ORIGINAL ARTICLE

Oral manifestations of human immunodeficiency virus in children: An institutional study at highly active antiretroviral therapy centre in India

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ABSTRACT

Context: More than 1000 children are newly infected with Human immunodefi ciency virus (HIV) every day, and of these more than half will die as a result of AIDS due to lack of access to HIV treatment. HIV disease varies considerably in children. Among those infected prenatally, some experience few or no symptoms for years, whereas in others the disease progresses rapidly. The risk factors that influence the development of such oral manifestations include, low CD4+ T cell count, xerostomia and lack of highly active antiretroviral therapy (HAART). **Aims:** To identify the oral manifestations of HIV in children receiving HAART. **Materials and Methods:** The study comprised 95 children receiving HAART. 95 HIV +ve children not receiving HAART and 95 HIV –ve children were also included for comparing the manifestations of HIV. **Statistical Analysis Used:** Statistical analysis was done using Fisher's Chi-square test. Probability value (*P* value) was obtained for the three groups. **Results:** The manifestations of HIV that were observed in children receiving HAART include dental caries (26%), periodontal diseases (23%), candidiasis (19%), hyperpigmentation (17%), ulcerative stomatitis (9%) and one case of mucocele. These manifestations were compared with HIV +ve children not receiving HAART and HIV –ve children to find manifestations with statistical significance. **Conclusions:** We conclude that HAART had increased the disease-free states in HIV +ve children on HAART promising them better life span. The incidence of oral lesions can further come down with adequate oral hygiene measures in HIV-infected children.

Key words: CD4 count, HAART, HIV oral manifestations, HIV, pediatric HIV

INTRODUCTION

Human immunodeficiency virus (HIV) infection is considered a pandemic by the World Health Organization (WHO). From its discovery in 1981 to 2006, acquired immunodeficiency syndrome (AIDS) has killed more than 25 million people. HIV infects about 0.6% of the world's population.[1] In 2005, AIDS claimed an estimated 2.4–3.3 million lives, of which more than 570,000 were children. Most of the cases are seen in sub-Saharan countries and developing nations.[2] Antiretroviral treatment reduces both the mortality and the morbidity rates of HIV infection, but routine access to antiretroviral medication is not available in all countries.[3]

HIV transmission in children occurs mainly through vertical transmission (mother to child). The risk of transmission by an infected mother occurring before or during birth (without medical intervention) is around 15–20%. Breast feeding by an infected mother increases the risk by 5–20% to a total of 20–45%.[4] In a study conducted in Brazil, vertical transmission was seen in 97.5% in children.[5] Studies in India had reported that vertical transmission is seen in 51 to 83% of children.[6-8]

Oral manifestations are amongst the earliest and most important indicators of HIV infection. At present three groups of oral manifestations are defined by Greenspan *et al,* based on their intensity and features [Table 1].[9]

The human immunodeficiency virus (HIV) was detected in children for the first time in 1982. Since then the infection has

Access this article online
Quick Response Code:
Website: www.jomfp.in
DOI: 10.4103/0973-029X.98499

Table 1: Classification of oral lesions in HIV by Greenspan

Group I	Group II	Group III
Oral candidiasis	Atypical ulcers	Diffuse osteomyelitis
Hairy leukoplakia	Salivarygland diseases	Squamous cell carcinoma
Kaposi sarcoma	Viral infections like CMV, HSV, HPV, HZV	Other rare lasions
Linear gingival erythema		
Necrotizing ulcerative gingivitis		
Necrotizing ulcerative periodontitis		
Non-Hodgkin lymphoma		

