Profiles of HIV-infected anti-retroviral therapy naïve children from Mumbai, India

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Original article

Background: **This study aimed to investigate the demographic profiles of human immunodifficiency virus (HIV) infected anti-retroviral therapy (ART) naïve children in our hospital and their relations to the clinical, immunological and nutritional status.**

Methods: **A cross-sectional study was conducted in an Integrated Counselling and Testing Center (ICTC) at a tertiary care hospital in Mumbai. ART naïve HIV positive children were enrolled in the study. The demographic profiles, clinical features, immunological (CD4%/CD4 count) and nutritional status of these children were recorded. The agreement between clinical, immunological and nutritional staging was determined using Cohen's kappa test.**

Results: **In 192 HIV-infected ART naive children enrolled with a median age of 9 years (range 3 months-14 years), 97.4% acquired infection through vertical transmission. The most common clinical presentation was fever (39.6 %), followed by generalized lymphadenopathy (32.3%), cough (22.4%) and diarrhoea (9.9%). Tuberculosis was seen in 22.9% of the children. The agreement was fair between clinical and immunological staging, and slight between nutritional, immunological and clinical staging.**

Conclusions: **Perinatal transmission is the most common mode of acquiring HIV infection in children. The Prevention of Parent to Child Transmission (PPTCT) program should be strengthened for lowering the transmission rate by providing extended ART to mothers during pregnancy and breast-feeding. Tuberculosis remains a major concern in HIV-infected children. The poor correlation between WHO clinical and immunological staging emphasizes the importance of making CD4 facilities available in HIV prevalent areas. Malnutrition cannot be used as a surrogate marker for predicting stage or severity as it is common at all stages of HIV disease.**

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Key words: **anti-retroviral therapy;**
CD4 count;
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Introduction

It has been reported that 3.4 million children were living with HIV at the end of 2011.[1] Approximately 142 000 children aged 0-14 years are living with human immunodifficiency virus (HIV) in India, including 14 000 new cases of HIV infections annually. Most of these children acquire HIV from their HIV-infected mothers during pregnancy, birth or breastfeeding. By effective interventions, the risk of mother-to-child HIV transmission can be reduced to 2%.[2] However, such interventions are not widely accessible or available in other resource-limited countries where the burden of HIV is the highest.[1] Globally, evidence suggests that although anti-retroviral therapy (ART) using single drug nevirapine is highly effective in reducing risk of transmission from about 45% to less than 10%,[3] addressing HIV/AIDS in infants and children below 18 months is a significant challenge. The Prevention of Parent to Child Transmission (PPTCT) program was launched in India in 2002. The program involved counselling and testing of pregnant women, detection of positive pregnant women, and the administration of a single dose of 200 mg nevirapine at the onset of labor to mother and a dose of 2 mg/kg to child after delivery to

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prevent mother to child transmission of HIV.[4]

Early ART for the prevention of HIV is contributive to the survival of infants. The National AIDS Control Organization (NACO) of India started the Early Infant Diagnosis (EID) program for the early diagnosis of HIV in 2010.[5] This program recommends that children born to HIV positive mothers should be diagnosed by DNA PCR earliest at 6 weeks, and ART must be given immediately to those with a positive result. As the 2012 NACO report, however, 86 000 children were eligible for ART, indicating a ART coverage rate of 40%.[6] The children born to HIV positive mothers before the initiation of EID program have missed ART and lost to follow-up, contributing to large pool of ART naive children in India. These children unless diagnosed would have been deprived of ART, and efforts should be made to enrol them in the Care and Support Services with the initiation of the EID program.

