RESEARCH PAPER

Profile of HIV Infected Children from Delhi and Their Response to Antiretroviral Treatment

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Objectives: (*i*) To study the clinical and immunological profile of HIV infected children attending the ART centre; (*ii*) To correlate CD4 count with clinical staging at diagnosis; and, *iii*) To study the clinical and immunological response to antiretroviral treatment.

Setting: Antiretroviral therapy (ART) centres of two tertiary care hospitals of Delhi.

Patients: 100 children attending the centres between December 2008 to June 2009.

Methods: The clinical features, immunological profile (CD4 count) and response to ART were recorded in a structured proforma.

Design: Prospective follow-up.

Results: Average age of enrolled children was 6.24 y (range 1-14 years) and mode of transmission was parent to child in 92%. Most common clinical presentation was fever (83%), cough (50.8%) and diarrhea (38.9%). Tuberculosis was the most common opportunistic infection seen in 11% of children. 59% of enrolled children were malnourished. Antiretroviral treatment (ART) was initiated in 33 children. Children who were initiated on ART had a significant improvement in both clinical and immunological staging at the 6 months follow up. Immunological response (rise in CD4 count) to ART was better in children with lesser degree of immunosuppression. The measure of agreement between the clinical and immunological stage at presentation was poor.

***Conclusions**:* Baseline CD4 counts rather than clinical staging can be a primary determinant for initiation of antiretroviral treatment in HIV infected children.

Key words: *Anti-retroviral treatment, CD4 count, Clinical stage, Outcome, Treatment.*

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Human immunodeficiency virus (HIV) infection is a growing concern in pediatric population and large number of children are registered and treated at Antiretroviral treatment (ART) centres across the country [1]. Despite the magnitude of illness, there is a lack of studies describing the correlation of clinical staging and immunological staging (CD4 count) in HIV infected children. We report the clinical and immunological profile of children attending ART clinics of two tertiary care centers of Delhi, along with their response to antiretroviral treatment.

METHODS

This was a prospective study conducted in ART clinics of two tertiary care hospitals of Delhi over a period of six months from December 2008 to June 2009. A sample size of 96 subjects (rounded to 100) was obtained with 95% confidence interval and 10% absolute precision (2 sided) in prevalence of diarrhea in HIV infected children, which was approximately 55% in a previous study [2]. The sample size was estimated using Power analysis and sample size (PASS) software. A total of 100 children aged less

than 18 years were enrolled in the study (50 each from two study centres). A clearance was obtained from institutional ethical committee. The study protocol was fully explained to parents/guardian and written informed consent was obtained.

The diagnosis of HIV was confirmed by ELISA using two different antigens (COMB HIV, TRI DOT) in children more than 18 months. In children less than 18 months, diagnosis was confirmed by positive DNA PCR (repeated twice with cessation of breastfeeding for minimum of six weeks). Demographic profile, clinical presentation and mode of transmission of enrolled children were recorded in a predesigned proforma. Anthropometric assessment was done and WHO classification for malnutrition was adopted to classify children into stunted, wasted and both stunted and wasted [3]. Children were categorized by their presenting complaints into clinical staging as per WHO clinical classification for HIV infected children [4]. Opportunistic infections were screened using Mantoux test, chest skiagram, microscopic examination of sputum, urine and stool. It also included the examination of skin and oral mucosa with scrapings for potassium hydroxide (KOH) mount preparation [4]. Baseline value of hemogram, serum bilirubin, serum aminotransferase, blood urea and serum creatinine was obtained in all children. Other investigations were planned as deemed necessary. CD4 count was estimated by FACS (fluorescent activated cell sorter) method (Becton-Dickinson). Immunological assessment was done in terms of CD4 counts as per WHO classification [4].

Children were started on ART as per National AIDS Control Organisation (NACO) guidelines [5]. Combination of two nucleoside reverse transcriptase inhibitor (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) was started. Children were monitored clinically weekly or monthly, depending on the clinical presentation. Children were observed for clinical improvement or detoriation, compliance with medications and for any adverse effects of ART. CD4 counts were repeated every 6 months.

Data were analyzed using SPSS version 17.0. All quantitative variables including age, weight, height and body mass index were compared by unpaired t-test; categorical variables like sex, mode of delivery and mode of transmission were compared by Chi-square test or Fisher's exact test. Variables like clinical staging, immunological staging and CD4 counts which were measured repeatedly (at presentation and at follow up) were analysed with repeated measure ANOVA followed by Tukey procedure at 5% level of significance to allow for multiple comparisons. To find the agreement between clinical staging and immunological staging, kappa statistic was applied. $P<0.05$ was considered as significant.

