The effect of nutritional status on the response to highly active antiretroviral therapy in human immunodeficiency virus-infected children at regional antiretroviral therapy centre in Northern India

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Received – 22 January 2017 Initial Review – 11 February 2018 Published Online – 08 March

ABSTRACT

Background: Effect of highly active antiretroviral therapy (HAART) on growth in children is well established but influence of prior nutritional status on the response to HAART is not well known. **Objective:** To determine the influence of prior nutritional status on the response to HAART in terms of growth and CD4 counts. **Methods:** It was a retrospective record review based study conducted at a regional ART centre at a tertiary care, teaching hospital in Northern India. Human immunodeficiency virus (HIV) positive children who were naïve to antiretroviral therapy and were initiated on treatment from January 2006 to December 2007 were included in this study. Age, weight, height and CD4 cell counts were recorded at the initiation of HAART and after 24 months of therapy. Data was analyzed using paired t-tests within the groups, Chi-square tests, and one-way analysis of variance. **Results:** Seventy-nine HIV positive children were included in the study. At baseline, 29% of children were normal weight, 27% moderately underweight and 44% severely underweight with mean CD4 counts 243.30±178.50, 282.95±173.69 and 215.11±85.71 respectively. After 24 months of HAART, mean CD4 cell counts as well as weight for age z scores increased significantly in all 3 groups with mean CD4 counts being 913.61±401.46, 931.24±363.54 and 775.31±424.43 respectively in the groups. There were no significant differences in CD4 counts in the groups both pre and post ART. **Conclusion:** Underlying malnutrition does not adversely affect growth and immunologic response (increase in CD4 count) to HAART in HIV-infected children.

Key words: *CD 4 counts, Height for age z-scores, Highly active antiretroviral therapy, Immunologic response, Nutritional status, Weight for age z-scores, Weight for height z-scores*

Human immunodeficiency virus (HIV) continues to be a major global health issue. As per World Health Organization, approximately 36.7 million people were living with HIV at the end of 2016 out of which 2.1 million were children below 15 years of age [1]. National acquired immuno deficiency syndrome (AIDS) Control Organization estimated 21.17 lakh people living with HIV in India in 2015, out of which 6.54% were children less than 15 years of age [2]. Malnutrition and growth failure are consequences of HIV infection in children and are characterized by poor linear and ponderal growth [3-7]. HIV infected children have high rates of malnutrition as compared to HIV uninfected children despite similar calorie intake [8]. Reduced appetite, side effects of medicines, depression, malabsorption and increased nutrient requirement during fever and infections are possible contributory factors [9]. The use of highly active antiretroviral therapy (HAART) has substantially improved survival in HIV-infected children [10]. Children on HAART show improved growth in height and weight [11-13]. They show significant CD4 cell percentage recovery, and suppression of viral loads [14-17]. Although the impact of HAART on growth is well established, the effect of prior nutritional status of HIV patients on the response to HAART in terms of increase in CD4 counts and improvement in nutritional status itself is less clear [18,19]. The objective of this study was to determine the role of nutritional status at the commencement of therapy on the clinical and immunologic response to HAART in HIV-infected children in India in terms of growth parameters and CD4 counts respectively.

MATERIALS AND METHODS

The study was conducted on children upto 12 years of age from Pediatric ART Centre at a tertiary care teaching Hospital, New Delhi, India. Children were eligible for HAART based on clinical and immunologic parameters after a diagnosis of HIV infection was made by HIV antibody testing if they were older than

18 months or by HIV deoxyribo-nucleic acid polymerase chain reaction (DNA PCR) testing if they were younger than 18 months. Presumptive diagnosis of severe HIV disease was made in those who could not afford DNA PCR if: The infant was confirmed HIV antibody positive and diagnosis of any AIDS-indicator condition(s) could be made or the infant was symptomatic with two or more of the following: (a) Oral thrush, (b) severe pneumonia, (c) severe sepsis [20]. HAART was started if patient had WHO clinical stage 3 or 4 disease and or CD4 cell percentage <25% in <12 months, less than 20 % in 12–35 months, less than 15% in 36–59 months and <350 cells/cu.mm in >5 years [20]. First-line Anti-RetroViral regimens used were: Regimen of 2 nucleoside reverse transcriptase inhibitors (NRTI) plus 1 NNRTI i.e. Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP) or Efavirenz (EFV) or Stavudine (D4T) + 3TC + NVP or EFV [20]. Adherence to treatment was assessed by caregiver reports and pill counts. Patients were evaluated at the clinic every month.

