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Evaluation of Stavudine (d4T)-Containing Antiretroviral Regimen on Serum Lipids in HIV-Infected Children in North West, Nigeria

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Abstract: **Effective evaluation of HIV antiretroviral regimen is very crucial for the achievement of an increased level of CD4 Count and reduction in the viral replication. The present study was aimed to evaluate the effect of stavudine-containing antiretroviral regimens on serum total cholesterol and triglycerides in HIV infected children in north-western Nigeria. Sixty HIV-infected children were divided into four (4) groups of fifteen (15) children each; 0-11 months, 1-4 years, 5-7 years and 6-11 years and 60 age matched HIV non-infected children were also recruited for the study. A structured questionnaire was used to obtain information on co-morbid medical conditions and mode of HIV transmission while serum total cholesterol and triglycerides were evaluated before treatment initiation and three months after. Mother-To child transmission of HIV (MTCT) was the major route of HIV infection in the HIV infected children with majority of the children been mixed fed. Total cholesterol levels were significantly decreased ($p<0.05$) while triglycerides were significantly higher ($p<0.05$) when compared with control groups at baseline. Three months after treatment initiation, a significant increase ($p<0.05$) was observed in the level of total cholesterol in the older age groups while a significant decrease was observed in total triglycerides level ($P<0.05$) to non infected levels which was more pronounced in the 0-11 months and 1-4 years age groups of the HIV-infected children when compared to baseline values. Evaluation and Monitoring of metabolic abnormalities in children on d4T-containing antiretroviral regimes can prevent premature treatment failure, poor adherence and drug induced hyperlipidemia.**

Keywords**: HIV/AIDS; Antiretroviral; Stavudine; Total Cholesterol; Triglycerides; Mother-to child transmission of HIV; North western Nigeria.**

I. INTRODUCTION

In the 1990s, many gains were achieved by the WHO/UNICEF's child survival programmes in immunization, oral rehydration therapy, promotion of breastfeeding, good weaning practices and growth monitoring. However, the HIV/AIDS pandemic is threatening these gains, felt more intensely in the sub-Saharan Africa [1]. HIV infection is a major contributing factor to childhood diseases and mortality [2]. An estimated 100,000 HIV-infected infants are born each year and 1.2 million children have been orphaned [3]. The HIV/AIDS pandemic continues to spread around the world at an alarming rate, and the number of people with the disease keeps growing significantly diffuse. There are 33.3million people globally living with HIV, out of which 22.5 million are living in Sub-Sahara Africa [4].

The vast majority of children (more than 90%) acquire the infection through mother-to-child transmission (MTCT) [5]. The rate of MTCT of the virus is affected by many factors including high viral load, low CD4 lymphocytes counts and related to increased exposure to maternal blood. Unscreened blood and blood products, infected medical or surgical equipments and certain traditional medical practices also put children at risk of being infected. An unknown but not inconsiderable number of children may become infected with HIV through sexual exploitation or abuse [1].

The advent of potent antiretroviral Drugs (ARVs) in 1996 has enabled the transformation of HIV from fatal to a chronic disease. Although not a cure, ARVs have dramatically reduced mortality and morbidity, prolonged lives and improved the quality of life of many [6]. ARVs are classified as Nucleoside or (nucleotide) reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). ARVs have been developed to target specific stages in the viral replication cycle [7]. An improved understanding of HIV pathogenesis has demonstrated the need for aggressive ARV therapy. The only regime potent enough is high active antiretroviral therapy (HAART) which involves combination of at least three ARVs [6]. NRTIs act as DNA chain terminators by blocking viral DNA replication [8]. They vary widely with regard to ARV activity, rates which viral resistance occurs and adverse effects [9]. Several adverse effects have been documented that are peculiar to each class of ARVs and are causing increasing concern in ARV drug use. Such effects include hepatic toxicity, derangements in lipid metabolism, osteoporosis and body habitus changes to mention a few [10].

This study therefore intends to evaluate the effect of NVP-containing ARV therapy on lipid profile in HIV infection in children as a basis for evaluation and monitoring of treatment before and during ARV therapy.

