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Pattern of adverse drug reaction in HIV-infected children on anti-retroviral therapy in Jos, Nigeria

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Abstract

Background: With the recommendation of highly active anti-retroviral therapy (HAART) as the standard of care for children infected with HIV, their quality of life has improved dramatically. However anti-retroviral (ARV) drugs used in HAART regimens are often associated with adverse drug reactions (ADRs), some of which may be life-threatening. This study aimed to determine the frequency and pattern of adverse drug reactions to ARVs in children in a large treatment centre in Nigeria. Methods: HIV-infected children initiated on ART between April 2008 and March 2013 at AIDS Prevention Initiative in Nigeria (APIN)-supported HIV clinic of Jos University Teaching Hospital, Jos, Nigeria were included in the study. Each child was followed up for a period of 12 months. A thorough symptom checklist, physical examination, and laboratory evaluation were done at baseline. We reviewed them on each scheduled monthly visit and on any event-triggered visit and assessed for adverse drug reactions. Routine laboratory evaluations were repeated at 3 months, 6 months, and 12 months after initiation of ART in accordance with monitoring guidelines. Results: Three hundred and eighty-two patients were initiated on first line ART within the stated period. One hundred and ninety-eight ADRs were observed in 139 (36.4%) patients after 12 months on ART. The commonest clinical ADRs observed were pallor (41.4%), skin rash (19.7%), vomiting (7.1%), diarrhoea (3.5%), and sleep disturbance (3.0%) while the commonest laboratory ADRs were severe anaemia (16.7%), elevated alanine transaminase (10.1%), thrombocytopenia (3.0%), and neutropenia (1.5%). About 45% of the ADRs were observed in the first 3 months of initiation of ART and about 75% in the first 6 months. Conclusion: ADRs were common in HIV-infected children that were initiated on ART in this study. Regular clinical and laboratory monitoring is necessary so that HIV-infected children on ART with ADRs can be identified early and managed appropriately in order to improve their overall treatment outcome.

Keywords

HIV, Anti-Retroviral Therapy, Adverse Drug Reaction, Children, Clinical, Laboratory, Nigeria

1. Introduction

The effect of human immunodeficiency virus (HIV) has become one of the major social and medical issues of our time since the discovery of the virus. HIV is contributing substantially to the rising child mortality rates in many areas of sub-Saharan Africa, reversing years of hard won gains in child survival [1]. UNAIDS estimated that 330,000

children were newly infected with HIV in 2012, 90% of them in Sub-Saharan Africa (SSA), with an estimated 3.3 million children <15 years infected at the end of 2012. [1] In Nigeria, 67,190 children were estimated to have been newly infected with HIV in 2011, accounting for about 20% of global burden of new HIV infection in children, with an estimated 260,000 children living with HIV at the end of 2011. [2]

With the recommendation of highly active anti-retroviral therapy (HAART) as the standard of care for children infected with HIV, [3], [4] their quality of life has improved dramatically as ART regimens suppress viral replication, provide significant immune reconstitution, and have resulted in a substantial and dramatic decrease in AIDS related opportunistic infections and deaths. However the drugs used in HAART regimens are often associated with adverse drug reactions (ADRs), some of which may be life-threatening. Adverse drug reactions can affect adherence to medication and consequently the outcomes of antiretroviral therapy. [5]-[7] Although ART is generally safe and tolerable in children, several ADRs have been observed. [8]-[12] Some of the mechanisms of ART-induced ADR include mitochondrial toxicity, hypersensitivity reaction, inhibition of lipid and adipocyte regulatory proteins, and cytochrome P450 interactions. [13]-[18]

There is insufficient awareness and inadequate training about drug safety monitoring among health care workers in Nigeria. Often, ADRs go unnoticed or are not reported. This study aimed to determine the frequency and pattern of ART adverse drug reaction in children in a large treatment centre in Nigeria.

