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Final Height and Associated Factors in Perinatally HIV-Infected Asian Adolescents

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Abstract

We analyzed final height (FH) of 273 perinatally HIV-infected Asian adolescents aged 18 years at their last clinic visit. By the WHO child growth reference, 30% were stunted, but by the Thai child growth reference, 19% were stunted. Half of those who were stunted at antiretroviral therapy initiation remained stunted over time. Being male and having a low baseline height-for-age z-score of <−1.0 were associated with low FH z-score.

Keywords

height; adolescents; perinatal; HIV; Asia

In developed countries, children living with HIV have shorter stature compared to uninfected children (1–4). In one study, perinatally HIV-infected US children (median age 12.6 years, 87% on antiretroviral therapy [ART]), were significantly shorter than HIV-

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exposed but uninfected children (4). Stagi et al., reported significantly reduced final height (FH; defined by bone age of at least 16 years for boys or 14 years for girls and height velocity of <1 cm per year) in perinatally HIV-infected Italian adolescents (median age 17.5 years, 75% using ART) (2). In adolescents living with chronic illnesses, short stature has been associated with worse prognosis (5), and low quality of life and self-esteem (6, 7). There are limited data on FH in HIV-infected children in the Asia-Pacific region. We report on FH, defined as height at 18 years of age (8), of PHIVA and predictors of lower FH z-score in a regional cohort.

METHODS

Participants were selected from the TREAT Asia Pediatric HIV Observational database (TAPHOD) (9). Details of the overall study design and description of the cohort have been previously published (9). TAPHOD contains information on demographic characteristics, anthropometric parameters, ART, CD4, HIV-RNA, and other clinical and laboratory outcomes. Ethics approvals were obtained at all 16 participating clinics in six countries (Cambodia, India, Indonesia, Malaysia, Thailand, and Vietnam), the data management and biostatistical analysis center (the Kirby Institute, UNSW Australia), and the coordinating center (TREAT Asia/amfAR, Bangkok). Participant consent and assent requirements followed the guidelines of the institutional review boards of the individual participating sites.

For this analysis, we included perinatally HIV-infected children who were initiated on highly active ART (HAART) regimens after 1 January 2003 and had height measurements at age 18–19 years. Children with a known or documented history of endocrine diseases (e.g., thyroid disease, growth hormone deficiency) were excluded. FH was defined as height at 18 years of age (8). Height-for-age z-score (HAZ) and weight-for-age z-score (WAZ) were calculated by using the 2007 World Health Organization (WHO) child growth reference (10). As the majority of PHIVA were from Thailand, we also performed a sub-analysis by using a 2002 Thai child growth reference (INMU-NutriStat program, Institute of Nutrition, Mahidol University, Thailand). Stunting was defined as HAZ <−2.0 (5). Baseline height at HAART initiation was defined as the height measurement closest to the date of HAART initiation, within six months before or within one month after HAART initiation.

Descriptive statistics were used to summarize characteristics of the HIV-infected children through adolescence, and linear regression models were used to examine the influence of the baseline characteristics on FH. Covariates were considered for inclusion in the final hazard model on the basis of an unadjusted association with FH z-score ($p < 0.10$). Final models used a backward stepwise elimination procedure and predictors were sequentially eliminated on the basis of the highest p-value. Analyses were performed using STATA Version 10 (Stata Corp, College Station, USA). Results are presented as adjusted hazard ratios (aHR); statistical significance was defined as $p < 0.05$.

RESULTS

Up to March 2013, 5030 children were enrolled in TApHOD and 320 PHIVA reached age 18 years or beyond at their last visit. Among these, 273 PHIVA who had height measurements at age 18 were included in this analysis. Sixty-percent were female, and the majority (92%) were from Thailand, with 4% from Cambodia, and 4% from India, Vietnam, and Malaysia. At HAART initiation, median (IQR) age was 11.4 (10.2–12.7) years, 53% were classified as WHO stage III/IV, and median WAZ was -2.6 (-3.7 to -1.3); median hemoglobin was 11.0 (10.0 – 12.0) g/dL, median CD4% was 5 (2 – 11)%, median CD4 cell count was 161 (23 – 226) cells/mm³, and median HIV-RNA was 5.0 (4.6 – 5.4) log₁₀ copies/mL. Sixty-eight percent were single or double orphans. Initial HAART regimens included nevirapine (57%), efavirenz (35%), and ritonavir-boosted lopinavir (8%). The three most common nucleoside reverse transcriptase inhibitors were lamivudine (93%), zidovudine (33%), and stavudine (58%). Children were on HAART for a median (IQR) duration of 7.3 (5.9 – 8.6) years.

