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Clinical and Immunological Efficacy of Highly Anti-Retroviral Therapy on Paediatric Patients at the University of Abuja Teaching Hospital, Gwagwalada

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Abstract

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A two year prospective study of children living with HIV/AIDS and on treatment with highly active anti-retroviral therapy (HAART) at the paediatrics out-patients special treatment clinic (POSTC) of the University of Abuja Teaching Hospital (UATH) Gwagwalada, was carried out to determine the clinical and immunological efficacy of HAART after the first 12 months on treatment. One hundred and seventy four patients comprising of 91 (52.3 percent) males and 83 (47.7 percent) females (m:f ratio1.2:1) who were eligible for treatment, were commenced on HAART. Their mean age (± SD) at recruitment was 4.9±1.4 years. The baseline weight of the patients increased by 30.2% from 12.7± 3.5kg to 18.2 ± 3.9kg with a net gain of 5.5kg after one year treatment on HAART. This increase reflects a shift from a baseline growth curve of less than 5th centile for age using the National Center for Health Statistics (NCHS) growth chart at commencement of HAART, to 25th centile value after 12 months of treatment. The mean height and body mass index (BMI) similarly showed remarkable increases from mean recruitment values of 99.2±24.8cm and 12.5±3.2kg/m^2 to 111.9±25.5cm and 18.0±2.7kg/m^2 respectively. CD4 cell count and its percentage increased from a mean baseline recruitment value of 243±104.2 cells/ml and 11.7 percent to 788.5±217.0 cells/ml and 28.8 percent respectively after the same duration of HAART. Positive correlations were seen between CD4 cell count and bodyweight ($r = 0.64$, $p < 0.01$), and between CD4 cell count and BMI and ($r = 0.65$, $p < 0.01$). The result shows effective and good outcome of HAART on paediatric HIV/AIDS patients. From the findings, it is recommended that there should be rapid scale up of HAART for paediatric HIV/AIDS patients across the country

Introduction

Before the advent of modern anti-retroviral (ARV) therapy, untreated HIV patients demonstrated continuously declining CD_4 cell count with increasing plasma level of circulating HIV ribonucleic acid (RNA), increased vulnerability to opportunistic infections and subsequent death.[1-3] However, since the mid-1990's, there have been major advances in the medical management of HIV disease with use of ARV drugs which not only suppress circulating HIV RNA with rebound increase in CD_4 cell count, but also dramatically reduce HIV related morbidity and mortality.[4-7] The treatment of people with HIV disease requires daily regimen of at least three or more drugs from two or more different groups, otherwise called 'Highly Active Antiretroviral Therapy' (HAART).[5,8] The use of these drugs combinations requires schedule dosing protocol that needs not only coordinated dietary intake but also highly committed paediatric caregivers and good adherence counseling practice to prevent emergence of drug resistance strain.[6,9-11]

Highly active antiretroviral therapy is currently the standard mode of treatment of HIV infection for achieving the best possible suppression of viral replication.[6,10] The goal of such therapy is to stop and reverse progression of the disease by sustaining maximum viral suppression, promote and restore normal growth and development, prevent opportunistic infections and improve the quality of life.[7-12] Good response to HAART also requires a drop of about 1 log (10 + fold) of viral load in the

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first week, 2 log by 2-3 weeks i.e. 400 copies/ml of blood in 2-3 weeks, and, < 50 copies per ml by 6 months of commencement of HAART.[13] This is usually followed by improvement in the clinical, immunological, and anthropometric profile of the patients. [13] Monitoring and evaluation of paediatric patients on HAART requires among others, clinical, anthropometric (weight, height/length, head circumference), immunological (CD_4 cell count and CD_4 percent) as well as virological (viral load) evaluations.[8,10,12] Such evaluations are needed at regular intervals for assessing the adequacy of the therapy as well as early detection of treatment failure.[6,9-12]

Several studies on both adult and children on HAART have shown dramatic improvement in both the clinical and anthropometric indices as well as immunological and virological profile of patients with good adherence.[14-19] Such improvement is evident from the study of Liotta *et al* [14] in their one year review of paediatric patients on HAART in a resource limited setting. They noted that after six months of commencement of HAART, 40% of their patients achieved viral load of below 400 copies/ml, while 60% had a CD_4 percent higher than 24%. Medecins Sans Frontieres study [15] obtained another excellent outcome in children placed on HAART in yet another study in a resource limited setting in seven Africa countries. They reported a median 10% and 12% gain in CD4 cell count within 6 and 12 months of commencement of HAART. Massaquoi *et al* [16] in their study among Kenyan children on HAART, noted a net gain in bodyweight of 1.8kg and 5kg after six and 12 months' therapy respectively.

