Persistence of Stunting after Highly Active Antiretroviral therapy (HAART) in HIV-infected children in South India

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ABSTRACT

Introduction

Growth failure is a common feature of children with human immunodeficiency virus type 1 (HIV-1) infection and is a sensitive indicator of disease progression. We studied the effect of Highly Active Antiretroviral therapy (HAART) on the growth and immunologic parameters of HIV-infected children in comparison with those not initiated on HAART.

Methodology

HIV-infected children from birth to 15 years of age referred to the clinics of Tuberculosis Research Centre at Chennai and Madurai were recruited after obtaining written informed consent from their parent/guardian. Clinical examination, anthropometric measurements and investigations (hematology, CD4, CD8 counts) were done and children eligible for antiretroviral treatment were started on a triple-drug regimen (Stavudine, Lamivudine and Nevirapine). All assessments were repeated at 12 months. Statistical analysis was done using SPSS, Version 11.0.

Results

253 HIV-infected children were enrolled of whom 102 children have complete data available. 49 were eligible for ART. Majority of children in ART and non-ART groups were in the 5-10 years age group (48% and 62% respectively).The prevalence of underweight (WAZ <-2), stunting (HAZ<-2) and wasting (WHZ<-2) among the ART eligible group was 81%, 52% and 56% respectively and among the non-ART group was 59%, 50% and 29% respectively at baseline. After 1 year of HAART, median WAZ increased significantly from baseline (-2.84 to -2.18] but HAZ did not increase proportionately. Children who were initiated on HAART at CD4 >15% had less severe stunting after one year. All growth indices worsened in the group not started on ART.

Conclusions

Chronic malnutrition is a common feature of pediatric HIV in India, both on and off HAART and needs to be managed concurrently. Earlier initiation of HAART may prevent irreversible stunting.

INTRODUCTION

- Failure to thrive is a common feature of children with HIV-1 infection. HIV infection adversely affects both weight gain and vertical growth velocity.
- Growth seems to be one of the most sensitive indicators of disease progression in children with acquired immunodeficiency syndrome (AIDS).
- The only effective treatment for growth-failure in children with HIV appears to be highly active antiretroviral therapy (HAART)
- Whether HAART would be able to completely reverse these changes, especially stunting, is unclear.

AIM

- To study the changes in height, weight and immunologic parameters of HIV-infected children initiated on highly active antiretroviral therapy compared to those not initiated on HAART.

METHODOLOGY

Design: Observational cohort study

Participants: HIV-infected children from birth to 15 years of age referred to the clinics of Tuberculosis Research Centre (TRC) at Chennai and Madurai, Tamil Nadu, south India from May 2004 to December 2007 were recruited after written informed consent from their parent or guardian.

Methods:

- History and clinical examination performed by a physician and anthropometric measurements done by a trained nutritionist.
- Complete blood counts (using automated hematology counter, ABX Pentra 60) and CD4, CD8 count (by standard flow cytometric methods using a FACS Count, Becton Dickinson India Ltd.) at baseline.
- Eligible children started on a simplified, nationally approved, triple-drug regimen at the nearest ART centre*.
- Followed every three months with clinical monitoring and anthropometry and laboratory investigations repeated every 6 months

Statistical analysis done using SPSS, Version 11.0. Data are expressed as median and inter quartile range (IQR) as well as proportions. The prevalence of under-weight, stunting and wasting was calculated for the different age groups and both sexes using Epi Info[TM] software (Version 3.4.3) and the severity classified based on z-scores.

Differences in the proportion of wasting, stunting and underweight between the ART and non-ART groups were tested with the Pearson Chi-square and the change in growth parameters using Wilcoxon Signed Rank Test. All the statistical tests were performed considering the actual numbers for which data was available. Receiver operating curve was constructed for relationship between weight gain and improvement in CD4 count following ART.

*** When to start ART in children, guided by CD4**
< 11 month Infants: if CD4 < 1500 cells/mm3 (< 25%)
12–35 months: if CD4 < 750 cells/mm3 (<20%)
36–59 months: if CD4 <350 cells/mm3 (15%)
> 5 years old: follow adult guidelines i.e. start ART if < 350 cells/mm^3 especially if symptomatic.

RESULTS

- 253 HIV-infected children were enrolled of whom 102 children have complete data available
- 49 children (median age 76 months) started on ART (ART group) - 39 on a stavudine based regimen (d4T+3TC+NVP) and 10 on a zidovudine based regimen (ZDV+3TC+NVP). 53 children (median age 72 months) not started on ART (non-ART group).

