Prevalence of Oral and Systemic Manifestations in Pediatric HIV Cohorts with and without Drug Therapy

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Abstract: The prevalence of orofacial and systemic manifestations and their association with drug therapy in pediatric HIV patients is scarce in the literature. The aim of the study was to determine the prevalence of oro-facial and systemic manifestations in HIV sero-positive children with and without highly active antiretroviral therapy (HAART). The study population consisted of 100 pediatric HIV patients (n=47 on HAART and n=53 not on HAART). The majority of the children (n=56) had at least one or more oro-facial manifestation associated with HIV. Oral candidiasis was the most common oral finding present in the HAART (14/33) and non-HAART groups (19/33). Recurrent aphthous ulcers was the only significant oral finding, present more in the HAART group. The percentage of children with upper respiratory tract infection was also more in the HAART group. The other lesions which were found to be significant were seborrheic dermatitis, pulmonary tuberculosis and otitis media. There was no significant difference in the participants' oral findings based on CD4 counts in the HAART and non- HAART groups. The prevalence of oral and systemic manifestations is a persistent feature associated with pediatric HIV, though of moderate intensity in those using HAART and may vary according to individual immune status.

Keywords: Candidiasis, children, HAART, HIV/AIDS, immunosuppression, oral lesions.

INTRODUCTION

Overall health of every individual has been guaranteed as a 'human right' through several international human rights treaties. The rapid spread of Acquired Immunodeficiency Syndrome (AIDS) or Human Immunodeficiency Virus (HIV) has led to a contravention of the human rights of men, women and infants alike, affected by the epidemic in numerous devastating ways. HIV infection manifests itself as a chronic course of disease with a long period of clinical latency, persistent viral replication and involvement of the central nervous system [1, 2]. The HIV/AIDS has spread worldwide as a complex public health hazard since it was first recognized in 1981. According to the global AIDS epidemic update of UNAIDS/WHO, there was an estimated 33.4 million people living with HIV as of 2008 [3]. Pediatric AIDS is defined as AIDS occurring in children less than 13 years [1, 4]. An estimated number of children under 15 years living with HIV in 2008 were approximately 2.1 million. HIV is posing a lifelong threat to children; it is the underlying reason for more than one-third of all deaths among children under the age of five years [4].

According to the 2011-12 annual report of the National AIDS Control Organization (NACO) in India, there was an estimated 2.39 million people infected with HIV in 2009, of which 4.4% were children. While the primary route of transmission of HIV infection is through the sexual route (88.2%), mother to offspring transmission accounted for 5.0% as estimated by NACO [5]. Vertical (mother to offspring) transmission of HIV may occur in utero, during labour and delivery or post-partum as a result of breast feeding [3, 6]. The determinants of transmission are multifactorial and are dependent on maternal immune response, viral load, viral phenotype, and obstetric factors [7].

In children due to their developmental stage with an immature immune system, they are prone to severe immunosuppression and consequently a more rapid and fulminant disease process. Several manifestations, including lesions affecting oral tissues, occur earlier in children than in adults and they facilitate the development of opportunistic infection mainly caused by the fungi [8]. The destruction of CD4 T lymphocyte cells in HIV infection is responsible for the development of oral manifestations in an individual [9]. Oral manifestations related to HIV have relatively declined and the oral health related quality of life of HIV positive

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victims has enormously improved following the introduction of the antiretroviral therapy (ART), especially the combination therapy known as the highly active antiretroviral therapy (HAART) [9-11]. Despite the introduction of HAART, growing numbers of children are still being born with HIV and this serious issue needs to be addressed especially in developing countries. This may be attributed to the difficulties in treatment adherence, lack of pediatric formulations, limited options of drugs available for children, dependence of caregivers for drug administration and specific toxicity in long-term therapy [12]. However, the early initiation of ART has been advocated by Violari *et al.* [13] with a strong evidence of reduced infant mortality and HIV disease progression.

