Original Article

Assessment of Physical Growth in Male Children Infected with Human Immunodeficiency Virus on Highly Active Antiretroviral Therapy in Abakaliki

Chijioke Ogodo Ogeh[1], Ifeoma I. Emodi[2], Maria-Lauretta Orji[1], Chijioke J. Nweke[3], Blessed U. Ogeh[4], Ogochukwu Nneka Iloh[2], Kenechukwu Kosisochukwu Iloh[2]

[1]Departments of Paediatrics, [3]Mathematics/Computer Science/Statistics/Informatics and,[4]Ophthalmology Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Ebonyi State, [2]Department of Paediatrics, College of Medicine, University of Nigeria, University of Nigeria Teaching Hospital, Ituku Ozalla Enugu State, Nigeria

Abstract

Background: Human immunodeficiency virus (HIV) infection causes a derangement in growth. Antiretrovirals promote immune function restoration and improvement in the quality of life. Variables such as poor adherence to drugs and unsuppressed viral load may negatively influence growth in HIV-infected children. The study aimed at determining the growth in HIV-infected males aged 8–17 years in Abakaliki who were on antiretrovirals. **Methods:** A case–control hospital-based study, involving 80 HIV-infected males aged 8–17 years who were matched for age and socioeconomic class with 80 HIV-uninfected controls. Growth parameters including the heights, weights, and body mass index (BMI) of subjects and controls were measured, and *Z* scores for age derived for height, weight, and BMI. **Results:** The mean height of subjects (1.420 ± 0.18 m) was significantly lower than that of controls (1.515 ± 0.17 m). The mean weight of subjects (35.09 ± 12.48 kg) was significantly low compared to controls (42.21 ± 12.95 kg). A significant difference was documented in the mean BMI for age among subjects (16.78 ± 2.12 kg/m^2) and controls (17.93 ± 2.27 kg/m^2). There was a significant relationship between CD4 count and growth (BMI) (P = 0.006) and between duration on highly active antiretroviral therapy and growth (P = 0.024). **Conclusion:** HIV-infected males had significantly impaired growth despite the use of antiretroviral drugs.

Keywords: Children, human immunodeficiency virus antiretroviral drugs, males, physical growth

Introduction

Human immunodeficiency virus (HIV) infection is caused by a virus that belongs to the family retroviridae, affecting the immune state and depleting the natural defense system.[1] HIV destroys the CD4 T-lymphocytes leading to cell-mediated immune incompetence known as Acquired Immune Deficiency Syndrome (AIDS) and even death.[1] In 2018, about 36.9 million people and about 1.8 million children <15 years were living with HIV in the same year.[2] It was estimated that 940,000 people living with HIV died from AIDS-related illnesses worldwide in 2018.[2] The majority of the people living with HIV (PLHIV) live in developing countries.[2]

In Sub-Saharan Africa, about 25.5 million people were infected with HIV and reside in Africa.[3] Among PLHIV globally, Nigeria has the second-largest HIV disease burden with 3.1 million people after South Africa which has an estimate of 6.8 million people living with HIV.[3] However, a current published Nigeria HIV/AIDS Indicator and Impact Survey, one of the largest population-based HIV/AIDS household surveys ever conducted, found the prevalence to be 1.4%.[4] Better surveillance was responsible for the apparent decline.[4] Approximately 150,000 people died from AIDS-related illnesses in Nigeria in 2017.[4] Mother-to-child transmission of HIV accounts for over 90% of paediatric HIV transmission in Sub-Saharan Africa.[2] Children can also be infected through contaminated and unsterilized needles and blood transfusions and sexual abuse.[5]

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Address for correspondence: Dr. Kenechukwu Kosisochukwu Iloh, College of Medicine, University of Nigeria, University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu State, Nigeria.
E-mail: kenechukwu.iloh@unn.edu.ng

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With the introduction of antiretroviral therapy (ART), there was a reduction in HIV replication, preservation of CD4 T-lymphocyte cell count/function, and restoration of immunity to fight infection, thereby promoting or restoring normal growth and development, as well as improving quality of life.[6-8] This led to a reduction in mortality and morbidity of HIV-infected children/adolescents as well as an increase in the number of adolescents living with HIV.[8]

