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Profile of HIV Infection in Children and Its Correlation with their CD4 Counts

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ABSTRACT

Objectives: (i) To study the clinical profile of human immunodeficiency virus (HIV) infection in children. (ii) To establish the pattern of correlation of these clinical features with the CD4 counts. (iii) To evaluate the effect of highly active antiretroviral therapy (HAART) on CD4 count of children at 6 months of therapy. **Material and methods:** Sixty-eight children enrolled at our ART centre or admitted at our hospital were enrolled for the study. Their case papers were reviewed. Complete clinical profile was obtained and baseline investigations including CD4 counts done. Children were then followed up and repeat CD4 levels done 6 monthly. The children were managed as per current guidelines. **Results:** The mean age at presentation was 6.54 ± 2.69 years. Male-to-female ratio was 2.579:1. Vertical transmission accounted for 95.58% of cases. Prolonged fever and chronic diarrhea were the most common symptoms and hepatosplenomegaly and lymphadenopathy were the most common signs. There was strong correlation between clinical and immunological staging ($p < 0.0001$). Failure to thrive, recurrent skin infections and abscesses were signs and symptoms at lowest CD4 levels. Orphan-hood ($p < 0.0001$) and socioeconomic status ($p = 0.0003$) significantly affected schooling among these children. Malnutrition, anemia and stunting were features of severe immunosuppression. HAART significantly raised the CD4 count at 6 months of therapy (paired 't' = 6.830, $p < 0.0001$) with best results at higher baseline CD4 levels. Gastritis was the most common (81.5%) adverse effect and the major cause of decreased compliance. Tuberculosis and candidiasis were the commonest opportunistic infections and pneumonia accounted for majority of hospitalizations (61.5%). **Conclusions:** Clinical and immunological staging have good correlation. The features of severe immunosuppression are failure to thrive, recurrent bacterial skin infections, abscesses, *Pneumocystis jirovecii* pneumonia, extrapulmonary tuberculosis, anemia and stunting. Orphan-hood and poor socioeconomic status affect schooling in these children. Early initiation of ART at higher baseline CD4 has best results. Gastritis is the major adverse effect causing decreased compliance.

Keywords: CD4 count, children, clinical features, HIV, immunological stage, malnutrition, schooling

The human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) epidemic is in its 4th decade. With the advent of highly active antiretroviral therapy (HAART), most of the countries have halted and begun to reverse the spread of HIV.[1] Although the number of new infections has been falling, levels of new infections overall are still high and with significant reductions in mortality, the number of people living with HIV worldwide has increased. CD count has been the most widely used parameter for monitoring patients. Whereas, the clinical presentation and the opportunistic infections at different CD4 levels have been well-established in adults, data regarding the same in children are lacking. Further, certain other nutritional, social and economical factors like malnutrition, immunization, anemia, parental death and schooling, etc. further complicate the issue in children. The advent of HAART has brought about a major change in the AIDS epidemic pattern. But, the efficacy of HAART and the factors affecting compliance to drugs in children, particularly in Indian setting, has not been well-documented.

The decision to initiate ART is based on the CD4 count of the child. If the facilities for CD4 count are not available, then clinical staging is used for deciding the timing for initiation of ART.[2] However, the best timing for initiation of HAART is still a subject of much debate.

In this study, we aim to establish the pattern of signs and symptoms, prevalence of anemia, malnutrition, vitamin A deficiency and the various opportunistic infections at various levels of CD4 counts in children.

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We will evaluate the effect of HAART in children, the adverse effects associated with these drugs in children and the factors affecting compliance to these drugs. We will also evaluate the factors which are associated with better improvements in CD4 counts in patients on HAART and try to establish their roles in determining the best timing for initiation of ART.