HIV: Human immunodeficiency virus; CMV: Cytomegalovirus; HSV: Herpes simplex virus; HPV: Human papilloma virus; HZV: Herpes zoster virus

spread rapidly and is now a significant cause of death within the pediatric group. Immunological immaturity of the child in the first months of life, and the difficulty of diagnosis in this period, makes this group characteristic separating them from adult population. In case of vertical transmission, the diagnosis of initial infection is often complicated. Early diagnosis is necessary for initiating highly active antiretroviral therapy (HAART), which also spares the babies from the toxicity of the antiretroviral drugs in negative cases. Though all infants born to HIV-positive mothers are initially seropositive, only 13–40% develop HIV infection.[10] The seropositive mothers passively transmit the anti-HIV antibodies to the neonates (by vertical and intrauterine transmission) and only one-third of these children are infected.[11] So the criteria for diagnosis in children less than 18 months of age include positive results on two separate determinations (excluding cord blood) from one or more of the following tests, namely HIV culture, HIV-DNA PCR, and HIV-p24 Ag or meeting the criteria for AIDS diagnosis based on 1987 AIDS surveillance definition, i.e., >18 months of age who is HIV antibody positive by repeated enzyme immunoassay (EIA) and confirmatory test (western blot or immune fluorescence assay) or by meeting any of the above criteria.[12]

Oral lesions in HIV/AIDS indicate the progress of disease process and therefore, have prognostic significance.[13] The risk factors that influence the development of such oral manifestations include, low CD4+ T cell count, xerostomia and lack of HAART. Opportunistic infections like oral candidiasis and herpetic viral infections are the commonly observed infections in children.[14]

With the successful introduction of HAART, oral health care providers are now more likely to encounter children and adolescents who live longer with HIV/AIDS. The treatment with HAART is primarily directed at inhibiting viral replication, as well as, preventing and managing opportunistic infections and malignancies.[15]

In case of children above the age of five years, a combination of Stavudine, Lamivudine, Nevirapine or Zidovudine, Lamivudine, and Nevirapine are given.[16] These drug combinations are given at a dosage of around 1 mg b.i.d per kilogram of body weight. In case of hypersensitivity to Nevirapine the drug combination is given without Nevirapine.

The adverse effects for Nevirapine are seen in the form of skin rashes in the hypersensitive children. Anemia is a common side effect seen in Zidovudine administration. Hemoglobin concentration is constantly monitored in the children who are given Zidovudine and its administration is stopped when the hemoglobin percentage falls below 9%. Adverse effects for Stavudine include fat loss, hepatitis and lactic acidosis.[16]

The advent of HAART had reduced the incidence and type of oral lesions as found in many studies. However, these studies are mostly done in adults and studies related to the incidence of oral lesions in children are few, particularly in India. In this context, oral lesions in HIV +ve children receiving HAART are studied. Differences in the incidence of oral lesions among the HIV +ve children receiving HAART and not receiving HAART were also studied. An attempt is also made to identify whether the oral manifestations were exclusive to HIV +ve children.

MATERIALS AND METHODS

The study comprised three groups of children with 95 children each. Group I consists of 95 children receiving HAART. Group II consists of 95 HIV +ve children not receiving HAART. Group III consists of 95 children without HIV.

Children in Group I (HIV +ve on HAART) were randomly picked at anti-retroviral therapy (ART) Center in Government General Hospital, Vijayawada, India. Written consent was obtained from the parents of these children before recording the cases. The age of these children ranged from five to fifteen years. The oral cavity was thoroughly examined by trained dental surgeons. The details taken from the children for subsequent analysis include age, CD4+ T cell count, oral lesions and therapeutic drugs used.

Children in Group II (HIV +ve without HAART) were selected to find the efficacy of HAART to reduce the incidence of oral manifestations. Group II consists of 95 children who came to the ART Center for first time without previous history of anti-retroviral therapy.

Children in Group III consist of 95 children without HIV. These children were selected from same age group and same socioeconomic status. These children were selected to identify whether the oral manifestations in HIV were exclusive to HIV +ve children.

