (ISRs) are the most common adverse events reported with the use of enfuvirtide. Their manifestation includes erythema, induration, ecchymosis, nodules, or cysts and may present with symptoms of pruritus, pain, or discomfort. A needle-free drug delivery system that may decrease the impact of ISRs is under investigation.[12]

Although few studies[13, 14] carried out in Nigeria have reported suspected adverse drug reactions to antiretroviral drugs, there is paucity of data in this area of pharmacovigilance . One of the studies identified peripheral neuropathy as the commonest ADR with tenofovir-based regimen being a risk factor for its development.[13] It was also found that ADRs are less likely to occur in stavudine or tenofovir based regimen than in zidovudine-based regimen. However the finding wasn't conclusive and the severity of the ADRs was not assessed in the study. Therefore, there is the need for more studies to be carried out with a view to adding to the body of evidence of adverse drug reactions to antiretroviral drugs among HIV-positive patients on ARVs in Nigeria.

The objectives of this study were to describe the profile of adverse drug reactions of ART in HIV-infected patients, assess their severity and identify the risk factors for the development of the adverse drug

reaction.

METHODS

Study design:

This study was carried out retrospectively and prospectively. The retrospective arm of the study, which spanned one year from July 2009 to June 2010, made use of data from the case notes of patients whose hospital numbers were selected using a web-based random sampling method. The prospective arm, on the other hand, made use of intensive reporting method (active phamacovigilance) with the aid of a data capture form from July to September, 2010.

Setting:

This study was carried out at the United States Presidential Emergency Plan For Aids Relief (PEPFAR) clinic in LUTH, which is one of the PEPFAR approved centres for the HIV relief program. The clinic runs from 8am to 4pm Monday to Friday with only Wednesday and Friday for enrolment of new patients who were treatment naïve. Tuesday clinics are for children only. No consultation on weekends and public holidays. Drugs are dispensed free of charge to about 13,000 registered HIV infected patients including men, pregnant and non pregnant women and children from different parts of Nigeria on monthly basis. Average number of daily clinic attendance was 200 – 250 and the number of new patients seen on enrolment days (Wednesday and Friday) was 5-8.

Population, Sample and Sampling:

Random sampling method was used to select patients whose data were captured prospectively and retrospectively.

The sample size of 138 as minimum was calculated from a standard formula[15], however the study made use of 188 as the sample size.

Ethical consideration:

Ethical Approval for this study was obtained from the research and ethics committee of Lagos University Teaching Hospital (LUTH). For the prospective arm of the studies, a written consent was obtained from each of the patients after a clear explanation of the study to them. The retrospective arm of the study did not require informed consent. However, confidentiality of the patient's data was assured.

Inclusion criteria:

The inclusion criteria for the prospective arm of the study were: being a new patient who were ARV-treatment naive but eligible to commence ART, having age above 18 years, not pregnant at the time of recruitment and readiness to give informed consent.

Data collection:

The prospective arm of the study lasted for 3 months (July-Sept., 2010). By means of interview and data capture forms, information was obtained by Doctors and Pharmacists of the clinic from the patients who made at least three visits to the clinic during the 3 months study period. All the patients enrolled into this study were given pharmacovigilance study (PVS) number for easy monitoring and follow up.

On the other hand, the retrospective aspect of the study which spanned one year (July 2009 – June 2010) made use of information retrieved from case notes of the patients whose hospital numbers were selected by a web-based random sampling method. This was done in the central data office of the PEPFAR clinic by randomly searching for reported ADRs between July 2009 – June 2010.

Outcomes variables:

For both studies, the information retrieved included demographic data such as age, sex, weight, height, occupation, educational background, ARV drugs being used, co-morbidities, concurrently used drugs or herbs, baseline medical laboratory tests and results before the commencement of ARV drugs such as CD4+ cells count, haemoglobin concentration, liver and renal function tests as well as the adverse drug reactions observed by the patients since their commencement of antiretroviral therapy.