At age 18 years the median FH was 164 (157 – 169) cm for males and 154 (149 – 157) cm for females (Table 1). As median standard FH by the WHO child growth reference was 176.5 cm for males and 163.2 cm for females, the percentages of males and females who had lower FH than the median FH by the WHO child growth reference were 99% and 95%, respectively. By the WHO child growth reference, median (IQR) HAZ was -1.6 (-2.5 to -1.0) for males and -1.4 (-2.1 to -0.9) for females. Eighty-three (30%) PHIVA were stunted. Among those who were stunted at age 18, median FH was 156 (153 – 158) cm for males and 147 (144 – 149) cm for females.

According to the Thai child growth reference, the standard median FH was 170 cm for males and 159 cm for females. The percentages of males and females in this study had lower FH than the median FH by the Thai child growth reference were 76% and 85%, respectively. By using the Thai child growth reference, median (IQR) HAZ at age 18 was -1.0 (-2.3 to 0.1) for males and -0.6 (-1.7 to -0.0) for females (Table 1). Fifty-three (19%) PHIVA were stunted; 29 of 110 males (26%) and 24 of 163 females (15%).

At HAART initiation, 194 of 273 children had available height measurements with median HAZ -2.2 (-3.2 to -1.4) (Table 1); 106 (55%) were stunted by the WHO child growth reference. Among these, 51 (48%) remained stunted at age 18 years. Of the 88 children without stunting at HAART initiation, 11 (12%) had stunting at age 18 years. Of the 79 of 273 children who did not have height measurements at HAART initiation, 21 (27%) were stunted at age 18 years (Figure 1).

Predictors of FH

In the multivariate analysis, being male (adjusted coefficient -0.25 , 95%CI -0.44 to -0.04) and having lower baseline HAZ (HAZ < -3.0 [adjusted coefficient -2.04 , 95%CI -2.56 to -1.52], HAZ -3.0 to < -2.0 [adjusted coefficient -1.12 , 95%CI -1.61 to -0.62], HAZ -2.0 to < -1.0 [adjusted coefficient -0.80 , 95%CI -1.22 to -0.39]) were associated with lower FH z-score. Age at HAART initiation, WAZ, WHO stage, duration of HAART, hemoglobin, CD4% and HIV-RNA at HAART initiation, as well as CD4% and HIV-RNA at

last visit, and parental vital status (both alive vs. single or double orphan), were not associated with FH.

DISCUSSION

By using the WHO child growth reference, one-third of the PHIVA were stunted at age 18 years. However, using the WHO child growth reference might lead to an over-estimation of the rate of stunting, as only one-fifth of the PHIVA were stunted at age 18 years when using the Thai child growth reference. Half of the PHIVA who were stunted at HAART initiation remained so at their FH measurement. Males and those with baseline HAZ < -1.0 had lower FH z-score.

The association between perinatal HIV infection and poor child growth is well known, but is insufficiently addressed in routine clinical care services in resource-limited settings. PHIVA in our study had lower HAZ at their FH measurement compared to data from Italian PHIVA (mean [SD] HAZ -0.4 [0.9]) (2), but were comparable to Brazilian PHIVA (mean [SD] -1.2 [1.18]) (5). Associated factors for FH in Brazilian PHIVA included having AIDS symptoms (5), but baseline CD4%, number and duration of antiretroviral regimens, and final CD4% were not associated with FH (5). Aupibul et al., reported only 58% in 179 HIV-infected Thai children who had growth failure, defined as WAZ and HAZ < 1.5 at ART initiation, had the cumulative probability of growth reversal, defined as having improvement of WAZ and HAZ > 1.5 WAZ, after five years of ART (11). Prevention and reversal of stunting should be higher priorities in pediatric HIV care programs.