RESULTS

The current study involves 95 children each in three groups. Group I consists of 95 HIV positive children with 43 males and 52 females [Figure 1]. In this study we found that 43% of HIV +ve children on HAART had presented with some form of oral lesion [Figure 2]. The lesions that were observed in these children include candidiasis, ulcerative stomatitis, dental caries, gingivitis, periodontitis, hyperpigmentation and mucocele. The total sample of 95 children in Group I were divided into two groups (Group IA and Group IB) based on their CD4+ T cell count at the time of oral examination. Group IA included patients with CD4+ T cell count less than 250 per cubic mm. Group IB included patients with CD4+ T cell count more than 250 per cubic mm. We found that 29% of these children were having their CD4+ T cell count less than 250 [Figure 3]. Statistical analysis was done using Fisher's Chi-square test, and probability value (*P* value) was obtained for all the lesions divided into two groups based on their CD4+ T cell count. Statistical analysis showed that patients with low CD4+ T cell counts (Group IA) had more number of lesions when compared to the patients with higher CD4 T cell count (Group IB). Finally, the antiretroviral drugs that were given to these patients were recorded, which include, Zidovudine, Lamivudine, Stavudine and Nevirapine [Table 2].

In the second part of the study, the oral manifestations of children in Group I (HIV +ve with HAART) were compared to that of Group II (HIV +ve without HAART). The manifestations that were observed in Group I were taken into consideration for comparing the incidence of oral manifestations. The statistical analysis using Fishers Chi-square test showed that hyperpigmentation was significantly more in children receiving HAART. Candidiasis, ulcerative stomatitis and gingival/periodontal lesions were more in HIV +ve children without HAART with statistical significance. However, the prevalence of dental caries was same in both the groups [Table 3].

In the third part of the study, the oral manifestations of children in Group I (HIV +ve with HAART) were compared to that of Group III (HIV -ve). The manifestations that were observed in Group I were taken into consideration for comparing the two groups.

Table 2: Highly active antiretroviral therapy (HAART) drugs used for the treatment

Regimen I	Regimen II	Regimen III (In Nevirapine sensitivity)
Zidovudine	Stavudine	Zidovudine & Lamivudine
Lamivudine	Lamivudine	Or
Nevirapine	Nevirapine	Stavudine & Lamivudine

Table 3: Incidence of oral lesions in HIV +ve and HIV –ve children

Oral lesions	With HAART	Without HAART	Chi-square value	*P* value	Inference
Candidiasis	16	27	3.637	0.05	Significant
Gingivitis/ Periodontitis	28	34	0.861	0.5	Not Significant
Dental caries	33	35	0.091	0.5	Not Significant
Ulcerative stomatitis	12	24	3.582	0.001	Significant
Hyperpigmentation	18	2	14.305	0.001	Highly Significant
Mucocele	1	0	1.005	0.1	Not Significant

