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Growth of HIV-Infected Children on Antiretrovirals Started Prior the Age of 2 Years

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Abstract

Objective: To study the effects of starting antiretroviral treatment (ART) prior the age of two years on the growth (height and weight) of HIV-infected children. **Methodology:** This was a retrospective cohort study. HIV-infected children on ART aged less than 15 years were divided into two groups Group 1 (G1) comprising children who started ART prior 2 years and Group (G2) those put on treatment thereafter. **Main Measures:** Percentage of children with growth retardation measured by Height for Age (H/A) and Weight for Age (W/A) < −2 standard deviation (SD) and associated factors of growth retardation. Statistical analysis was performed using SPSS 20 software, with $p < 0.05$ considered statistically significant. **Results:** In total, we included 90 subjects. The median age was 10 years with a slight female predominance (51.2%). Most children were asymptomatic at the time of the study (96.6%), compliant with treatment (81%), 54.8% of children were on cotrimoxazole, 33% knew their status. At initiation, underweight was predominant in group 1 compared to group 2 (52% versus 29.5%; $p = 0.015$). Conversely, stunted growth predominated in G2 compared to G1 but without significant difference (38% versus 50%; $p = 0.147$). At the time of our study (median age of 10 years), catch-up height and weight predominated in G1 compared to G2; only a small proportion remained below −2SD (4% versus 18.2%; $p = 0.015$ and 9% versus 29.5%; $p = 0.006$ respectively for underweight and stunted growth). **Conclusion and Global Health Implications:** Growth retardation was common at ART initiation. Catch-up in height was more evident in the early treatment group. Initiation of ART before the age of 2 years rather influences children's height than weight. The result of this study further emphasizes the need of early ART and closed clinical monitoring to better assess the impact of ART in areas with high rates

of undernutrition.

Keywords

Growth, Height and Weight, HIV, Antiretrovirals, Children, 2 Years Old

1. Introduction

Acquired immunodeficiency syndrome (AIDS) is a pandemic that has been raging for several decades and remains today a real public health problem in the world [1]. Progress has been made in the response to HIV, notably access to treatment has reduced by more than half the number of new infections as well as the HIV-related mortality rate worldwide. Thus, in 2023, UNAIDS (United Nations Organization for the Fight against AIDS) estimated at 1.5 million children under the age of 15 [2]-[4]. In Cameroon, HIV prevalence is 2.7% [5], the total number of children living with HIV aged less than 15 years is rounded up at 26 000 of whom 40.9% are under antiretroviral therapy [5]. HIV-infected children frequently show symptoms during their first year of life, including growth retardation, an early and frequent manifestation of HIV/AIDS in children; in fact, growth restriction is an independent factor of disease progression. The impact and benefits of ART on clinical anthropometric parameters have been described with effects as early as during the first 12 months of treatment and in parallel, long terms benefits have been recorded. Overall, the recovery of weight for age z-score and percentiles have been highlighted in many settings. But many limitations of these benefits have also been reported in case of delayed treatment, pre-treatment weight and height impairment [6] [7]. A study carried out in the United States by Sharon *et al.* in 2005 found that children aged less than 2 years at the start of ART had a significant improvement in the recovery of growth rate compared to those initiated on ART at an older age [8]. In Thailand, Thanyawee *et al.*, during a study on early initiation of ART versus delayed initiation in HIV-infected children (HIC) above 1 year old found an average gain in weight and height of 2.2 kg respectively and 5.4 cm in the first year in the early treatment group versus 2.1 kg and 4.9 cm in the delayed treatment group 1 [9]. Therefore, the timely of ART initiation and the clinical stage at initiation is a determinant of the growth but also the duration as benefit on weight were recovered at one year of treatment from subnormal to normal while it requires 2 years for height [10] [11]. Since 2015, the WHO recommends early treatment for all people living with AIDS (as soon as the diagnosis is made, regardless of the clinical and/or immunological stage [12]. Lacking specific data in Cameroonian context, we designed a study which objective was to evaluate, in our context, the effect of early start of ART on growth of HIV-infected put on antiretroviral prior their second birthday versus thereafter, in order to improve timely ART treatment amongst HIV infected children in the era of test and treat.