There were several limitations to this study, including the predominance of data from a single country, and the lack of parental height data, patient pubertal stage, and bone age. Using additional bone age data (2) could be more accurate to identify FH compared to only use a single height measurement at age 18 years. In addition, height measurements were not standardized across the clinical sites, and were collected during routine care over time and by multiple providers. We did exploratory data analysis to verify whether the height at age 18 years is an appropriate definition to represent as a final height. The median difference between last height measurement and age 18 was 0.8 cm, during the 19 months interval. Therefore, the definition that we use a single height measurement at age 18 years is quite accurate. Moreover, the majority of children were initiated on HAART late (between ages 10–12 years) and half of them were classified as WHO stage III/IV with severe immune suppression at baseline. In combination with our limited sample size, it is consequently difficult to fully evaluate the impact of younger age at HAART initiation on low FH.

In conclusion, by the WHO international child growth reference, one-third of PHIVA in this regional cohort were stunted at the age of 18 years and almost half of those who were stunted at HAART initiation remained stunted over time. The association of stunting with being male emphasizes the importance of age and sex disaggregation of HIV outcomes data in order to better understand the HIV disease outcomes and guide interventions. More aggressive efforts to improve earlier diagnosis and access to HIV care and supplemental nutrition support in the Asia-Pacific region could prevent stunting in future generations.

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Figure 1.

Stunting outcomes by WHO child growth reference standards

Final height was defined as height at the age of 18 years.

Stunting was defined as height-for-age z-score of <-2.0 (5)

Table 1

Height and prevalence of stunting in children at HAART initiation and at age 18 years old, by WHO and Thai child growth reference standards

Baseline characteristics			
Median (IQR) age at HAART initiation, years	11.4 (10.2–12.7)		
% WHO stage III/IV	53%		
Median (IQR) CD4% at HAART initiation	5 (2–11)%		
	WHO child growth reference	Thai child growth reference	p-value
At HAART initiation, overall (N=194)			
Median (IQR) height, cm	129 (121–141)		
Median (IQR) HAZ	−2.2 (−3.2 to −1.4)	−1.9 (−3 to −1.0)	<0.0001
Number (%) stunted	106 (55%)	94 (49%)	
At HAART initiation, male (N=80)			
Median (IQR) height, cm	130 (121–139)		
Median (IQR) HAZ	−2.3 (−3.0 to −1.5)	−1.8 (−2.5 to −1.1)	<0.0001
Number (%) stunted	44 (55%)	38 (48%)	
At HAART initiation, female (N=114)			
Median (IQR) height, cm	129 (121–143)		
Median (IQR) HAZ	−2.2 (−3.6 to −1.28)	−2.0 (−3.3 to −0.9)	<0.0001
Number (%) stunted	62 (54%)	56 (49%)	
Final height			
At age 18 years, overall (N=273)			
Median (IQR) height, cm	157 (152–164)		
Median (IQR) HAZ	−1.5 (−2.2 to −0.9)	−0.8 (−1.7 to 0.0)	<0.0001
Number (%) stunted	83 (30%)	53 (19%)	
At age 18 years, male (N=110)			
Median (IQR) height, cm	164 (157–169)		
Median (IQR) HAZ	−1.6 (−2.5 to −1.0)	−1.0 (−2.3 to 0.1)	<0.0001
Number (%) stunted	38 (35%)	29 (26%)	
At age 18 years, female (N=163)			
Median (IQR) height, cm	154 (149–157)		
Median (IQR) HAZ	−1.4 (−2.1 to −0.9)	−0.6 (−1.7 to 0.0)	<0.0001
Number (%) stunted	45 (28%)	24 (15%)	

HAART: highly active antiretroviral therapy, HAZ: height-for-age z-score, IQR: interquartile range; WHO: World Health Organization.

Stunting was defined as height-for-age z-score of <−2.0 (5)