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Original Article

Age and HIV stage at initiation of highly active antiretroviral therapy determine non-reversal stunting at 3 years of treatment

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Abstract

Background Highly active antiretroviral therapy (HAART) has been reported to improve growth, especially in the first 2 years of treatment. It is not clear whether catch up growth is maintained after 2 years of HAART.

Objective To assess growth in stunted children with HIV after 3 years of HAART and analyze possible risk factors for non-reversal of stunting.

Methods This study was done from May 2016 to April 2017 to follow children with HIV who started HAART between January 2009 and April 2014, and continued for 3 years. Inclusion criteria were children with HIV, aged < 18 years, compliance to the regimen, and stunting. Exclusion criteria were patients lost to follow up or who died prior to 3 years of HAART. Non-reversal of stunting was defined as HAZ ≤ -2SD after 3 years of HAART. Possible risk factors for non-reversal were analyzed using Chi-square test with P<0.05, as well as risk ratio (RR) and 95% confidence intervals (CI).

Results Of 150 HIV-infected pediatric patients, 115 were on HAART and 55 (47.8%) were stunted at HAART initiation. Of the 55 stunted and HAART-treated children, 31 (56.4%) were male. Baseline median age was 3.6 years (interquartile range 0.37-8.48). Non-reversal occurred in 32 (58.2%) subjects. Multivariate Cox regression model analysis showed predictors of non-reversal after 3 years of HAART to be age >2 years (RR 16.05; 95%CI 2.89 to 89.02; P=0.002) and HIV stage III-IV (RR 8.93; 95%CI 1.47 to 54.37; P=0.017).

Conclusion The HAART initiation at age >2 years and HIV clinical stage III-IV at diagnosis are risk factors for non-reversal of stunting after 3 years of HAART. **[Paediatr Indones. 2018;58:180-5; doi: http://dx.doi.org/10.14238/pi58.4.2018.180-5]**.

Keywords: *HIV; stunted; HAART; three-year observation; non-reversal*

In the last two decades, Indonesia has seen a concentrated HIV epidemic expand into a generalized one, as a result of the growing number of women of childbearing age who are infected with HIV.[1,2] The cumulative number of children under 15 years of age with HIV in Indonesia from 1987 to 2014 was reported to be as many as 1,647, of whom 1,206 were under the age of five years.[3] *The World Health Organization* (WHO) noted that only 21-25% of children infected with HIV received antiretroviral therapy.[4] Although HAART improves the survival of children with HIV, optimizing health and quality of life of pediatric survivors remains a major challenge.[5] Without effective treatment, an estimated one-third of children with HIV die in the first year of life, and about half die in the second year.[6]

Several studies reported growth improvements in children with HIV after HAART initiation. Mwiru *et al.* found that children with HIV showed

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improvement in metabolism in the first 6 months of HAART.[7] Similarly, Suryani *et al.*[8] observed growth improvement for 12 months, and Sari et al. showed growth improvement at 24 months of HAART.[9]

Although studies have reported growth and nutritional care improvements within 2 years of HAART, other studies noted that stunting may occur after such time.[7,10,11] A study of 225 HIV-infected children found a probability of 58% for growth reversal among 179 subjects with growth failure at entry, while the rest remained in growth failure. Age, sex, and clinical category at the time of ART initiation were not risk factors for reversal.[12] Therefore, we aimed to assess if non-reversal of stunting occurred in children with HIV after three years of HAART and to examine risk factors for non-reversal of stunting.

Methods

The study was a part of a prospective cohort study which followed children with HIV who initiated HAART between January 2009 and April 2014, in particular, those with stunting. The study was conducted from May 2016 until April 2017 in the Allergy Immunology Division, Department of Child Health, Sanglah Hospital, Denpasar, Bali. Subjects were part of the eligible population who met the following inclusion criteria. Children with HIV aged < 18 years, good HAART compliance, stunted at the time of HIV diagnosis, and whose parents were willing to participate. Exclusion criteria were lost to follow up or died during observation. In addition to HAART, all children received daily zinc supplementation.

We collected subjects' age, sex, weight, height, height-for-age z-score (HAZ) to determine stunting, recent opportunistic infection, recent anemia, CD4+, nutritional status, family economic status, HIV clinical stage at the start of ART, and 3 years of data to determine linear growth pattern, and risk factors for non-reversal of stunting. All data were collected from the subjects' medical records. The variables were defined as follows:

- Stunted: HAZ <-2SD according to the WHO Child Growth Standard.[13] Stunting was determined at the time of diagnosis and calculated using the *2005 WHO Anthro and Anthroplus software*.
- Opportunistic infection: an infection in a person with poor immunity, which would normally not cause infections in those with normal immunity.[14]
- Anemia: determined based on the WHO criteria for HIV clinical stage 3, in which hemoglobin was < 8 g/dL.[15]
- Nutritional status: determined using the Waterlow formula, in which actual body weight was divided by ideal body weight. Ideal body weight was determined using the *WHO Growth Chart* for body weight over height.[16]
- Family economic status: the economic ability to meet the needs of all family members. Our subjects were assumed to have similar economic status, since all subjects used government health care insurance.
- HIV clinical stage: determined based on the WHO clinical stage category.[15]
- Non-reversal of stunting: HAZ <-2SD after 3 years of HAART.