II. MATERIALS AND METHODS

A cross-sectional study was conducted on HIV infected children attending the paediatric HIV clinic of Murtala Muhammad Specialist Hospital. A total of 60 HIV infected children and 60 HIV non infected age matched children were used as controls. The subjects were grouped into four groups on basis of age, 15 subjects each; 0-11 months; 1-4 years; 5-9 years and 10-12 years. Blood samples were obtained from study subjects before NVP-containing regime initiation on basis of biochemical evaluation, CD4 percentage and clinical evaluation. Blood samples were collected three months after for evaluation of serum cholesterol and triglycerides level. Blood samples (3mls) was obtained from infected and control subjects, it was delivered into plain blood containers and allowed to clot. After clot retraction, blood was centrifuged at 3000 rpm for 5 minutes and sera was harvested into clean tubes and stored at 2-8 C prior to analysis. Sera obtained were used for estimation of serum total cholesterol by the enzymatic colorimetric method [11] and triglycerides by the glycerol phosphate oxidase method [12]. Statistical analysis was performed using the SPSS version 16.0 software.

III. RESULTS

The mode of transmission in the HIV infected children are shown in table I. Findings of the study revealed that ninety three percent (93.33%) of HIV infected children acquired the infection through Mother-To-Child Transmission with 1.67 % acquiring the infection through blood transfusion. The Studied children did not have any co-existing medical condition observed. The mean ± Standard deviation of serum total cholesterol and triglycerides of HIV infected and control groups for different age groups at baseline and three months after treatment initiation are shown in table II and table III respectively. The total mean triglycerides of the HIV infected groups (170.5±89.6) were significantly higher ($P<0.05$) while mean total cholesterol levels (122.2±38.0) were significantly lower ($P>0.05$) when compared with control groups at baseline. Three months after treatment with d4T-containing regime of antiretroviral therapy, a significant increase ($P<0.05$) was observed in the total mean serum total cholesterol levels (139.3±48.9) while the mean total levels of serum triglycerides was significantly decreased ($p<0.05$) to non infected levels when compared with their baseline values.

A significantly higher level ($p<0.05$) of serum triglyceride were observed in all the age groups while a significantly higher ($p<0.05$) levels of total cholesterol was observed in the all age groups except 0-11 months group when compared to their age matched controls. The same level of total cholesterol was observed in all the age groups at base line. However three months after d4T-antiretroviral regime a significantly higher total cholesterol levels ($p<0.05$) were observed in the older age groups 5-9 and 10- 12 years. A significantly lower levels of triglycerides ($p<0.05$) were observed in the 0-11 months, 1-4 years and 10-12 years age groups after three months treatment when compared to their baseline values.

TABLE I: MODE OF TRANSMISSION OF HIV IN HIV INFECTED CHILDREN

Mode of transmission	Number	Percentage (%)
Mother-to-child	56	93.33
Transfusion	1	1.67
Undetermined	3	5.00
Total	60	100

TABLE II: EFFECT OF d4T-CONTAINING ANTIRETROVIRAL REGIME ON TRIGLYCERIDE LEVELS OF HIV INFECTED CHILDREN

Age group	Mean Baseline values mg/dl	Mean 3 months treatment mg/dl	Mean Non infected mg/dl
0-11 months N-15	137.8±101.8[f]	93.3±57.3[a]	84.0±34.6
1-4 years N=15	213.3±90.6[f]	119.9±31.2[a]	114.0±29.6
5-9 years N=15	175.9±80.2[f]	161.6±58.3[b]	124.0±32.7
10-12 years N=15	155.0±62.6[f]	130.5±60.9[a]	120.0±39.3
Total	170.5±89.6	126.6±57.0	126.5±18.7

n=60 Results expressed are mean±SD

[f] (comparison with non infected aged matched groups; $p<0.05$); [a] (comparison with baseline values of each age group; $p<0.05$); [b] (comparison with baseline of each age group; $p>0.05$)