2. Method

2.1. Study Design and Population

This was a monocentric retrospective cohort and analytical study. The study was carried out in the pediatric department of the Essos Hospital Centre in Yaoundé within the Approved Treatment Center for antiretroviral therapy (ACT). The ACT is a specialized and a referral Centre in Prevention of mother-to-child transmission (PMTCT) of HIV and for care of children living with HIV. This study was conducted for 3 months, from March to May 30, 2018 and covered a period of 12 years from 2005 to 2017. Patients enrolled were responding to the following criteria: being HIV-infected children aged 15 years or less, on ART and follow up at Essos Hospital Centre, Files with key missing data were excluded. The children included were then divided into 2 groups. Group 1 started ART before 2 years and Group 2 started treatment after the second birthday.

2.2. Procedure

After obtaining ethical clearance, under the number 2018/04/CE-CHE we began the recruitment. In absence of exclusion criteria, written informed consent was obtained. The data was collected during a face-to-face interview by the research investigator. The main variables were 1) sociodemographic; 2) therapeutic and clinical according to the 2007 WHO clinical staging. With regards to anthropometric variables relating to growth, we evaluated weight and height. These parameters were reported as percentiles (weight-for-age; height-for-age) using the Center for Disease Control and Prevention growth charts. The results obtained in percentiles were converted into standard deviation; the 3 and 97 percentiles corresponding respectively to −2SD and +2SD [13]; 3) Biological: CD4: we used the WHO classification of immunological status. Viral load: the virological status was assessed as undetectable at a threshold < 60 copies/ml.

Definition of Operational Terms

Child: any individual under the age of 15; Stunted: height-for-age index less than −2SD. Underweight: weight-for-age index below −2SD. "Normal" height growth: height-for-age index greater than −2SD. "Normal" weight growth: weight-for-age index greater than −2SD; Group 1: children initiated on ART before the age of 2 years ; Group 2: children initiated on ART after the 2nd birthday.

2.3. Statistical Analysis

Data analysis was done using Excel, SPSS and Stata 12 software. The qualitative variables were expressed in the form of numbers and proportions; as for the quantitative variables, the distributions were represented by their mean. The comparison between the proportions was made using the chi-square test. To determine the association between the W/A, H/A greater than −2SD and the independent variables, we used logistic regression. All the variables associated with a normal weight and height in univariate analysis were introduced into the same logistic

regression model to find the determinants of a W/A and H/A > −2SD. The significance level was set at 5%.

2.4. Ethical Considerations

This study protocol was submitted to the institutional review board of EHC and the ethical was approved under the number 2018-04/CE-CHE. In addition, we obtained a research authorization from the administrative authorities of the Yaoundé EHC. All eligible persons have been explicitly built on the interest of our study. Participant approval was obtained and recorded in an informed consent form.

3. Results

3.1. Study Population

3.1.1. Participant Inclusion Diagram

In our study, we targeted 115 subjects from the available files. Nine of them were unusable. Of the remaining 106, we definitively recruited 90 subjects because of refusal to participate (n = 6), ineffective phone numbers (N = 5) and deaths (4).

3.1.2. General Characteristics of the Population

We included a total of 90 subjects including 46 (51.1%) girls and 44 (48.9%) boys with a male/female sex ratio of 0.95. 52% of the children were initiated before the age of 2; the average age at initiation was 10 months. For children initiated after the age of 2 years (48%), the age at initiation varied between 2 and 13 years, with an average age of 6 years. At the time of the study the age of the children varied between 2 and 15 years with a median of 10 years, with 25% lived with both parents. Most of the children were in school. Regarding the status of the parents, of the 56 mothers whose status could be collected, 2 were HIV-negative (3.6%), in the case of the fathers, 40% were HIV-negative.