2. Material and Methods

2.1. Background of Study Area

The study was carried out at AIDS Prevention Initiative in Nigeria (APIN)-supported HIV clinic of Jos University Teaching Hospital, Jos, Plateau State, Nigeria. The program cares for patients in and outside Plateau state in the North-central zone of Nigeria. HIV care, treatment and support services are free for all patients enrolled in the program.

2.2. Study Design

This was an observational cohort study.

2.3. Ethical Consideration

A written informed consent was obtained from each parent/guardian for use of data for research. Ethical clearance was obtained from the Ethics committee of Jos University Teaching Hospital.

2.4. Patient Selection and Data Collection

HIV-infected children enrolled in the paediatric ART program and initiated on ART between April 2008 and March 2013 were the subjects of the study. HIV was confirmed by either deoxyribonucleic acid Polymerase Chain Reaction (PCR) for children <18 months or Western blot for children ≥18 months. They were initiated on ART based on WHO and Nigerian guidelines. [3], [4] A thorough symptom checklist and physical examination were done at baseline before initiation of ART. A complete blood count (CBC), liver function test (LFT), serum electrolytes, urea and creatinine (E, U & Cr), serum glucose, lipid profiles; and $CD4^+$T cell count and $CD4^+$T cell percent were determined at baseline before initiation of ART. The CBC was done with Mindray 3200 Auto Haematology Analyzer (Shenzhen Mindray Bio-Medical, Shenzhen, China) while the biochemistry tests were done with Roche COBAS C311 Auto Analyser (Roche Diagnostics, GmbH Mannheim, Germany). Flow cytometry was used to determine $CD4^+$T cell count and the $CD4^+$T percent (Partec, GmbH Munster, Germany).

At ART initiation, patients and their caregivers were counseled on the ADRs of the drugs they were initiated on and asked to return to the clinic immediately they observe any of the reactions. All the children on ART were reviewed on each scheduled monthly visit and on any event-triggered visit and assessed for adverse reactions using symptom checklist and physical examination. Routine laboratory evaluations were repeated at 3 months, 6 months, and 12 months after initiation of ART in accordance with monitoring guidelines. [4] Further laboratory evaluations were done for those with adverse reactions if necessary. Adverse drug reactions were managed according to established guidelines. [4]

2.5. Assessment of Adverse Drug Reaction

Adverse drug reaction to ART may be confused with worsening symptoms of HIV infection, new opportunistic or intercurrent infections, drug-drug interaction, or immune reconstitution inflammatory syndrome (IRIS). A patient was assessed to be having ADR if he/she developed new symptoms after initiation of ART or has a known side effect of a particular drug after excluding other causes. Laboratory adverse reactions were determined by comparing the baseline laboratory indices with subsequent measurements after initiation of ART in accordance with WHO and Nigerian guidelines. [3], [4]

2.6. Statistical Analysis

Data obtained were analyzed using EpiInfo version 3.5.1. The Kruskal-Wallis test was used for continuous variables while chi-squared test was used to test significance of associations. P value <0.05 was considered significant.

3. Result

Three hundred and eighty-two patients were initiated on first line ART within the study period. There were 190 (49.7%) males and 192 (50.8%) females. The mean age of the patients was 4.72±3.95 years. The mean age for the

males was 4.46±3.86 years and for the females 4.97±4.03 years (P = 0.20). The number and proportion of children initiated on various ART regimens are as in Table 1. Table 1 shows the characteristics of the patients.

