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Gingival status: An indicator of disease progression and its correlation with the immunologic profile in HIV-infected children on antiretroviral therapy

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To determine the gingival health of human immunodeficiency virus (HIV) infected children and how it correlates to CD4 percentages in vertically infected children with HIV undergoing combination antiretroviral therapy. Two hundred and fifteen HIV positive children on antiretroviral therapy, of both sexes from seven to fifteen years old were evaluated for their gingival status using the Gingival Index. Children were divided into three groups; mild, advanced and severe depending on their absolute CD4 count and CD4 percentage. Statistically significant association was observed between CD4% category (mild, advanced and severe) and gingivitis (P < 0.001). More number of children in mild CD4% category were found to have mild gingivitis. Based on the results of our study the prevalence and distribution of gingivitis was high, this data will helps us in formulating a preventive as well as therapeutic programme for these children who have untreated oral lesions.

Key words: Human immunodeficiency virus (HIV), gingivitis, antiretroviral therapy, oral lesions.

INTRODUCTION

Approximately 33 million adults (most of them parents) are now living with HIV worldwide and more than 15 million children are orphaned by AIDS (UNAIDS/WHO, 2008; UNAIDS/UNICEF, 2005). India too is in the grip of the HIV/AIDS epidemic. Mother-to-child transmission (MTCT) is the largest source of HIV infection in children below the age of 15 years (UNAIDS, 1998). According to National AIDS Control Organization (NACO), about 30,000 infants are estimated to acquire HIV infection each each year (NACO, 2004). Oral manifestations are often among the first symptoms in human immunodeficiency virus (HIV) infected patients (Kozinetz et al., 2000) and have been associated with immune suppression (Moniaci et al., 1990). The distribution of some of the specific oral manifestations is reported to differ between adults and children (Ramos-Gomez, 2002). Oral health is an essential component of health throughout life. Poor oral health and untreated oral diseases and conditions can

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Table 1. WHO classification of HIV associated immunodeficiency using CD4 count.

Classification of HIV-associated immunodeficiency	Age-related CD4 values			
	≤ 11 months (CD4%)	12 - 35 months (CD4%)	36 - 59 months (CD4%)	≥ 5 years (cells/mm^3 Or CD4%)
Not significant	>35	>30	>25	>500
Mild	30-35	25-30	20-25	350-499
Advanced	25-29	20-24	15-19	200-349
Severe	<25	<20	<15	<200 or <15%

have a significant impact on the quality of life. They can affect the most basic human needs, including the ability to eat and drink, swallow, maintain proper nutrition, smile, and communicate (NIDCR, 2015).

The prevalence of oral manifestations in HIV infected adults tends to vary from country to country. Studies in Africa showed a wide range of prevalence rates from 1.5 to 94% (Hodgson and Rachanis, 2002). However, in HIV infected children, the prevalence of oral manifestations in developed countries has been reported to be as high as 72% (Ketchem et al., 1990; European Collaborative Study, 1991). Comparable studies in children from developing countries including Africa, indicated variations in the occurrence of oral manifestations, for example 61% in Brazil (Costa et al., 1998) 55% in Romania (Flaitz et al., 2001), 49% in Thailand (Khongkunthian et al., 2001) and 63% in South Africa (Naidoo and Chikte, 2004). Few studies describe the gingival health of HIV infected children. Linear gingival erythema, necrotic ulcerative gingivitis and necrotic ulcerative periodontitis are among the lesions which are strongly related to HIV infection (Classification and diagnostic criteria for oral lesions in HIV infection, 1993). Severe periodontal manifestations do not occur in HIV infected children (Fonseca, 1996; Schoen et al., 1995). HIV targets primarily CD4 lymphocytes, although significant quantities of HIV probably reside in lymphoid elements throughout infection period. In infected adults, CD4 cell counts decline as the disease advances, making them useful markers of the progress of the infection.

Younger children normally have higher CD4 counts than older children and adults. As a result, the CD4 count by itself is not a reliable marker in pediatric cases. CD4% is the preferred measurement in children < 5 years old, as it varies less in them than in older children. At ≥ 5 years of age, either CD4% or absolute CD4 count can be used but CD4 count is preferred (Howell et al., 1992). There is limited data correlating the relationship between the gingival status, oral and perioral lesions to their absolute CD4 lymphocyte count and CD4 percentage of HIV infected children from India. Hence the aim of this study was to assess the prevalence of soft tissue and gingival lesions in 215 vertically infected children with HIV undergoing combination antiretroviral therapy and the relationship of CD4 lymphocyte levels.

