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Weight as predictors of clinical progression and treatment failure: Results from the TREAT Asia Pediatric HIV Observational Database (TApHOD)

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Abstract

Objective—To evaluate the value of time-updated weight and height in predicting clinical progression, immunological and virological failure in children receiving combination antiretroviral therapy (cART).

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Methods—We used Cox regression to analyse data of a cohort of Asian children.

Results—2608 children were included; median age at cART was 5.7 years. Time-updated weight for age Z score <−3 was associated with mortality ($P < 0.001$) independent of CD4%; and <−2 was associated with immunological failure ($P \leq 0.03$) independent of age at cART.

Conclusion—Weight monitoring provides useful data to inform clinical management of children on cART in resource-limited settings.

Keywords

HIV; cohort; pediatric; z score; disease progression

INTRODUCTION

According to the World Health Organization[1, 2] there was a 20-fold increase in the number of people receiving antiretroviral therapy (ART) in low- and middle-income countries between 2003 and 2011. The ability of these countries to sustain long-term HIV care with ART requires monitoring the progression of disease in patients and their response to treatment.[3] In developed countries, frequent CD4 T-cell count and viral load are used to monitor patients,[4, 5] but these tools are not consistently available in developing countries, and providers may have to rely more heavily on clinical parameters, including height and weight, to monitor progress. In such settings, where it is hoped that the scale-up of ART will continue,[6] the extent to which routinely available height and weight monitoring could help predict progression of pediatric HIV disease is unclear.

Few studies examined the association between growth velocity during the first few months of combination antiretroviral therapy (cART) use and the risk of subsequent death or treatment failure.[7-9] However, the predictive value of weight and height as two variables changing through the study has not been described. We analysed data from the TREAT Asia Pediatric HIV Observational Database (TApHOD) to assess the value of time-updated weight and height in predicting clinical progression, and immunological and virological failure in children receiving cART at age <15 years.

METHODS

Study Population

TApHOD is an observational cohort study of HIV-infected children in Asia that has been described elsewhere.[10] Up to March 2012, TApHOD included 4385 children and adolescents receiving care at 18 pediatric clinics in Cambodia (n = 3), India (n = 1), Indonesia (n = 2), Malaysia (n = 4), Thailand (n = 5), and Vietnam (n = 3). These sites are predominantly public or university-based pediatric HIV referral clinics. Ethics approval is obtained at the sites, TREAT Asia/amfAR (coordinating center), and the Kirby Institute (data management center). Patient consent is deferred to the individual participating sites and their institutional review boards.

For this analysis we included children younger than 15 years at cART initiation with a first visit and cART start after January 1, 2003, and who had >3 months of follow-up and at least

one recorded post-baseline weight and height measurement during the follow-up. The database included information up to March 31, 2012.

Endpoints

Our clinical endpoints were a) progression to a new/recurring WHO stage 4 event after at least 6 months on cART to reduce the number of immune-reconstitution events, or b) death after at least 3 months on cART to reduce the inclusion of cases with high early mortality due to the severity of pre-cART HIV disease. We considered progression to a new/recurring WHO stage 4 event and mortality as separate outcomes. Immunologic failure was defined as a confirmed decline of ≥5 percentage points from the peak CD4%, or a failure to increase CD4% by ≥5 percentage points from baseline in children with previous severe immune suppression (CD4% < 15%), all after a cART duration of >6 months. Virological failure was defined as the presence of a HIV viral load ≥1000 copies/ml after >9 months of cART. The choice of 6 and 9 months is because of the time-lag period until immunological and virological deterioration occurs following cART and also because of the testing intervals at the sites.