MATERIAL AND METHODS

The study was conducted at the Dept. of Pediatrics, SN Medical College, Agra and ART Centre, SN Medical College, Agra in collaboration with National JALMA Institute for Leprosy and Other Mycobacterial Diseases, (Indian Council of Medical Research), Agra. A sample size of 68 was obtained assuming noncentrality parameter delta = 2.53, type 1 error = 0.05, power (1-β) = 0.90, effect size (d) = 0.40 and a t (critical), one-tailed test = 1.68. Children less than 15 years of age were enrolled in the study as per the classification by UNAIDS.[1] Known HIV-positive children attending the ART Centre, SN Medical College and those children who were diagnosed as HIV-positive during the course of their management in the hospital were included in the study. Institutional Thesis and Ethical Committee cleared the study. The study protocol was explained to the parent/guardian in detail and informed, written consent was obtained from them. Data was obtained from the parents/guardians as per the predesigned questionnaire and by referring to their records for investigations. A detailed history covering all aspects was taken. Complete physical examination including anthropometry was done. Investigations were accessed from the records of the patient. If not available, investigations were carried out at SN Medical College. CD4 count of the child was done using the Becton Dickinson's automated fluorescence activated cell sorter (FACS), at National JALMA Institute for Leprosy and other Mycobacterial Diseases. Protein energy malnutrition (PEM) was graded on the basis of weight for age (independent activities period [IAP] grading). Anemia was taken as hemoglobin <8 g/dL according to National AIDS Control Organization (NACO) guidelines.[2] Opportunistic infections were diagnosed based on the standard protocol and investigations available. Each patient was assigned a clinical and an immunological stage as per World Health Organization (WHO) criteria. Children were followed up at monthly intervals and investigations including CD4 counts repeated at 6-monthly intervals. ART naïve children who were eligible for initiation of ART as per the current guidelines were initiated on appropriate treatment as per NACO guidelines.[2] Pearson's correlation coefficient (r) was used to analyze the degree of correlation of clinical and immunological stages. Independent sample *t*-test was used to compare the means of 2 distinct qualitative groups like males and females. Categorical variables were compared by using Chi-square test. Cochran-Armitage Chi-square test for trend was preferred, when one of the variables followed ordinal distribution. To compare the pre- and post-treatment CD4 values, we have used paired *t*-test. To perform all these functions, MedCalc version 11.6 and SPSS version 16 statistical packages were utilized.

RESULTS

The mean age at the time of diagnosis was 6.735 ± 2.75 years for males and 6.05 ± 2.53 years for females, with no significant difference between the groups ($p > 0.05$). Whereas, 72.06% of children in our study were males, only 27.94% were females. Vertical transmission was the predominant mode of transmission of HIV in our study accounting for 95.58% of cases. The remaining 3 (4.41%) had acquired HIV through transmission of infected blood/blood products.

Prolonged fever was the predominant symptom in HIV-positive children (42.64%). Chronic diarrhea (41.17%), prolonged cough (25%), not gaining weight (17.61%), recurrent skin infection (17.61%) and ear discharge (17.61%) were some of the other common symptoms that were present in these children. On examination of these children, the most commonly noted signs were hepatosplenomegaly and lymphadenopathy, both being present in 47.06% children. Oral candidiasis and signs of vitamin A deficiency were both present in 27.94% of children. Other signs noted included pyoderma (26.42%), pneumonitis (26.42%), otitis media (17.68%), dental caries (17.68%), aphthous ulcers (8.82%) and scabies (5.888%). On classifying these children into clinical stages based on WHO clinical staging criteria, majority (35.3%) of children in our study, belonged to clinical stage 3 and 21 (30.88%) children belonged to clinical stage 2; 16.17% and 17.65% children were in clinical stage 1 and 4, respectively. There was no significant variation in clinical staging in different age groups ($p = 0.491$). At the time of enrollment in our study, 23 (33.82%) children were not having any immunosuppression; 13.23%, 22.06% and 30.88% children were having mild, advanced and severe immunosuppression, respectively. Immunological stage was neither dependent on the age of the child ($p > 0.05$), nor was it dependent on the mode of acquisition of HIV ($p = 0.46$). There was a strong association between the clinical and the immunological staging of HIV in

children, i.e., with worsening CD4 status, clinical stage of the child's infection advanced (r = 0.6708 and p < 0.0001) (Table 1). While prolonged fever and chronic diarrhea were the commonest presenting symptoms in children from across all immunological stages, 2 symptoms which were more common in children with severe immunosuppression and less common in others were 'failure to thrive' and 'recurrent skin infections' in 38.09% and 28.57% of children with severe immunosuppression. Hepatosplenomegaly and lymphadenopathy were the commonest clinical signs irrespective of the CD4 status of the children. Pyoderma and abscesses were signs, which were predominantly seen only when CD4 count of the children were very low. Pyoderma was seen in as many as 52.38% of children whose CD4 levels were consistent with stage of severe immunosuppression, whereas, at stages of no immunosuppression and mild immunosuppression, it was seen in less than 10% of the cases (Table 2).

