World Journal of Nutrition and Health, 2016, Vol. 4, No. 1, 22-26
Available online at http://pubs.sciepub.com/jnh/4/1/5

DOI:10.12691/jnh-4-1-5

Poor Physical Growth among Perinatally HIV-infected Girls despite Anti-retroviral Therapy in Enugu, South-East Nigeria

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Abstract ***Background:*** Perinatally acquired HIV infection is associated with early and progressive reductions in weight and height and features of endocrine dysfunction such as pubertal delay. Impairment of growth is a marker of advanced HIV disease and require proper evaluation. The aim of this study was to assess the physical growth of perinatally HIV-infected females aged 8-18 years. ***Materials and methods:*** A cross sectional study involving 100 HIV-infected girls aged 8-18 years and 100 un-infected counterparts matched for age and social class. Weight and height were measured to assess the nutritional status of study participants and BMI calculated, Data analysis was done with SPSS version 20 (Chicago IL). Significant levels were assumed at p-values less than 0.05. ***Results:*** The mean height of the subjects and controls were 139.19 ± 14.31cm and 145.67 ± 13.09cm respectively (p=0.001). The mean weight of the subjects and controls were 33.56 ± 11.12kg and 37.68 ± 11.07kg (p=0.009) respectively. ***Conclusions:*** Perinatally HIV infected females have significantly lower weight and height for age z scores than HIV uninfected controls.

Keywords: *physical growth, peri-natal, HIV, girls, poor*

Cite This Article: Iloh O N, Ubesie AC, Iloh KK, Emodi IJ, Ikefuna AN, and Obumneme-Anyim I., "Poor Physical Growth among Perinatally HIV-infected Girls despite Anti-retroviral Therapy in Enugu, South-East Nigeria." *World Journal of Nutrition and Health*, vol. 4, no. 1 (2016): 22-26. doi: 10.12691/jnh-4-1-5.

1. Introduction

Human immunodeficiency virus (HIV) is a lymphotropic and neurotropic retrovirus that belongs to the retroviridae family and causes an infection that affects several organs and systems. [1] HIV infection causes both humoral and cell mediated immune incompetence over time leading to acquired immune deficiency syndrome (AIDS) and subsequently, death. [1] It has become a pandemic and a significant cause of childhood morbidity and mortality in Africa. [2]

An estimated 2.1 million adolescents, aged between 10 and 19 years were living with HIV in low and middle income countries by the end of 2012. [3] Eighty-two percent of these adolescents are in sub-Saharan Africa and 58% of them are females. [4] In Nigeria, about 3.2 million people were living with HIV by the end of 2013, representing the largest epidemic in West Africa [5].

Mother-to-child (vertical) transmission is responsible for approximately 90% of paediatric HIV transmission in sub-Saharan Africa. [6] Other routes of transmission are contaminated needles, blood transfusion and sexual activities. [7] The natural progression of vertically acquired HIV infection appears to be in two forms. AIDS can be slowly progressive, taking about 2-15 years to develop depending on the individual. [8] The second and more aggressive form is characterized by early conversion to AIDS within two years and an increased risk of opportunistic infections and mortality. [9] Investigators have hypothesized that a greater proportion of children infected through breastfeeding would be slow progressors, compared to those with in-utero infection. [10]

The introduction of highly active antiretroviral therapy (HAART) has drastically reduced HIV disease associated morbidity and mortality in children. [11] There has been a documented reduction in deaths from AIDS related illnesses by 21% between 2005 and 2011. [12] Therefore an increasing number of perinatally HIV-infected children now enter adolescence, a period defined by the World Health Organization (WHO) as being between 10 and 19 years of age. [13] Perinatally acquired HIV infection is associated with early and progressive reductions in weight and height and features of endocrine dysfunction such as pubertal delay. [14] Impairment of growth is a marker of advanced HIV disease and require proper evaluation. [15] Growth impairment have implications on the reproductive health of young girls later in life. It has been shown that females with short stature have significantly higher rates of cephalo-pelvic disproportion. [16] They are also at increased risk of delivering birth weight babies with attendant morbidity and mortality. [17] Significant gaps exist in the literature regarding growth impairment among HIV-infected young females on anti-retroviral therapy in developing countries. The outcome of studies conducted

in developed countries may not be applicable to developing countries because of underlying poverty and malnutrition. [18,19] This led to the hypothesis that the magnitude of impairment of physical growth among HIV infected young females may be worse in resource limited countries like Nigeria. This study therefore, sought to assess the physical growth of perinatally HIV-infected females aged 8-18 years in Enugu, South-East Nigeria.