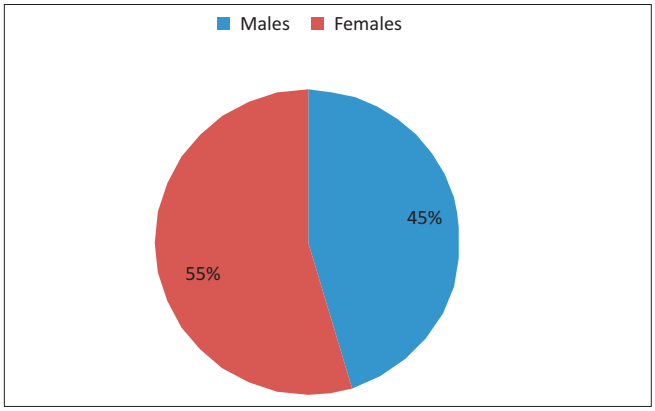

Figure 1: Male to female ratio of the study group

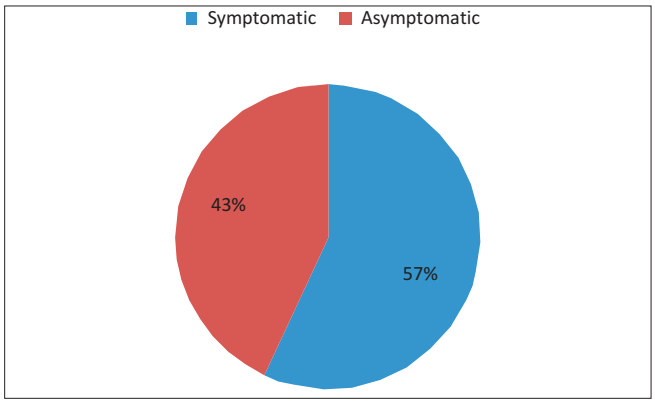

Figure 2: HIV status of the study group

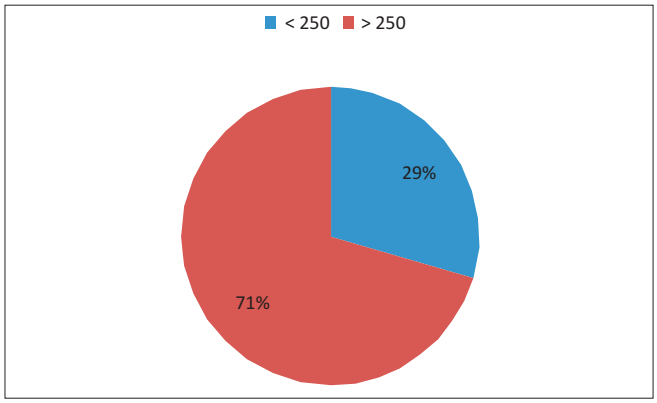

Figure 3: CD4+ T cell count of the study group

Candidiasis, ulcerative stomatitis and hyperpigmentation were not observed in HIV –ve children. Dental caries and gingival/periodontal lesions were more in HIV +ve children with HAART with a statistical significance [Table 4].

DISCUSSION

The advent of HAART had reduced the mortality and morbidity rates in HIV positive individuals. This is due to the reduction of HIV viral load and consequent recovery of immune system.[17] Patients receiving HAART are protected to some extent ag ainst, candidiasis, salivary gland disease, Kaposi's sarcoma, and oral hairy leukoplakia.[18] The prevalence of all oral lesions has decreased by more than 30% since the introduction of HAART.[19] However, the prevalence of HIV salivary gland disease has seen a slight increase in its incidence, while, the incidence of some lesions like oral candidiasis, aphthous ulcers, and Kaposi's sarcoma has remained the same.[20]

The diagnosis of initial infection in children is established by PCR. However, antiretroviral drugs are not given to children below the age of 5 years. The CD4+ T cell count of these children are monitored and necessary instructions are given to the parents of these children. However, antiretroviral drugs in the form of syrups are given to infants with low CD4+ T cell count.

A high frequency of oral lesions in HIV-positive patients was reported by Marcenes *et al*,,[21] who examined 51 patients and observed oral lesions in 76.5% of cases. However, in a study conducted by Pinheiro *et al*,[22] only 33.5% of HIV-positive patients exhibited oral lesions.

In the current study we found that only 43% of the children infected with HIV were symptomatic and 57% were asymptomatic [Figure 2]. Oral lesions that were observed in symptomatic children include candidiasis, ulcerative stomatitis, dental caries, gingivitis/periodontitis, hyperpigmentation and mucocele [Figure 4].

