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Therapeutic Drug Dilemma and Pharmaceutical Mediation in HIV-Positive Children in Nigeria University Teaching Hospital

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ABSTRACT

Background: In spite of advances in the use of combined antiretroviral drugs in the management of human immunodeficiency virus (HIV) infection, drug therapy problems (DTPs) cause hindrance in the developing countries including Nigeria.

Objective: The present study assessed DTPs and pharmacists' intervention impact among HIV-positive children on combined antiretroviral therapy (cART) in the University of Ilorin Teaching Hospital (UITH), Ilorin, Nigeria. Eighty HIV-positive children on cART, attending Institute of Human Virology, Nigeria (IHVN) Clinic of UITH, and refilled their prescriptions based on Paediatric Pharmacy Order Form (PPF), were enrolled into the study.

Methodology: The DTPs encountered among those children were collected through personal interaction with the children/caregivers, patients' medical folders and PPF. The DTPs observed at baselines were tailed using pharmaceutical interventions at 2 and 4 months.

Result: The children studied were mostly males (60.0 %) with a median age of 3.16±0.74 years. Zidovudine backbone regimen was frequently prescribed first-line cART. At baseline, 39.0% of the children had DTPs with an average number of 2.3±4.7 per child. Of the 39.0% DTPs encountered, 6.4% were directly related to PPF. Dosage too low (1.3%), dose not indicated (1.3%), ineffective drugs (1.3%), inappropriate drug adherence (21.3%), adverse drug reactions (10.0%) and dosage too high (3.8%) were the DTPs observed at baseline 0-month. In the last 4th month after pharmacists' intervention, all DTPs were completely resolved among the children including those related to PPF.

Conclusion: The pharmacist's mediation in the management of DTPs significantly improved health of the HIV-positive children in this hospital.

INTRODUCTION

The burden of Human Immunodeficiency Virus (HIV) remains the highest health dilemma worldwide. HIV infects the body and ultimately leads to signs and symptoms of Acquired Immunodeficiency Syndrome (AIDS) disease, if left untreated [1]. Combined antiretroviral therapy (cART) are blended of three or more drugs taken concurrently to reduce the ability of the virus to replicate, thereby enhancing the body in combating the diseases. This also represents the gold standard of care of antiretroviral drugs for HIV-positive children [2]. The use of cART prolongs advancement to AIDS and the average survival period (Ramana *et al*.) [3]. The

antiretroviral drugs were often associated with a number of problems including pill burden and complex regimens. In addition to these challenges are the Drug Therapy Problems (DTPs). In the treatment of HIV infection, like other chronic diseases, DTPs could be adverse drug reactions, dosage too low, drug interaction, unnecessary drug therapy, need for additional drug therapy, dose not indicated, ineffective drug, dosage too high or/and inappropriate drug adherence. These problems could occur during drugs prescription, drugs handling over to patients and during administration of drugs by the patients. The clinical outcomes of DTPs are increase in patients' hospital duration, rise in healthcare costs, and decrease in patients' quality of life, aggravation of patients' well-being, occurrence of drug resistance, therapeutic failure, drug toxicities, organ damage and ultimately premature death.

Earlier researchers had revealed the importance of monitoring DTPs in HIV-positive individuals on cART. The studies of Montessori *et al*. [4]. reported that in addition to availability of cART, an effective cART programme requires adequate supervision of the potential adverse reactions to these drugs. The authors therefore opined that strategies including continual better understanding and management of current drug with adverse reactions could improve treatment duration. However, with the use of cART, some distinct adverse drug reactions have been reported by previous researchers (Subbaraman *et al*. [5]. and Borras-Blasco *et al*. [6]. Thus, preventing DTPs, healthcare cost may be reduced and lives preserved. This study was performed to assess DTPs and pharmacists' intervention impact on HIV-positive children using cART, with the view to ascertaining their well-being in the UITH, Nigeria.

METHODOLOGY

This is a prospective study carried out among HIV-positive children on cART for twelve months in the Institute of Human Virology Nigeria (IHVN) Clinic of the University of Ilorin Teaching Hospital, Nigeria between December 2015 and October, 2016. The IHVN Paediatric Clinic holds every Monday and supported by Management Sciences for Health (MSH). National Agency for the Control of AIDS (NACA) and Axios Foundation (NACA, 2013). The children enrolled ranged from 1 to 14 years, confirmed to be HIV positive through clinical and laboratory tests. The children/caregivers where be ready to be tailed up. Exclusion criteria were children with co-morbidities and those who are older than fourteen years. The study was done in the HAART Pharmacy Unit when children/caregiver visited to refill their prescriptions. The children and caregivers (for children less than eight years) were comprehensively informed about the purpose of the study and written consents/assents were obtained from them. Of the 80 children enrolled into the study, Drug Therapy Problems were collected at baseline as previously reported by Cipolle [7] and Mekonnen *et al*. [8]. The researchers (pharmacists) were able to identify DTPs among these children through personal interview of the children/caregivers, children medical folders and use of Paediatric Pharmacy Order Form (PPF).