2. Materials and Methods

2.1. Study Site and Design

The study was carried out in the Paediatric HIV clinic of the University of Nigeria Teaching Hospital, Ituku/Ozalla, Enugu, Nigeria. It was cross sectional and descriptive, done over a period of six months (between August 2014 and January 2015). The study subjects were HIV-infected females aged eight to eighteen years. Perinatal HIV diagnosis was made in our subjects if DNA PCR for children below 18 months or ELISA for those above 18 months were positive and the mothers HIV positive at the time of delivery. Other routes of transmission must have been excluded. The controls were HIV-uninfected females who were matched for age and social class and without chronic diseases such as sickle cell anemia, chronic kidney disease or asthma attending the children outpatient clinic. The social class was assigned to the subjects and controls using social classification system as proposed by Oyedeji. [20] This classification uses maternal and paternal highest education attainment and occupation.

2.2. Sample Size Determination

The sample size was calculated using the formular [21]

$$N=\frac{z^2pq}{d^2}$$

Where N = the uncorrected sample size estimate for an infinite population
z = 1.96 standard normal deviate
p = the proportion in the target population estimated to have a particular characteristic. If there is no reasonable estimate then 50% is used (i.e. 0.5)
q = 1.0-p
d = the desired precision or tolerable error (taken as 0.05)

$$N=\frac{(1.96)^2 \text{ x}(0.5)\text{x}(0.5)}{(0.05)^2}$$

$$N=\frac{3.84 \text{ x } 0.5 \text{ x } 0.5}{0.0025}$$

$$N=384.$$

However, since the sample was drawn from a finite population of HIV infected adolescents numbering less than 10,000 a second formula correcting the sample size for a finite population was used thus:

$$Nf=\frac{n}{1+(n/N)}$$

Where nf = Sample size for a finite population
n = desired sample size for a population more than 10,000
N = The estimate of the population size which in this case is the total number of HIV infected females aged 8-18 years in UNTH Enugu and was approximately 135.

Hence

$$nf=\frac{384}{1+(384/135)}$$

$$nf=100$$

The minimum sample size was thus 100.

2.3. Sampling Method

The WHO clinical staging was based on the WHO case definitions for HIV surveillance and clinical staging in children. [22] Standardized clinical parameters based solely on patient clinical features were used to sort patients from stage 1 (asymptomatic) to stage 4 (AIDS). [22] Patients were assigned a particular stage if they presented with at least one clinical condition in that stage's criteria. [22] CDC immunological classification was categorized from stage 1 to stage 4 based on the immunological classification for HIV related disease in adults and children using absolute CD4+ T- lymphocyte counts.22 Stage 1 represented CD4 cell count of >500cells/µl, stage 2 represented CD4 cell count of 200 -349 cells/µl while stage 3 represented CD4 cell count of 350-499cell/µl and stage 4 < 200cells/µl. [22]

The HIV-uninfected females (controls) were enrolled from the Children Outpatient Clinic after informed consent from caregivers and assent from the controls were obtained. HIV counselling and testing (HCT), was offered to the controls according to the National algorithm. The determine ™ HIV1/2 (Alere) rapid test kit (100% sensitivity and specificity 97.8%) was used to test for HIV antibody.[133] An initial positive test was followed by one confirmatory test (Uniglod with a sensitivity of 100% and specificity of 99.7%) to confirm the HIV status of the child. A second negative test was then followed by a third tie-breaker, stat-pak (sensitivity of 100% and specificity of 100%) to confirm the HIV status of the child. Post-test counseling was done and those confirmed to be HIV positive were referred to the paediatric HIV clinic for further evaluation and treatment. The HIV negative controls on the other hand were subsequently enrolled and matched for age and social class with the subjects.

Growth parameters (weight and height) were measured by the researchers to assess the nutritional status of both subjects and controls. Participants stood erect wearing only light clothing and leaning on nothing while their weight was recorded on a battery-powered digital scale to the nearest 0.1kg (Seca, Inc, Columbia, MD, USA). The scale was reset to zero after every ten measurements. Height measurements were taken using a stadiometer (Seca Inc, Columbia, MD, USA) with the participants standing erect, without shoes, heels together and back as straight as possible. The heels, buttocks, shoulders and back of the head were touching the wall. The eye-ear plane was perpendicular to the wall while the head piece was moved down to touch the child's head.