Table 4: Differences in incidence of oral lesions in HIV +ve children with and without HAART

Oral lesions	Children with HIV on HAART	Children without HIV	Chi-square value	*P* value	Inference
Candidiasis	16	0	17.471	0.001	Highly Significant
Gingivitis/ Periodontitis	28	15	5.079	0.2	Significant
Dental caries	33	28	0.603	0.5	Not Significant
Ulcerative stomatitis	12	0	12.808	0.001	Highly Significant
hyperpigmentation	18	0	19.808	0.001	Highly Significant
Mucocele	1	0	1.005	0.1	Not Significant

Candidiasis is the most common manifestation of HIV infection both in adults and children. Previous studies had shown that the incidence of candidiasis in children varies between 20 and 72%.[23-26] The most common form of oral candidiasis is pseudomembranous form (oral thrush) followed by angular cheilitis, papillary hyperplasia, chronic hyperplastic

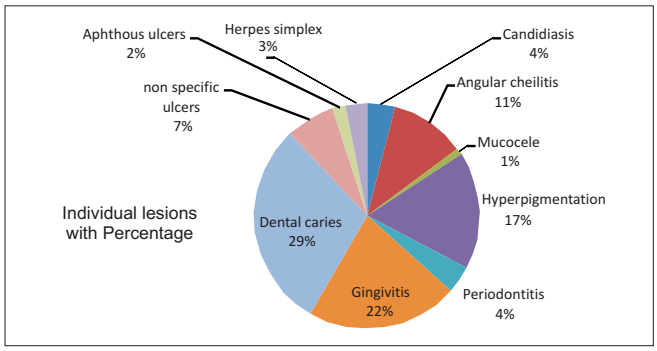

Figure 4: Oral lesions seen in the current study

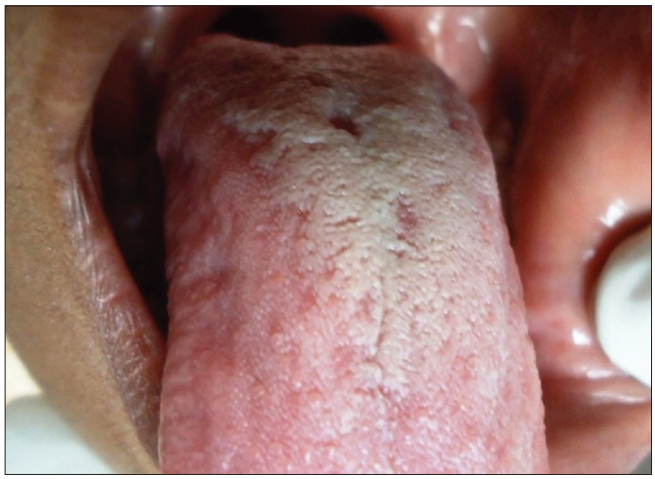

Figure 5: Candidiasis seen on the dorsal surface of tongue in HIV child

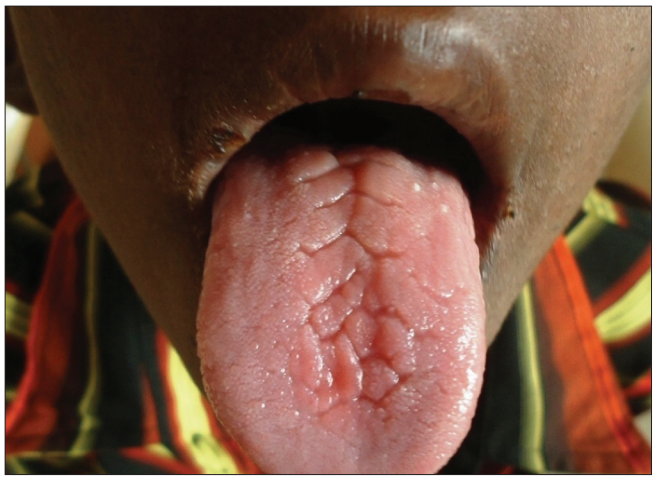

Figure 6: Fissured tongue with angular cheilitis

candidiasis, erythematous candidiasis and median rhomboid glossitis. Many studies had shown that oral thrush is a marker for rapid HIV disease progression and death.[25,26] In the current study we observed that 17 out of 95 children had some form of oral candidiasis. Out of the 17 lesions that were observed, 9 were pseudomembranous candidiasis [Figure 5], 2 were erythematous candidiasis and 6 were angular cheilitis [Figure 6]. This accounts for only 19% in the total number of patients observed in our study. The CD4+ T cell counts of these children with HIV infection ranged from 92 to 336. Statistical analysis with Fisher's Chi-square test showed that candidal lesions are significantly more in children with low CD4 + T cell counts (Group IA) when compared to children with higher CD4 + T cell count (Group IB) with a *P* value of <0.005.