Oral manifestations are one of the most primitive clinical indicators of HIV infection and its progression in children [14]. The oral cavity being easily accessible, allows early diagnosis, prediction of immune status, prevention and timely therapeutic intervention to be provided for the progression of HIV infection to AIDS [15]. As oral signs and symptoms may have predictive value that is independent of the various disease markers, recognition of these oral signs during routine examinations may allow early intervention and reduction in morbidity in this vulnerable population [16]. Very few studies have assessed the oral manifestations of pediatric HIV infection in a developing country like India [17, 18]. Further research is needed to emphasize the importance of oral manifestations as predictors of disease progression and its relation with systemic manifestations. To address this issue, the present study was done in order to determine the frequency and nature of the different oro-facial and systemic manifestations in HIV sero-positive children with and without HAART in South India.

MATERIALS AND METHODS

Study Design and Ethical Considerations

This is a descriptive study designed to determine the prevalence of oro-facial and systemic manifestations in 100 pediatric HIV patients from four centers in the country. The institutional committee for ethics and research, Amrita Institute of Medical Sciences, Cochin, India approved the protocol of the study and authorization was procured from the director of the centers where the study was carried out. All the children in the study were included after obtaining the informed consent for clinical examination and photographic documentation from the children's parents or legal guardians.

Study Population

The study group included 100 HIV sero-positive patients over a period of 18 months (July 2011 to December 2012). All the children enrolled in this study were between 2-12 years of age and had definitive diagnosis for HIV infection confirmed either by enzyme-linked immunosorbent assay (ELISA)/ Western Blot/ HIV Tri-dot tests. The children were selected from the following four centers in India: Asha Kirana Hospital, Mysore, Karnataka; Mar Kundukulam Memorial Research and Rehabilitation Center, Thrissur, Kerala; Cancer and AIDS shelter society (CASS), Kottayam, Kerala; and Kerala state AIDS control society (KSACS), Kottayam, Kerala. This was a convenient sample as it is difficult to determine the HIV status of children in a general population due to ethical concerns. Some of the unfortunate AIDS victims were either orphaned or abandoned and were well cared by these support centers. Majority of the children who were on HAART (mean duration on HAART was 4.3 months) were selected from the hospital setting. This hospital based sample were out-patients who were undergoing regular check-ups. A combination therapy or HAART with nucleoside reverse transcriptase inhibitors such as combivir (zidovudine + lamivudine combination) and/or lamivudine + stavudine and non-nucleoside reverse transcriptase inhibitors such as nevirapine/ efavirenz were the prescribed drug regimens.

On the days of the examination, all children with formerly approved informed consent, those who were out-patients and those who were residents in the institutions, were included. Thus, this study consisted of two categories of patients; HAART and non- HAART patients. Those children requiring urgent medical attention were excluded from the study. The study was done by strictly abiding by the rules put forward by each center and adequate steps were taken to ensure patient confidentiality. All the patients were recorded with a numerical code in order of participation in the study and no record were kept to link between numerical codes and patients' identity. No invasive investigative procedure was done on the patient as per the conditions forwarded by all the centers in which the study was conducted.

Diagnostic Procedures and Clinical Examinations

Examinations were performed by two trained examiners (dental surgeons) and the findings were recorded. The examination procedure was standardized for validity, reliability and reproducibility of the data before and during the screening (Kappa value=0.81). On commencement of the study, all medical history pertaining to the patients were recovered. Data on the demographics, systemic manifestations, family history, drug history, pattern of feeding and immunological marker (CD4 cell count) were obtained from the medical records and was recorded onto a preformatted case sheet. The most recently obtained CD4 cell counts (but not that which was taken before 3 months) were taken into consideration.