From the baseline data of DTPs, the 31 children identified to have DTPs were tailed up for four months by the researchers (pharmacists) using detailed drug counselling on clinic visitation for prescription refill every two months. The children/caregivers were counselled on drug-drug interactions, cART adherence, simplification of drug regimens, management of cART side reactions and drug-food interactions. An assessment was made on the cART drugs supplied to the children/caregivers during prescription refills. These drugs were compared with those written on PPF to detect prescription of wrong drugs. In addition, the clinician was directly contacted by the researchers when errors were found in the PPF and the errors resolved with the clinician. In the last fourth month, a post evaluation studies were carried out to investigate the impact of the pharmacists'

intervention in resolving DTPs. Where any DTP was associated with the clinician, the clinician was contacted and the error discussed for resolution.

The following format was applied in data collection comprising four areas.

i. Biodata form: This was used to capture data on children's age, education and gender.

ii. PPF: The form was used to obtain information on cART adverse reactions and types of cART used by the children.

iii. Clinical evaluation Form: The form assessed the clinical staging of the children.

iv. Drug Therapy Problems Evaluation Form: The information on drug and patient-related problems were received using this form. Prior to the study, Ethical Review Committee of University of Ilorin Teaching Hospital approved the study.

Data analysis

Frequency distributions, means and standard deviations were the descriptive statistics computed from the questionnaires and sample profiles. Student's t-test was used for inferential statistics.

RESULTS

At the period of the study, ninety children were receiving cART in the Institute of Human Virology Nigeria (IHVN) Clinic of the institution, but only eighty (48 males and 32 females) were worthy enrolled. Among the 80 children tailed for four months, mean age at baseline was 3.16±0.74 years (Table **1**).

Most (72.6%) of the children had mild and adequate immune suppression of the disease (stages 1 and 2) and only few (27.4%) were at the severe and advanced forms of the infection (stages 3 and 4). This indicates that AIDS was uncommon among the children studied. Only eight (10%) children started treatment with the second line therapy (protease inhibitors), 93.7% on nucleoside analog reverse transcriptase inhibitors (NRTIs) and 6.3% had nucleotide analog reverse transcriptase inhibitors (NtRTIs) therapy. Lopinavir boosted ritonavir was the commonest protease inhibitor prescribed. Mean duration on cART was 2.39 years, with most children on Zidovudine-Nevirapine based regimen 57 (71.3%).

Table 1. Percentage distribution of children by WHO clinical staging and antiretroviral therapy combination.

Variable	N (%)
WHO Clinical Staging	
Stage 1	25 (31.3)
Stage 2	33 (41.3)
Stage 3	16 (20.0)
Stage 4	6 (7.4)
Combined Antiretroviral Therapy	
Zidovudine-Nevirapine based regimen	57 (71.3)
Zidovudine-Efavirenz based regimen	14 (17.4)
Zidovudine-Lopinavir/ritonavir-based regimen	1 (1.3)
Tenofovir-Lopinavir/ritonavir-based regimen	4 (5.0)
Tenofovir-Efavirenz based regimen	1 (1.3)
Abacavir-Lopinavir/ritonavir based-regimen	3 (3.7)

The prevalence of adverse reactions to cART was 10.0% (Table **2**).

Table 2. Adverse reactions of cART drugs among the children.

Adverse Reactions	N (%)
Fever	1 (1.3)
Rashes	3 (3.8)
Reddish eye	1 (1.3)
Body weakness	1 (1.3)
Abdominal pain	2 (2.5)

The prominent effect observed in the children was rashes followed by abdominal pain. Others include fever, body weakness and reddish eye. These reactions were frequent to all the regimens used for the children.

Table 3. Drug therapy problems of HIV infected children in UITH, Nigeria.

Types of DTP Encountered	*Baseline[a]	2 Months[b]	4 Months[c]	P-Value
Unnecessary drugs	-	-	-	
Additional drugs	-	-	-	
Ineffective drugs	1(1.3)	-	-	
Dose not indicated	1(1.3)	-	-	
Dosage low	1(1.3)	-	-	
Drug adverse reactions	8(10.0)	-	-	
Dosage high	3(3.8)	-	-	
Inappropriate adherence	17(21.3)	2(2.5)	-	0.027[ab]

The occurrence of DTPs observed at baseline among the children is provided in Table **3**. of the 80 HIV-positive children on cART, 39% (31) had DTPs. The DTPs recorded were ineffective drug, doses not indicated, dosage too low, adverse drug reactions, dosage too high and non-adherence. Non-adherence 17 (21.3%) was the commonest DTP noted in these children, while dose related problems had the least. About 6.4% of the DTPs detected were associated with Paediatric Pharmacy Order Form-PPF (clinicians 'errors observed while filling the form for pharmacy refills), others were obtained during children/care givers' interview (patients-oriented problems). Thirty-one children had 72 DTPs with the incidence rate of 39%. Children identified to have had 1, 2 or 3 DTPs were 2 (6.5%), 17 (54.8%) and 12 (38.7%), respectively. The average DTPs identified per child was 2.3±4.7.