Table 1: Characteristics of Children eligible and not eligible for ART at baseline (n=102)

	ART Group	**Non-ART Group**
	N=49	**N=53**
Age (in months) *Median,(IQR)*	76 (42, 110)	72 (48, 108)
	(%)	(%)
Age wise distribution (%)		
< 3 years	18	6
3 – 5 years	20	21
5 – 10 years	48	62
>= 10 years	12	11
Weight for age 'Z' score *Median, (IQR)*	-2.86 (-3.25, -2.21)	-2.28 (-3.23, -1.50)
< -2 (%)	81*	59
>= -2 (%)	19*	41
Weight for height 'Z' score *Median, IQR*	-2.18 (-3.08, -1.65)	-1.29 (-2.28, -0.27)
< -2 (%)	56*	29
>= -2 (%)	44*	71
Height for age 'Z' score *Median, IQR*	-2.25 (-3.42, -0.46)	-2.21 (-3.48, -1.10)
< -2 (%)	52	50
>= -2 (%)	48	50
BMI 'Z' score *Median, IQR*	-3.04 (-4.90, -2.23)	-1.45 (-3.06, -0.18)
< -2 (%)	78*	41
>= -2 (%)	22*	59
CD_4%, median, IQR	14 (8, 18.5) *	17 (14, 29)
CD_4 count, median, IQR	408 (185, 921) *	642 (388, 1306)

(cells/mm^3)		

* (p = <0.01) compared to non-ART group

Table 2. Nutritional status at baseline and the end of 1 year in both groups of children (proportions)

	ART (n=49)		**Non-ART (n=53)**	
	Baseline	**1 year**	**Baseline**	**1 year**
Weight for age 'Z' score*	**%**	**%**	**%**	**%**
< -2	82	57*	43	57**
>=-2	18	43*	57	43**
Height for age 'Z' score				
< -2	50	62	46	46
>=-2	50	38	54	54
Weight for height 'Z' score*				
< -2	59	12*	17	17
>=-2	41	88*	83	83
BMI 'Z' score*				
< -2	79	42*	27	42**
>=-2	21	58*	73	58**

* p=< 0.01 compared to baseline

** p=< 0.05 compared to baseline

Table 3: Nutritional status at baseline and the end of 1 year in both groups of children (median values)

Growth parameter	**ART**		**Non-ART**	
	Baseline	**1 year**		
Weight for age 'Z' score *Median, IQR*	-2.84 (-3.25, -2.21)	-2.18 (-2.80, -1.72) *	-1.85 (-2.82, -1.28)	-2.12 (-2.48, -1.68)
Height for age 'Z' score *Median, IQR*	-2.02 (-3.38, -0.68)	-2.27 (-3.35, -1.16)	-1.76 (-3.18, -1.10)	1.80 (-2.84, -1.22)
Weight for height 'Z' score *Median, IQR*	-2.41 (-3.12, -1.63)	-1.08 (-1.75, -0.26) *	-1.08 (-1.50, -0.07)	-1.32 (-1.78, -0.92)
BMI 'Z' score *Median, IQR*	-3.04 (-5.24, -2.24)	-1.50 (-3.14, -1.50) *	-1.15 (-2.13, -0.37)	-1.73 (-2.54, -0.98)
CD4 cell% Median, IQR	14 (8.0,18.0)	30 (25, 36.0) *	23 (18.5, 30.50) **	25 (21.0, 33.5)**
CD4 cell count Median, IQR	408 (195.0, 896.0)	1138 (726.0, 1506.0) *	946 (591.5, 1315.0)	863 (542.5, 1253.0)
Hemoglobin Median, IQR	10.0 (8.85, 11.35)	11.7 (10.10, 12.40) *	11.2 (9.8, 11.8) *	11.5 (10.92, 12.2) *