Oral examination consisted of inspection and palpation of the oral cavity and facial structures using disposable mouth mirrors, probes, tweezers, sterile cotton swabs and head light. Photographs were taken in some cases. Oral lesions were diagnosed based on the presumptive diagnostic criteria formulated by the EC-Clearinghouse and WHO collaborative workgroup on oral manifestations of pediatric HIV infection [19, 20]. Following the oral examination, advices on oral health care (in their local language) were given to the child's parents or guardians as necessary and were informed about the existing oral conditions and referrals were made accordingly.

Statistical Analysis

All data were systematically entered and analyzed using Statistical Package for Social Sciences, version 16.0 (SPSS

Inc., Chicago, IL, USA). Descriptive statistics were calculated for all variables. Chi-square test was used to determine the association in the occurrence of oral and systemic lesions between the HAART and non-HAART groups. The Student's t-test was performed to compare the mean differences in normally distributed data. The Mann–Whitney U-test was applied to assess the statistical differences between the groups of patients when the data were not normal. The level of significance was set at 0.05 for all statistical tests.

RESULTS

The study population consisted of 100 HIV sero-positive subjects, of which, 47 were included in the HAART group and 53 in the non-HAART group. All the patients had acquired HIV infection *via* vertical transmission that may be either during pregnancy, labor or postnatally during breast feeding. Feeding patterns were recorded. Approximately 74% of patients were only breast fed, 6% patients were only bottle fed and 20% were both breast and bottle fed. There were 60 males (31 HAART and 29 non-HAART) and 40 females (16 HAART and 24 non-HAART). Ages ranged from 2 to 12 years with a mean age of 7.6 ± 2.73 years. Twenty-two patients were between the age group of 2-5 years and 78 patients were between 6-12 years of age. The sample characteristics of the study groups are given in Table **1**. HIV status of the parents showed that majority of the children's both mother and father were HIV positive (n=93) and only mother was positive for the remaining children (n=7) (Table **1**).

Table 1. Demographic Characteristics of the Study Population

Variables	HAART n=47 n (%)	Non-HAART n=53 |n (%)	P-Value
Age groups			
2-5 years	6 (12.8)	16 (30.2)	0.030*
6-12 years	41 (87.2)	37 (69.8)	
Gender			
Male	31 (66.0)	29 (54.7)	0.174
Female	16 (34.0)	24 (45.3)	
CD4 counts			
≤200	14 (29.8)	14 (26.4)	0.708
>200	33 (70.2)	39 (73.6)	
Feeding pattern			
Breastfed	38 (80.9)	36 (67.9)	0.338
Bottle	2 (4.3)	4 (7.5)	
Combination	7 (14.9)	13 (24.5)	
Sample source			
Hospital based out-patients	34 (72.3)	36 (67.9)	0.631
Institutionalized	13 (27.7)	17 (32.1)	

*P< 0.05 (statistically significant).

The majority of the children (n=56) had at least one or more oro-facial manifestation associated with HIV. Oral candidiasis (OC) was the most common oral finding present in the HAART (14/33) and non-HAART groups (19/33). The different clinical forms of candidiasis including pseudomembraneous candidiasis (PC), erythematous candidiasis (EC) and angular cheilitis (AC) were noticed. EC was the most common type present in a total of 24% patients. PC was present in 9 % and AC was seen in 11% cases. There was no statistically significant difference in the antifungal treatment for OC among the HAART and non-HAART groups (p=0.55). The medical history revealed that, in addition to the 5 patients taking antifungal treatment, 71 patients were taking multivitamin and iron supplements and a total of 56 patients were taking antibiotics. Antitubercular regime was prescribed to 15 patients and 7 patients were taking salbutamol. The prevalence of the oral findings including the different clinical forms of candidiasis individually and in combination among the HAART and non- HAART groups are given in Table **2**.