Table 1. *Characteristics of the patients*

Characteristics	Total (%)
Sex	
Males	190 (49.7)
Females	192 (50.3)
Age group	
<1year	92 (24.1)
1-5years	152 (39.8)
6-10years	99 (25.9)
11-15years	39 (10.2)
Regimen	
ZDV/3TC/NVP	268 (70.1)
ZDV/3TC/LPV/r	8 (2.1)
ZDV/3TC/EFV	76 (19.9)
d4T/3TC/NVP	24 (6.3)
d4T/3TC/EFV	6 (1.6)

ZDV = Zidovudine 3TC = Lamivudine NVP = Nevirapine LPV/r = Lopinavir/ritonavir EFV = Efavirenz d4T = Stavudine

One hundred and ninety-eight ADRs were observed in 139 (36.4%) patients after 12 months on ART. The commonest clinical ADRs observed were pallor (41.4%), skin rash (19.7%), vomiting (7.1%), diarrhoea (3.5%), and sleep disturbance (3.0%) while the commonest laboratory ADRs were severe anaemia (16.7%), elevated alanine transaminase (10.1%), thrombocytopenia (3.0%), and neutropenia (1.5%). The drugs most commonly implicated in ADR were ZDV and NVP. Table 2 shows the pattern of ADRs observed.

Table 2. *Pattern of adverse drug reactions*

ADRs^	Total (%)	Drugs implicated
Clinical		
Pallor*	82 (41.4%)	ZDV
Skin rash/Steven Johnson syndrome	39 (19.7%)	NVP
Vomiting	14 (7.1)	ZDV
Diarrhoea	7 (3.5%)	ZDV, LPV/r
Sleep disturbance	6 (3.0%)	EFV
Abdominal discomfort	5 (2.5%)	ZDV
Headache	5 (2.5%)	EFV
Jaundice#	2 (1.0%)	NVP
Others	6 (3.0%)	
Laboratory		
Severe anaemia (Hb <8g/dl)*	33 (16.7%)	ZDV
Elevated ALT (>41IU/L)#	21 (10.1%)	NVP, EFV
Thrombocytopenia (<100,000/mm^3)	6 (3.0)	ZDV
Neutropenia (<1000/mm^3)	3 (1.5%)	ZDV
Hyperglycaemia	2 (1.0%)	ZDV, LPV/r
Hyperlipidaemia/Hypercholesterolaemia	2 (1.0%)	d4T, LPV/r

^Some children had more than one ADR
*Pallor and severe anaemia were merged
#Jaundice and elevated ALT were merged

Although more females had ADRs compared to males, the difference was not significant: females 74 (38.5%), males 65 (34.2%), P = 0.38. No significant difference was also observed in the frequency of ADRs based on the age group of the patients (P = 0.85); however older patients had more of central nervous system ADRs while younger patients had more of gastrointestinal ADRs. Most of the ADRs were observed within 6 months of initiation of ART. Eighty-eight (44.4%) of the ADRs were observed within 3 months of initiation of ART, 57 (28.8%) within 4-6 months, and 53 (26.8%) within 7-12 months. Table 3 shows the age and sex distribution of ADRs.

Table 3. *Age and sex distribution of ADRs.*

Characteristics	Total (%)	ADRs	No ADRs	*P* value
Age				0.38
<1 year	92 (24.1)	31	61	
1-5 years	152 (39.8)	58	94	
6-10 years	99 (25.9)	34	65	
11-15 years	39 (10.2)	16	23	
Sex				0.85
Female	192 (50.3)	74	118	
Male	190 (49.7)	65	125	

4. Discussion

One hundred and ninety-eight ADRs were observed in 139 (36.4%) patients giving a ratio of 0.52 ADR per patient. This was lower than what was previously reported in Nigeria [12], [19] and other parts of the world. [20]-[22] ADR rate of 45.5-71.1% was reported in India [20], [21] while a rate of 45% was reported in Switzerland. [22] Our observed rate was however similar to 34.5% reported in Brazil [23] and 39.7% reported in Manipal Karnataka, India. [24] The high rate of ADRs observed in this study and in other studies shows that ADRs are quite common in HIV-infected patients initiating ART. It is therefore very important to inform patients and their caregivers about ADRs during adherence counselling prior to initiation of ART. This will improve the knowledge of patients and their caregivers on ADRs and help to reduce the number of patients that will discontinue ART as a result of ADRs. It will also help them to promptly seek medical intervention especially if the ADR is severe or life-threatening. Healthcare workers providing care and treatment to HIV-infected children need to be trained and retrained on ADRs from ART so that they can recognize them early and manage them appropriately.