*$p < 0.01$

**$p < 0.05$

Figure 1: Change in height for age after 1 year in children on and off ART

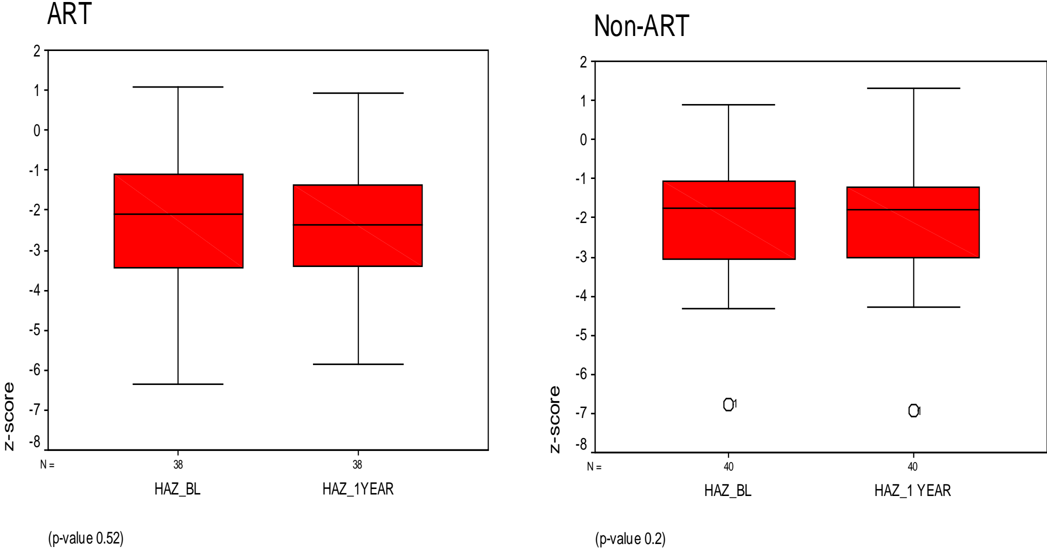


Figure 2: Change in height for age after 1 year among those on ART, classified by baseline immune status

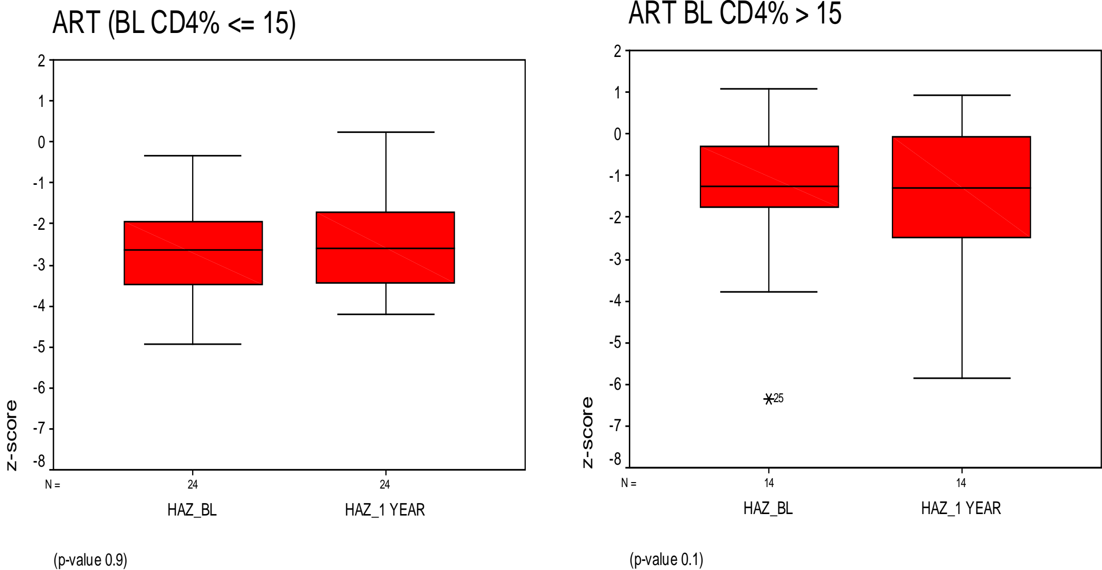


Figure 3: Change in weight for age after 1 year in children on and off ART

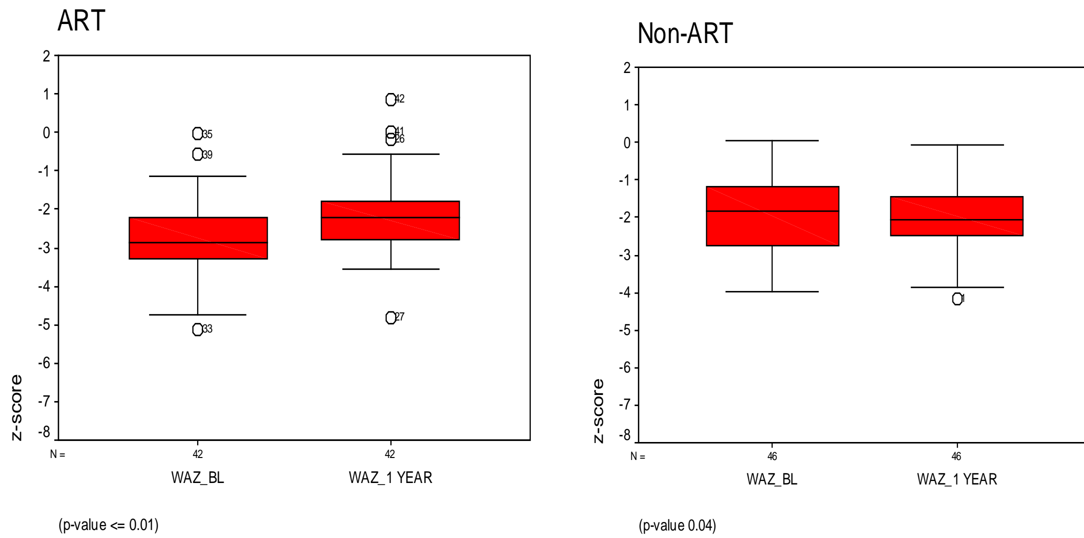


Figure 4: Change in weight for age after 1 year among those on ART, classified by baseline immune status