Table 1. Common Clinical Features at Different Grades of Immunosuppression

WHO immunological stage	Common symptoms		Common clinical signs	
	Symptoms	Number of children	Clinical signs	Number of children
No immunosuppression (n = 23)	Prolonged fever	08 (34.78%)	No abnormality	06 (26.08%)
	Chronic diarrhea	04 (17.39%)	Lymphadenopathy	06 (26.08%)
	Ear discharge	04 (17.39%)	Hepatosplenomegaly	05 (21.74%)
	Asymptomatic	03 (13.04%)	Otitis media	05 (21.74%)
Mild immunosuppression (n = 9)	Chronic diarrhea	06 (66.67%)	Lymphadenopathy	05 (55.55%)
	Prolonged fever	03 (33.33%)	Hepatosplenomegaly	04 (44.44%)
	Recurrent oral ulceration	03 (33.33%)	Oral candidiasis	04 (44.44%)
	Asymptomatic	02 (22.22%)	No abnormality	03 (33.33%)
Advanced immunosuppression (n = 15)	Prolonged fever	08 (53.33%)	Signs of vitamin A deficiency	07 (46.67%)
	Recurrent chest infection	05 (33.33%)	Hepatosplenomegaly	06 (40%)
	Chronic diarrhea	05 (33.33%)	Lymphadenopathy	06 (40%)
	Ear discharge	06 (40%)	Pneumonitis	06 (40%)
Severe immunosuppression (n = 21)	Chronic diarrhea	13 (61.9%)	Hepatosplenomegaly	14 (66.67%)
	Failure to thrive	08 (38.09%)	Lymphadenopathy	13 (61.9%)
	Prolonged fever	10 (47.61%)	Oral candidiasis	11 (52.38%)
	Recurrent skin infection	06 (28.57%)	Pyoderma/Abscesses	11 (52.38%)

Table 2. Correlation of the WHO Clinical Stage and WHO Immunological Stage of the HIV-positive Children

	WHO clinical stage 1 (n = 11)	WHO clinical stage 2 (n = 21)	WHO clinical stage 3 (n = 24)	WHO clinical stage 4 (n = 12)
Stage of no immunosuppression (n = 23)	10	09	03	01
Stage of mild immunosuppression (n = 9)	01	04	04	NIL
Stage of advanced immunosuppression (n = 15)	NIL	07	06	02
Stage of severe immunosuppression (n = 21)	NIL	01	11	09

Pearson's correlation coefficient 'r' = 0.6708, 95% CI for 'r' = 0.515 to 0.784, $p < 0.0001$. Concordance correlation coefficient = 0.6488, C_b(accuracy) = 0.9672 (Very strong association).

Sixty-three out of 65 children (96.92%) acquiring HIV infection through mother-to-child transmission were delivered vaginally and only 2 (3%) were delivered by cesarean section. A total of 89.2% children had received breastfeeding in infancy (43.07% - exclusive breastfeeding, 46.15% - mixed feeding).

A majority (52.94%) of families of children in our study belonged to socioeconomic Class IV (Kuppuswamy socioeconomic scale). There was no significant variation in clinical stages among children of different socioeconomic classes (p = 0.274). Sixteen percent of children in our study were orphans, i.e., had no alive parent. They were being taken care of by grand-parents, siblings (elder) or uncle/aunt. No child was staying at orphanage. Nearly 42.6% of children had both their parents alive. Eight (11.76%) had lost their mothers and 20 (29.41%) had lost their fathers, thus implying that 57.3% children had lost one or both of their parents. Sixty out of 68 children in our study were of school-going age. Whereas, 84% of children whose both parents were alive were enrolled at school, only 9% of children who had no alive parent were enrolled at school, while 62.5% and 26.6% of children who were survived only by their fathers and mothers, respectively were enrolled at school. All children whose families belonged to socioeconomic Class I or II were enrolled at school; 83.33% of those belonging to socioeconomic Class III had school enrollment. But when it came to socioeconomic Class IV and V, only 38.7% and 25% were enrolled at school, respectively (Table 3). Only 47.06% of children had completed immunization for their age as per the National Immunization Schedule.