In a longitudinal pilot study involving adult population in Nigeria, Osaro[17] observed a net gain in weight and body mass index (BMI) of 13.3kg and 5.1kg/m^2, respectively among HIV infected persons after 48 weeks of treatment on HAART; the net gains also correlated positively with the CD4 cell count. In the same study, the incidence in underweight was found to decline from a baseline value of 46 percent to 1 percent after the same duration of treatment. A study by Amenyah and co-workers [18] in another group of adult population in Ghana noted a 2.5 percent increase in bodyweight, 15 percent increase in BMI, and 78.9 percent increase in CD4 cell count after 6months treatment with HAART. While many other studies reported improvement in bodyweight and CD4 cell count on commencement on HAART,[14-19] Maia et al[20] observed loss in subcutaneous fat, which was clinically interpreted as weight loss in adult population they studied. This weight loss they observed was however more pronounced in patients started on mono and dual ARV drugs than those on HAART.

Since no such study has been reported in children in Nigeria, the present study was undertaken to examine the clinical and immunological efficacy of HAART in HIV infected children after one year of administration of these drugs at UATH. It is envisaged that the outcome of the study will assist health care providers in evaluating and predicting the efficacy of HAART within a given time period as well as providing base line information for other workers.

Materials and Methods

This prospective study was conducted at the paediatric outpatient special treatment clinic (POSTC) of the University of Abuja Teaching Hospital (UATH), Gwagwalada over a two-year period, November 1, 2005 to October 31, 2007. The hospital is a 350-bed capacity tertiary health institution sub-serving Federal Capital Territory (FCT), Abuja and neighboring states of Nassarawa, Kogi, Benue, Niger, and parts of Kaduna. The paediatric outpatient unit of the hospital is made up of general paediatric outpatient and POSTC for HIV/AIDS children. It started offering free paediatric HIV/AIDS services from April 2005, courtesy of United State government through President's Emergency Plan for AIDS Relief. Deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) test for early diagnosis of HIV infection in children less than 18 months was also made available to the center.

The subjects were paediatric patients aged two months to 15 years who were attending POSTC and were positive for HIV infection either by serological method for children from 18 months and above, or by both serology and DNA PCR test for those less than 18months. They also met WHO/ National guideline for commencement of HAART in children.[10,12,21] Sera obtained from the patients were screened for the presence of HIV 1 or 2 antibodies using commercially available recombinant antigen based double rapid test (STATPAK by *Chembio Diagnostic System INC*, New York, and *Determine* by Abbot Laboratories, Japan) with sensitivity and specificity of 100 percent. DNA PCR test amplifies and detects the HIV pro-viral DNA sequences within the mononuclear cells in the blood, and it is a gold standard test for diagnosis of HIV infection in infants in developed countries.[10,12] The test is 100 percent sensitive by 4 to 6 weeks of postnatal life.[10,12] Excluded from the study were all HIV exposed but not infected infants, and those positive infected children who did not meet WHO/ National guideline for commencement on HAART.

Patients were recruited over a 12 months period, and follow up was also a period of 12 months. At recruitment, clinical and baseline investigations were carried out. These included: general physical, anthropometric measurements (weight, length/ height), immunological assessment (CD4 cell count and CD4 percent), and haematological profile (full blood count, and differential). WHO clinical staging, [10,12,21] an international four stage system that classifies the severity of HIV infection in children was applied for all recruited subjects (Appendix).

While weight was taken using beam weighing scale accurate to the nearest 0.01kg, recumbent length was carried out with infantometer made up of a flat board with a fixed head plate and movable foot plate. Height was taken with Marsden standiometer (supplied by Marsdens, 01-289-1066) and accurate to 0.1cm. CD4 cell count was carried out using automated Partec Cyflow easy Count Kit (*Partec Code No 05-8401 Western Germany*). For the purpose of this study, only the clinical, anthropometric and immunological profiles of the recruited subjects were recorded subsequently at 3, 6, and 12 month intervals. Viral load, a very important and good monitoring assay was not carried out for all patients because of cost. Only few patients with evidence of immunological failures were subjected to viral load testing. Body weight and height/length comparisons were carried out using NCHS growth chart. [22]

The sample size was calculated using this formular by Araoye. [23]

$n = z^2 pq/d^2$; where n = the desired sample size (when the population is greater than 10,000).

z= the standard normal deviate, usually set at 1.96 corresponding to 95% confidence level.

p= the proportion in the target population estimated to have a particular characteristics. For the present study, the average prevalent rate from two studies in countrywas used, (1.5% from Angyo *et al* [24] and 5.7% from Oniyangi *et al* [25]). The average of the two being 3.6%.

q = 1.0-p .

d = degree of accuracy desired, set at 0.05.