Linear gingival erythema was present in 16 children (17% in the HAART group and 15.1% in the non- HAART group). Distinctive oral hyperpigmentation was present in 8 children; 8.5% in the HAART group and 7.5% in the non-HAART group. Oral hairy leukoplakia (OHL) was seen 4% of cases. Ulcerative lesions including recurrent aphthous ulcers and herpes simplex infection were seen in 17% of patients. Recurrent aphthous ulcers was the only statistically significant oral finding, present more in the HAART group than in the non- HAART group (p = 0.02).

Clinical findings regarding systemic lesions were recorded as given in Table **3** and in that, approximately 18% were clinically normal or without any systemic manifestations. Generalized lymphadenopathy was the most common systemic manifestation present in 85% of the patients. The percentage of children with upper respiratory tract infection was more in the HAART group than in the non- HAART group (p<0.001). The other lesions detected elsewhere in the body in our cohort which was found to be statistically significant (p<0.05) were seborrheic dermatitis (20%; 14 in HAART group and 6 in non- HAART group), pulmonary tuberculosis (19%; 14 in HAART group and 5 in non- HAART group) and otitis media (14%; 10 in HAART group and 4 in non- HAART group). Viral infections affected the HAART group (n=4) more than the non-HAART group (n= 1). In addition, parotid enlargement was present more in the non- HAART group (n=9) than in the HAART group (n=4). Pruritic eruptions and petechiae were present in 5% of patients each. Epistaxis was noticed in 3.8% of patients in the non- HAART group. Molluscum contagiosum contributed to 4.3% in the HAART group and 1.9% in the non- HAART group.

The mean duration of HAART in our sample was 4.3 months and this was correlated with the presence of oral lesions. Oral candidiasis (p<0.001), linear gingival erythema (p=0.01) and recurrent apthous ulcers (p=0.03) were significantly evident in those who were on HAART for less than 4 months than those who were on HAART for more than 5 months. There was a significant decline in the presence of oral lesions with respect to longer duration of HAART treatments (p<0.001). The CD4 counts were available for all the 100 participants. Of these, 28 patients had CD4 counts below 200 and were considered severely immunosuppressed and 72 had counts above 200. The minimum CD4 count recorded was 46 (for a 12 year old) and the maximum was 1647(not immunosuppressed for a 2.5

Table 2 Oral Findings in HAART (n= 47) and Non- HAART (n= 53) Groups

Oral Lesions	HAART (n=47) n (%)	Non-HAART (n=53) n (%)	Total n=100 n (%)	P Value
Candidiasis	14 (29.8)	19 (35.8)	33 (33.0)	0.52
Pseudomembraneous	1 (2.1)	2 (3.8)	3 (3.0)	0.63
Angular cheilitis	2 (4.3)	3 (5.7)	5 (5.0)	0.74
Erythematous	7 (14.9)	10 (18.9)	17 (17.0)	0.60
PC+ EC	2 (4.3)	0 (0)	2 (2.0)	0.13
PC+AC	0 (0)	1 (1.9)	1 (1.0)	0.34
EC+AC	1 (2.1)	1 (1.9)	2 (2.0)	0.93
PC+AC+EC	1 (2.1)	2 (3.8)	3 (3.0)	0.63
Linear gingival erythema	8 (17.0)	8 (15.1)	16 (16.0)	0.79
Hyperpigmentation	4 (8.5)	4 (7.5)	8 (8.0)	0.86
Oral hairy leukoplakia	3 (6.4)	1 (1.9)	4 (4.0)	0.25
Recurrent aphthous ulcers	10 (21.3)	3 (5.7)	13 (13.0)	0.02*
Herpes simplex infection	3 (6.4)	1 (1.9)	4 (4.0)	0.25
Non-diagnostic lesions	2 (4.3)	1 (1.9)	3 (3.0)	0.49
Any lesion	30 (63.8)	26 (49.1)	56 (56.0)	0.14
Asymptomatic (no oral lesion)	17 (36.2)	27 (50.9)	44 (44.0)	0.14

*P ≤ 0.05 (statistically significant).
PC: Pseudomembraneous candidiasis; AC: Angular cheilitis; EC: Erythematous candidiasis.