TABLE III: EFFECT OF d4T-CONTAINING ANTIRETROVIRAL TREATMENT ON TOTAL CHOLESTEROL ON HIV INFECTION IN CHILDREN

Age group	Mean Baseline values mg/dl	Mean 3 months treatment mg/dl	Mean Non infected mg/dl
0-11 months N-15	123.9±38.1[b]	106.8±36.5[e]	103.0±34.2
1-4 years N=15	122.8±30.1[b]	142.8±32.5[g]	155.4±22.2
5-9 years N=15	126.0±42.5[b]	164.4±62.0[g]	197.0±42.0
10-12 years N=15	122.9±38.7[b]	144.1±39.5[g]	160.0±34.6
Total	122.2±38.0	139.3±48.9	156.0±33.5

n=60 Results expressed are mean±SD

[b] (comparison with non infected age matched groups; $p>0.05$); [e] (comparison with baseline values; $p>0.05$); [g] (comparison with baseline values; $p<0.05$)

IV. DISCUSSION

The understanding of HIV disease and the modes of management continue to change as new drugs become available. One of the challenges which accompany implementation of antiretroviral therapy in settings with limited resources is the monitoring and evaluation of metabolic complications or toxicities [13]. Complications at onset of antiretroviral therapy can lead to premature interruption or poor adherence to treatment, evaluation therefore becomes a heavy task. The present study revealed that over ninety percent of HIV infected children became infected through Mother-To-Child-transmission. This finding correlates with UNAIDS [1] data which showed that the vast majority of children under 13 years of age (more than 90%) acquired HIV infection through Mother-to-child-transmission. CDC guidelines [14] also showed that HIV trends by transmission group in children are primarily vertically acquired. A reason for this finding in this setting is probably due to high burden HIV in the study area and many mothers don't seek medical attention because of fear of stigmatization. Studies have shown an increased risk of transmission of HIV from infected mothers to babies through breast milk, therefore avoidance of breast feeding lowers the risk of HIV transmission from an infected mother [15]. Evidence has shown that mixed feeding is associated with higher risk of HIV infection and consequently increased metabolic complications caused by HIV virus [16]. Replacement feeding causes bruising to the intestinal tract of the child thereby facilitating absorption of the HIV virus found in breast milk into the child's circulatory system. Contrary to the findings of this study most of the infected children are being breast fed thereby increasing risk of metabolic complication. Removal of an infant from breast milk is culturally and hygienically not feasible.

Triglycerides studied in the present study were significantly higher while total cholesterol levels were lower at baseline. Three months treatment with d4T-containing antiretroviral therapy resulted in a significant decrease in triglyceride and increase in total cholesterol to almost normal value which was more pronounced in the younger children (0-4years of age). Impaired lipid metabolism as evidenced by elevated triglyceride caused by HIV disease itself has been reported by Hadigan [17]. This often results to increased hepatic triglyceride leading to hepatic steatosis hence diminished hepatic function resulting in mitochondrial toxicity [18]. A lower level of triglycerides and higher levels of cholesterol observed in the present study shows ameliorative effect of the stavudine containg antiretroviral therapy and an evidence of improved immunological response of the HIV infected children.. Among the Nucleoside reverse transcriptase inhibitors (NRTIs) stavudine (d4T) is most commonly associated with hyperlipidemia in adults [19]. Findings of the present study at baseline correlates well with this report as a higher level of total cholesterol was observed as the children grow older. The variation of total cholesterol status with age group might have resulted from changes of body habitus with age, feeding habits and diet, immune reconstitution and viral suppression of child during treatment. Nevarapine (NVP) and to a lesser extent efavirenz (EFV) were reported to be associated with increased HDL-C levels over time and have potential antiatherogenic effects [19].

V. CONCLUSION

It can be concluded that stavudine containing ART regimes were able to revert HIV infection associated metabolic changes of high triglyceride and low cholesterol levels in the HIV infected child. However, older children are at risk of developing hyperlipidemia which the younger children are at risk of developing hepatotoxicity (hepatic steatosis). However, ART can be well tolerated and can improve the general well being and quality of life of the HIV infected child. Its side effects can be managed along with other childhood diseases. However it is worth noting that a HIV infected child is exposed to antiretroviral drugs very early in life and is therefore at risk of facing lifelong treatments. Evaluation and monitoring of children on antiretroviral therapy would therefore have positive gains.

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