Weight and height measurements were converted into age- and sex-standardized z scores. For height-for-age z score (HAZ) the WHO 2006/2007 Child Growth Standards were used.[11] WHO 1977 Standards were used for weight-for-age z scores (WAZ), to allow for scoring children >10 years of age.[12] The applicability of the 1977 growth references was previously assessed in this cohort by comparing WAZ from both the WHO 1977 and the WHO 2006/2007 reference curves in children <10 years, and the two WAZ standards gave similar results.[13] Baseline values were the values closest to the starting date of cART within the 3 months prior through 1 month after initiation. For CD4%, the post-cART window was restricted to 1 week after. Severe anemia was defined as having a hemoglobin level <6.50 g/dL (Grade ≥3), according to the US NIH Division of AIDS 2004 toxicity grading criteria.[14] cART was defined as therapy with a triple nucleoside reverse transcriptase inhibitor (NRTI) regimen, or two NRTIs plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI).

Analyses

We used Kaplan-Meier life-tables and Cox regression for time-to-event analyses and calculated the incidence of the outcome of interest. Follow-up began after 3 months on cART for mortality, after 6 months on cART for clinical progression and immunological failure, and after 9 months on cART for virological failure. Follow-up data were censored at the date of endpoint or last follow-up visit for the analysis of clinical progression and at the date of endpoint or time of the last available measurement for the analysis of immunological and virological failure.

To identify factors associated with the endpoints, we conducted four different Cox proportional hazard regression analyses, using both WAZ and HAZ as time-updated variables, as well as CD4%, except in the analyses for immunological failure. Other factors considered for inclusion in the univariate analysis were sex, orphan status, primary caregiver, age, history of severe anemia, WHO clinical stage and CD4 T-cell count at cART

start. Covariates were included in the final model on the basis of an unadjusted association with the outcome of interest (P <0.10). Analyses were performed using STATA Version 10 (Stata Corp, College Station, USA). Results are presented as adjusted hazard ratios and statistical significance was defined as $P < 0.05$. We also conducted a sensitivity analysis and excluded children with missing values for all key variables.

RESULTS

Patients Characteristics at cART Initiation

A total of 2608 children were included in the analysis. At cART initiation, the median age was 5.7 years (13% were <18 months) and 540 (19%) children had a previous WHO stage 4 event. The majority of children were from Thailand (43%) and Vietnam (26%). For 2197 children with available data, the baseline median CD4% was 9% (IQR: 3%-15%); 1122 (51%) had CD4% <10%. Forty-three percent of children were cared for by parents and 12% by grandparents. Thirty-nine percent had both HAZ <−2 and WAZ <−2. An additional 12% had only WAZ <−2, and 8% had only HAZ <−2. Of the initial cART regimens used, 95% were NRTI-NNRTI and 4% were NRTI-PI combinations.

Change in WAZ and HAZ

Children had a median of 12 (IQR: 7-18) weight measurements and 8 (IQR: 4-13) height measurements after cART initiation during the follow-up perid. For 1312 children with anthropometric measurements available before and up to two years after treatment, the median WAZ increased during the first 18 months by 1.39 SD unit ($P < 0.001$) and then stabilized. The median WAZ increased from −2.8 at cART start to −2.0 at 6, −1.8 at 12, −1.4 at 18 and −1.4 at 24 months on treatment. The increases in HAZ went from −2.4 at cART initiation to −2.3 at 6, −2.2 at 12, −2.0 at 18 and −1.9 at 24 months ($P < 0.001$). Over this period of time, the growth velocity was similar in children with WAZ and HAZ scores of < −2 or ≥-2 at cART initiation.

Clinical Progression

A total of 2608 children with >3 months of follow-up were included in the analysis for mortality and 2243 children with >6 months of follow-up in the analysis of progression to a WHO stage 4 event. Overall, 55 experienced a new/recurring WHO stage 4 event and 107 patients died. The incidence of stage 4 events was 0.6 (95% CI: 0.5-0.8) and of mortality was 1.0 (95% CI: 0.9-1.2) per 100 child-years. The most common causes of death were related to opportunistic infections. Disseminated mycosis (n = 9), HIV encephalopathy (n = 7), chronic herpes simplex infection (n = 6), and pneumocystis pneumonia (n = 6) were the most common stage 4 events. In Cox regression, only time-updated CD4% <25% ($P \leq 0.02$), and not WAZ or HAZ, was associated with progression to a new/recurring WHO stage 4 event (Table 1). Time-updated WAZ <−3, CD4% <15%, and baseline WHO clinical stage 4 were independently associated with an increased risk of death (all $P \leq 0.001$) (Table 1). Sensitivity analyses produced similar results showing increased risk of death for children with time-updated WAZ <−3.