RESULTS

All the 100 children were brought for follow up till 6 months. Their mean age of presentation was 6.24±2.93 (range 1-14) years, 33% were below 5 years and there were 70 males. 41 children were asymptomatic at diagnosis, of the rest only two required hospitalization for non-resolving pneumonia.

Nutritional status was normal in 41 children. Among the rest 59 children, 13 (22%) were wasted, 23 (38.9%) were stunted, and 23 (38.9%) were both wasted and stunted. Severe wasting and severe stunting were present in 12/59 (20.3%) and 8/59 (13.5%) children. Mean body mass index in children more than 5 years was 13.92.

The possible mode of transmission was parent to child in 90 children, blood transfusion in 4 children, unsafe injection practices in 1 child and in 5 children, the mode of transmission was not clear. Majority of children were born by vaginal delivery (93%) with only 2% born by cesarean section. Five children were orphans brought to our centre by local non-governmental organisation and their birth and family details were not available.

Common clinical symptoms at diagnosis were fever (83%), cough (50.8%) and diarrhea (38.9%). Skin manifestations were observed in 6.7% of children and included pyoderma, extensive warts and molluscum contagiosum. Mucosal presentations include oral ulcerations (44.1%) and candidiasis (14.7%). Tuberculosis was the most common opportunistic infection diagnosed in 11% of

children. Parotitis and acute suppurative otitis media were seen in one child each.

Age wise distribution of baseline mean (SD) CD4 count was 961.6 (535.1) [1-5 years]; 659.4 (544.7) [5-9 years]; 603.3 (500.1) [9-13years]; 422 (226.3) [above 13 years]. Baseline CD4 count was significantly higher in children less than 5 years (P=0.003). ***Table* I** depicts the relation between clinical staging and immunological staging at presentation. Agreement between the clinical and immunological stage at presentation was poor (κ 43.6%).

Thirty three children were initiated on ART. Compliance with medications was good and none developed any adverse reaction to ART. Of these, 28 were started on ART based on clinical staging (clinical stage III, 22 and stage IV, 6) and 5 children were started ART based on immunological criteria (CD4 guided). 22 children were started on combination of lamivudine, stavudine and nevirapine; seven children started on combination of lamivudine, zidovudine and efavirenz; and three children on combination of lamivudine, stavudine and efavirenz. Efavirenz based therapy was started in children diagnosed with tuberculosis and they were reverted back to nevirapine based therapy after completion of antitubercular treatment. ART combination was based on availability of ART in the centre. 70% [23] of children who were initiated on ART were malnourished (stunted, wasted, or both). Mean (SD) hemoglobin level in children on zidovudine based ART was 8.75 (1.28) g/dL and those on stavudine based ART was 8.6 (2.68) g/dL.

Children who were initiated on ART had a significant improvement in both clinical and immunological staging at the 6 months follow up (P=0.001). There was a significant rise in CD4 count at the six month follow up in these children. However, the rise in CD4 count was not related to stage of clinical presentation at diagnosis (***Table* II**). Mean (SD) increase in CD4 count for children on ART was 317.4 (155.1) per cu mm. In children who were not initiated on ART (n=67), there was no change in either clinical or immunological staging at the follow up. The mean (SD) decline in CD4 count in this group was 106.4 (333.8) per cu mm (P=0.015).

In children on ART, CD4 count at the follow up varied significantly with the immunological stage of presentation (P=0.04). Rise in CD4 count was inversely related to the degree of immune suppression at onset. Children with better baseline CD4 count had a better rise in CD4 count in response to ART. However, no difference was observed among the clinical stages in relation to CD4 counts at presentation and at follow up (***Table* II**).

DISCUSSION

Clinical profile of HIV infected children in our ART centre was similar to those reported earlier [6]. However, in our study, 41% of children were asymptomatic with normal nutritional status. This is in contrast to another study from India which revealed prevalence of underweight, stunting and wasting of 63%, 58% and 16%, respectively [7]. This could be attributed to early diagnosis of illness in the asymptomatic stage as large number of children are diagnosed positive because of their parents' HIV status [8]. Moreover, these children are

TABLE I CLINICAL AND IMMUNOLOGICAL STAGING AT PRESENTATION

	Immune stage 1	Immune stage 2	Immune stage 3	Immune stage 4	Total
WHO stage 1	47	16	2	1	66
WHO stage 2	0	3	1	2	6
WHO stage 3	0	7	9	6	22
WHO stage 4	0	1	0	5	6
Total	47	27	12	14	100

kappa 43.6% form agreement between WHO staging and immune staging at presentation.