With the above formula a sample size of 200 was generated. With the studying population of less than 10,000, the final sample estimate (nf) was further applied in the calculation of sample size:

nf = n/1+(n)/(N)

where:

nf = the desired sample size when the population is less than 10,000.

n= the desired sample size when the population is more than 10,000.

N = the estimate of the population size.

The minimum sample size calculated = 166.

Allowing for 10% attrition risk = N/1-f.

Where: N = Calculated sample size. f= 10% non response = 0.1.

Minimum sample size calculated was 174.34, approximately 174.

Data entry and analysis was conducted using SPSS program version 7.5 that provided frequency distribution, means, standard deviations, correlation co-efficient, $\div^2$ test of significance and p values.

Results.

A total of 174 patients comprising 91 (52.3 percent) males and 83 (47.7 percent) females were enrolled and started on HAART during the study period. The mean age and body weight at recruitment were 4.9±1.4 years and 12.7±3.8kg, while that of CD_4 count and its percentage were 243.9±104.2 cells/ml and 11.7 percent, respectively (Table 1). More than 50 percent of the patients had WHO clinical stage 3 diseases, and BMI of 12.5±3.2kg/ m^2. Both the mean weight- and height -for-age of the subjects at

Table 1

Characteristics of Recruited Patients

Variables	*Males*	*Females*	*Whole study population.*
Sex	91	83	174
Age in years	5.2 ± 0.7	4.6 ± 2.0	4.9 ± 1.4
Weight (Kg)	13.1 ± 1.8	12.3 ± 5.2	12.7 ± 3.5
Height (cm)	103.4 ± 12.4	95. 7 ± 37.2	99.2 ± 24.8
BMI (Kg/m^2)	13.1 ± 1.8	12.3 ± 3.7	12.7 ± 3.1
CD_4 cell count (cells/ml)	216.7 ± 104.2	231.2 ± 109.7	243.9 ± 106.7
CD_4 %	11.3	11.7	1.5
WHO clinical staging	3	2	3

Values are means ± standard deviations BMI: Body Mass Index

recruitment were below the 5th centile for their age using NCHS growth chart indicating severe wasting and stunting.

Anthropometric Changes during 12 Months' Treatment with HAART.

Table IIa shows the anthropometric changes after one year treatment with HAART. There was a steady increase in the mean values of all the variables studied (the bodyweight, the length/height, BMI, CD4 cell count and its percentages). Body weight increased from mean value of 12.7±3.8kg to 18.2±3.9kg with a net gain of 5.5kg, while height and BMI also showed a steady increase from baseline values of 99.2±24.8cm to 111.9±25.5cm, and 12.5±3.2kg/m^2 to 18.0±2.3kg/m^2. When percentage increases in all the parameters studied were considered, there was 9.9 percent increase in bodyweight at three months and 30.2 percent increase by one year. The mean height also increased from 2.1 percent at three months to 11.3 percent at the end of one year. Using NCHS growth chart, the weight- for- age increased from below the 5th centile growth curve to 25th centile, while the length/height also increased from 5th centile to 15th centile using the same NCHS growth curve.

Changes in CD4 cell count and WHO Clinical Staging during 12 Months' Treatment with HAART

CD_4 cell count and its percentage showed a steady increase from 243.7±104.2 cells/ml to 788.5± 21.7cells/ml and from 11.5 percent to 28.8 percent after one year of treatment with HAART (Table 11b). The CD_4 cell count increased by 57.3 percent to 69.1 percent at 6 and 12 months respectively, its percentage also increased from 48.2 percent at 6 months to 59.4 percent at the 12th month. The exception to this increase was the WHO clinical staging which showed a decreasing trend from stage 3 to stage 1 disease after a year treatment. The decrease was an impressive one signifying

Table IIa

Anthropometric Changes during 12 Months' Treatment with HAART.