Immunological and Virological Failure

The analysis of immunological failure was based on 1876 children with >6 months follow-up and available CD4 tests after cART. During a median time of 4.2 years, 164 (9%) had immunological failure for an incidence rate of 2.5 (95% CI: 2.1-2.9) per 100 child-years; approximately half (n = 80) occurred within 2-4 years after cART initiation. Time-updated WAZ <−2 ($P \leq 0.03$) and age <5 years at cART initiation ($P \leq 0.001$) were associated with immunological failure (Table 2). The analysis of virological failure was based on 1694 children with >9 months of follow-up and available viral load. Of these, 450 (27.0%) developed virological failure during a median follow-up duration of 3.5 years. The failure incidence rate was 9.2 (95% CI: 8.4-10.1) per 100 child-years. In Cox regression, time-updated CD4 <25% ($P < 0.001$) and age <5 ($P \leq 0.001$) years at cART initiation and male sex ($P = 0.011$) were predictors of virological failure (Table 2). The results from the sensitivity analyses were comparable to those observed in the above analyses.

DISCUSSION

In this multicenter analysis of 18 pediatric ART clinics in the Asia region, 39% of children had both HAZ and WAZ <−2 at cART initiation. We found that children with a time-updated WAZ <−3 had a significantly increased hazard of subsequent mortality, and those with WAZ <−2 a significantly increased risk of immunological failure. This relationship was independent of the most recent CD4%, and WHO clinical stage, CD4% and age at cART initiation. WAZ was not associated with an increased risk of virological failure or progression to a new/recurring WHO stage 4 event.

There was a significant increase in WAZ and HAZ over time, reflecting the clinical efficacy of cART. The effect of cART on growth of HIV-infected children has been investigated previousely.[15-20] cART is generally associated with improved growth parameters, except in the case of ritonavir, where drug toxicities have been shown to interfere with caloric intake and weight.[16]

It is well-documented that low weight-for-age at cART initiation correlates with HIV disease prognosis in children.[21-25] There is also evidence that poor growth in the first few months of cART is an indicator of disease progression that often precedes CD4 T-cell count decline.[18] In a study by Benjamin and colleagues,[26] height growth increase was strongly associated with reduced risk of subsequent clinical progression and immune reconstitution, and was weakly associated with declines in HIV viral load in US children receiving cART. Changes in WAZ were not associated with pediatric HIV outcomes in a study by Musoke *et al* [27] among Ugandan children. Our study showed no association between WAZ and progression to WHO stage 4 event in the multivariate model. This lack of association could merely be due to the small number of children who progressed to a stage 4 event.

Given the important relationship between HIV, nutrition, growth, functional status and clinical progression in children living with HIV, WHO recommends that early nutritional assessment and support should be an integral part of the care plan of an HIV-infected infant or child.[28] Identifying early signs of malnutrition and children with severe deficits in weight may help HIV care teams focus their attention on higher-risk children and prevent deaths.

Young children, age <5 years at cART initiation, had higher rate of immunological and virological failure. Studies elsewhere showed that younger age is a predictor of immunological[29,30] and virological failure.[31,32] This may have been related to the poorer adherence, inaccurate drug dosage, and complications of malnutrtion in younger age group. Selection bias towards inclusion of children who do well enough to defer starting therapy until later ages may also account for better immunological and virogical response to cART in older children.