METHODOLOGY

215 HIV infected children between the ages of 5 and 13 years attending a specialized pediatric out-patient clinic at Tertiary care hospital were examined for examined the prevalence of soft tissue and gingival lesions and their relationship to the Absolute CD4 count and CD4 percentages. Their CD4 percent and absolute CD4 count was obtained from their medical records within 3 months of oral examination. The study was approved by the Ethical Committee for Research. Parents /Guardians were requested to give written permission for the examiner to access medical and dental information about the child. These children were also grouped depending on the CD4 percentage into mild, advanced and severe (Table 1).

ART in children, guided by CD4

1. < 11 month infants: If CD4 < 1500 cells/mm^3 (< 25%).
2. 12 to 35 months: If CD4 < 750 cells/mm^3 (< 20%).
3. 36 to 59 months: If CD4 < 350 cells/mm^3 (15%)
4. > 5 years old: Follow adult guidelines i.e. start.
5. ART if < 350 cells/mm^3 especially if symptomatic.
6. Initiate ART before CD4: drops below 200 cells/mm^3

Paediatric formulations were provided at ART center at Indira Gandhi Institute of Child Health. The drugs supplied are fixed dosed combinations (FDC) available in India which are stavudine-based regimens (National Aids Control Organization (NACO) guidelines for HIV care and treatment in infants and children) (Table 2). It has been recommended that in order to scale up the treatment of children, this will be used until zidovudine (AZT) based regimens are available and recommended globally, as the preferred choice for children. As NACO will supply drugs to be used for children in the national programme, it is recommended not to cut adult drugs once paediatric formulations are available at ART centers. FDC tablets supplied under the national initiative based on the CD4 count and percentages and correlated with clinical staging will cover > 5 kg children (based on weights). For children < 5 kg body weight, ARVs have to be in form of syrups or suspension.

In the 2006 WHO guidelines for treatment of infants and children, several drugs have been recommended for use, based on evidence - NRTI (d4T, 3TC, AZT, ABC) ; NNRTI (NVP, EFV) and PIs (LPV/r, NFV,SQV). There is little data on other ARV drugs for use in

Table 2. National AIDS Control Organization (NACO) guidelines for HIV care and treatment in infants and children.

Formulation of FDC's available for pediatric HIV use in India			
Formulation	**Stavudine (D4T) (mg)**	**Lamivudine (3Tc) (mg)**	**Nevirapine (NVP) (mg)**
FDC 6 (baby tablet)	6	30	50
FDC 10 (tablet)	10	40	70
FDC 12 (Junior tablet)	12	60	100
FDC 30 D4T (adult tablet)	30	150	200
FDC 30 AZT (adult tablet)	300	150	200

children. The recommended preferred first-line ARV regimens for infants and children are: Regimen of 2 NRTI plus 1 NNRTI, AZT + 3TC + NVP or EFV, D4T + 3TC + NVP or EFV. AZT should not be given in combination with D4T. EFV is not currently recommended for children < 3 years of age or < 10kg, and should be avoided in post-pubertal adolescent girls who are either in 1st trimester of pregnancy or are sexually active and not receiving adequate contraception. EFV is used to substitute NPV when anti-tuberculous treatment has to be provided concomitantly. However, after 2 weeks of completion of ATT, EFV should be switched back to NVP, (NACO, 2007).

Study design

Comparative study samples were chosen based on simple random sampling and then stratified.

Inclusion criteria

Perinatally infected children with HIV undergoing combination antiretroviral therapy.

Exclusion criteria

HIV infected children not on antiretroviral therapy, unco-operative, critically ill patients. The soft tissue oral lesions were diagnosed using the classification and diagnostic criteria as described by the Collaborative Work group on the Oral Manifestations of Pediatric HIVInfections (Ramos-Gomez et al., 1999). Soft tissue lesions diagnosed were only upon clinical findings. Data collected included sex, age, plaque accumulation, gingival health and oral and perioral lesions.