Symptomatic HIV infection in children is associated with initial and subsequent reductions in weight, height, and body mass index (BMI).[9] It has been reported that delayed physical growth in HIV-infected children/adolescents results in poor self-image and low self-esteem mainly when they are among their peers.[9] This may be related to the psychological and social change experienced during adolescence, whereby the adolescent spends time thinking about physical growth and body image because they want peers' acceptance. Some studies have reported that males were more vulnerable to poor growth than females and called for further research into this finding.[10-12] Furthermore, the existing studies on assessing physical growth in male adolescents infected with HIV were reported in developed countries.[13-15] The study aimed to assess physical growth in HIV-infected males aged 8–17 years in Abakaliki. It hopes to provide information that will guide paediatricians in counselling caregivers and/or HIV-infected adolescents. It will also provide data that may help create awareness and sensitization in the community on early diagnosis and prompt enrollment in HIV care.

Methods

Study area

This study was conducted in the paediatric HIV clinic and children outpatient (CHOP) department of the Federal Teaching Hospital, Abakaliki (FETHA) and Mile Four Mission Hospital, Abakaliki, Ebonyi State.

Study population

The study populations were male children infected with HIV attending the paediatric HIV specialty clinic in both hospitals aged 8–17 years, while the controls were HIV-uninfected males aged 8–17 years who were matched for age and socioeconomic class in both hospitals who were without chronic kidney disease, sickle cell anemia (SCA), asthma, chronic liver disease, and cerebral palsy attending the CHOP clinic.

Sample size determination

Sample size was determined using Jaykan and Tamoghna method.[16]

$$\text{Sample size}\,(n)=\frac{r+1}{r}\times\frac{(P^*)(1-P^*)(Z_\beta+Z_{\alpha/2})^2}{(P_1-P_2)^2}$$

Where r = ratio of control to cases (subjects), 1 for an equal number of cases and control.

P^* = Average proportion exposed

$$\frac{\text{Proportion of exposed cases}+\text{proportion of control exposed}}{2}$$

50% (0.5) was used when there was no recognizable estimate.

Z_β = normal standard variate for significant level as identified in the previous section. i.e., normal standard variate for the power of 80%, which is equal to 0.84.

$Z_{\alpha/2}$ = normal standard variate for significant level as identified in the previous section, i.e., normal standard variate at 95% confidence level = 1.96.

$P_1 - P_2$ = different in proportions or effect size identified from previous studies.

P_1 = is proportion in cases (subjects) (0.17).[17]

P_2 = is proportion in controls (0.04).[17]

n = minimum sample size.

$$n=\frac{1+1}{1}\times\frac{(0.5)(1-0.5)(0.84+1.96)^2}{(0.17-0.04)^2}=232$$

Furthermore, a second formula[18] correcting the sample size for a finite population was used because the first formula was drawn from a finite population of HIV-infected children numbering <10,000 population thus:

$$\text{nf}=\frac{n}{1+(n/n_E)}$$

Where,

nf = represent sample size for a finite population.

n = represent a population greater than 10,000 participants.

n_E = estimated total number of HIV-infected males aged 8–17 years in FETHA and Mile Four Hospital were approximately 105 (61 + 44).

Hence,

$$\frac{232}{1+(232/105)}=73$$

The minimum sample size was thus 73.

Non responders rate.

$$n\times\frac{10}{100}=7.3$$

Therefore, the actual minimum sample size of cases (subjects) was 80.

However, the sample size was allocated proportionally (William, 1977) to the two hospitals under study thus:

Let N_1 be the number of HIV patients aged 8–17 years in FETHA and N_2 be the number of HIV patients aged 8–17 years Mile four, n = minimum sample size = 80, and N total number of HIV patients aged 8–17 years in the two hospitals = 105.

Therefore, the sample size for each hospital is given by:

For FETHA,

$$n_1 = \frac{n \times N_1}{N} = \frac{80 \times 61}{105} = 46 = 57.5\%$$

For Mile Four,

$$n_1 = \frac{n \times N_2}{N} = \frac{80 \times 44}{105} = 34 = 42.5\%$$

The same proportion was used for the selection of the control.