Data analysis:

The data generated was subjected to statistical analysis using computer software package, Statistical Package for Social Science, SPSS Version 17. The Frequency, proportion & percentage, were used to analyse the variables generated such as proportion of male to female patients, proportion of each ADR to total ADR reported and others. Naranjo's scale was used to assess causality of the adverse drug reactions, WHO Severity scale was used to assess severity and multiple logistic regression was used to assess the risk factors for the development of the adverse drug reactions.

RESULTS

Socio-demographic characteristics:

A total of 188 patients (Prospective-51; Retrospective-137) were studied.. Most of them were middle aged, literate and of female gender (table 1)

Table 1: Demographic characteristics of the patients attending APIN clinic

Demography	Prospective	Retrospective
Number of Patients (n)	51	137
Gender		
Male	21 (41.2%)	56 (40.9%)
Female	30 (58.8%)	81 (59.1%)
Age		
≤ 20 years	2 (3.9%)	1 (0.7%)
21-40 years	34 (66.7%)	100 (73%)
41-50 years	6 (11.8%)	24 (17.5%)\
51-60 years	9 (17.6%)	12 (8.5%)
Pregnancy		
Pregnant subjects	7 (13.7%)	5 (6.2%)
Non-pregnant subjects	44 (86.3%)	76 (93.8%)
Education		
Literate	48 (94.1%)	107 (78.1%)
Illiterate	3 (5.9%)	30 (21.9%)
$CD4^+$ Cells Count		
< 200	35 (68.6%)	28 (20.4%)
> 200	16 (31.4%)	109 (79.6%)

Antiretroviral regimens:
Table 2 shows the different antiretroviral drug combinations used in all the patients, the frequency and the percentages of patients that used them. The table also shows the proportion of patients that used herbal medicine and other drugs concomitantly with the antiretroviral drugs.

Table 2: Types of antiretroviral drugs and other drugs / herbs used concomitantly*

Antiretroviral therapy	Prospective	Retrospective
Zidovudine/ Lamivudine/ Nevirapine	27 (52.9%)	50 (36.5%)
Zidovudine/ Lamivudine /Efavirenz	7 (13.7%)	21 (15.3%)
Zidovudine/ Lamivudine /Saquinavir	8 (15.7%)	-
Tenofovir/ Lamivudine /Efavirenz	3 (5.9%)	15 (10.9%)
Tenofovir/ Emtricitabine /Efavirenz	6 (11.8%)	22 (16.1%)
Zidovudine/Lamivudine/Abacavir	-	15 (10.9%)
Ritonavir/Zidovudine/Saquinavir	-	12 (8.8%)
Others	-	17 (12.4%)
Herbal medicine		
Yes	6 (11.8%)	10 (7.3%)
No	45 (88.3%)	127 (92.7%)
Concomitantly Used Drugs		
None	38 (74.5%)	78 (56.9%)
Cotrimoxazole	3 (6%)	42 (30.7%)
Fluconazole	4 (7.8%)	7 (5.1%)
Others	6 (11.7%)	10 (7.3%)

* The percentages may not add up to 100% or unity because more than one combination was used in some of the patients due to treatment failure or toxicity.

Table 3 shows the suspected adverse drug events and their frequency of occurrence in both arms of the study. Dizziness was the most frequently reported adverse effect followed by body weakness, anaemia and skin rash.

Table 3: Frequency table of suspected adverse drug events on different organ system

Organ system affected	Prospective (f, %) n= 51	Retrospective (f, %) n=137	Total (f, %) n=188
Gastrointestinal system			
Mouth ulcer	1 (0.65%)	-	1 (0.37%)
Abdominal pain	1 (0.65%)	3 (2.61%)	4 (1.48%)
Nausea and Vomiting	13 (8.39%)	7 (6.09%)	20 (7.41%)
Diarrhoea	1 (0.65%)	12 (10.43%)	13 (4.81%)
Haematological system			
Anaemia	16 (10.32%)	14 (12.17%)	30 (11.11%)
Skin and appendages			
Jaundice	5 (3.23%)	2 (1.74%)	7 (2.59%)
Body itching / Pruritus	12 (7.74%)	14 (12.17%)	26 (9.63%)
Fever	5 (3.23%)	3 (2.61%)	8 (2.96%)
hyperpigmentation	-	4 (3.48%)	4 (1.48%)
Lipodystrophy	-	5 (4.35%)	5 (1.85%)
Skin eruption/Rash	15 (9.68%)	11 (9.57%)	26 (9.63%)
Central nervous system			
Dizziness	30 (19.35%)	17 (14.78%)	47 (17.40%)
Fatique	14 (9.03%)	6 (5.22%)	20 (7.41%)
Paraesthesia	3 (1.94%)	10 (8.70%)	13 (4.81%)
Weakness	28 (18.06%)	4 (3.48%)	32 (11.85%)
Headache	7 (4.52%)	3 (1.94%)	10 (3.73%)
Tremor	1 (0.65%)	-	1 (0.37%)
Restlessness	3 (1.94%)	-	3 (1.11%)
Total	155 (100%)	115 (100%)	270 (100%)