To further reduce mother to child transmission of HIV, a change was made in the policies of the PPTCT program since 2013. If a pregnant woman is found to be HIV positive she is referred to the ART centre and started on multiple drug ART consisting of at least three drugs irrespective of her CD4 count. And her child after delivery is subjected to nevirapine prophylaxis for 6 weeks, after which the child is referred for DNA PCR testing under the EID program.[3]

HIV is heterogenic epidemic and has different clinical and immunological presentations in different parts of the world. Both clinical and immunological profiles have been extensively studied in adults but the data in children are limited. The clinical manifestations of these ART naïve HIV positive children and their correlation with CD4 count/CD4% would be helpful in better understanding this disease. The present study was conducted to investigate the correlation of clinical, immunological and nutritional profiles in ART naïve children.

Methods

A cross-sectional study was conducted in an Integrated Counselling and Testing Center (ICTC) at a tertiary care hospital in Mumbai, India from April 2011 to September 2012. The study was approved by the institutional ethics committee. An ICTC is an entry point to prevention, treatment and care, where a person is counselled and tested for HIV and if positive, is referred for ART. Infants born to HIV positive mothers are also referred to the ICTC to be registered under the EID program, where samples are taken for DNA PCR. The CD4 testing facility for HIV positive children is also available at the ICTC.

The study protocol was explained to parents/guardians and those who gave written informed consent for their children were enrolled.

Age, gender and weight of the child were recorded. The probable mode of transmission was determined by taking history from parents/guardians and mother's HIV status. The clinical history was obtained by taking the details from each pediatric examination sheet.

Children were categorized into different clinical stages according to WHO clinical classification for HIV-infected children.[7] CD4 count/CD4% was estimated using BD FACSCalibur™ (Beckton Dickinson, Franklin Lakes, NJ, USA). Immunological staging was done according to WHO Immunological classification.[7] Under this classification, immunosupression was graded as not significant, mild, advanced and severe. CD4% was considered for children up to 5 years old, whereas CD4 count was for children more than 5 years old. Nutritional status of each child was determined on the basis of weight for age. The weight for age was calculated by Advanced Pediatric Life Support (APLS) formula, and graded as normal nutrition and grade I, II, III and IV malnutrition according to the Indian Association of Pediatrics (IAP) guidelines. IAP designates a weight of more than 80% of expected for age as normal. Grades of malnutrition are grade I (71%-80%), II (61%-70%), III (51%-60%) and IV (≤50%) of expected weight for that age.[8] On the basis of age, the children were divided into two groups: up to five years old and more than five years old. Demographic profiles of all children were studied. The clinical, immunological and nutritional parameters were compared.

Statistical analysis

CD4%/CD4 count of children in each clinical stage was analyzed and comparison between the clinical stages was done using ANNOVA followed by Tukey's (parametric) or the Kruskal-Wallis test followed by Dunn's test (non-parametric). Normality of the data was assessed by the Kolmogorov-Smirnov test. To find the agreement between clinical, immunological and nutritional staging, Cohen's kappa test was used. Statistical analyses were made using Graph pad Instat Version 3.0.

Results

One hundred and ninety two HIV positive ART naïve children were enrolled in the study. The age range was from 3 months to 14 years. The median age of presentation was 9 years.

One hundred and ten (57.3%) children were males. There was no significant difference in CD4

Table 1. Demographics of the enrolled HIV-infected ART naïve children

Variables	No.	Median CD4%*	Median CD4 count*	WHO classification of immunodeficiency			
				NS	Mild	Advanced	Severe
Gender							
Male	110	17 (*n*=31)	516.8 (*n*=79)	37	21	23	29
Female	82	17.9 (*n*=23)	446.6 (*n*=59)	23	19	16	24
Total	192			60	40	39	53
Age up to 5 (y)							
0-1	15	16	-	0	1	4	10
>1-3	15	22	-	4	5	2	4
>3-5	24	13	-	5	6	1	12
Total	54			9	12	7	26
Age >5 (y)							
>5-7	29	-	583.8	15	8	4	2
>7-9	21	-	455.2	8	1	4	8
>9-11	43	-	460.9	13	9	13	8
>11-13	26	-	525.8	9	9	3	5
>13	19	-	379.2	6	1	8	4
Total	138			51	28	32	27

*: CD4% in children up to 5 years old and CD4 count in children >5 years old. NS: not significant; ART: anti-retroviral therapy.