Study design

The study is a case–control hospital-based study.

Study duration

The research work was carried out within six months (September 2018 to February 2019).

Sampling method

All eligible study participants scheduled for Mondays and Thursdays in FETHA, Thursdays in Mile Four Mission Hospital, and children attending CHOP were consecutively enrolled until the estimated minimum sample size was reached.

Study procedure

Males infected with HIV aged 8–17 years (subjects) who met the inclusion criteria were enrolled consecutively during the weekly paediatric HIV clinic. Before recruitment into the study, the researcher obtained informed consent from the parents/caregivers and assent from the populations. At this stage, the details and reason for the study were explained to the researcher's populations and their caregivers. The caregivers were also informed that participation in this study was voluntary, and they would not be penalized if they refuse to give consent/assent for participation. After that, a Case records containing detailed information on the biodata of the subject, history of diagnosis, sociodemographic profile, and relevant laboratory data including CD4 count and viral load was then completed by the researcher.

Oyedeji Social Classification System[19] was used to determine the social class of each participant. They were then subdivided into the upper, middle, and lower socioeconomic classes. Those in upper social class were represented by classes 1 and 2, 3 for the middle class, while classes 4 and 5 were defined as lower social class. Each score has two variables, occupation, and level of education of both parents/caregivers.[19]

The clinical staging and immunological classification of subjects into the paediatric HIV clinic were retrieved from the children's case notes. The WHO clinical staging was as documented by WHO case definitions for clinical staging system and HIV surveillance in children.[20] Recognized clinical features were used to group them from Stage 1 (asymptomatic) to Stage 4 (AIDS) according to WHO criteria.[20] The subjects were assigned to a specific stage if they had at least one clinical feature in that stage's criteria. The WHO immunological classification was categorized from "not significant suppression" to "severe suppression" based on the revised immunological classification for HIV-related disease in children and adolescents using absolute CD4+ T-lymphocyte counts. Stage 1 (not significant) represented CD4 cell count of >500 cells/mm^3, stage 2 (mild) represented CD4 cell count of 350–499 cells/mm^3, stage 3 (advanced) represented CD4 cell count of 200–349 cells/mm^3, while stage 4 (severe) represented CD4 cell count of < 200 cells/mm^3.[20]

The HIV-uninfected males (controls) matched for age and social class were enrolled from the CHOP clinic of both hospitals after informed consent from parents/caregivers and assent from the controls had been retrieved by the researcher. For HIV counselling and testing, the controls had a pretest counselling which was done routinely by the treatment support staff, and then, they had serial consecutive rapid diagnostic tests according to the National guideline on HIV counselling and testing to determine their HIV status.[21] To confirm the HIV status of the child, the initial positive test was followed by one more confirmatory test (Unigold™ with a sensitivity of 100% and specificity of 99.7%).[22] If the second test was negative, a third tie-breaker test was then used, which has a sensitivity of 100% and specificity of 100% to confirm the HIV status.[19] Post-test counselling was done. Controls confirmed to be HIV infected were referred to the paediatric HIV clinic for further counselling and enrolled in HIV care. On the other hand, the HIV-uninfected controls were also counselled and subsequently enrolled and matched for age and social class with the subjects (HIV-infected). A case record form was then completed for them by the researcher. None of the controls enrolled was HIV positive.

The researchers measured the weight and height of both the subjects and controls to determine the physical growth. The study participants stood erect on a battery-powered digital scale set to the nearest 0.1 kg wearing only light clothing and leaning on nothing while their weight was read off from the scale and recorded on the case form.[23] After every ten readings, the scale was reset to zero to avoid errors. A known weight was placed on the scale every day before use and periodically while in use.

We measured the heights of the study population using the stadiometer.[23] Each participant was bare footed, stood erect, With heels brought together, and the back as straight as possible while the back of the head, shoulders, buttocks, and heels were touching the wall. As the headpiece was moved down to touch the child's head, the eye–ear plane was placed perpendicular to the wall, and readings were recorded on the case form. The measurements were then recorded to the nearest 0.1 cm.