Variable	*Values at recruitment*	*Values at 3 Months (% increase)*	*Values at 6 Months (% increase)*	*Values at 12 Months(% increase)*
Age (years)	4.9±1.4	5.0±2.3	5.3±2.4	5.9±1.7
Weight(kg	12.7±3.2	14.9±4.5(14.8)	15.9±31.8(20.1)	18.2±3.9(30.2)
Height (cm)	99.2±24.8	101.3±25.1 (2.1)	103.7±25.3(4.3)	111.9 ±23.9(11.3)
BMI(kg/m^2)	12.5±2.3	14.0±3.8(10.7)	15.8±3.8(20.9)	18.0±2.7(30.5)

Values are means + standard deviation

Table IIb

Changes in CD4cell count and WHO Staging during 12 Months' Treatment with HAART

Variable	*Values at recruitment*	*Values at 3 Months (% increase)*	*Values at 6 Months (% increase)*	*Values at 12 Months (% increase)*
Age (years)	4.9±1.4	5.0±2.3	5.3±2.4	5.9±1.7
CD4cell count	243.9±106.2	461.2±108.5(47.1)	570.8±281.1(57.3)	788.5±217.3(69.1)
CD_4 cell %	11.7	17.2(32.0)	22.6(48.2)	28.8(59.4)
WHO clinical	3	2	1	1

Values are means ± standard deviations

improvement in the clinical condition. Body weight and BMI showed a strong positive correlation with CD_4 cell count [r = 0.64, p< 0.001; r = 0.61, p < 0.001 respectively]. There was no correlation between CD_4 cell count and height, (r =0.003, p < 0.05).

net gain in BMI of 5.4 ± 0.1kg/m² (29.8 percent total increase), and increase in height from 99.2±24.8cm to 107.9±23.9cm, (8.1 percent) after one year treatment. Several other workers have testified to the effectiveness of HAART in improving

Appendix

Revised WHO Staging of HIV/AIDS for Infants and Children

Clinical State 1: Asymptomatic stage with persistent generalized lymphadenopathy or hepatosplenomagaly.

Clinical Stage 11: Disease is manifested by popular puritic eruptions, seborrhea dermatitis, fungal nail infections, angular chelitis, lineal gingival erythema, extensive human papilloma virus (HPV) or mollscum infection (>5percent of body area/ face), recurrent oral ulceration (>2episode/ 6months), parotid enlargement, herpes zoster (>1episode /12months), recurrent or chronic upper respiratory infections (URTI): otitis media, otorrhoea, sinusitis (>2episodes /6months).

Clinical Stage 111: Features include unexplained moderate malnutrition (-2SD or Z score) not responding to standard therapy, unexplained persistent diarrhea (>14days), unexplained persistent fever (intermittent or constant, >1month, oral condidiasis, oral hairy leukoplakia, pulmonary tuberculosis, severe recurrent presumed bacteria pneumonia (>2episodes/12months), acute necrotizing ulcerative gingivitis/periodontal, lymphoid interstitial pneumonitis, unexplained anemia (<8gm/dl), neutropenia (<10000/mm³), or thrombocytopenia (<30,000/mm³) for >1month, HIV cardiomyopathy, and HIV related nephropathy..

Clinical Stage IV: Consist or unexplained severe wasting or severe malnutrition (-3SD or Z score) not responding to standard treatment, pneumocystic pneumonia, recurrent Severe bacterial infections (>2 episodes/12months, excluding pneumonia), chronic orolabial or cutaneous herpes simplex virus (lasting >1month), extra pulmonary tuberculosis, Kaposi sarcoma, esophageal candidiasis, central nervous system toxoplasmosis, cryptoccocal meningitis, any disseminated endemic mycosis, cryptosporidiosis or isosporiasis (with diarrhea >1month), cytomegalovirus virus infection of organs other than the liver, spleen, lymph nodes (and onset age >1month) disseminated mycobacterial disease other than tuberculosis, candida of trachea, bronchia or lungs, acquired recto-vesico fistula, cerebral or B cell non-Hodgkin lymphoma, HIV encephalopathy, and progressive multifocal leucoencephalopathy.

