Research Article

Height at three years of Highly active antiretroviral has a strong correlation with height at diagnosis in children with HIV infection

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Abstract:

Background

Study shown that stunting in children with human immunodeficiency virus might persisted until age 18 years, despite the course of highly active antiretroviral therapy (HAART).

Aims

To compare stunting proportion at diagnosis and at three years after HAART in children with HIV infection aged below five years.

Methods.

The study was done in Sanglah Hospital, Bali - Indonesia. Inclusion criteria: HIV infection, started HAART in 2009 to 2015, age 1 month to 5 years, had no major congenital anomaly, and parents consented. The cohort were divided into groups of children aged <2 years and >2 years, then followed for 3 years. Chi square analysis was used to test a difference between groups at diagnosis and three years after HAART. Mc Nemar test was used to analyze the difference within children group between two times measurement.

Results

From 146 eligible children, 77 completed three years of observation (37 in the <2 years and 40 in the > 2 years group). No difference of stunting proportion was found between the two age groups at diagnosis (59.45% vs 72.50%, P=0.229, 95%CI -7.85% to 32.67%), but significant difference found at 3 years (32.43% vs 65.00%; P=0.045, 95%CI 10.22% to 50.71%). In age < 2 years group, stunting reduced significantly at 3 years (difference -27.02%; P=0.0063; 95% CI - 43.18 to -10.87), but not in children age > 2 years (difference -7,50%; P=0.5078; 95%CI -22.02 to 7.02).

Conclusion:

In children ages two to five years, stunting proportion remains unchanged after three years of HAART.

Keywords: Stunting, Children, HIV, HAART

Introduction

The success of Highly active antiretroviral (HAART) in survival during HIV epidemic in children is well known.[1-5] Whether it is able to maintain or improve the quality of life needs to be elucidated. Growth in term of weight for age z score (WAZ or WHZ) were significantly improved on cohort of children with HIV infection who used HAART. The cohort mostly was done in one or two years of observation. The linear growth failure or stunting recovery were not as satisfying as weight gain.[5-10]

A remarkable finding emerged from a large cohort of Asian children presenting the persistence of stunting after HAART was instituted. This persistence of stunting was documented at the age of 18 years where growth does not occur. Children who were not stunting at HAART initiation might also experienced stunting by the age of 18 years.[11]

There is an ongoing debate whether linear growth was improved after HAART institution, in especially in younger age. We wanted to obtain more information from younger age group, which dominated our cohort. Our previous study documented that stunting in children with median age 31 months might persist early in the first year of HAART initiation and also developed in those who were not stunting at the beginning.[12]

In the current study, we wanted to assess whether the stunting proportion at diagnosis was different from the three years of HAART in children aged under five years. The results will contribute as an evidence for the role of early stunting to the persistency of stunting in longer term.

Methods

Study population

This study is a part of a longitudinal cohort which was done to follow 215 children with HIV infection in Sanglah Hospital in Indonesia, who were diagnosed with HIV based on clinical symptom and HIV Antibody test or HIV-1 PCR RNA. The Udayana University/Sanglah hospital

participated in TREAT Asia pediatric HIV observational database, in which we documented the data for this study analysis.

Eligibility criteria

The subjects were randomly included if aged less ≤5 years at diagnosis, starting HAART, having height documentation routinely at least three months apart, and has had documentation at least one year, had no major congenital anomaly, and parents consented for participation.

Study group

Subject was divided into two groups, consisting children aged ≤ 2 years and aged > 2-5 years.

Follow up

Follow up was done for height measurement. Children was considered drop out if died, migrated from Bali Province, or lost to follow up. Lost to follow up was defined as height documentation was not available in one year since previous clinic visit.

Those who did not complete three years observation if they died, transfered or lost to follow up before finished three years observation were excluded from analysis for this study. Height at diagnosis was determined as explanatory variable while height at three years was determined as response variable. Height was measured either in erect position for children older than 2 years or recumbent for children younger than 2 years. Stunting was defined as height for age z score less than -2SD according to age and sex WHO reference.(ref)

Statistics

Chi squared test was used to compare stunting proportion between the two age groups at diagnosis, as well as at three years of HAART. The Mc Nemar statistic was used to compare stunting proportion at diagnosis and three years of HAART within group of children aged ≤ 2 years and > 2 years. The significance of statistical analysis was considered at $P<0.05$ and 95% confidence interval (95%CI). Statistical analysis was carried out in MedCalc version 19.03

Ethical aspect.