Only 17.64% of children in the study had no malnutrition (weight for age more than 80% of expected). Out of the remaining, 30.8%, 19.1%, 23.5% and 8.8% children suffered from Grade I, II, III and IV PEM, respectively. As evident from Table 4, proportion of children with higher grades of malnutrition increased significantly in children with increasing clinical stages of infection (p = 0.0013). A similar association was found between the immunological stage and the severity of malnutrition (p = 0.0038). However, such positive association was not found between the socioeconomic status and the severity of malnutrition (p = 0.3123). Table 5 shows that stunting was present in 25% of the children; 70.59% of children who had stunting were having CD4 counts consistent with the stage of severe immunosuppression (p = 0.0004). The prevalence of anemia was 30.9% in our study with the largest proportion of these anemics having CD4 counts consistent with stage of severe immunosuppression (66.67%). Signs of vitamin A deficiency were present

Table 3. Variables Affecting the Child's Schooling

Variables	Children enrolled at school (Number of children [%])	Children not enrolled at school (Number of children [%])
Surviving parent/s*		
Both parents	22 (84.61)	04 (15.38)
Father only	05 (62.5)	03 (37.5)
Mother only	04 (26.66)	11 (73.33)
No surviving parent	01 (9.09)	10 (90.9)
Socioeconomic status of the family†		
Socioeconomic Class I	02 (100)	NIL
Socioeconomic Class II	01 (100)	NIL
Socioeconomic Class III	15 (83.33)	03 (16.67)
Socioeconomic Class IV	12 (38.71)	19 (61.29)
Socioeconomic Class V	02 (25)	06 (75)
Severity of the disease‡		
WHO clinical stage 1	05 (50)	05 (50)
WHO clinical stage 2	11 (52.38)	10 (47.62)
WHO clinical stage 3	15 (75)	05 (25)
WHO clinical stage 4	01 (11.11)	08 (88.88)

*Survival of parents vs. schooling: $\chi^2 = 23.429$, DF = 3, $p < 0.0001$.

†Socioeconomic status of family vs. schooling: $\chi^2 = 14.378$, p = 0.0006, χ^2 (trend) = 12.257, p = 0.0005.

‡Clinical severity vs. schooling: $\chi^2 = 10.271$, p = 0.0164, χ^2 (trend) = 0.653, p = 0.4190.

Table 4. Prevalence of PEM in HIV-positive Children and Factors Affecting It

Variables	PEM (IAP classification)					
	No PEM	Grade I PEM	Grade II PEM	Grade III PEM	Grade IV PEM	
Clinical severity of disease*						
WHO clinical stage 1	06 (54.54%)	02 (18.18%)	03 (27.27%)	NIL	NIL	11
WHO clinical stage 2	04 (19.04%)	09 (42.86%)	05 (23.8%)	03 (14.28%)	NIL	21
WHO clinical stage 3	02 (8.33%)	08 (33.33%)	03 (12.5%)	09 (37.5%)	02 (8.33%)	24
WHO clinical stage 4	NIL	02 (16.67%)	02 (16.67%)	04 (33.33%)	04 (33.33%)	12
Immunological stage†						
No immunosuppression	08 (34.78%)	09 (39.13%)	05 (21.74%)	01 (4.35%)	NIL	23
Mild Immunosuppression	02 (22.22%)	04 (44.44%)	02 (22.22%)	01 (11.11%)	NIL	09
Advanced immunosuppression	02 (13.33%)	04 (26.67%)	04 (26.67%)	04 (26.67%)	01 (6.66%)	15
Severe immunosuppression	NIL	04 (19.05%)	02 (9.52%)	10 (47.61%)	05 (23.8%)	21
Socioeconomic status of the family‡						
Class I	01 (50%)	NIL	NIL	01 (50%)	NIL	02
Class II	01 (100%)	NIL	NIL	NIL	NIL	01
Class III	06 (31.58%)	05 (26.31%)	04 (21.05%)	04 (21.05%)	NIL	19
Class IV	02 (5.55%)	14 (38.89%)	08 (22.22%)	08 (22.22%)	04 (11.11%)	36
Class V	02 (20%)	02 (20%)	01 (10%)	03 (30%)	02 (20%)	10

*Clinical stage vs. Grade of PEM: χ^2 = 32.233, DF= 12, Contingency coefficient = 0.567, p = 0.0013.