We did not observe any difference in the sex distribution of ADRs. Previous studies reported that ADRs were more common in females as a result of physiological differences between males and females and influences of sex hormones on drug metabolism. [21], [25] These studies were however done in adults in whom physiological difference between males and females and the influence of sex hormones on drug metabolism would be evident whereas in our study

90% of the patients were prepubertal children. Also we did not observe any significant difference in the frequency of ADRs in the different age groups. A previous study in Nigeria had reported that younger children experienced ADRs more than older children. [12] However, we observed that younger children had more of gastrointestinal (GI) ADRs while older children had more of central nervous system (CNS) ADRs. This may be because GI ADRs can easily be noticed by the caregiver whereas CNS ADRs are not easily noticeable and a child has to be old enough to be able to recognize them.

About 45% of the ADRs were observed in the first 3 months of initiation of ART and about 75% in the first 6 months. This is similar to what was previously reported. [12], [21], [22], [24] Most cases of ADRs are as a result of an expression of intrinsic intolerance rather than a delayed toxic accumulation process. [26] ADRs usually occur early after initiation of ART; therefore patients that are initiated on ART need to be monitored very closely especially in the first 6 months. This is even more important in children since they and their caregivers may not recognize the ADRs.

Pallor was the most common ADR we observed in our patients but less than half of patients with pallor had severe anaemia (haemoglobin <7g/dl in children aged 6-59 months and <8g/dl in children aged 5-14 years) that necessitated drug switch. Sixteen (27.1%) of the patients that developed severe anaemia required blood transfusion. Almost all the severe anaemia occurred within 6 months of initiation of ART, all were attributable to ZDV. Children that are initiated on ZDV-containing regimen should therefore be monitored very closely for anaemia with haemoglobin or haematocrit check every month especially in the first 6 months so that those with severe anaemia can be identified early and managed appropriately.

Skin rash was the second most common ADR we observed, occurring in 19.7% of our patients but only one patient had Steven Johnson syndrome. This rate was lower than what was previously reported in Jamaica [27] and United Kingdom. [28] This could be because all our patients on NVP were placed on once daily dosage in the first 2 weeks of treatment. With the increasing use of fixed dose combinations (FDCs) in many paediatric ART programs in resource-limited countries, the administration of once daily NVP in the first 2 weeks of treatment may become difficult if NVP syrup is phased out. National ART programs should therefore retain single NVP syrup or paediatric tablet in their recommended regimen. This is especially important because of the use of daily NVP prophylaxis in the prevention of mother-to-child transmission of HIV.

Elevated ALT was the third most common ADR we observed, occurring in about 10% of our patients but only 3 patients had elevated ALT >5 times the upper limit of normal which is the level that suggests hepatotoxicity. Many ARV drugs can cause hepatotoxicity but the non nucleoside reverse transcriptase inhibitors like NVP and EFV are usually implicated. This is buttressed by the fact that all the patients that had hepatotoxicity were on NVP. The 3 patients were switched to EFV which though can also cause hepatotoxicity but to a lesser extent. Co-infection with hepatitis B and C are known to increase the hepatotoxicity to antiretroviral medications. [29], [30] HIV-infected children should therefore be screened for hepatitis B and C prior to initiation of ART so that those at increased risk of hepatotoxicity will be placed on safer regimens and monitored closely.

5. Conclusion

ADRs were common in HIV-infected children that were initiated on ART in this study. Most of the ADRs were observed within 6 months of initiating ART. The most common ADRs observed were anaemia, skin rash, and elevated ALT levels. Regular clinical and laboratory monitoring is necessary so that HIV-infected children on ART with ADRs can be identified early and managed appropriately in order to improve their overall treatment outcome.

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