Children were included once informed consent was given by parent or caregiver. Institutional Review Board (IRB) of Kerti Praja Foundation and Sanglah-Hospital Ethical-Committee issued the ethical clearance for the study.

Results

There were 215 children with HIV infection during the study but only 146 were considered eligible for the study. Seven children died, 60 were lost to follow up, and 2 transferred out. Only 77 (52.7%) of eligible children completed three years observation and had analysis. Flow chart of the study was shown on Figure 1.

Study subjects characteristic was shown in **Table 1**. Difference of stunting proportion between children aged ≤ 2 years and > 2-5 years at diagnosis was assessed using Chi squared test, as depicted in **Table 2**. **Table 2** shown that there was no difference of stunting proportion at the time of diagnosis between children aged ≤ 2 years and > 2-5 years (59.45% vs 72.50%, P=0.229, 95%CI -7.85% to 32.67%). However, at three years of HAART, difference of stunting proportion between children ≤2 years and >2 years to five years was significant (32.43% vs 65.00%; P=0.045, 95%CI 10.22% to 50.71%).

To ensure the difference of stunting proportion between the two age groups at the time of diagnosis and three years after HAART, we delivered McNemar z test, as designated on **Table 3.** The McNemar test indicated the stunting proportion was reduced significantly in children aged ≤ 2 years, while stunting proportion in children aged >2-5 years, was reduced but non significant statistically. To further analyse the relationship between the linear growth at diagnosis and after three years of HAART, comparison is shown of height at diagnosis and height at three years of HAART (**Figure 2)**. The correlations were positive and strong for both age groups (r=0.86 and 0.83, 95% CI 0,5 to 0,8 and 0,4 to 0,6 respectively with both P<0.0001). The scatter plot diagrams indicated the slope of the fitted lined for children ≤ 2 years of age was sharper than children aged >2 to 5 years.

These data indicated height attainment at three years of HAART was easier to reach for children aged ≤ 2 years.

Discussion

Stunting was a global issue and has been a target to reduce by 40% in 2025.(ref) HIV infection in children contributed significant proportion of stunting. Considering a gap of antiretroviral distribution among women and children globally,[5] stunting in HIV infected children has consistently challenged pediatric practices. As growth is a characteristic of the childhood, many aspects threatened growth in HIV infection also need to be identified during this period.

Many previous pediatric HIV reports shown benefit of HAART on growth.[13-16] These reports exhibited limitations in term of evidenced horizontal instead of linear growth (benefit WAZ and WHZ more than or instead of HAZ), delivered in a relative short term (one to two years observation), and using wide age range. As height reflected a no-return process that occured in the growth plate,[17,18] it was very important to carefully study whether stunting in HIV has different mechanism over a chronic lack of nutrition. This perspective was built based on Bunuparadah study,[11] which shown a persistency of stunting in children by the age of 18 years. The persistence occured irrespective if the children were or were not stunting at the start of HAART. Bunuparadah study indicated a pitfall in linear growth observation during childhood. As much as 52% of children who started HAART at 11 years or older remained stunted. Another 12% became stunted and 27% of children who did not have height record at the beginning of the study were found stunted at age 18 years.This study, however, has been done in children who started HAART by the age of eleven years. Stunting in children younger is not known. A cross sectional study done by Vedaswari, showed that age was a predictor to non reversal at three years of HAART.[19]

First five years has been considered as an utmost important period in childhood where growth and development mostly take place. Based on Bunuparadah and Vedaswari studies, we compared two groups of children under five years of age for linear growth outcome based on each

group growth pace and showed little difference of growth trajectory between children aged ≤ 2 years and >2 to 5 years.

Our study also showed that children under five years, when grouped as younger and older one, can exhibit different outcome in linear growth despite no difference at diagnosis . Despite a three observation we were able to demonstrate the failure to overcome stunting in relatively short period despite HAART. Our study was in contrast to McGrath and other studies,[13-15] which describing the benefit of starting HAART in younger age for growth reconstitution. However these studies mostly were done as two years observation. In our setting, we also started HAART earlier, nonetheless, the growth rate apparently has been programmed to follow the slow pace over longer period although the slope of the fitted line was sharper in younger age. Our finding was also in accordance to Boetigger findings[16] with regards to failure of observing height increment over two years observation in children using HAART. Such failure was also documented in European study.[20]

In many settings, observing children for a long period was a significant challenge as most children are lost to follow up dominated as in our setting. Our project first aim was to identify shifting of stunting proportion during HAART in children younger than five years of age. We sought to identify whether this younger age group also shown the typical growth failure for longer duration. In our setting, children with HIV infection came at earlier age compared to other countries in Asia.[9,11] We have complemented for Bunuparadah study by expanding knowledge to the younger age group.