†Immunological stage vs. Grade of PEM: χ^2 = 29.141, DF = 12, Contingency coefficient = 0.548, p = 0.0038.

‡Socioeconomic status of the family vs. Grade of PEM: χ^2 = 18.201, DF = 16, Contingency coefficient = 0.46, p = 0.3123.

Table 5. Comparison of Stunting, Anemia and Vitamin A deficiency with the CD4 Status

Features		Number of children (%)			
		No immuno-suppression	Mild immuno-suppression	Advanced immuno-suppression	Severe immuno-suppression
Stunting	Yes (n = 17)	02 (11.76)	00	03 (17.65)	12 (70.59)
	No (n = 51)	21 (41.18)	09 (17.65)	12 (23.53)	09 (17.65)
Anemia	Present (n = 21)	03 (14.28)	01 (4.76)	03 (14.28)	14 (66.67)
	Absent (n = 47)	20 (42.5)	08 (17.02)	12 (25.53)	07 (14.89)
Signs of vitamin A deficiency	Present (n = 19)	03 (15.78)	02 (10.52)	05 (26.32)	09 (47.37)
	Absent (n = 49)	20 (40.82)	07 (14.28)	10 (20.41)	12 (24.49)

in 27.9% of the children. There was no significant association between the immunological stage and the prevalence of manifestations of vitamin A deficiency (p = 0.1565).

As depicted in Table 6, 23.5% of the HIV-positive children had no opportunistic infection at the time of enrollment in the study, 27.9% children suffered from 1 opportunistic infection and the rest 48.5% had more than 1 opportunistic infections at the time of being enrolled in the study. The chances of acquiring an opportunistic infection increased significantly as the immunological status of the children deteriorated (p < 0.001). The most common opportunistic infections in these children were pulmonary tuberculosis (27.94%) and oral candidiasis (27.94%). Other common opportunistic infections were pneumonia (20.6%), recurrent skin infections (17.65%), otitis media (16.18%), persistent diarrhea (16.18%), extra-pulmonary tuberculosis (10.29%), scabies (5.88%) and *Pneumocystis jirovecii* pneumonia (4.41%). Pulmonary tuberculosis, candidiasis and otitis media were present at all immunological stages with greater prevalence

at higher levels of immunosuppression. Pneumonia was more prevalent in children with advanced (33.33%) and severe (33.33%) immunosuppression. All children suffering from *P. jirovecii* pneumonia were having CD4 levels consistent with stage of severe immunosuppression. Extrapulmonary tuberculosis had higher prevalence among children with severe immunosuppression (19.05%). There were a total of 29 children whose pre-treatment CD4 and 6 months post-treatment CD4 values were available. Paired CD4 counts of the children pre-treatment and 6 months post- treatment were compared. Mean CD4 count of these children before starting ART was 384.655 ± 268.645. The mean CD4 count of the same group of children after receiving ART for 6 months was 604.241 ± 322.380 with a mean increase of 219.586 ± 173.127. We applied paired sample *t*-test and obtained 't' = 6.830 and $p < 0.0001$ (Table 7).

The mean rise in CD4 count was maximally seen in the age group of 5-10 years (273.823 ± 169.041). There was a significant improvement in CD4 levels on receiving ART

Table 6. Prevalence of Opportunistic Infections at Different Grades of Immunosuppression

Opportunistic infections	Grades of immunosuppression			
	No immuno-suppression (n = 23)	Mild immuno-suppression (n = 09)	Advanced immuno-suppression (n = 15)	Severe immuno-suppression (n = 21)
No opportunistic infection	13 (56.52%)	02 (22.22%)	01 (6.67%)	NIL
P. jirovecii pneumonia	NIL	NIL	NIL	03 (14.28%)
Pulmonary TB (including miliary TB)	04 (17.39%)	01 (11.11%)	03 (20%)	11 (52.38%)
Extrapulmonary TB	01 (4.25%)	01 (11.11%)	01 (6.67%)	04 (19.05%)
Oral/pharyngeal candidiasis	02 (8.69%)	03 (33.33%)	03 (20%)	11 (52.38%)
Recurrent bacterial skin and soft tissue infections	03 (13.04%)	01 (11.11%)	02 (13.33%)	08 (38.09%)
Otitis media	03 (13.04%)	02 (22.22%)	04 (26.67%)	02 (9.52%)
Infective persistent diarrhea	01 (4.25%)	01 (11.11%)	02 (13.33%)	07 (33.33%)
Bacterial pneumonia	01 (4.25%)	01 (11.11%)	05 (33.33%)	07 (33.33%)