Table 3. Systemic Findings in the Body of 100 HIV Pediatric Patients in HAART and Non-HAART Groups

Oral Lesions	HAART (n=47) n (%)	Non-HAART (n=53) n (%)	Total n=100 n (%)	P Value
Lymphadenopathy	42 (89.4)	43 (81.1)	85 (85.0)	0.25
Upper respiratory tract infection	32 (68.1)	16 (30.2)	48 (48.0)	<0.001*
Fever	11 (23.4)	10 (18.9)	21 (21.0)	0.57
Seborrheic dermatitis	14 (29.8)	6 (11.3)	20 (20.0)	0.02*
Pulmonary tuberculosis	14 (29.8)	5 (9.4)	19 (19.0)	0.01*
Otitis media	10 (21.3)	4 (7.5)	14 (14.0)	0.04*
Parotid enlargement	4 (8.5)	9 (17.0)	13 (13.0)	0.20
Lower respiratory tract infection	3 (6.4)	4 (7.5)	7 (7.0)	0.82
Pruritic eruptions	2 (4.3)	3 (5.7)	5 (5.0)	0.74
Viral infections	4 (8.5)	1 (1.9)	5 (5.0)	0.12
Petechiae	2 (4.3)	3 (5.7)	5 (5.0)	0.74
Molluscum contagiosum	2 (4.3)	1 (1.9)	3 (3.0)	0.48
Epitaxis	0 (0)	2 (3.8)	2 (2.0)	0.17
Asymptomatic (no systemic lesion)	2 (4.3)	16 (30.2)	18 (18.0)	<0.001*

*P< 0.05 (statistically significant).
Note: There were patients with more than one systemic finding.

year old). There was no statistically significant difference in the participants' oral findings based on CD4 counts in the HAART and non- HAART groups. In children with CD4≤ 200, oral candidiasis was observed in 28.6% in the HAART group and 50% in the non-HAART group. OHL was evident only in the non- HAART group (7.1%). Children with at least one or more oral lesion was observed in 50% in the HAART group and 57.1% in the non- HAART group.

Interestingly, in participants with CD4 > 200, oral findings was more evident in the HAART group (69.7%) than in the non- HAART group (46.2%). OHL and herpes simplex infection were seen only in the HAART group (3.0% and 6.1% respectively). (Table **4**)

The Collaborative Workgroup on the oral manifestations of pediatric HIV infection reached a consensus, based upon available data, as to the presumptive and definitive criteria to diagnose the oro-facial manifestations of HIV infection in children [20]. The oro-facial lesions diagnosed in our cohort with reference to this consensus classification are as follows:

Group 1 (Lesions commonly associated with pediatric HIV infection) All oro-facial lesions in this group were seen in our cohort. EC (24%), PC (9%), AC (11%), herpes simplex infection (4%), linear gingival erythema (16%), parotid enlargement (13%), recurrent aphthous ulcers (13%).

Group 2 (Lesions less commonly associated with pediatric HIV infection) Bacterial odontogenic infections (13%), seborrheic dermatitis (20%), viral infections (5%) and molluscum contagiosum (3%). The other lesions in this group which were not present in our cohort were xerostomia

Table 4. Comparison of the Oral Findings Among HAART and Non- HAART Groups Based on CD4 Counts