Table 2. Correlation between immunological and clinical staging

WHO clinical stage	Age (y)	Number	Median CD4% /CD4 count*	WHO immunological stage			
				NS	Mild	Advanced	Severe
I	≤5	27	22.0%	9	7	5	6
	>5	56	672.5	36	12	7	1
II	≤5	7	17.9%	0	2	2	3
	>5	24	404.5	10	9	3	2
III	≤5	12	10.5%	0	3	0	9
	>5	39	220	3	5	16	15
IV	≤5	8	10.0%	0	0	0	8
		19	206	2	2	6	9

*: CD4% in children up to 5 years old and CD4 count in children > 5 years old. NS: not significant; Kappa (*k*)=0.27, 95% confidence interval=0.18-0.4.

count/CD4% between males and females, hence stratification by gender was not necessary (Table 1). The possible mode of transmission was parent to child in 187 (97.4%) children, blood transfusion in 3, and undetermined transmission in 2. In 60 (31.3%) children, immunodeficiency was not significant. Moreover, 40 (20.8%), 39 (20.3%) and 53 (27.6%) children had mild, advanced and severe immunodeficiency respectively according to WHO immunological staging (Table 1). The number of children with advanced and severe immunodeficiency was larger in children of 5 years old than in those of more than 5 years old (P=0.0251).

The agreement was fair between clinical and immunological staging (k=0.27). CD4 count (CD4% in children aged ≤5 years) declined with deterioration of WHO clinical stages of the disease (P<0.0001, the Kruskal-Wallis test followed by Post hoc Dunn's test) (Table 2). In the present study, 68 (35.4%) children were asymptomatic. Of these children, 25 were up to 5 years old with a median CD4% of 22% and 43 were more than 5 years old with a median CD4 count of 597. WHO Immunological staging showed that 35, 15, 11, and 7 children had non-significant, mild, advanced and severe immunosuppression, respectively (Table 3).

Table 3. Correlation of clinical profile with WHO immunological staging

Variables	Number (%)	WHO immunological staging			
		NS	Mild	Advanced	Severe
Asymptomatic	68 (35.4)	35	15	11	7
Symptomatic*	124 (64.6)	25	25	28	46
Fever	76 (39.6)	8	15	17	36
Cough	43 (22.4)	6	7	12	18
Diarrhoea	19 (9.9)	3	2	5	9
Skin lesions	7 (3.6)	3	1	0	3
Herpes zoster	6 (3.1)	2	2	2	0
Lymphadenaopathy	62 (32.3)	6	12	15	29
Hepatosplenomegaly	14 (7.3)	1	2	3	8
Pneumonia	10 (5.2)	2	2	0	6
Brochiectasis	1 (0.5)	0	0	1	0
Tuberculosis (TB)	44 (22.9)	5	6	9	24
Pulmonary TB	23	2	4	6	11
Extrapulmonary TB	18	3	2	2	11
Disseminated TB	3	0	0	1	2
Kaposis sarcoma	1 (0.5)	0	0	1	0

*: Some patients presented with more than one sign and/or symptom. NS: not significant.

Table 4. Correlation of nutritional status with clinical and immunological status

Variables	Number	Malnutrition grade			
		Normal+Grade I	Grade II	Grade III	Grade IV
WHO immunological stage					
NS	60	16	11	13	20
Mild	40	4	9	15	12
Advanced	39	8	6	9	16
Severe	53	4	19	10	20
Total	192	32	45	47	68
WHO clinical stage					
I	83	24	21	17	21
II	31	4	9	9	9
III	51	2	6	17	26
IV	27	2	9	4	12
Total	192	32	45	47	68

NS: not significant. Kappa (*k*)=0.04 agreement between nutritional and immunological staging [95% confidence interval (CI): 0.00-0.13]; Kappa (*k*)=0.1267 agreement between nutritional and clinical staging (95% CI: 0.04-0.21).