Table 7. Efficacy of HAART and the Variables Affecting Response to Treatment

Variables	No. of children	Pre-HAART CD4 (mean ± SD)	Post-HAART CD4 (mean ± SD)	Change in CD4 due to treatment (mean ± SD)	P value
Age					
3-5 years	5	415.00 ± 334.829	551.40 ± 420.409	136.40 ± 212.647	p = 0.224
5-10 years	17	435.706 ± 267.149	709.529 ± 314.848	273.823 ± 169.041	p < 0.0001
10-15 years	7	239.000 ± 197.065	386.285 ± 116.914	147.285 ± 115.448	p = 0.015
Clinical stage					
1	04	653.75 ± 377.792	957.00 ± 371.064	303.250 ± 46.133	p = 0.001
2	10	358.800 ± 216.034	550.70 ± 238.325	191.90 ± 152.569	p = 0.003
3	14	340.500 ± 249.469	566.357 ± 318.65	225.859 ± 208.65	p = 0.001
4	01	185.000	259.000	NA	NA
Within stage, p < 0.001; between stages, p = 0.094					
Immunological stage					
No immunosuppression	8	693.500 ± 275.935	961.875 ± 308.351	268.375 ± 94.892	p < 0.0001
Mild immunosuppression	6	376.500 ± 96.529	480.333 ± 139.648	103.833 ± 128.207	p = 0.104
Advanced immunosuppression	8	319.500 ± 120.844	552.875 ± 199.415	233.375 ± 212.364	p = 0.017
Severe immunosuppression	7	113.143 ± 65.098	360.429 ± 229.498	247.286 ± 212.979	p = 0.022
Within stage, p < 0.001; between stages, p < 0.001					

Table 8. Hospitalization in HIV-positive Children

Variable	Number of admissions N = 13 (%)
WHO clinical stage of disease	
Clinical stage 1	NIL
Clinical stage 2	NIL
Clinical stage 3	05 (38.46)
Clinical stage 4	08 (61.54)
Immunological status of the child	
No immunosuppression	NIL
Mild immunosuppression	NIL
Advanced immunosuppression	02 (15.39)
Severe immunosuppression	11 (84.61)

in children irrespective of their clinical stages. The mean rise in CD4 levels in children with no, mild, advanced and severe immunosuppression were 268.375 ± 94.892, 103.833 ± 128.207, 233.375 ± 212.364 and 247.286 ± 212.979, respectively. Of those who reported at follow-up after starting ART, 49.09% experienced adverse effects to ART. The commonest reported adverse effect was gastritis, which was present in 81.5% of those who reported adverse effects. It was the most common event causing decreased compliance to HAART.

A total of 13 (19.12%) children in our study required hospitalization during the 1½ year study period. The most common indication for hospitalization was pneumonia, responsible for 61.5% of the hospitalizations. Of these, 38.46% of children were in clinical stage 3 and 61.54% were in WHO clinical stage 4. No child with HIV in clinical stage 1 or 2 required hospitalization. It was seen that 15.4% of children who required admission had CD4 levels consistent with stage of advanced immunosuppression and the rest 84.6% children who were hospitalized had CD4 levels consistent with stage of severe immunosuppression (Table 8).

DISCUSSION

The mean age at diagnosis was 6.54 ± 2.69 years. Most of these children were diagnosed as a part of screening after parental diagnosis. Delayed diagnosis implies delayed initiation of treatment. In the study by Shah et al, mean age at diagnosis was 4.5 ± 2.9 years.[3] The male-to-female sex ratio in our study was 2.579:1, which is similar to previous studies.[4-7] However, this difference is not statistically significant (p = 0.7965) at the current sample size. As many as, 95.58% of children in our study had acquired the infection through mother-to-child transmission. Previous studies showed a significant transmission to occur through blood transfusion,[8-10] which has decreased now, due to compulsory screening of donor blood for HIV.