The current study was in line with our previous findings showing time to the peristency and new stunting occured in the first year of HAART.[12] We found that in the first year, the stunting persistency has been documented in a 59% of subject, while a 25% documented a new stunting. This mean as much as 25% of children who live with HIV had stunting although they were not at the beginning of HAART with implications for HIV Program.[12]

Preventive steps can be taken as shown by Bunuparadah when closure of the growth plate has occurs as the child ages. Further research on larger number of children can be done to seek deeper mechanism of stunting in children with HIV infection. Multifactorial reasons such as chronic lack of nutrition -either in the calorie amount, or, chronic inflammationin HIV infection has been proposed that might play a role not by the chemical mediators released during the event only but also the preceeding phenomenon.[21] Serum zinc status and result of clinical trial despite failure of supplementation contributed to another possible mechanism, such as zinc signaling failure[22-26] and so proper management may be optimized.

Our study limitations includes not to observe calorie intake. However, as our center was a part of TApHOD study, we have done regular survey about feeding practices which shown similarity across Asia. Nutritional advice and food supplement were part of the clinic regular program. Lost to follow up was high, accounting 41% of the eligible participants, however, the distribution of the lost to follow up was similar between the groups.

In conclusion we have shown that children aged between 2 and five years were unable to thrive from stunting after three years commencing HAART.

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Table 1. Subject characteristic

Characteristic	Age ≤ 2 years (n=37)	Age 2 to 5 years (n=40)
Age at diagnosis , month, median (IQR, range)	31 (37.2, 4-58)	
Sex, girl, n (%)	17 (45.9)	15(37.5)
Clinical category		
Stage 3-4, n (%)	30(81.0)	28(70.0)
Stage 1-2, n (%)	7(19.0)	12(30.0)
CD4 level at diagnosis, cell/mL, median (IQR, range)	163 (468,2-1997)	
Immune suppression at diagnosis		
Severe -Advance, n (%)	27 (72.9)	34 (85.0)
Mild to moderate, n (%)	10 (27.1)	6 (15.0)
Hemmoglobin at diagnosis, g/dL, median (IQR, range)	10 (2, 2.1-14)	
Anemia at diagnosis, n (%)	33 (89.2)	35 (87.5)
Undernutrition at diagnosis, n (%)	25 (67.6)	25 (62.5)
Height at diagnosis, cm, mean (SD)	83.9(14.9)	
Height at three years, cm, mean (SD)	108.6 (9.5)	
Stunting at diagnosis, n (%)	22 (59.4)	29 (72.5)
Stunting at three years, n (%)	15 (40.6)	26 (65.0)
Firstline HAART ever, n (%)	35 (94.5)	35 (85.0)
Second-line HAART, n (%)	2 (5.5)	6 (15.0)

Table 2. Stunting proportion at diagnosis in children aged ≤2 years and >2 to 5 years

Group	Stunting Proportion	Proportion difference	Chi-squared	DF	P value*	95% CI
At diagnosis						
≤2 years (n=37)	59.45%	13.05%	1.445	1	0.229	-7.85% to 32.67%
>2 to 5 years (n=40)	72.50%					
At three years						
≤2 years (n=37)	32.43%	32.57%	8.05	1	0.045	10.22% to 50.71%
>2 to 5 years (n=40)	65.00%					

** Chi-squared test, two sided test, CI, Confidence interval*

Table 3. Comparison between stunting proportion at diagnosis and after three years of HAART in children with HIV infection aged ≤2 years and > 2 to 5 years

Group	Stunting Proportion	Difference proportion	P value*	95% CI
≤2 years (n=37)				
At diagnosis	59.45%			
At three years of HAART	32.43%	-27.02%	0.0063	- 43.18 to -10.87
≥2 to 5 years (n=40)				
At diagnosis	72.50%			
At three years of HAART	65.00%	-7,50%	0.5078	-22.02 to 7.02