The oral hygiene status of the study participants was assessed using the Simplified Oral hygiene index OHI-S (Simplified Debris (plaque) Index DI-S and Simplified Calculus Index CI-S) as described by Greene-Vermillion (1967) The Gingival Index of Loe and Silness (1963) was used to assess the severity and prevalence of gingivitis by examining the qualitative changes. (that is, severity of the lesion) of the gingival soft tissue and scored on a four point scale 0 to 3 as follows:

0 = No inflammation i.e. normal gingival.
1 = Mild inflammation i.e. slight change in colour, slight oedema with no bleeding on probing.
2 = Moderate inflammation i.e. redness, oedema and glazing, with bleeding on probing.
3 = Severe inflammation i.e. marked redness and oedema, with ulceration and a tendency to spontaneous bleeding.

All the GIs were determined by the same trained and calibrated examiner, using a disposable mouth mirror, tongue depressor, and a periodontal probe. The index for gingival inflammation was the sum of the scores divided by the number of teeth. A score from 0.1 to 1.0 = mild inflammation; 1.1 to 2.0 = moderate inflammation, and 2.1 to 3.0 signifies severe inflammation. The data was analyzed. Associations between CD4 levels and clinical parameters were determined using the using Chi square test and values of $P < 0.05$ were considered statistically significant.

RESULTS

Two hundred and fifteen children, 119 males and 96 females, between 5 and 13 years old were examined. The 215 HIV infected children were classified according to their degree of immune suppression into mild immune suppression (122), advanced immune suppression (64) and severe immune suppression (29). Statistically significant association was observed between CD4% category (mild, advanced and severe) and gingivitis ($P < 0.001$). More number of children in mild CD4% category was found to have mild gingivitis (Table 3). In the mild stage of the disease, 64% of children had no gingivitis, 71% had mild gingivitis and 59 and 25% had moderate and severe gingivitis.

In advanced stage of the disease, 36% of children had no gingivitis, 22% had mild gingivitis, 27 and 46% had moderate and severe gingivitis. In severe stage of the disease, 0% of children had no gingivitis, 6% had mild gingivitis, 9 and 14% had moderate and severe gingivitis. Overall prevalence of number of children with no gingivitis was 5%, children with mild gingivitis was 42 and 31% with moderate gingivitis and 22% with severe gingivitis (Table 4). Prevalence of various oral manifestation (Table 5); oral candidiasis-pseudomembranous was 17 (8%), erythematous was 8 (4%), angular chelitis 11 (5%), followed by oral ulcers 24 (11%), herpes simplex 12 (6%), necrotizing ulcerativeperodontitis 8 (4%), parotid enlargement 1 (0%) and hairy leukoplakia (0%). Some of the children were presented with two or more different types of lesion.

Table 3. Correlation between CD4% category (mild, advanced and severe) and severity of gingivitis.

Gingivitis	Classification of HIV associated immunodeficiency based on CD4%						Total	χ^2	P-value
	Mild		Advanced		Severe				
	n	%	n	%	n	%			
No gingivitis	7	64	4	36	0	0	11	31.473	< 0.001*
Mild gingivitis	64	71	20	22	6	7	90		
Moderate gingivitis	39	59	18	27	9	14	66		
Severe gingivitis	12	25	22	46	14	29	48		

Table 4. Severity of gingivitis and gender distribution.

Severity	Male	Female	Prevalance (%)
No gingivitis	5	6	5
Mild gingivitis	53	37	42
Moderate gingivitis	36	30	31
Severe gingivitis	25	23	22

Table 5. Prevalence of oral manifestations.

Oral manifestations	Total		Gingivitis					
			Mild		Advanced		Severe	
	n	%	N	%	n	%	n	%
Candidiasis								
Pseudomembranous	17	8	3	1	5	2	9	4
Erythematous	8	4	-	0	2	1	6	3
Angular cheilitis	11	5	2	1	3	1	6	3
Herpes simplex	12	6	2	1	4	2	6	3
Hairy leukoplakia	0	0	0	0	0	0	0	0
Enlargement of parotids	1	0	0	0	0	0	1	0
Necrotizing ulcerative periodontitis	8	4	0	0	3	1	5	2
Oral ulcers	24	11	6	3	9	4	9	4

DISCUSSION

Oral manifestations are common in children infected by HIV and are associated with serious immunosuppression and AIDS (Valdez et al., 1994; Teles, 1996). The introduction of highly active antiretroviral therapy (HAART) in the mid 1990s was an important landmark with therapeutic effects and dramatic changes in the clinical prospects of HIV infection. The rate of HIV-related oral manifestations has declined following the introduction of HAART (Schmidt-Westhausen et al., 2000). Gingivitis has been shown to occur with a high frequency and greater severity in HIV-infected children (Kline, 1996; Ceballos-Salobrena et al., 2000; Petersen et al., 1994; Elderidge and Gallagher, 2000; Flaitz et al., 2000, Flaitz et al., 2000; Vierla et al., 1998).