Adopted from: Interim WHO Staging or HIV/AIDS Case Definitions for Surveillance African Region WHO/HIV/2005.02
http:www.who.int/hiv/pub/guidelines/clinicalstaging.pdf

Discussion

The clinical effectiveness of HAART was demonstrated in this study and compared favourably with results obtained in respect to other paediatric cohorts in Africa, United State, and Europe.[14-19,23-27] From the anthropometric point of view, the mean bodyweight of the recruited infants increased from 12.7 ± 3.5kg to 18.2 ± 3.9kg with a net gain of 5.5kg (30.2 percent total increase) after one year treatment with HAART. This equally translates to increase in growth curve from 5th centile value to 25th centile, a

the anthropometric indices of patients.[14-19,26-33] Studies by Massaquoi et al [16] from Kenya, and Renner and co-workers [19] from Ghana noted a net increase in body weight of 1.8kg and 5.0kg after 6 months and 12 months treatment, and 45 percent in body weight after one year treatment. These findings appeared similar to 5.5kg and 30.2 percent net increase in weight observed in the present study, and buttress the effectiveness of HAART in paediatric patien Another study by Osaro[17] reporting on ad

population in Nigeria, also recorded a significant gain in weight and BMI of 13.3kg and 5.13kg/m^2 respectively, following one year administration of HAART.

Growth is an important prognostic indicator for children with HIV.[34-35] In particular, height velocity is an independent predictor of survival when control for age, viral load and CD4 count are made.[35] In the present study, although there was increase in height, the increase was however not as remarkable as that of the weight and BMI. A study by Van Rossum et al [27] on the efficacy of HAART on paediatric patients, also observed non-significant increase in the HAZ score when compared to WAZ score, and attributed such changes to the short follow up period involved in their study. HAART by inducing quantitative and qualitative immune restoration in HIV/AIDS patients will directly and indirectly improve both the general well being and anthropometric profile of the individual.

Research result has demonstrated a variety of growth patterns in HIV infected children.[34-35] A European studyon infants and childhood weight and height showed significant lower values in HIV positive children; the differences persists and increases with age.[35] Other studies on such children have reflected growth patterns including acute wasting, slow weight gain, and chronic slow linear growth.[34-35] The findings in the present study are in keeping with previous ones [34-35] where HIV infected children were noticed to have their anthropometric indices (the body weight, length/height) below the 5th centile growth curve using the international (NCHS) [22] growth chart at recruitment. The endemicity of childhood malnutrition in most developing countries[12,36] is further compounded by HIV infections which not only decreases food intake from its anorexia, mouth ulcers/oral thrush, but also increases nutrient loss from malabsorption, chronic diarrhea, HIV enteropathy, as well increase in metabolic rate from infections and infestations which releases cytokines that mediate weight loss.

Following HIV infection, the CD_4 cell count decreases while the HIV RNA rises significantly.[1-3] As the disease progresses, the circulating CD_4 T cells level drops to a level where opportunistic infections set in.[2,3,10,12] During the latter stage of HIV infection, the CD_4 cell counts continuously decline to levels of less than 200 cells /mm^2 in older children, a level at which an individual is deemed to have severe immune depression with AIDS.[2,3,10,12] In this study, more than 50 percent of the cases were in WHO stage 3 disease with severe immunosuppression and a mean $CD_{4\ \text{cell count of}\ 243.7\ \pm}$ 106 cells/cmm. On commencement of HAART, the mean CD_4 cell count and its percentage steadily increased to near normal value of 788.5 ± 217 cells/mm^3 and 28.8 percent (69.1 percent and 59.4 percent total increase respectively) at 12 months on treatment, with the greatest increase occurring in the first 6 months of commencement of HAART. The remarkable increase in CD4cell count in the first six months of treatment with HAART in this study is in keeping with findings from Kenya by Rinn et al [32] and Puthankit [33] and co-workers from Thailand. While Liotta and co-workers [14] observed 24 percent increase in CD4cell count after 6 months of therapy, the present study recorded 57.3 percent at 6 months and 69.1 percent at 12 months, and a Ghanaian study [18] noted increase of 78.9 percent after 6 months on HAART. The differences in the increase might not be unconnected to the age of patients, since CD4cell count varies with age. CD4 cell count is the primary target of HIV and HAART by acting in the various stages of HIV replication within the CD4 cell will produce a rebound increase in the cell count especially during the initial period of treatment when the viral load is still very high.[10,12] The strong positive correlation seen between CD4cell count and both weight and BMI has also been reported by other workers.[12,15,27,32] As suggested by some [26,29,31] weight can be used to successfully to monitor children on HAART in most poor African settings where CD4 cell measurement might not be visible because of cost.

It is therefore concluded from our study that in view of excellent outcome of HAART on paediatric patients, there should be a rapid scale up of HAART across the nation as record shows that only five percent of infected children are receiving anti-retroviral therapy.

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