3.1.3. Distribution of Weight and Height According to Age at Initiation (Table 1)

For children initiated before the age of 2 years Group 1, we find that: 52% had a weight deficit at ART start against 4% at the time of the study. Thus, these children almost all regained their weight on ART. On the other hand, 15/44 (34%) were stunted at ART start versus 4/44 (9%). Thus, after initiation of ART, almost all children have caught-up in height.

Table 1. Distribution of weight and height according to age at initiation.

	SD	Initiated before 2 years		Initiated after 2 years		p value
		N	Freq	N	Freq	
Weight at initiation	Below normal for age (<−2SD)	24	52.0%	13	29.5%	0.0150
	Normal for age (>−2SD)	22	48.0%	31	70.5%	0.0017

Continued

Current Weight	Below normal for age (<−2SD)	2	4.0%	8	18.2%	0.0155
	Normal for age (>−2SD)	44	96.0%	36	81.8%	0.0155
Height at initiation	Below normal for age (<−2SD)	15	38.0%	18	50.0%	0.1476
	Normal for age (>−2SD)	24	62.0%	18	50.0%	0.1476
Current Height	Below normal for age (<−2SD)	4	9.0%	13	29.5%	0.0066
	Normal for age (>−2SD)	42	91.0%	31	70.5%	0.0066

3.1.4. Habits and Events at the Time of ART

Of the 90 children at the time of our study, 81% had good compliance and 19.3% had interrupted their treatment, 33.7% knew their "HIV" status at the state of complete disclosure 24.4% had never been hospitalized for more than 24 hours and 54.8% were on cotrimoxazole at the time of the study (Table 2).

Table 2. Habits and events associated to normal weight for age.

		Weight for normal age		**p value**
		YES (47)	NO (7)	
ARV protocol	ABC + 3TC + LPVr	9	0	0.126
	AZT + 3TC + LPVr	10	4	
	AZT/ABC/D4T + 3TC + NVP	19	3	
	Other	9	0	
Hospitalization	0 hospitalization	12	3	0.285
	1st hospitalization	15	2	
	2 to 4 hospitalizations	14	0	
	At least 5 hospitalizations	6	2	
Treatment interruption	Yes	3	5	0.021
	No	44	2	
Compliance	Good	36	6	0.621
	Bad	9	1	
Cotrimoxazole	Yes	23	4	0.685
	No	24	3	
ART start before age 2	Yes	18	2	0.619
	Not	29	7	

3.1.5. Factors Associated with Normal Weight for Age

In view of the results of the univariate analysis, starting ART before the age of 2 years did not influence the weight of the children in our study (Table 2). In addition, children who did not interrupt their treatment had a greater chance (OR (95% CI); 2.856 (1.84 - 4.42)) of having a normal weight for age compared to those who had interrupted, regardless of the age of initiation (Table 3).

Table 3. Factors associated with normal weight for AGE.

		Weight for AGE		Odds Ratio	p value	CI (95%)
		YES (47)	NO (7)			
Treatment interruption	YES	3	5	2.856	<0.001	[1.84; 4.42]
	NO	44	2	Ref		

3.1.6. Factors Associated with Normal Height for Age

The interruption of treatment and the start of ART before the age of 2 years were the main factors influencing height of the children of our entire study population (Table 4 and Table 5). The multivariate analysis reveals that: 1) children who do not interrupt their treatment were more likely (OR (95% CI; 2.72 (1.78 - 4.15))) to have a normal height than those who interrupt their treatment regardless of is the age of initiation. 2) those who started treatment after the age of 2 years had lower chance (OR (95% CI; 0.078 (0.001 - 0.45))) of reaching a normal height than those who started treatment before the age of 2 years.

Table 4. habits and events related to height for age normal.

		Height for normal age		**p value chi-square**
		Yes (46)	No (8)	
ARV protocol	ABC + 3TC + LPVr	8	1	0.182
	AZT + 3TC + LPVr	11	3	
	AZT/ABC/D4T + 3TC + NVP	21	1	
	Other	6	3	
Hospitalization	0 hospitalization	12	3	0.318
	1st hospitalization	14	3	
	2 to 4 hospitalizations	14	0	
	At least 5 hospitalizations	6	2	
Treatment interruption	Yes	5	2	0.000
	No	44	3	
Compliance	Good	35	7	0.608
	Bad	39	1	
Cotrimoxazole	Yes	23	4	1
	No	23	4	
ART before age 2	Yes	14	6	0.016
	No	32	2	

Table 5. Factors associated with normal Height for age.