The measurements were then recorded to the nearest 0.1cm.

Body Mass Index (BMI) or Quetelets index for age was calculated using the formula. [23]

$$\text{BMI} = \frac{\text{Weight in kilograms}}{(\text{Height})^2 \text{ in metres}}$$

Z scores were then derived for the weight, height and BMI for age and compared with the WHO 2007 reference values. [24] Acute malnutrition (wasting) was defined as weight-for-length/height and BMI Z scores <-2 while chronic malnutrition (stunting) was defined as HAZ<-2 [24].

2.4. Ethical Approval

Ethical approval was obtained from the Health Research and Ethics Committee of UNTH.

2.5. Consent/Assent

Details of the study were explained to each study participant and their parents/guardians. Participants were enrolled if consent was obtained from their parents/guardians and assent obtained from the child.

2.6. Data Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 18 for windows. Frequencies, percentages, means and standard deviations were generated for categorical and continuous variables. Means of continuous variables (age, height, weight and BMI). All tests were two-tailed and significant p values were set at less than 0.05.

3. Results

Two hundred females were enrolled (100 HIV infected subjects and 100 HIV uninfected controls). They were aged 8 -17 years. The mean age of the subjects at study enrolment was 11.3 ± 2.3 years. The mean at HIV diagnosis among the subjects was 6.1 ± 3 years. Eighty-six of the subjects (86%) were on HAART and the mean duration on HAART was 4.7 ± 2 years.. Eighty-six of the subjects (86%) and 86 controls (86%) respectively were in the upper socio economic class while 14 (14%) were in the lower socio economic class.

Table 1 shows a comparison of the mean anthropometric values of the subjects and controls. The mean height of the subjects and controls were 139.19 ± 14.31cm and 145.67± 13.09cm respectively (t=3.343, df=1, p=0.001). The mean weight of the subjects and controls were 33.56 ± 11.12kg and 37.68 ± 11.07kg (t=2.621, df=1, p=0.009) respectively.

Seventeen subjects (17%) compared to 4 controls (4%) were stunted (p = 0.003). Twelve subjects (12%) compared to 9 controls (9%) had under-nutrition while six subjects (6%) and 14 controls (14%) were overweight/obese (p = 0.151) as shown in Table 2.

Table 3 compares the weight and height z-scores of subjects based on their HAART, clinical and immunologic status. There was no significant difference in the mean height z score between the subjects on HAART and those who were not on HAART (p = 0.38). Similarly, the weight z score did not differ significantly between those on HAART and those not on HAART (p = 0.39). WHO clinical stage assessment done in the course of the study revealed that all subjects were in either clinical stage 1 or 2, having been on HAART for a mean duration of 4.7 ±2 years. There was no significant difference in height z scores of the subjects (p = 0.52, p = 0.26) on comparison of clinical and immunologic stages.

Table 1. Comparison of the anthropometric measurements of subjects and controls

Variables	Subjects Mean ± SD	Controls Mean ± SD	t	p value
Height(cm)	139.19 ± 14.31	145.67 ± 13.09	3.343	0.001
Weight(kg)	33.56 ± 11.12	37.68 ± 11.07	2.621	0.009
BMI(kg/m$^{2)}$	16.92 ± 2.92	17.44 ± 3.45	1.143	0.254
Height for age Z – score	-0.94 ± 1.38	0.01 ± 1.13	5.293	< 0.001
Weight for age Z – score	-0.94 ± 1.48	-0.29 ± 1.07	3.574	< 0.001
BMI for age Z – score(kg/m^2)	-0.63 ± 1.59	-0.42 ± 1.22	1.037	0.301

cm=centimeter, kg = kilogram, SD = standard deviation. BMI = body mass index.