DISCUSSION

World Health Organization (WHO) Clinical Staging System in children is proposed for baseline evaluation of patients care [9]. Puthanakit *et al*. [10]. showed that progression to moderate or high immune suppression is common among older HIV-positive children. While about 50% developed relative immune suppression, 20% had critical immune suppression. Similar to the present study, was the report of Eticha *et al*. [11] that majority (62.2%) of the children were males. The various cART utilized in the setting of this study was contrary to the studies conducted in Port Harcourt, Nigeria by Okafor *et al*. (2014) in which abacavir based regimen was substituted for stavudine based regimen. Nevirapine-associated rashes was the commonest drug adverse reaction that occurred in this study. This was in agreement with an earlier report of Modak *et al*. [12]. whereby rashes had the largest percentage of adverse reactions. Also, Thuret [13] and Parsode *et al*. [14]. reported that Nevirapine based regimen is related with rashes. Unlike the study of Subbaraman *et al*. in which hepatotoxicity was the highest effect observed among the patients. Other side reactions identified were abdominal pain, fever, red eye and body weakness. These results conformed with Chatterjee *et al*. (2012) who reported transient maculo-papular skin rashes, clinical jaundice and peripheral neuropathy as major adverse reactions.

The prevalence of skin rashes (3.8%) observed in this study was lower than that of Pierre *et al*. [15]. In Jamaica with 12.9% and 9.0% in India by Shah [16]. Almost three quarters (71.3%) of the children involved in this study were on a nevirapine-based regimen, as part of the recommended first-line paediatric cART in Nigeria. This finding corroborates with the result obtained by Subbaraman *et al*. [5]. who reported that Nevirapine is frequently used Non-Nucleoside Reverse Transcriptase Inhibitor in poor-resource countries, being cheap compared to efavirenz. The low prevalence of nevirapine-induced rashes observed in this study may be due to long-term use of this drug and its gradual decrease over time of therapy. This also

validates the continual use of nevirapine-based regimen for cART initiation. This incidence was lower than the rates reported among HIV-positive children in Nigeria by Oshikoya *et al*. [17]. with 47.5%, Srikanth *et al*. [18]. observed 34.1% in Kadapa, Sharma *et al*. [19]. noted 71.1%) in India while Meneze *et al*. [20]. recorded 34.5% in Brazil. This shows that the range of adverse reactions to cART vary in the same country, from one nation to another and between developed and developing countries. The variations in the rates may be explained by the differences in the methodology of the studies, the population studied, the cART regimens prescribed, duration on cART and the definition of adverse drug reactions used in each study.

Of the 80 HIV-positive infants on cART, 31 had DTPs. The DTPs observed were ineffective drug, doses not indicated, dosage too low, adverse drug reactions, dosage too high and non-adherence. Non-adherence was the commonest DTP observed in these infants and the least was found in dose related problems. About 6.4% of the DTPs observed were associated with Pediatric Pharmacy Order Form-PPF (clinicians 'errors observed while filling the form for pharmacy refills), others were obtained during children/care givers' interview (patients-oriented problems). The incidence rate of DTPs was 39%. This value was lower compared with the observation of Bello *et al*. (2014) in Nigeria among HIV adult population who reported high incidence rate of DTPs of 90.6%. Furthermore, the studies by Mok and Minson [21] and Carcelero *et al*. [22]. revealed high incidence rates of DTPs. The reasons for low DTPs compared with adults in other settings in this study could be attributed to relatively low children number used. Also, due to larger number of HIV-positive adult population, the clinicians were always hurrying to attend to the patient consultations during the clinic days; hence errors could occur when filling the standardized prescription forms.

The pharmacists' intervention was successful as all the DTPs related with the use of PPF were eliminated at the first follow up (2 months). Also, non-adherence to medications only was eliminated at the second follow up (4 months), while other DTPs were all eliminated at first follow up. The interventions conducted on PPF with the clinicians were through the pharmacists in charge of the Highly Active Antiretroviral Therapy (HAART) Pharmacy. Counselling of children/caregivers on drug adherence and adverse drug reactions were carried out by the researchers (pharmacists). Children/caregivers' counselling (67 out of 72, 93.6%) was frequent intervention conducted by the researchers. Consulting the prescriber for dose related problems and change of drugs (5 out of 72, 6.4%) were the second most important interventions accomplished by the pharmacists to resolve and prevent DTPs. At the last fourth month, all the problems were completely resolved.

Non-adherence was common DTPs observed in this study, whereas the reports of Bello *et al*. [23] in Nigeria and Nicolas *et al*. [24]. in Germany revealed generic drug substitution as the commonest DTP encountered. The rationale could result to the fact that children do not make choice of their drugs (generic or branded) as far as the drug is palatable with less pill burden. The success of the pharmaceutical intervention conducted by the researchers/pharmacists in charge of HAART to resolve DTPs in the present study was very great (100%) compared to other studies of Nwaozuzu *et al*. [25]. with 55% and 61.2% for Bello *et al*. [23].

CONCLUSION

The pharmacists' mediation in the management of DTPs significantly improved health of the HIV-positive children in this hospital.

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