The study was conducted as a retrospective record review of all HIV infected children who were naive to antiretroviral therapy, and who started treatment between January 1st, 2006 and December 31st, 2007. Age, weight, height and CD4 cell counts were recorded at the initiation of HAART and after 24 months of therapy. Undernutrition was defined as "underweight" (weight for age < −2 standard deviations (SD), "stunting" (height for age < −2 SD) and "wasting" (weight for height < −2 SD). Underweight served as indicator for overall nutrition. Weight-for age z-scores (WAZ), height for age z-scores and weight for height z scores were calculated using WHO growth references 2010 [21].

Once patients had fulfilled the inclusion criteria, they were divided into 3 groups based on WAZ. Normal weight was defined as a WAZ between −2 and + 2 SD, moderate underweight as a WAZ between −2 and −3 SD and severe underweight as a WAZ of < −3 SD [21]. Growth and CD4 cell counts were compared among these 3 patient groups both pre and post ART. Software used was Microsoft office excel 2007 and Statist version 1.4.1. Differences between the groups at baseline were determined by one-way analysis of variance (ANOVA) testing for parametric variables, and chi-square tests for categorical variables. Changes in mean values from baseline to month 24 were evaluated for each of the patient groups with paired t-tests. Unpaired t-tests and one-way ANOVA were used to compare changes in mean values between the different groups. A 2-tailed p<0.05 was considered statistically significant. Confidence intervals (CI) were noted at the 95% level.

RESULTS

Eighty eight children were put on HAART between January 1st, 2006 and December 31st, 2007. At 24 months, data was available for 79 children only as 3 children had died, 2 were lost to follow-up and 4 were transferred to other ART centres during the study period. So a total of 79 children were included in the study.

Patients were divided into three groups (normal weight, moderate underweight and severe underweight) based on their baseline WAZ. Number of patients were significantly more in "Severe underweight group" (n=35, 44.30%). Overall 71% (56) were underweight, 58.2% (46) were stunted and 38.0% (30) were wasted. Baseline patient characteristics are shown in Table 1. Sex distribution was homogeneous, Age and CD4 counts were comparable in all three groups. CD4 count was not affected significantly in underweight patients, and there was no significant correlation between weight and CD4 counts (Pearson correlation coefficient is −0.04). All three expired children belonged to severe underweight group but cause of expiry could not be found.

Weight for age after 24 months of HAART are shown in Fig. 1. Weight for age increased significantly in all three groups, from 19.03±4.18 to 21.85±3.67(mean difference: 2.82, p<0.001) in normal weight group, 16.69±4.53 to 20.57±4.90 (mean difference: 3.88, p<0.001) in moderate underweight group and 13.03±3.95 to 18.57±4.12 (mean difference: 5.54, p<0.001) in severe underweight group.

Height for age improved in all three groups but improvement was not significant. Weight for height improved significantly in both the underweight groups (p<0.05). At 24 months, there was no significant difference in the weight for age among the three groups. Fig. 2 shows CD4 counts after 24 months of HAART in three patient groups. Mean CD4 cell counts increased significantly in all three groups: From a mean of 243.30±178.50 to 913.61±401.46 (p <0.001; CI: 72.95–164.07) in normal weight group, from 282.95±173.69 to 931.24±363.54 (p<0.001; CI: 74.29–155.49) in moderate underweight group and from 215.11±85.71 to 775.31±424.43 (p<0.001; CI: 28.4–140.61) in severe underweight group. Table 2 shows that there were no significant differences in CD4 count among the groups both: Pre-ART and 24 month post ART.

DISCUSSION

The prevalence of underweight, stunting and wasting in ART-naïve patients were 71%, 58.2%, 38% respectively. The rates

Table 1: Baseline characteristics (age, weight and CD4 counts) of the study population

Characteristics	All patients (%)	Normal weight (%)	Moderate underweight (%)	Severe underweight (%)	p value
No of children	79	23 (29.11)	21 (26.58)	35 (44.30)	p<0.05
Age (years)	7.14±2.96	6.65±2.33	6.86±3.05	7.63±3.26	NS
Sex					
Male	59 (74.68)	17 (73.91)	15 (71.43)	27 (77.14)	NS
Female	20 (25.32)	6 (26.09)	6 (28.57)	8 (22.86)	
CD 4 counts per mm^3	241.35±143.87	243.30±178.50	282.95±173.69	215.11±85.71	NS

Age and CD4 counts are expressed as mean±SD, ANOVA was used to compare the three groups. SD: Standard deviation, NS: Not significant, ANOVA: Analysis of variance