BMI was calculated using the formula.[24]

$$\text{BMI} = \frac{\text{Weight (kg)}}{(\text{Height})^2 \text{ (m)}}$$

The weight, height, and BMI for age *Z* scores were determined and compared with the WHO 2007 reference values using the WHO AnthroPlus Software.[24-28]

Ethical approval

Before commencing the study, the institutional ethical approval was obtained from the Research and Ethics Committee of the FETHA and a permission letter from Mile Four Mission Hospital.

Confidentiality

The confidentiality of information and data retrieved from the study participants were emphasized to all study participants and were kept throughout and after the study. All the essential data relating to the survey were kept safe by the principal investigator. The study participants were assigned identification numbers and their data coded using their initials and identification numbers.

Data analysis

The data obtained was transferred into an electronic database using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM SPSS Statistics for Windows, version 20.0. Armonk, NY: IBM Corp) and then analyzed. The difference in means for continuous variables (age, height, weight, and BMI) for controls and subjects was compared using Student's *t*-test. The odds ratio was used to ascertain the odd in favor of the controls over the subjects. The effect of social class, immunological status, clinical stage, and duration on highly active ART (HAART) on physical growth was modeled using multivariate and logistic regression, respectively. The relationship between physical growth and viral load was tested using the Chi-square. All test statistics were conducted at a 0.05 level of significance. Charts and tables were used in the presentation of the results.

Results

The age and social class of the study participants

One hundred and seventy-two males comprising 82 HIV infected (subjects) and 90 HIV-uninfected (controls) were recruited over six months (September 2018 to February 2019). Two males out of the 82 subjects were excluded from the study because parents/caregivers did not give consent, while 10 males out of the 90 controls were also excluded from participating in the study because five males did not give consent/assent, three males were SCA patients, one was a known asthmatic patient, and one was on the steroid for SCA nephropathy.

Therefore, eighty HIV-infected subjects and eighty HIV-uninfected controls within the same age bracket of 8–17 years were enrolled for the study and matched for age and socioeconomic class. Majority of the subjects and controls (70%) were pre/early adolescent (8–14 years) stage of life, while (30%) of the study participants were in middle adolescence (15–17 years). Forty-eight of the subjects (60%) and 48 controls (60%), respectively, were in the lower socioeconomic class, while 32 (40%) were in the upper socioeconomic class, but none of the participants was from the middle class as depicted in Figure 1.

The frequencies of different variables of the subjects

Table 1 shows the clinical characteristics of the subjects. All the subjects were of mother-to-child transmission of HIV. Sixty-four (80%) were on the first line of HAART, and only three had been on HAART for less than six months. Thirty-eight (47.5%) were HIV clinical staging 1, while one (1.25%) subject was in stage 4. The immunological status was assessed using CD4 count and it showed that majority of the subjects (49, 61.25%) had non significant (CD4 count >500 cells/mm^3) immunological staging and 5 (6.25%) had severe (CD4 count <200 cells/mm^3) immunological staging. Additionally, more of the 43 (55.8%) subjects had unsuppressed viral load, while 34 (44.2%) had an suppressed viral load.

The physical growth profile of the study participants

Table 2 depicts a comparison of the physical growth of controls and subjects. The mean height for the controls and subjects were 1.515 ± 0.17 m and 1.420 ± 0.18 m, respectively. The difference between them was statistically significant (t = 3.350,