The clinical features in our study were similar to previous studies.[3,7-9,11-13] There was a very strong correlation between the clinical and the immunological stages of HIV in children (correlation coefficient, r = 0.6708, p < 0.0001). A previous study had showed good correlation.[9] When we assessed the clinical features with regards to CD4 count, we noticed that while most of the signs and symptoms were present at all CD4 levels, 'failure to thrive', 'recurrent skin infection (pyoderma)' and 'abscesses' occurred when CD4 levels of the children fell very low (stage of severe immunosuppression).

On analysis of the variables affecting schooling in these children, we found that orphan-hood (p < 0.0001) and poor socioeconomic status (p = 0.0003) were significant contributor to school absenteeism. In contrast, clinical severity as determined by higher clinical staging did not affect school absenteeism.

PEM was present in 82.36% of children. The factors affecting the severity of malnutrition were clinical stage (p = 0.0013) and immunological stage (p = 0.0038) implying that it's the severity of infection evidenced by clinical and immunological stages that is a significant contributor towards malnutrition in children. Stunting and anemia were late features in HIV. Children in stage of severe immunosuppression accounted for 70% and 66.67% of cases of stunting and anemia, respectively. Signs of vitamin A deficiency occurred early in the course of the disease.

The chances of acquiring an opportunistic infection increased significantly as the immunological status of the children deteriorated (p < 0.001). The most common opportunistic infections in these children were pulmonary tuberculosis (27.94%) and oral candidiasis (27.94%). This is in accordance with previous studies.[7,8,14] Pulmonary tuberculosis, candidiasis and otitis media occurred at higher CD4 levels but their prevalence increased with increasing levels of immunosuppression. Pneumonia was more prevalent in children with advanced (33.33%) and severe (33.33%) immunosuppression. All children suffering from *P. jirovecii* pneumonia and extrapulmonary tuberculosis were seen when CD4 levels fell to the stage of severe immunosuppression (19.05%). All the opportunistic infections occurred at greater frequency than the Pediatric AIDS Clinical Trials Group (PACTG) study trial.[15]

HAART resulted in significant rise in CD4 levels after 6 months of therapy. The maximum response to HAART was seen in the age group of 5-10 years. There was significant rise in CD4 count irrespective of the clinical staging. But, the best response of HAART in terms of raising CD4 count was seen when therapy was initiated in children with lesser immunosuppression, i.e., higher baseline CD4 count. Hence, early initiation of ART at higher CD4 levels may be more beneficial rather than waiting for the CD4 count to fall below the current cut-off as per WHO guidelines. Gastritis was the most commonly reported adverse effect of HAART and it was also the major cause of decreased compliance to therapy. About 19% of HIV-positive children required admission every year with pneumonia being the most common cause of admission among them. Average duration of hospital stay was 8.84 ± 4.35 days. The frequency of hospitalization increased as the clinical and immunological stage of the child's illness increased; 38.46% of children requiring admission were in clinical stage 3 and 61.54% were in WHO clinical stage 4. No child with HIV in clinical stage 1 or 2 required hospitalization. Similarly, 15.4% and 84.6% of admitted children had CD4 levels consistent with advanced and severe immunosuppression, respectively.

CONCLUSION

The clinical and immunological stagings have good correlation and hence in the absence of facilities for carrying out CD4 count, clinical staging is a suitable alternative for monitoring these children. The timing of appearance of various clinical features with regards to the CD4 count can be summarized as follows: *Mild immunosuppression*: Vitamin A deficiency, pulmonary tuberculosis, candidiasis, otitis media, decreased weight for age, hepatosplenomegaly and lymphadenopathy; *Advanced immunosuppression*: Bacterial pneumonia; *Severe immunosuppression*: Anemia, stunting, pyoderma, abscesses, *P. jirovecii* pneumonia and extrapulmonary tuberculosis. HAART causes significant rise in CD4 count at 6 months of treatment. The best effect is seen when HAART is initiated at higher baseline CD4 count. HAART is very well-tolerated in children with good compliance. Gastritis is the major limiting side effect. Early diagnosis and early initiation of treatment will reduce the morbidity and mortality associated with HIV.

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