Children included in this analysis benefitted from well-structured, mainly university-based, referral hospitals for HIV care, so results from this study may not be generalizable to children treated in primary care centers or rural areas. In addition, our analysis is based on routine monitoring data. Consequently, some of the data were collected retrospectively and were incomplete. The lack of data on adherence also limited our analysis.

In conclusion, we demonstrated that current WAZ, a low-cost, basic measurement of child development already being done in most pediatric HIV health care settings, can predict mortality and immunological failure independently from current CD4 T-cell counts and age at cART initiation. Our findings support that the observation of WAZ <−2 SD at any time during follow-up should be considered a serious warning of disease progression risk when monitoring responses to cART in resource-limited settings. Clinicians in settings with reduced access to laboratory monitoring can assign greater value to the weight parameter as a useful marker for high-risk children.

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Abbreviations

TREAT Asia	Therapeutics Research, Education, and AIDS Training in Asia
TApHOD	TREAT Asia Pediatric HIV Observational Database
cART	combination antiretroviral therapy
WAZ	weight-for-age z score
HAZ	height-for-age z score
NRTI	nucleoside reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
PI	protease inhibitor
IQR	interquartile range

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Table 1

Multivariate analysis of the association between WAZ and HAZ with clinical progression.

Characteristics	Progression to new/recurrent WHO stage 4 (n = 2243)			Death (n = 2608)		
	Rate/100 py (events/py)	Adjusted hazard ratio (95% CI)	*P* value	Rate/100 py (events/py)	Adjusted hazard ratio (95% CI)	*P* value
Sex						
Male				1.2 (63/5185)	*1.28 (0.87-1.89)*	0.21
Female				0.8 (44/5207)	*1.0*	
WAZ [a]						
< −3SD	1.5 (20/1357)	1.60 (0.70-3.67)	0.24	4.0 (74/1856)	5.14 (2.61-10.12)	<0.001
≤ −3 to < −2 SD	0.4 (8/1857)	0.64 (0.27-1.54)	0.33	0.6 (15/2343)	1.38 (0.65-2.92)	0.40
≥ −2SD	0.5 (27/4941)	1.0		0.3 (18/5790)	1.0	
HAZ [a]						
< −3SD	1.4 (19/1328)	1.54 (0.65-3.66)	0.33	3.3 (60/1808)	1.43 (0.74-2.77)	0.28
≥ −3 to < −2 SD	0.6 (12/2097)	0.93 (0.43-2.02)	0.86	0.9 (24/2653)	0.96 (0.90-1.86)	0.90
≥ −2SD	0.5 (24/4597)	1.0		0.4 (21/5322)	1.0	
CD4 T-cell percentage [a]						
< 10	2.7 (15/566)	8.08 (3.58-18.24)	<0.001	6.6 (62/940)	24.84 (11.77-52.39)	<0.001
10-14	1.7 (10/605)	5.15 (2.15-12.30)	<0.001	1.6 (13/816)	7.49 (3.12-17.98)	<0.001
15-24	0.7 (18/2514)	2.39 (1.14-5.01)	0.02	0.4 (13/3020)	2.19 (0.93-5.17)	0.07
≥ 25	0.3 (12/4448)	1.0		0.2 (9/5156)	1.0	
Highest WHO clinical staging at cART start						
Stage 1/2	0.6 (28/4726)	*1.0*		0.6 (33/5222)	*1.0*	
Stage 3	0.6 (16/2838)	*0.78 (0.42-1.45)*	*0.43*	0.8 (24/3090)	0.81 (0.48-1.38)	0.44
Stage 4	1.2 (11/895)	*1.89 (0.95-3.77)*	*0.07*	2.4 (50/2079)	2.21 (1.41-3.46)	0.001
Anemia at cART start						
Yes				2.0 (8/393)	*1.23 (0.58-2.57)*	0.59
No				1.0 (73/6974)	1.0	

PY, person-years; WAZ, weight-for-age z score; HAZ, height-for-age z score; CI, confidence interval. Variables listed are those significant at the p <0.10 alpha level in the univariate model. For those variables which did not remain significant in the adjusted model, the hazard ratios are shown in italic. These adjusted hazard ratios were obtained by adding and removing each insignificant variable to the final model. The study factors of interest, WAZ and HAZ were included in the final model, irrespective of their *P* values.