The relationship between adverse drug events and ARVs in the prospective study is shown in table 4. The most common adverse drug events: dizziness, body weakness, anaemia and skin rash were mainly associated with antiretroviral regimen of AZT/3TC/NVP.

Table 4: Relationship between suspected ADRs and antiretroviral regimen used (Prospective)

Adverse drug reactions	AZT/ 3TC/ EFV	AZT/ 3TC/ NVP	AZT/ 3TC/ SQV	TDF/ 3TC/ EFV	TDF/ FTC/ EFV	Total
Gastrointestinal tract						
Nausea and Vomiting	4	7	1	0	1	13 (25.5%)
Haematological system						
Anaemia	2	10	3	0	1	16 (31.4%)
Skin and appendages						
Jaundice	0	4	1	0	0	5 (9.8%)
Skin eruption/Rash	0	12	2	1	0	15 (29.4%)
Hyperpigmentation	0	2	0	0	0	2 (3.9%)
Body itching	2	7	2	1	0	12 (23.5%)
Central nervous system						
Fever	1	3	1	0	0	5 (9.8%)
Dizziness	4	17	1	2	6	30 (58.8%)
Fatique	2	9	0	1	2	14 (27.5%)
Paraesthesia	0	1	1	1	0	3 (5.9%)
Weakness/tiredness	1	21	3	0	3	28 (54.9%)
Headache	1	0	2	0	0	3 (5.9%)
Tremor	0	0	0	0	1	1 (1.9%)

* AZT- zidovudine, 3TC- lamivudine, EFV- efavirenz, NVP- nevirapine, SQV- saquinavir, TDF- tenofovir, FTC- emtricitabine.

Assessment of the severity and causality of the adverse drug events shows that most of the adverse drug reactions were mild but few were severe and some were moderate (Table 5)

Table 5: Assessment of severity and causality of the adverse drug reactions (Prospective)

Severity/ Causality	No of patient (n=51)	Percentage (%)
Severity		
Mild	39	76.5
Moderate	10	19.6
Severe	2	3.9
Total	51	100
Causality (Naranjo's algorithm)		
Probable	19	42.9
Possible	18	38.1
Doubtful	14	19
Total	51	100

Table 6 shows the results of the assessment of risk factors for the development of adverse drug reactions. ARVs regimen of AZT/3TC/NVP, $CD4^+$ cells count of 200 cells/mm^3 or less and female gender were risk factors for the development of ADRs.

Table 6: Risk factor assessment for development of ADRs*

Risk factor	P-value (Prospective)	P-value (Retrospective)
Age		
< 20	0.9989	-
21_30	0.9974	0.1321
31_40	0.3816	0.0793
41_50	0.9985	0.0684
51_60	0.9985	0.2395
ARV drug combinations		
AZT/3TC/NVP	0.0099	0.8551
AZT/3TC/EFV	0.9974	0.4486
AZT/3TC/ABC	-	0.0173
AZT/3TC/SQV	0.8118	-
AZT/RTV/SQV	-	0.6420
TDF/3TC/EFV	0.0616	0.8137
TDF/FTC/EFV	0.9952	-
Education		
Illiterate	0.9965	0.9945
Literate	1.0000	0.9944
CD4 COUNT		
CD4≤200	0.0005	0.0347
CD4≥200	0.9984	0.0543
SEX		
Male	0.9988	1.000
Female	0.0010	0.021

*Any of the variables with p-value greater than 0.05 (5%) is not considered a risk factor and vice versa.