		Height for normal age		**Odds Ratio**	**p value**	**Confidence interval**
		YES (46)	NO (8)			
Treatment interruption	Yes	2	3	2.72	**<0.001**	[1.78; 4.15]
	No	44	5			

Continued

ART started before the age of 2 years	Yes	14	6	0.078	**0.019**	[0.001; 0.45]
	No	32	2			

4. Discussion

The aim of our work was to study the growth of children put on antiretroviral treatment before the age of 2 years at Essos Hospital Centre. It emerges from this work that: early initiation of ART promotes catch-up in stature and weight; in addition, discontinuation of treatment influences weight and height independent of age of initiation. Regarding sociodemographic data, our study allowed us to find a female predominance. This result is similar to that previously obtained in the same site with a female predominance (52%) amongst HIV-infected children but contrary to the findings of Weigel *et al.* in Malawi [14] [15]. The average age of our participants was 9 years old. This trend is above the findings of Thanyawee *et al.* which was 6.4 years [9]. Almost all (96%) of the children were born to HIV-positive mothers thus perinatally infected. This figure is close to that of Kazadi *et al.* who found a frequency of 95.7% [16]. The rate of underweighted children under 2 years old at the start of ART compared to those over 2 years old is comparable to the profile described by Jesson *et al.* in South Africa in 2015 [17]. In addition, we recorded a high frequency of stunting in children older at initiation (50%) compared to those under 2 years old (38%) but statistically not significant. Thus, our results differ from those of Jesson *et al.* who found in a similar study that children initiated on ART before the age of 5 years were more affected by growth retardation compared to those initiated after 5 years with a significant difference [17]. Our analysis made it possible to highlight an improvement in height and weight under ART both in children initiated on ART before the age of 2 years than in those initiated after 2 years. These results can be superimposed on those found in other studies carried out in sub-Saharan Africa [18]-[20]. These positive effects of ART on height and weight growth are key indicators of a good response to treatment.

4.1. Weight and Interruption of Treatment

However, the effect of the interruption on growth differs according to the authors; some highlight its interest in optimizing treatment: Coton *et al.* [21] in a study found that interrupting ART over time after initiation at an early age showed good clinical and immunological responses after resumption of treatment compared to the deferred treatment group. Penezzato *et al.* in 2014 during a study on the optimization of ART in HIV-infected children found that children who interrupted their treatment had similar growth than those who had continuous treatment [22]. These differences could be explained by the duration of the interruption which length varies in various studies from less than 3months to 33 weeks [21]. Indeed, Dalton *et al.* found that a "short" interruption duration did not compromise growth [23].

4.2. Age at Initiation

The age of initiation to treatment did not influence the weight of the children in our study. Our results differ from those found by Diniz *et al.* in Brazil [24] who found that young age at initiation was a predictor of greater weight catch-up. Similarly, Nachman *et al.* [8] in a study similar to ours reported that children under 2 years of age were more likely to catch up on their weight compared to older ones. Some authors in the European context claim that it would take up to 5 years of exposure to ART to catch up to normal height [25].

5. Conclusion and Global Health Implications

At the end of this study, we can conclude that the catch-up of height was poorer compared to weight. Our results further highlight the age at initiation of ART as a predictor of better catch-up growth, with significantly improved chances in children starting antiretroviral treatment before the age of 2 years. Despite significant improvement in growth after ART, some of these children remained below normal for weight and much higher for height, even in the best-response age-group.

In addition, continuous treatment without interruption is associated with a normal W/A and H/A whatever the age at initiation thus highlighting the importance of lifelong adherence counseling. All these findings stress the recommendations to start the treatment as early as possible in children even as early as the neonatal period with a closely clinical and biological monitoring of children under ART.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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