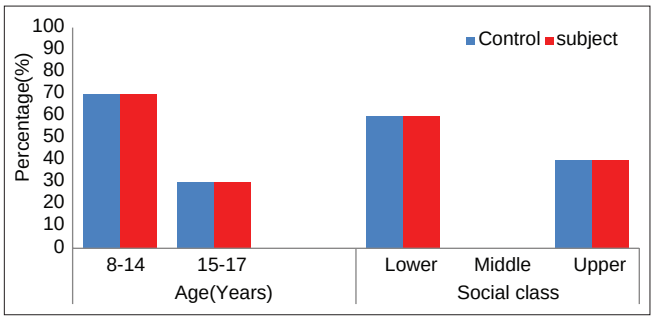

Figure 1: Social class and age profile of the study participants

Table 1: Clinical characteristics of the subjects

Characteristics	Categories	Frequency (%)
ART regimen	First line	64 (80.00)
	Second line	16 (20.00)
Duration on ART	Less than six months	3 (3.75)
	Six months to five years	36 (45.00)
	Greater than five years	41 (51.25)
Clinical stages	1	38 (47.50)
	2	19 (23.75)
	3	22 (27.50)
	4	1 (1.25)
Immunological status (CD4 count)	Not significant	49 (61.25)
	Mild	14 (17.50)
	Advanced	12 (15.00)
	Severe	5 (6.25)
	Total	80 (100.00)
Viral load	Suppressed	34 (44.20)
	Unsuppressed	43 (55.80)
	Total	77 (100.00)

Not significant: >500 ml/mm^3, Mild: (350-499) ml/mm^3, Advanced: (200-349) ml/mm^3, Severe: <200 ml/mm^3, Suppressed: ≤1000 copies/ml, Unsuppressed: >1000 copies/ml. ART: Antiretroviral therapy

P = 0.001). Furthermore, the mean weight for controls and subjects were 42.21 ± 12.95 and 35.09 ± 12.48 kg, respectively. The difference between them was statistically significant (t = 3.540, P = 0.001).

Relationship between physical growth with social class, immunological status, clinical staging, and duration of highly active antiretroviral therapy in subjects

Table 3 shows a multivariate regression analysis of the physical growth on social class, immunological stages, clinical stage, and HAART duration. It shows that CD4 count and duration on HAART were significant. These indicate significant relationships between physical growth, CD4 count, and HAART duration but not with social class and clinical stages.

Relationship between viral load and physical growth

Table 4 shows the relationship between viral load and physical growth. There was a significant relationship between viral load and height for age. But there was no significant relationship between in contrast between viral load and BMI for age with $P > 0.05$.

Table 2: Comparison of physical growth of the controls and subjects

Variables	Participant		*t*-statistic	*P*
	Controls	Subjects		
Height (m)	1.515±0.170	1.420±0.180	3.350	0.001
Weight (kg)	42.210±12.950	35.090±12.480	3.540	0.001
BMI (kg/m^2)	17.930±2.270	16.780±2.120	4.035	<0.001
Weight for age Z-score	0.238±0.730	−0.170±0.500	3.216	0.002
Height for age Z-score	0.069±1.400	−1.340±1.230	6.758	<0.001
BMI for age Z-score	−0.133±1.040	−0.780±1.220	3.628	<0.001

Values are mean±SD. BMI: Body mass index, Subjects: HIV-positive, Controls: HIV-negative, HIV: Human immunodeficiency virus, SD: Standard deviation

Discussion

This study assessed HIV-infected males' physical growth (subjects) compared with HIV-uninfected males (controls).

This study's findings showed that stunting and underweight were more common in subjects than controls with P = 0.001. The difference in growth pattern between the two groups can be attributed to opportunistic infections (OIs) and immune dysfunction induced by HIV, resulting in increased protein metabolism and energy diversion away from growth. The subjects' reduced height and weight in this study compared well with observations by Anyabolu *et al*.[29] among HIV-infected children in Ife, Oyo State, Nigeria, who also noted that more of the HIV-infected children were stunted, wasted, and underweight compared to the controls (P = 0.001). This finding in the index study was corroborated by Newel *et al*.[30] and Iloh *et al*.[31] who studied HIV-infected female adolescents in Enugu, Southeast Nigeria.

Isanaka *et al*.[32] suggested that disturbances to energy balance may be a factor in stunting of growth in HIV-infected children, while Newell *et al*.[30] found that OIs and HIV-induced immune dysfunction will lead to increased protein catabolism and diversion of nutrients away from growth.