DISCUSSION

This study highlights the common adverse reactions associated with the use of antiretroviral drugs in a resource poor setting. Dizziness was the most frequently reported adverse event in both arms of the study followed by body weakness, anaemia, rash, pruritus, nausea and vomiting and fatigue. The high occurrence of dizziness as an adverse event could be due to the fact that many of the antiretroviral regimens are based on efavirenz which has been found to cause dizziness.[8] Also, anaemia, nausea and vomiting are known adverse effects of zidovudine[16, 17] while rash is a common adverse effect of nevirapine[18]. Therefore, their reported high occurrence is in order since nevirapine and zidovudine are components of most of the ARV regimens used in the clinic. The ARV combination of zidovudine+lamivudine+nevirapine is a first line regimen recommended by the national guideline[19] and is commonly used in the setting except for those who could not tolerate nevirapine or are tuberculosis-infected. The high occurrence of rash reported in this study is in line with previous studies including a study from Tanzania.[20]

An important finding from our study was that development of adverse drug reaction was significantly associated with female gender, $CD4^+$ cells count below 200 cells/mm^3 and antiretroviral drug combination of Zidovudine + lamivudine + nevirapine. Although, majority of the ADRs occurred in subjects between the ages 21-40, they were not significant. Hence age was

not considered a risk factor for the development of ADRs to ARVs in this study. This is contrary to the finding from another study carried out in South Africa in which majority of the ADRs occurred in the elderly.[21]

Educational status was not found in this study to be a predisposing factor to development of ADRs to ARVs. Despite the fact that most of the patients used were literate, ADRs still occurred. However, certain workers have reported that illiteracy was a risk factor to the development of ADRs to antiretroviral drugs in their studies though they could not directly correlate the illiteracy status and the cause of increased ADRs in their study population.[22] The low CD4 count observed as a predictor of adverse drug reaction to ART confirms a similar finding in a previous study[23] However, another study[24] carried out in Nigeria could not significantly associate ADRs with age, gender and CD4 count.

Majority of the reported adverse effects in both arms of the study occurred in patients who took zidovudine-based regimens containing nevirapine or efavirenz. This result is in line with that of a previous Nigerian study[13]. Similarly, another study associated nevirapine and efavirenz with high incidence of adverse reactions.[25]

The severity score of the adverse drug reactions showed that majority of the ADRs were mild and did not require the discontinuation of the drug.

The few (3.9%) reports of severe ADRs is similar to the findings from a previous longitudinal two year study (2003-2005) on adverse events in HIV-Infected persons receiving ARVs in a large urban slum in Nairobi from where it was established that majority of the patients experienced adverse drug events, with only 6% having severe toxicity.[26] Causality assessment revealed that majority of the adverse events were either probable or possible according to Naranjo's algorithm.[27]

The association of the ART combination of AZT/3TC/NVP with development of ADRs could be due to the fact that it was the most prescribed medication.

An important limitation of this study was the lack of adequate laboratory data due to irregular measurement of viral load, $CD4^+$ cell count and other laboratory parameters to determine adverse drug reaction. For effective monitoring of adverse drug reactions it is recommended that laboratory analysis of blood samples for relevant laboratory indices like liver function test, full blood count etc, should be carried out on a regular basis (monthly or at most every three months). Viral load and CD4 count determination should be more regular at least every 3 month to facilitate correlation of their values with therapeutic outcome.

Due to association of ARVs regimen of AZT/3TC/NVP with development of ADRs, fewer patients should be placed on this combination while TDF/3TC/EFV which was better tolerated should be preferred as first line.

CONCLUSION

The most common adverse event to antiretroviral drugs was dizziness followed by body weakness, anaemia, skin rash, body itching, lipodystrophy, nausea and vomiting. Most of the ADRs were mild. ART combination of zidovudine + lamivudine + nevirapine/efavirenz, female gender and $CD4^+$ cells count of $\leq$ 200 cells/ml were risk factors for the development of adverse drug events

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