Ulcerative lesions recorded in the current study include, herpes simplex, aphthous ulcers and non-specific ulcers. Chronic persistent infection with herpes simplex virus (HSV-1) is common in patients with HIV infection [Figure 7]. Lesions may appear as grouped blisters that rupture, crust, and heal in 7 to 10 days. Once severely immunosuppressed, HIV-infected individuals often experience chronic lesions that continue to expand and form large, painful ulcers and crusted erosions which are 2 to 10 cm or larger.

Aphthous ulcers are common in children infected with HIV. These aphthous ulcers tend to be larger and more painful when compared to the lesions seen in HIV -ve children.[27] The occurrence of non-specific ulcers in HIV infection is reported in many studies. Although the exact reason for non-specific ulcers is not known, they are attributed to be the adverse effect of antiretroviral drugs or due to the deficiency of vital nutrients. Delgado *et al*,[28] published the histopathological, immunohistochemical (IHC) and *in-situ* hybridization (ISH) data of 25 cases of oral ulcers in HIV-positive patients, with clinical and microscopic features similar to ulcers not otherwise specified (NOS)/necrotizing ulcerative stomatitis (NUS). Their results showed that CD68+ macrophages, followed by CD8+ T cells, were the predominant inflammatory cells indicating their role in the pathogenesis of these ulcers through abnormal immune response in the oral mucosa. In the current study we observed that 9% of the children had ulcers in various regions of the oral cavity. Statistical analysis showed that patients with low CD4+ T cell counts (Group IA) had more number of oral ulcers (*P* value <0.001) when compared to patients with higher CD4+ T cell count (Group IB).

Earlier studies reporting the incidence of dental caries in HIV-infected children were conflicting. Fine *et al*,[29] examined over 100 HIV-infected participants aged 2 to 15 years at six-month intervals and found no difference with respect to caries. However, Eldridge *et al*,[30] in their study reported that caries prevalence was high in HIV-infected children. They concluded that these children should be considered as high caries risk and receive appropriate dental care, in terms of both treatment and preventive services, following confirmation of seropositivity. In the present study we found that 33 (26%) out of 95 HIV +ve children on HAART had dental caries [Figure 8]. Twelve out of these 33 children had rampant dental caries involving almost all the teeth. Dental caries was the most predominant finding that was recorded in the current study making 26% of the total number of cases. Statistically patients with low CD4+ T cell counts (Group IA) had high incidence of dental caries (*P* value <0.005) when compared to patients with higher CD4 T cell count (Group IB).

Gingivitis and periodontitis are also common in children infected with HIV.[31] Schoen *et al*,[32] in their study found that, except for the prevalence of linear gingival erythema, the periodontal findings are similar to their HIV-negative household peers and to the general pediatric population. However, Mataftsi *et al*,[33] reported that the prevalence and course of periodontal lesions had been modified. They stated that higher prevalence of opportunistic microorganisms has been frequently detected in the subgingival flora of HIV-infected individuals, probably due to the immune status of those patients, as colonization and overgrowth of atypical