The mean height in subjects was noted to be significantly lower compared to controls. The subjects' chronicity of HIV infection may have negatively influenced their physical growth more than the control group. Ferrand *et al*.[33] stated that growth failure might be the distinguishing factor in subjects who have had the illness for a longer time than the uninfected group. These findings were corroborated by Majaliwa *et al*.[9] and Stagi *et al*.,[34] who found that growth in height is affected in individuals with HIV infection. Similar results

Table 3: Regression analysis of physical growth on social class, immunological stage, clinical stage, and duration on highly active antiretroviral therapy

Variable	Physical growth				Multivariate test		
	Z-score for BMI		*Z*-score for height				
	β	*t* (*P*)	β	*t* (*P*)	Δ	*F*	*P*
Intercept	−2.396	−2.135 (0.036)	−1.247	−1.005 (0.318)	0.369	59.79	<0.001
Social class	0.161	0.625 (0.534)	0.250	0.880 (0.382)	0.991	0.312	0.733
CD 4 count							
Not significant	1.270	2.074 (0.042)	0.900	1.330 (0.188)	0.774	3.194	0.006
Mild	1.061	1.645 (0.104)	0.139	0.195 (0.846)			
Advance	0.850	1.269 (0.209)	0.624	0.842 (0.403)			
Clinical stage							
Stage I	1.359	1.061 (0.292)	−0.533	−0.376 (0.708)	0.917	1.029	0.409
Stage II	0.799	0.614 (0.541)	−0.830	−0.577 (0.566)			
Stage III	0.642	0.512 (0.610)	−0.965	−0.696 (0.489)			
Duration on HAART	0.102	2.800 (0.007)	0.034	0.853 (0.396)	0.899	3.929	0.024

P<0.05 indicates a significant coefficient. β: Value of regression coefficient, Δ-Wilks lambda statistic, t: *t*-test statistics, F: *F* test statistic, *P*: Significant value, and the last each categorical variable is the reference category. BMI: Body mass index, HAART: Highly active antiretroviral therapy

Table 4: Relationship between viral load and physical growth for subjects

Viral load	Height for age		Total	Measures of relationship		
	Stunting	Normal		Statistic	Value	*P*
Suppressed	2	32	34	χ^2	9.283	0.002
Unsuppressed	15	28	43			
Total	17	60	77			

Viral load	BMI for age				Total	Statistic	Value	*P*
	Severe underweight	Moderate underweight	Normal	Overweight				
Suppressed	1	2	31	0	34	χ^2	3.816	0.282
Unsuppressed	4	6	32	1	43			
Total	5	8	63	1	77			

P<0.05 implies a significant relationship. Subjects: HIV-positive, BMI: Body mass index, HIV: Human immunodeficiency virus

were also observed among perinatally HIV-infected males by Ferrand *et al*.[33] and Mbwile[17] in Zimbabwe and Tanzania, respectively, in Africa.

Similarly, the mean weight in subjects in this study was found to be significantly lower than controls. The survey by Majaliwa *et al*.[9] corroborated with this index study and observed that malnutrition which is a feature of HIV infection affects the hypothalamic–pituitary–gonadal axis resulting in decreased physical growth.

Additionally, BMI in this index study was significantly lower in the subjects than in the control groups. Mbwile[17] in Tanzania documented a similar finding where he documented lower BMI for age *Z* score in HIV infected than the HIV uninfected.

Thus, chronicity of HIV infection, malnutrition, and OIs may explain the reported difference in mean height, weight, BMI scores, and *Z*-scores between subjects and controls.

In the index study, there was also a significant positive association between physical growth and duration on HAART ($P = 0.024$). This finding may be that long duration on ART regimen may lead to the restoration of immune mechanism and reduction in OIs resulting in improvement of physical growth. This was corroborated by Brady *et al*.[35] that the main reason for the progression of HIV infection in children is the reduction of CD4 cells and increased viral load, which may result in OIs AIDS. These were similar to Ebonyi *et al*.'s findings,[36] which noted that after nine months on HAART, there was a significant reduction in the percentage of children with low BMI for age ($P = 0.006$). Only 2.5% still had low BMI after nine months of HAART compared to 18.2% at the beginning of HAART. Majority of subjects in this index study had been on HAART for an average of 5.8 years. This suggests that HAART improves physical growth but does not reverse growth failure caused by HIV.

Conclusion

HIV-infected males have significantly lower weight, height, and BMI than HIV-uninfected males. The effect of HIV on growth may persist despite antiretroviral therapy.

Limitation

The study was a case–control hospital-based study with only one assessment of physical growth. A prospective cohort study with multiple interval assessments would have given more information on the derangement in the physical growth of HIV-infected children.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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