**McNemar test; CI,Confidence interval*

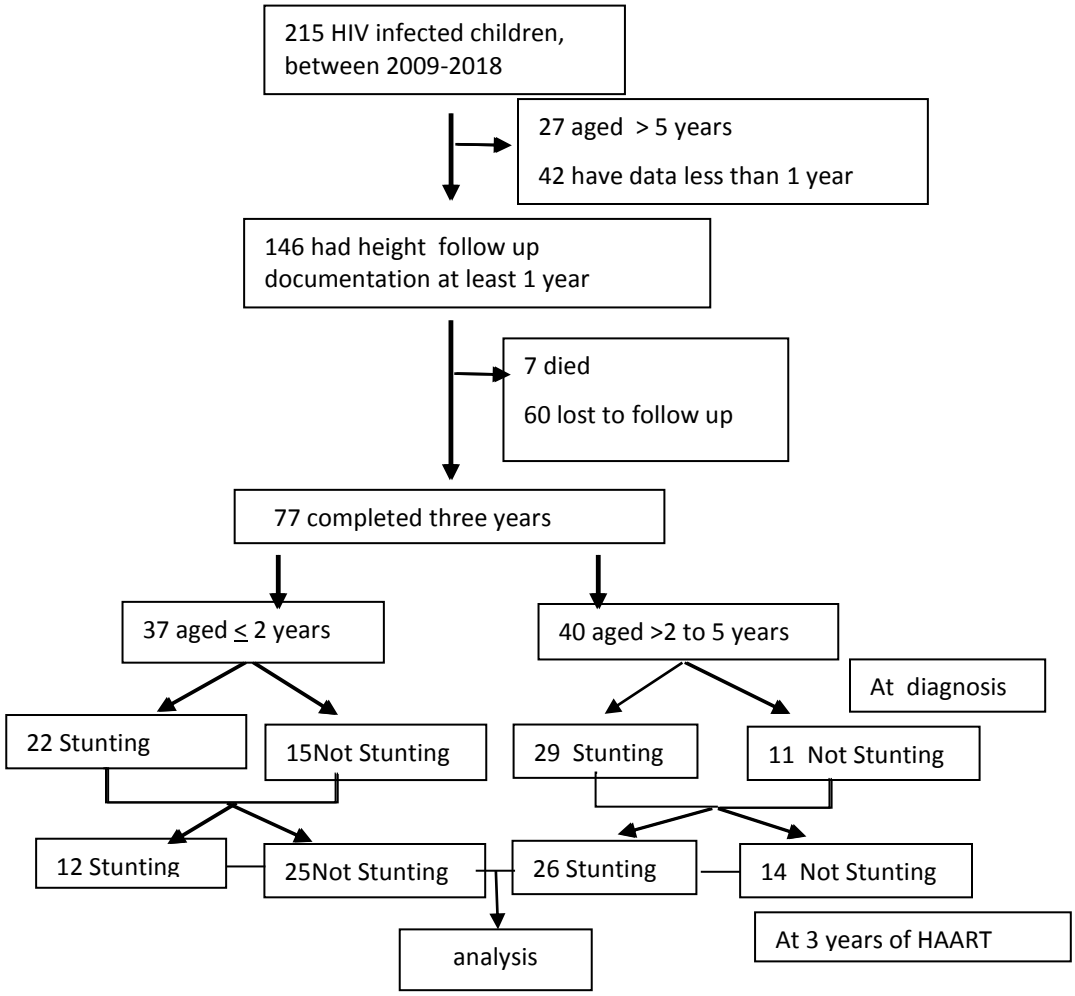

Figure 1. Flowchart of the study

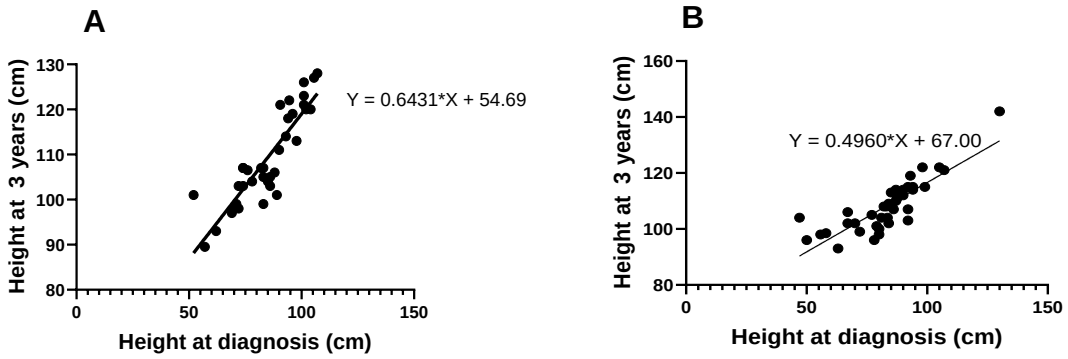

Figure 2. Scatter plot diagram of height at three years of HAART and height at diagnosis for children ≤ 2 years (A) and >2 to 5 years (B).