Table 2. Proportion of subjects and controls with acute and chronic malnutrition

	Subjects n (%)	Controls n (%)	χ^2	P value
Chronic malnutrition				
Stunted	17 (17%)	4 (4%)	8.99	0.003
Normal	83 (83%)	96 (96%)		
Total	100 (100%)	100 (100%)		
Acute malnutrition			z-score	
Undernourished	12 (12%)	9 (9%)	0.692	0.490
Normal Weight	82 (82%)	77 (77%)	0.876	0.379
Overweight/obese	6 (6%)	14 (14%)	-1.886	0.059
Total	100 (100%)	100 (100%)		

Table 3. Height and weight z-scores of the subjects according to their HAART, clinical and immunological parameters

Parameters	Number of subjects	Height z-score	p-value	Weight z-score	p-value
HAART					
Yes	86	-0.89	0.38	-0.89	0.39
No	14	- 1.24		-1.26	
WHO clinical staging					
I	75	-0.80	0.52	-0.70	0.17
II	18	-1.03		-1.21	
Immunological staging					
<200	19	-1.19	0.26	-1.53	0.14
200 - 349	21	-1.24		-0.85	
350 -499	19	-1.05		-1.15	
≥ 500	41	-0.61		-0.61	

4. Discussion

This study assessed the physical growth and sexual maturation of perinatally HIV-infected females (subjects) compared to HIV-uninfected controls. It was observed that the subjects weighed less (p=0.009) and were shorter (p=0.001) than the controls. The negative effects of HIV disease on physical growth have been documented. Possible explanations for this effect include secondary infections and HIV induced immune dysfunction leading to increased protein catabolism and diversion of energy away from growth. [25,26] The reduced height and weight of the subjects in the index study compared well with observations by Anyabolu *et al* [27] among HIV infected children in Nigeria. Lower height and weight among perinatally HIV infected females were also observed by Ferrand and colleagues [28] and Mbwile [29] in different African countries and across eight countries in Europe. [30] The similarity in the observations across different countries and continents shows that HIV affects height and weight irrespective of ethnic origin and technological advancement.

However, there was no significant difference in the proportion of subjects and controls that had various forms of acute malnutrition. This is in spite of the subjects having significant lower mean weight for age z-scores. This observation can be explained by higher proportion of controls than subjects being overweight/obese: an observation, which showed a trend but failed to achieve statistical significance. Conversely, a significant proportion of the subjects compared to controls were stunted. This suggests that the negative effects of HIV on stunting may not be compensated by the use of HAART. Stunting is a reflection of poor linear growth and might be the only manifestation of chronic HIV infection in an otherwise seemingly healthy adolescent. [31] A recent study of perinatally HIV-infected Asian adolescents older than 18 years at their last clinic visit revealed that as high as 30% of the adolescents were still stunted. The study noted that half of the adolescents who were stunted at antiretroviral therapy initiation remained stunted over time. [32] It has been shown that children who began anti-retroviral therapy in later childhood are typically unable to regain their height potential. [33] The mean duration of HAART among the subjects in this study was 4.7 ± 2 years, suggesting late initiation of treatment in our population of HIV-infected children.

Expectedly, there was no difference in the mean BMI z-scores of the subjects and controls (p=0.254). This is because, the subjects were significantly more stunted and weighed less than the controls. Mbwile [29] in Tanzania on the contrary observed lower BMI Z scores in subjects than controls. However, the controls in the Tanzanian study were not matched for socio economic classes with the subjects. This may have resulted in selection bias for nutritionally advantaged controls from higher socio-economic class.

There was no significant difference in the height z score between the subjects on HAART and those who were not (p = 0.38). Similarly, the weight z score did not differ significantly between those on HAART and those not on HAART (p = 0.39). This could partly be explained by the fact that 86% of the study subjects were on HAART while only 14% were not on HAART. WHO clinical stage assessment done in the course of the study revealed that all subjects were in either clinical stage 1 and 2 having been on HAART for a mean duration of 4.7 ±2 years. There was no significant difference in height z scores of the subjects' clinical and immunologic stages. Similarly there was no significant difference in weight z scores of subjects according to their clinical and immunologic stages. The relatively long duration of HAART among this cohort of client (mean duration of 4.7 ±2 years) connotes sufficient time for not just improvement in the clinical staging but also for catch up growth.

5. Conclusions

Perinatally HIV infected females had significantly lower weight and height for age z scores than HIV uninfected counterparts. A higher proportion of the subjects than controls were also stunted. However, there was no significant difference in the anthropometric parameters of subjects based on their HAART, clinical and immunologic status. The effect of HIV on linear growth may persist despite anti-retroviral therapy.

Acknowledgements

We acknowledge the children who participated in this study and their families.

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