The common clinical presentation was fever (39.6%), followed by generalized lymphadenopathy (32.3%), cough (22.4%), and diarrhea (9.9%). Tuberculosis was seen in 44 (22.9%) children. The median CD4 count in children (>5 years) with tuberculosis was 260.5 and CD4% (≤5 years) was 10%. In 5 children with tuberculosis, immune suppression was not significant.

Fourteen (7.3%) children up to 5 years old showed normal weight for age according to the classification of malnutrition issued by the Indian Association of

Pediatrics (IAP) with a mean CD4 count of 783.3 (>5 years) and mean CD4% of 24.6. The median CD4% was 17%, 14.5%, 11% and 18.1%, respectively in children up to 5 years old with grade I, II, III and IV malnutrition. In children more than 5 years old with grade I, II, III and IV malnutrition, the median CD4 count was 697, 431, 399.5 and 327.5 cells/μL, respectively. However, the agreement was slight between nutritional and immunological grading (k=0.04) and also between nutritional and clinical staging (k=0.1267) (Table 4).

Discussion

The present study was undertaken to investigate the demographic, nutritional, clinical and immunological profiles of HIV positive children before ART. WHO has recommended ART for all newly diagnosed HIV positive children from 2010.[9] The present study gives a perspective of cohort of HIV positive ART naïve children. Due to initiation of the Early Infant Diagnosis (EID) program developed by the National AIDS Control Organization (NACO), it is difficult to find HIV positive ART naïve children in different age groups.

In the present study, vertical transmission was the major mode of transmission. The findings in this study were similar to those reported elsewhere.[10-12] The high vertical transmission may be due to ineffective nevirapine regimen as combined ART in reducing MTCT.[13]

The high transmission rate may also be attributed to other factors. For example, older children in our study may have missed the PPTCT program. Some mothers deliver at home and are not diagnosed with the disease during pregnancy and some even do not receive a single dose of nevirapine as they present directly in the late stage of labor with unknown HIV status. Moreover, a breast feeding mother without receiving ART contributes to the high positivity of HIV infection in children.

To deal with pediatric HIV infection, the most effective measure would be contraception methods to prevent unwanted pregnancy followed by maximum possible reduction in MTCT rate. Therefore, HAART can be used to further reduce MTCT during pregnancy in addition to extended ART for mothers who want to breast feed their children. A single dose of nevirapine should be used as an option only for mothers coming directly in labor.

Blood transfusion is the possible mode of transmission for 1.6% of children. Compulsory screening of blood for HIV has been started in India since 1989. This has significantly reduced the transfusion transmitted cases. Lodha et al[14] found that despite mandatory screening, 30% of children were infected due to the presence of sero-negative window period during which the antibodies are not detectable but the donor is infectious. The three cases in the present study may be due to the same reason.

The median age of children at presentation in our study was 9 years, which is older than that in other studies from India.[10,11,15] The PPTCT program launched in 2002 provided access to HIV testing services to all pregnant women enrolled into Ante Natal Care (ANC) along with provision of ARV prophylaxis with a single dose of nevirapine at the time of delivery to mother and Syrup NVP to the baby. These services were rapidly scaled-up across India during NACP-III (2007-2012). The children born to HIV positive mothers before the advent of this program would have missed early ART. These children unless and until diagnosed in future were deprived of ART.[3] According to the 2012 NACO report, 86 000 children were eligible for ART out of which there was an estimated 40% ART coverage rate.[6]

Most children living with HIV AIDS (CLHA) presenting at ICTC belong to the poor socioeconomic strata. The parents of these children are daily-wage labourers and every visit to the hospital is a loss of wage to them. According to USAIDS case study report of slums in India, the urban poor lack access to health care because they could not pay for it. Also, the poor in India have great difficulty in comprehending the nature of their illness and understanding their course of treatment.[16] All these factors could have resulted in older age at presentation to the ICTC and delay in initiation of ART. The other Indian studies were conducted before the initiation of the EID program which may have resulted in a younger median age at presentation.[10,14,15]

The correlation between WHO clinical and immunological staging in our study was (k=0.27) not as good as that reported in the literature.[17] In this study, 114 children were classified into WHO clinical stage I and II, and 29 (25.4%) of them had advanced or severe immunosuppression. These children would have missed ART if immunological monitoring was not available. This finding emphasizes the need of making CD4 facilities available in HIV prevalent areas. Our study supports the WHO recommendation for initiation of ART based on CD4%/CD4 counts as clinical staging is a poor marker.