In our study, prevalence of mild gingivitis was 42%, moderate gingivitis was 31% and severe gingivitis was 22%. Candidiasis is the most common oral manifestation in HIV-infected children (Leggot, 1992; Murray et al., 1992; Moniaci et al., 1993; Santos et al., 1997) and its prevalence ranges from 20 to 72% (Chan et al., 1994). In our study, pseudo membranous candidiasis was present in 17 (8%) cases and erythematous and angular chelitis was present in 8 (4%) and 11 (5%) of the cases. Pseudo membranous candidiasis was the most common type,

which is in agreement with Valdez et al. (1994) and Santos et al. (1997). Erythematous candidiasis and angular cheilitis were present in 44.4% of the cases of candidiasis, in accordance with the study by Valdez et al. (1994).

The onset of gingival and periodontal diseases in individuals infected with HIV-1 is inversely proportional to their immunological status, i.e., as the immune system becomes more compromised, the individual becomes more susceptible to diseases. Portela et al. (2001) demonstrated that patients with gingival changes presented leukopenia and severe immune suppression. The relationship between low CD4 and the presence of conventional gingivitis has also been observed by Howell et al. (1996). However, Vieira et al. (1996) found no connection between suppression of the immune system and gingivitis. In our study we found statistically significant correlation between the CD4% category (mild, advanced and severe) and Gingivitis ($P < 0.001$). More number of children in mild CD4% category was found to have mild gingivitis. The oral lesions may have had a negative impact on the nutritional health of the children by reducing food intake as a result of discomfort during eating (Mugrditchian et al., 1992; Winter and Miller, 1994). Massarente et al. (2011) observed that children and adolescents with more severe manifestations of AIDS present with a worsened oral health-related quality of life as a result of oral symptoms as well as increased functional, emotional and social limitations.

In a similar study conducted by Damle et al. (2010) to evaluate the oral health status as an indicator of disease progression in HIV positive children, they concluded that oral health status in HIV children deteriorated with the decline in CD4 counts. It should be noted that regular dental care in HIV infected individuals result in better oral health with no greater cost than regular attendance (Hastreiter and Jiang, 2002). Limitations of our study include the lack of comparisons to non HIV infected children with similar socioeconomic background and oral hygiene index was not recorded. High prevalence of gingivitis in our study was due to poor immunity and lack of good oral hygiene practice, most of these patients brush once daily with unfluoridated or fluoridated toothpaste. None of the patients had ever visited a dentist. In cases of painful oral lesions the patients would only rinse their mouth with water and not brush their teeth. Limitations of our study is that the study subjects were not compared with non HIV infected children because the hospital was a tertiary health care centre for HIV infected children and the number of non HIV infected children who visited the facility were very minimal.

Conclusion

In India there is limited data concerning gingival health oral soft tissue lesions and their relationship to CD4 lymphocyte levels in HIV infected children. Our study established baseline data about the oral health in these children, based on which a comprehensive oral health programme can be planned to cater for these patients needs. HIV has overwhelming effect not only on the children but also on their families, with the absence of preventive measures and lack of timely intervention, these children have had to bear the pain because of these oral lesions which has affected their general health and quality of life.

RECOMMENDATION

Since these patients were never screened by a general dentist or a pediatric dentist, it is highly essential to set up a dental home for these patients in their ART center for anticipatory guidance, regular checkups and periodic recall and reinforcement of good oral hygiene practices. Oral health is vital part of general health and well being and hence paediatric dentist's role is pivotal in treating these patients for prevention and timely management of these oral lesions so that oral functions are not impaired. Pediatric dentists should be a part of primary health care team to provide oral health care for these children.

Conflicts of interest

Authors have none to declare.

Abbreviations

ART, Anti retroviral therapy; **HAART,** highly active antiretroviral therapy; **3TC,** lamivudine; **ABC,** abacavir; **ALT,** alanine amino transaminase; **AZT,** azidothymidine (also named zidovudine); **D4T,** stavudine; **EFV,** efavirenz; **LPV/r,** lopinavir/ritonavir; **NFV,** nelfinavir; **NRTI,** nucleoside reverse transcriptase inhibitor; **NNRTI,** non-nucleoside reverse transcriptase inhibitor; **NVP,** nevirapine; **SQV,** saquinavir.

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