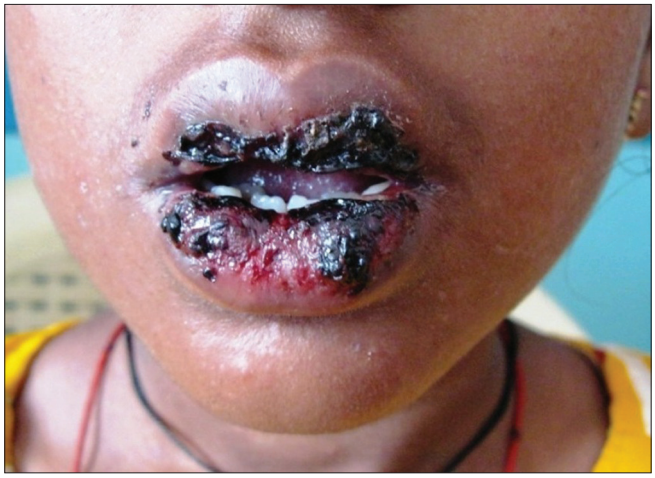

Figure 7: Ulcerative stomatitis

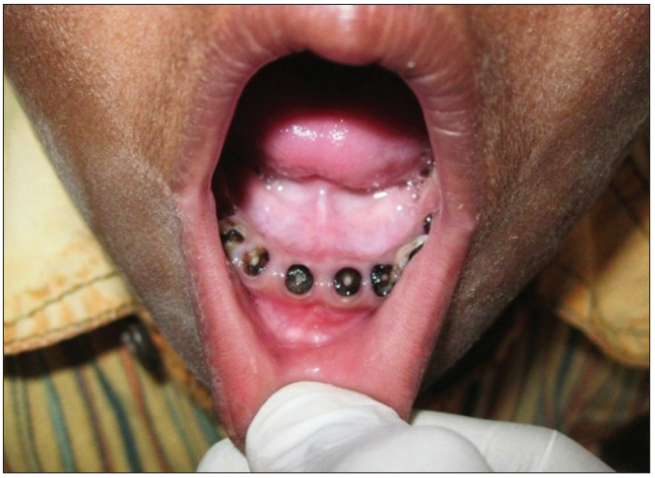

Figure 8: Rampant dental caries involving the deciduous teeth

pathogenic species is facilitated by immunosuppression. In the present study, we found that 28 children (23%) had periodontal problems either in the form of gingivitis or periodontitis. Out of these 28 children, 4 children had showed signs and symptoms of periodontitis. The statistical analysis of these patients showed that patients with low CD4+ T cell counts (Group IA) had more gingival and periodontal diseases (*P* value <0.005) when compared to patients with higher CD4 T cell count (Group IB).

Oral melanin pigmentation in HIV patients had been well documented by many researchers in their studies. Oral pigmentation in HIV patients may be due to the use of antifungal agents or due to the antiretroviral drugs.[34-36] It has been further suggested that cutaneous manifestations, including oral hyperpigmentation, might be a marker of immune suppression, since it was associated with a low CD4+ T cell count.[35,36] Ranganathan *et al*,[37] presented data on the prevalence of hyperpigmentation in a cohort of HIV-seropositive patients in India. The study group consisted of 1700 consecutive HIV/AIDS patients attending the YRG CARE, Chennai, India, over a period of 6 years (1998–2004). In their study they observed that 24.6% of HIV-infected children had hyperpigmentation. In the current study, we observed that 28 out of 95 HIV-infected children (17%) had oral pigmentation [Figure 9]. The statistical analysis of these patients showed that patients with low CD4+ T cell counts (Group IA) had slightly higher incidence of pigmented areas (*P* value <0.01) when compared to patients with higher CD4 T cell count (Group IB).

Among other findings, we observed a case of mucocele in a nine-year-old child in the floor of the oral cavity. Mucocele in HIV-infected individuals were reported in many studies. Surgical intervention is not required for these lesions as they heal on immune recovery.[38]

In the current study some of the lesions like oral hairy leukoplakia, oral warts (papilloma) and linear gingival erythema were not observed. These lesions are considered to be the pathognomic features of HIV infection. However, we did not come across these lesions in the current study of 95 HIV-infected children.