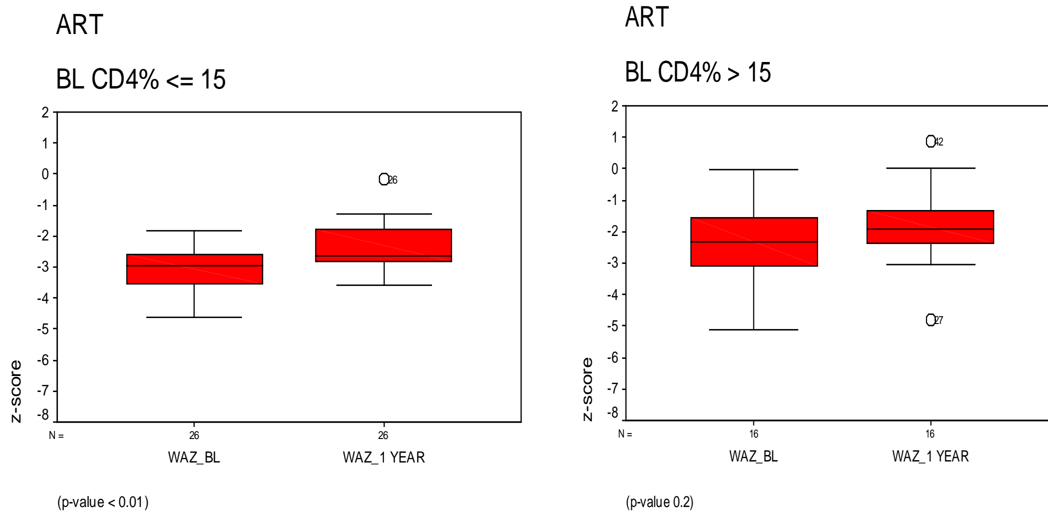
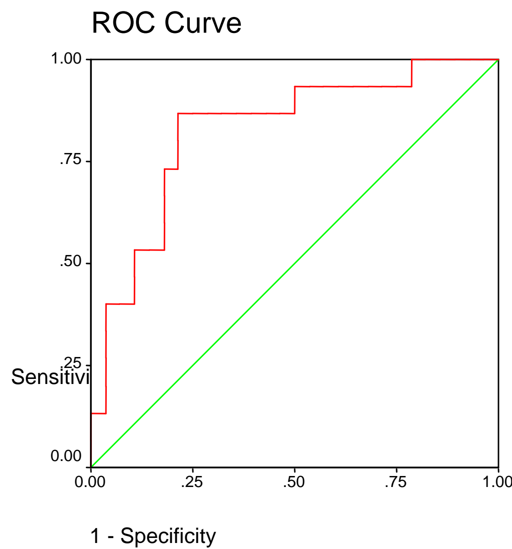


Fig 5: Receiver Operating Curve depicting the relationship between increase in CD% and weight, post HAART



Footnote: Area under the curve 0.82 indicating good correlation.

SALIENT FINDINGS

- Our study has confirmed that HAART has a beneficial effect on the growth and immunologic parameters of HIV-infected children.
- While weight improves significantly after HAART, this is not so with height. Stunting is less reversible than wasting and the negative impact of chronic infection and malnutrition on height appears to be long-lasting.
- Weight gain occurred when HAART was initiated irrespective of baseline CD4%, but the final weight for age was higher in the group with CD4>15%. This stresses the need to start HAART at an earlier stage for better growth.

- Improvement in immune status (CD4%) and weight gain showed a significant correlation after initiation of ART. Weight gain could be used as a surrogate marker for CD4% increase as the sensitivity and specificity of an increase in weight of 11% to predict an increase of CD4% of 10% from baseline was 78 and 73% respectively.

CONCLUSION

- While HAART has a positive effect on the growth of HIV-infected children, stunting persists, which suggests that it may not be reversible.
- Attention needs to be paid to making nutritional counselling, nutritional supplementation and sustainable nutritional interventions an integral part of our therapeutic strategies.