Table 2: Comparison of CD4 Counts in normal weight, moderate underweight and severe underweight groups

Group n=79	Normal weight n=23	Moderate underweight n=21	Severe underweight n=35	p value
CD4 count at start	243.30±178.50	282.95±173.69	215.11±85.71	NS
CD4 count after 24 months	913.61±401.46	931.24±363.54	775.31±424.43	NS
% increase in CD 4 count	73.38	69.71	72.22	NS

CD4 counts are expressed as mean±SD, ANOVA was used for comparison among groups. SD: Standard deviation, ANOVA: Analysis of variance

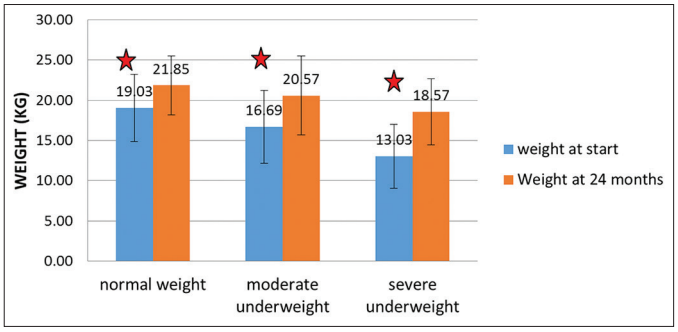

Figure 1: Changes in weight after 24 months of highly active antiretroviral therapy, ★ p<0.001 significant statistically (Student t-test), Whiskers denote standard deviation

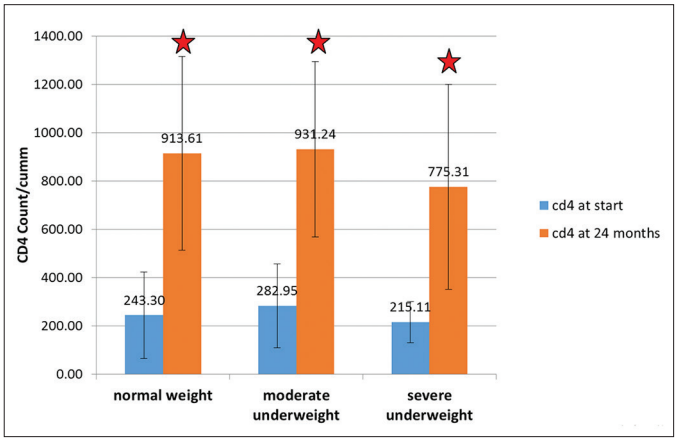

Figure 2: CD4 counts in all three patient groups before and after 24 months of highly active antiretroviral therapy. ★ p<0.001 statistically significant (Student t-test), Whiskers denote standard deviationS

of underweight and stunting were almost similar to a study conducted in South India by Padmapriyadarsini *et al*, which were 63% and 58% respectively but higher than that found in south Africa study conducted by Naidoo *et al.* [6,19]. This shows that malnutrition in HIV infected children is more prevalent in India as compared to Africa.

The present study showed that 24 months after starting treatment with HAART, there was statistically significant increase in weight of children in all three groups which means that underlying malnutrition did not affect response to HAART in terms of growth. This observation was similar to that found in a study from Africa conducted by Naidoo *et al.,* 2010 [19]. Whereas study conducted in South India by Bandopadhyay *et al.*, 2008 showed that the nutritional response to HAART was poorer in malnourished children as compared to nutritionally normal counterparts [18].

Present study also showed that CD4 counts increased significantly in all three groups meaning thereby that underlying malnutrition did not affect the immunologic response to HAART too. Similar results were found in studies from Africa by Naidoo *et al* and Singapore by Paton *et al* [17,19].

Small sample size was the major limitation of our study. Moreover being a retrospective study, we couldn't collect the data of patients who expired or lost to follow-up. More studies are needed as only few studies have been conducted in this area and results of different studies vary.

CONCLUSION

Our study showed that underlying malnutrition did not affect nutritional and immunological response to HAART. Clinical implication of this study lies in provision of nutritional supplements to HIV patient's along with HAART as supplements will be useful if further studies show poor response to HAART in malnourished children.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Aaradhana S, Ravi S, Vishnu M, Divya J, Kriti M. The effect of nutritional status on the response to highly active antiretroviral therapy in human immunodeficiency virus-infected children at regional antiretroviral therapy centre in Northern India. Indian J Child Health. 2018; 5(2):95-98.