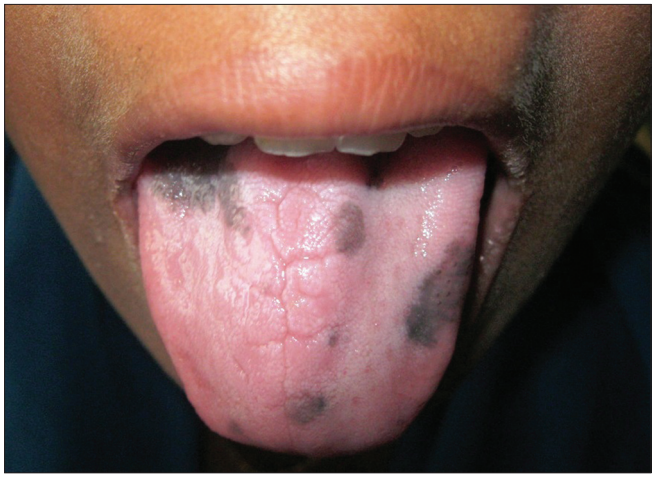

Figure 9: Hyperpigmentation seen on the dorsal surface of the tongue

A reduction in the prevalence of oral lesions has been reported in HIV-infected patients receiving HAART.[22,34,36,37] In the present study, the regular use of HAART had probably reduced the prevalence of oral lesions, especially oral hairy leukoplakia and pseudomembranous candidiasis. The reduction in the prevalence of oral lesions is attributed to the immune recovery on treatment with HAART.[22,34] Moura *et al*,[39] also reported that the incidence of hairy leukoplakia is less in patients with regular use of HAART. Similarly, Nicolatou-Galitis *et al,*[40] in Greece reported less number of oral lesions in patients receiving HIV protease-inhibitor drugs.

An attempt is made to identify oral lesions with statistical difference between the three groups. In this context, the findings of HIV +ve children receiving HAART were compared with HIV +ve children not receiving HAART [Table 3] and HIV –ve children [Table 4].

Table 3 shows oral lesions observed in Group I (HIV +ve children receiving HAART) and Group II (HIV +ve children not receiving HAART) children with their statistical significance. The findings from this table clearly show the efficacy of HAART to reduce the incidence of oral lesions. Our findings from this table correlate with those of Rwenyonyi *et al*,[41] who reported similar findings in their study.

Table 4 shows oral lesions observed in Group I (HIV +ve children receiving HAART) and Group III (HIV -ve children) children with their statistical significance. Children without HIV (normal cohorts) had not shown candidiasis, ulcerative stomatitis and hyperpigmentation. This finding clearly shows that candidiasis, ulcerative stomatitis and hyperpigmentation (children receiving HAART) are exclusive to HIV infection as observed in many studies.

CONCLUSION

In the current study we observed a high incidence of periodontal diseases and dental caries when compared to other lesions such as candidiasis, non-specific ulcers and other lesions. This might be attributed to the poor oral hygiene practice by these children coming from lower socio-economic classes. However, this is a positive finding, considering the fact that periodontal diseases and dental caries can be kept under control through meticulous oral hygiene practices. The children as well as the caretakers in the current study were given adequate oral hygiene instructions and we believe that incidence of oral lesions can further come down in HIV +ve children through proper oral hygiene practices.

ACKNOWLEDGMENTS

We sincerely thank Dr. Sathyanarayana, HOD of General Medicine, Government General Hospital, Vijayawada for allowing us to carry out this study. We also thank the staff of Art Centre, Government General Hospital, Vijayawada, for extending their support to the study.

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How to cite this article: Ponnam SR, Srivastava G, Theruru K. Oral manifestations of human immunodeficiency virus in children: An institutional study at highly active antiretroviral therapy centre in India. J Oral Maxillofac Pathol 2012;16:195-202.

Source of Support: Nil. **Conflict of Interest:** None declared.