Characteristics of subjects were presented descriptively in tables for the variables of age, sex, and HIV clinical stage, as well as tuberculosis, anemia, chronic diarrhea, CD4+, and nutritional status. Linear growth patterns during 3 years of HAART was presented as a graph. We calculated the proportion of non-reversal of stunting in our subjects. Possible risk factors for non-reversal were analyzed by Chi-square test. Covariates were considered for inclusion in the multivariate model if one or more categories exhibited a P value <0.1 in the bivariate model and were retained if 1 or more categories exhibited a P value <0.05 in the adjusted model.[17] Risk ratio (RR) of associated factors was determined with 95% CI. Analyses were done with *SPSS version 18 software*. This study was approved by the Medical Ethics Committee of Universitas Udayana/Sanglah Hospital, Denpasar.

Results

A total of 150 children were in the data cohort. Of these, 118 children were alive and 115 children had received HAART. At baseline, 55 (47.8%) children were stunted at HAART initiation, hence, they were included in our study. Only 23 (41.8%) subjects achieved growth reversal after 3 years of HAART

Table 1. Demographic and clinical characteristics of stunted, HIV-infected children at the time of HAART initiation

Clinical characteristics	(N=55)
Sex, n (%)	
Male	31 (56.4)
Age at baseline, n (%)	
≤ 2 year	12 (21.8)
> 2 year	43 (78.2)
Anemia at baseline, n (%)	
Yes	8 (14.5)
No	47 (85.5)
Nutritional state at baseline, n (%)	
Severe-moderate malnutrition	38 (69.1)
Well-nourished	17 (30.9)
Chronic diarrhea at baseline, n (%)	
Yes	5 (9.1)
No	50 (90.9)
Tuberculosis at baseline, n (%)	
Yes	21 (38.2)
No	34 (61.8)
CD4+ level, n (%)	
< 15% or < 200 cells/μL	39 (70.9)
≥ 15% or ≥ 200 cells/ μL	16 (29.1)
HIV stage at baseline, n (%)	
Stage I-II	8 (14.5)
Stage III-IV	47 (85.4)
Mean HAZ (SD)	-3.27 (0.9)
Stunting after 3 years of HAART initiation, n (%)	
Reversal	23 (41.8)
Non-reversal	32 (58.2)

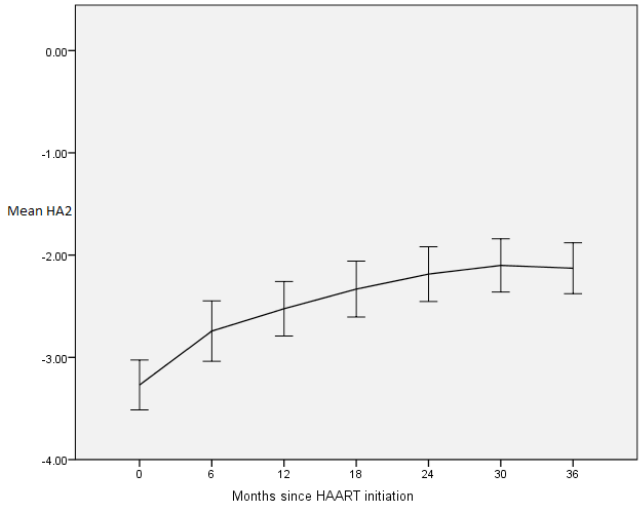
initiation. Characteristics of the 55 subjects are shown in **Table 1**.

The mean HAZs during the follow up period are shown in **Figure 1**. Upon on HAART initiation, mean HAZ improved for the first 6 months, then stabilized with only minimal improvements in linear growth over the 3 years of HAART. The trajectory of HAZ over the 3-year observation tended to plateau.

Table 2 shows the factors associated with non-reversal of stunting. Multivariate Cox regression analysis of the 55 children who were stunted at baseline revealed that the strongest predictors for non-reversal of stunting were age>2 years (RR 16.05; 95%CI 2.89 to 89.02; P=0.002) and HIV stage III-IV at HAART initiation (RR 8.93; 95%CI 1.47 to 54.37; P=0.017).

Discussion

Stunting is defined as height for age below minus 2 SD, according to *The WHO Child Growth Standard*. Stunting indicates a failure to achieve potential linear growth as a result of suboptimal health and/or nutritional conditions.[13] Children with HIV infection have a higher risk of stunting compared to uninfected children. In Tanzania, 36.6% of children infected with



	0	6	12	18	24	30	36
Mean HAZ	-3.27	-2.74	-2.52	-2.33	-2.19	-2.10	-2.13
Mean change	0	0.53	0.22	0.19	0.14	0.09	-0.03
% Stunted	100	81.8	74.5	61.8	65.5	61.8	58.2