TABLE II MEAN (SD) CD4 COUNTS AT PRESENTATION AND FOLLOW UP

Presentation	Children on ART (*n*=33)				Children not on ART (*n*=67)			
Staging	No.	CD4 pre Mean (SD)	CD4 FU Mean (SD)	Change CD4 Mean(SD)	No.	CD4 pre Mean (SD)	CD4 FU Mean (SD)	Change CD4 Mean (SD)
WHO stage								
Stage I	1	287.8(120.5)	597.8 (213.8)	310 (151.6)	65	979.9 (528.0)	875.9 (528.0)	-108.1 (338.6)
Stage II	4	287.8 (120.5)	597.8 (213.8)	310 (151.6)	2	407 (69.3)	354. (107.5)	-53 (38.2)
Stage III	22	292.3 (122.8)	578.8 (22.5)	286.5 (136.7)	0	NA	NA	NA
Stage IV	6	258.2 (227.8)	695.0 (366.1)	436.8 (188.8)	0	NA	NA	NA
Immunological stage								
Stage I	0	NA	NA	NA	47	1141.6 (529.6)	950.7 (443.9)	- 194 (343.3)
Stage II	9	391.9 (41.5)	749.3 (163.9)	357.4(143.4)	18	542.3 (164.2)	659.5 (275.6)	125 (210.3)
Stage III	10	305.5 (82.5)	550.4 (197.7)	244.9 (126.8)	2	544.0 (296.9)	545(91.9)	1.0 (205.5)
Stage IV	14	202.6 (167.0)	546.1 (295.2)	343.5 (171.7)	0	NA	NA	NA
Total	33	285.4 (141.4)	602.8 (247.8)	317.4 (155.1)	67	962.8 (520.2)	860.4 (420.6)	-106.4 (333.6)

Significance: On ART - WHO staging (pre and FU): Within group P = 0.00; between group P =0.9; Immune staging (pre and FU): - Within group P =0.00; between group P = 0.04; Not WHO staging (pre and FU):- Within group = 0.52, between group 0.09; Immune staging (pre and FU): Within subject P = 0.76, between subjects P <0.001.

also supported by non governmental organisations which provide good nutritional rehabilitation to them. However, more studies are required to determine whether nutritional rehabilitation early in the course of illness would improve the nutritional status of HIV infected children.

Clinical and immunological improvement to antiretroviral in our study is similar to previous Indian studies [9,10]. However, we observed that improvement in CD4 count was better among children with higher baseline CD4 count i.e. lesser degree of immunosupression. Similar observations have been reported in adults by Lawn, *et al*. [11], but seldom reported in children. This could be attributed to overwhelming opportunistic infections observed with higher degrees of immunosupression. Hence earlier detection and higher baseline CD4 count might improve the outcome of antiretroviral treatment.

WHO has laid down guidelines for initiation of ART based on the clinical staging (stage III/IV) and immunological staging *i.e.* CD4 counts in stage 1 and II [5]. In view of poor measure of agreement observed between the clinical and immunological staging at presentation in our study, we emphasise the need for CD4 count rather than clinical staging in guiding the initiation of antiretroviral treatment in children. Moreover, improvement in CD4 counts was better among children with higher baseline CD4 count i.e. lesser degree of immunosupression. Hence, earlier detection and higher baseline CD4 count might improve the outcome of antiretroviral treatment. Moreover, WHO clinical staging was designed for use in resource limited settings where access to laboratories is poor. Reliability of clinical staging for initiation of ART is hence debatable.

The limitations of our study include small sample size and the short study period. Provision of free-of-cost medicines, efforts of large number of social organisation, and achievement of universal treatment access has indeed resulted in excellent compliance and scheduled regular follow up visit [12]. Availability of CD4 count assay is limited to tertiary care hospitals and cheaper and newer methods for estimation of CD4 count are being developed [13]. CD4 guided initiation of ART irrespective of clinical staging might ensure full benefits of ART and might delay the progression of disease to advanced stage.

WHAT IS ALREADY KNOWN?

- HIV infection is a growing concern in Indian children.

WHAT THIS STUDY ADDS?

- Baseline CD4 counts should be used as a primary determinant for initiating antiretroviral therapy in HIV infected children.

Our study concludes that baseline CD4 counts rather than clinical staging can be a primary determinant for initiation of antiretroviral treatment in HIV infected children. However, we recommend further studies with longer follow up and larger sample size.

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