The number of children of up to 5 years with advanced and severe immunosuppression (61.1%) was larger than that of children more than 5 years old (42.8%). Tovo[18] have reported that the highest mortality is seen in infancy and those who survived infancy remained

well for several years. This finding supports the WHO recommendation for early diagnosis and treatment of the disease.

The most common clinical presentation of the disease was fever followed by generalized lymphadenopathy and cough, which are similar to those reported in other studies.[11,17,19] In the present study, 14 children had hepatosplenomegaly, and 10 had pneumonia including pneumocystis carinii (PCP) pneumonia (2 children). Six children had herpes zoster and 7 children had other skin lesions. One child was diagnosed with Kaposi's sarcoma.

Tuberculosis is the most common opportunistic infection HIV-infected people worldwide.[20] The prevalence of tuberculosis in our study was about 22.9%, which is similar to that reported in other studies.[10.19] The median CD4 count was 260.5 in children more than 5 years old and the median CD4% was 10% in those up to 5 years old were similar to those reported elsewhere.[21,22] In our study, 44 (22.9%) children suffered from tuberculosis, i.e. pulmonary tuberculosis in 23 children, extrapulmonary 18, and disseminated in 3. Of these children, 33 had advanced or severe immunosuppression, but 11 had non-significant or mild immunosuppression. The 11 children developed tuberculosis, indicating that it is probably a co-infection and not an opportunistic infection. Hence, in India where tuberculosis is endemic and children with normal immune system can also develop tuberculosis, symptoms and signs suggestive of the disease should be carefully watched for even in early stages of immunosuppression.

The percentage of asymptomatic children in Indian studies varied from 11.3% to 41%.[10,11,15,19] In the present study, 35.4% of the children were clinically asymptomatic.

HIV/AIDS is associated with biological and social factors that affect the individual's ability to consume and acquire food. These biological and social factors lead to poor nutritional status and weight loss, which are important causes of morbidity in individuals infected with HIV, resulting in a poor quality of life.[23] In our study, 92.7% of the children were malnourished. This finding is comparable to the study by Shah et al.[19]

The synergistic relationship between nutrition and the immune system has long been recognized, but in our study the correlation of nutritional grading with immunological and clinical staging was slight.

Padmapriyadarsini et al[24] also reported that while immune status and malnutrition showed a slight correlation, the presence of moderate stunting or undernutrition could not be used to predict disease severity accurately.

Our study also shows that at early stages of the disease with higher CD4 counts, malnutrition is a substantial problem in most children (grade III or IV malnutrition). Hence, nutritional intervention is needed even at an early stage of the disease. Malnutrition cannot be used as a surrogate marker for predicting disease stage or severity as it is common at all stages of HIV infection.

The clinical profile of HIV-infected children is helpful in better understanding the disease and its management. Perinatal transmission is commonly seen for HIV infection in children. The PPTCT program should be strengthened to provide effective contraception to prevent unwanted pregnancies and reduce the MTCT rate by providing extended ART to mothers during pregnancy and breast-feeding. Malnutrition is a major problem in HIV infected children in India, it should be targeted early to reduce morbidity in these children but it cannot be used as a surrogate marker for predicting the severity of the disease. Tuberculosis remains a major concern in HIV-infected children. The poor correlation of WHO clinical and immunological staging emphasizes the importance of making CD4 facilities available in HIV prevalent areas.

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