[a] Included as a time-updated variable.

Table 2

Multivariate analysis of the association of WAZ and HAZ with immunological and virological failure.

Characteristics	Immunological failure (n = 1876)			Virological failure (n = 1694)		
	Rate/100 py (events/py)	Adjusted hazard ratio (95% CI)	*P* value	Rate/100 py (events/py)	Adjusted hazard ratio (95% CI)	*P* value
Age at cART start, years						
<1.5	3.6 (27/742)	3.0 (1.71-5.33)	<0.001	13.9 (55/396)	2.47 (1.74-3.52)	<0.001
1.5-4.9	3.1 (56/1785)	2.08 (1.33-3.26)	0.001	12.3 (163/1330)	1.53 (1.19-1.97)	0.001
5-8.9	2.0 (50/2533)	1.07 (0.68-1.67)	0.77	6.6 (124/1888)	0.83 (0.64-1.08)	0.17
≥9	1.9 (31/1610)	1.0		8.5 (109/1282)	1.0	
Sex						
Male	2.8 (92/3242)	*1.22 (0.89-1.67)*	*0.22*	11.1 (259/2331)	1.28 (1.06-1.54)	0.01
Female	2.1 (72/3428)	*1.0*		7.5 (192/2565)	1.0	
WAZ [a]						
< −3SD	3.8 (43/1135)	2.25 (1.35-3.75)	0.002	12.7 (96/754)	1.24 (0.91-1.68)	0.17
≥ −3 to < −2 SD	2.9 (46/1564)	1.61 (1.06-2.44)	0.03	9.5 (110/1152)	1.11 (0.86-1.43)	0.44
≥ −2SD	1.96 (75/3818)	1.0		8.4 (244/2890)	1.0	
HAZ [b]						
< −3SD	3.2 (38/1204)	1.23 (0.72-2.10)	0.46	12.4 (102/823)	1.06 (0.78-1.44)	0.73
≥ −3 to < −2 SD	2.8 (50/1755)	1.22 (0.80-1.84)	0.35	10.0 (129/1286)	1.14 (0.89-1.46)	0.30
≥ −2SD	2.2 (75/3479)	1.0		7.8 (206/2638)	1.0	
CD4 T-cell percentage [b]						
<10	2.6 (83/3184)	1.00 (0.51-1.97)	0.99	42.3 (34.2-52.3)	7.89 (5.78-10.76)	<0.001
10-14	1.5 (17/1128)	0.50 (0.23-1.09)	0.08	23.3 (18.4-29.6)	4.36 (3.17-6.00)	<0.001
15-24	2.0 (21/1075)	0.66 (0.32-1.39)	0.27	10.0 (8.5-11.7)	2.24 (1.75-2.88)	<0.001
≥25	3.4 (11/326)	1.0		4.4 (3.7-5.3)	1.0	

PY, person-years; WAZ, weight-for-age z score; HAZ, height-for-age z score; CI, confidence interval. Variable listed are those significant at the p <0.10 alpha level in the univariate model. For those variables which did not remain significant in the adjusted model, the hazard ratios are shown in italic. These adjusted hazard ratios were obtained by adding and removing each insignificant variable to the final model. The study factors of interest, WAZ and HAZ were included in the final model, irrespective of their *P* values. The overall *P* value for CD4% in the analysis of immunological failure was 0.04.

[a] Included as a time-updated variable.

[b] Included as a time-updated variable in the analysis of virological failure and as a fixed variable taken at cART initiation in the analysis of immunological failure.