Figure 1. Mean HAZ over the 3-year follow up period after HAART initiation

Table 2. Predictors of non-reversal of stunting

Characteristics	Bivariate[a]		Multivariate[b]	
	Risk ratio (95%CI)	P value	Risk ratio (95%CI)	P value[c]
Age >2 years	2.76 (1.64-4.64)	0.001	16.05 (2.89-89.02)	0.002
Anemia	1.41 (0.87-2.28)	0.225	NA	
Severe-moderate malnutrition	1.28 (0.73-2.26)	0.262	NA	
CD4+ level	0.64 (0.35-1.17)	0.138	NA	
Chronic diarrhea	1.07 (0.50-2.28)	0.623	NA	
Tuberculosis	1.33 (0.84-2.09)	0.176	NA	
HIV stage III-IV	2.07 (1.19-3.60)	0.048	8.93 (1.47-54.37)	0.017

[a]By Chi-square analysis; [b]By Cox regression analysis; [c]Only characteristics with P value ≤ 0.1 in bivariate analysis were included in the multivariate analysis

HIV were stunted, compared to 21.8% of children who were not infected with HIV.18 McDonald *et al.* studied 2,387 infants born from HIV-infected mothers for 21 months in Tanzania. They found that stunting occurred in 8.7 months of observation, and the risk factors for stunting in these infants included low maternal education, poverty, low birth weight, HIV infection, and male gender.[18] The age of 6 to 24 months is the most critical period for linear growth in children, and the time of peak incidence of stunting in children in developing countries.[19] In this study from a database of 150 children with HIV infection, we found 36.7% children with stunting at time of HAART initiation. Similarly, Aurpibul *et al.*[10] reported 42% in Thailand, but an African study found an even higher proportion of children with stunting, 76.3%.[12]

The goal of administering HAART to HIV-infected children is to prolong life and ensure that they achieve sustained growth and development.[19] In a Dar es Salaam study in 2004, HIV-positive children without ART therapy had a higher proportion of stunting.[14] Prendergast *et al.* assumed that the phenomenon of stunting occurred due to a state of low-grade inflammation, due to HIV infection as a result of enteropathy.[20] HIV infection may result in stunting, despite having good nutrition and a normally functioning endocrine system. Several studies described positive short-term responses of HAZ to ART.[21] Kabue *et al.* found that administering ART resulted in improvement in HAZ in all subjects who had at least 6 months Of follow-up, and again at 12 months follow-up, respectively.[22] Similar results were found by Suryani *et al.*,[8] who observed children with HIV infection for 12 months, and Sari *et al.*,[9] who observed children with HIV infection for 24 months. However, few studies reported a growth response to ART beyond 24 months.[22] Sutcliffe *et al.* reported that after starting ART, nutritional status improved in both weight and height, but even after two years of ART, approximately 50% of children remained stunted.[23] With a longer period of observation, we found that in 58.2% of children, stunting was not reversed, despite receiving ART for 3 years. Mwiru *et al.* also reported that after ART initiation, child anthropometry *z*-score profiles improved, however, HAZ scores did not reach the normal value even after 6 years of follow up.[7]

Some factors were associated with reversal of growth failure. Aurpibul et al. found that a nevirapine-based regimen was a significant predictor of reversal of growth failure after initiating ART.[12] In our study, all subjects received WHO-recommended first-line, antiretroviral drugs in the form of two NRTIs and one NNRTI, including zidovudine, lamivudine and nevirapine. Children with HIV infection may have underlying chronic conditions or opportunistic infections, including anemia, tuberculosis, and chronic diarrhea, all of which can result in growth faltering by inadequate food intake and increased resting energy expenditure.[22] Diarrhea is the most common chronic condition among HIV-infected children, causing acute weight loss through water and electrolyte loss, leading to poor growth.14 Diarrhea was associated with weight-for-age *z*-scores (WAZ) <-2SD.[14] However, we found that anemia, tuberculosis, chronic diarrhea, and malnutrition at the time of ART initiation were not associated with non-reversal of stunting in this population. Similarly, Mwiru *et al.* found that anemia, tuberculosis, and chronic diarrhea were not associated with growth outcome.[7]

Age >2 years at HAART initiation was a significnt predictor of non-reversal of stunting in our study, similar

to findings of Mwiru *et al.*[7] Better growth outcomes among younger children could be related to the duration of infection, allowing them to more effectively absorb nutrients after viral suppression by ART. The longer duration of HIV infection in older children may further require more time to reserve the damage, implying a more prolonged metabolic cost.[7,24]

Sunguya *et al.* found that advanced HIV stage was a risk factor for stunting. At advanced stages, a child may succumb to poor linear growth, even with adequate food availability, due to frequent opportunistic infections. These severe opportunistic infections may lead to increased energy expenditure at rest.[14] This result was similar to our finding that stage 3 and 4 HIV at HAART initiation was a significant risk factor for non-reversal of stunting. In contrast, Diniz et al. reported a greater height catch-up after starting HAART in subjects with clinically advanced disease at baseline.[25]

A limitation of our study was not including parental, family, or caregiver data, as another study found that family situation was related to growth.26 In conclusion HAART initiation at age >2 years and HIV clinical stage III-IV at diagnosis are risk factors for non-reversal of stunting after 3 years of HAART.

Conflict of interest

None declared.

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