Oral Lesions	CD4 ≤ 200 (n=28)		CD4 > 200 (n=72)		Total (n=100) n (%)
	HAART n (%)	Non-HAART n (%)	HAART n (%)	Non-HAART n (%)	
Candidiasis	4 (28.6)	7 (50.0)	10 (30.3)	12 (30.8)	33 (33.0)
Pseudomembraneous	0 (0.0)	1 (7.1)	1 (3.0)	1 (2.6)	3 (3.0)
Angular cheilitis	1 (7.1)	1 (7.1)	1 (3.0)	2 (5.1)	5 (5.0)
Erythematous	2 (14.3)	3 (21.4)	5 (15.2)	7 (17.9)	17 (17.0)
PC+ EC	0 (0.0)	0 (0.0)	2 (6.1)	0 (0.0)	2 (2.0)
PC+AC	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.0)
EC+AC	0 (0.0)	0 (0.0)	1 (3.0)	1 (2.6)	2 (2.0)
PC+AC+EC	1 (7.1)	2 (14.3)	0 (0.0)	0 (0.0)	3 (3.0)
Linear gingival erythema	2 (14.3)	2 (14.3)	6 (18.2)	6 (15.4)	16 (16.0)
Hyperpigmentation	2 (14.3)	2 (14.3)	2 (6.1)	2 (5.1)	8 (8.0)
Oral hairy leukoplakia	0 (0.0)	1 (7.1)	1 (3.0)	0 (0.0)	2 (2.0)
Recurrent aphthous ulcers	2 (14.3)	1 (7.1)	8 (24.2)	2 (5.1)	13 (13.0)
Herpes simplex infection	1 (7.1)	1 (7.1)	2 (6.1)	0 (0.0)	4 (4.0)
Non-diagnostic lesions	1 (7.1)	0 (0.0)	1 (3.0)	1 (2.6)	3 (3.0)
Any lesion	7 (50.0)	8 (57.1)	23 (69.7)	18 (46.2)	56 (56.0)
Asymptomatic(no oral lesion)	7 (50.0)	6 (42.9)	10 (30.3)	21 (53.8)	44 (44.0)

and periodontal diseases like necrotizing ulcerative gingivitis, necrotizing ulcerative periodontitis or stomatitis.

Group 3 (Lesions strongly associated with HIV infection but rare in children) OHL (4%) was the only finding in this category. The other lesions like neoplasms, Kaposi's sarcoma, non- Hodgkin's lymphoma and tuberculosis related ulcers were not evident.

The positive predictive values for oral and systemic diseases in our pediatric cohort were calculated. Of the 56 patients with any oral lesion, 50 had some systemic disease and of the 44 patients with no oral lesions, 32 had some systemic manifestation. The predictive value of an oral lesion for systemic disease was 0.89 and the predictive value of systemic disease for the presence of an oral lesion was 0.73.

DISCUSSION

The epidemiology of pediatric HIV infection is associated with several factors such as the prevalence of HIV among woman in the child bearing age, the ingestion of antiretroviral medications during pregnancy, the availability and effective use of antiretroviral and prophylactic therapy and finally the use of clinical and laboratory measures to monitor therapy. In developing countries, almost half of all infected individuals are women of child bearing age. Little or no antiretroviral medications are available for these women and the children usually do not have the access to life saving drugs later in life [21]. For those children who have access to treatment, generic HAART was found to be safe, effective and relatively well tolerated [22]. Oral manifestations of HIV are common, may represent the first clinical symptoms of the disease and sometimes precede systemic manifestations [15]. Although oral manifestations of HIV infection in adults have been well documented, little is known about oral lesions in children in India. Regardless of the gender, race and age, reduced morbidity and mortality have been linked to increased use of HAART [23]. Yet, the risk factors, primary mode of transmission, patterns of seroconversion and the response of surrogate markers to HAART, such as CD4 count and HIV RNA levels, differs greatly between adults and children [24]. In our study, the duration of HAART therapy had a significant effect on the patients' oral lesions. Those children who were on HAART for less than 4 months had significantly more oral lesions than those under HAART for more than 5 months.

In this study, we reviewed the oro-facial and systemic manifestations in 100 HIV positive children with and without HAART from different centers of the country, particularly in South India. In 100 patients examined, 47% were taking HAART and 53% were selected as the non-HAART group. The initiation of HAART was based on low CD4 count percentage, a high viral load or due to the presence of clinical symptoms. In our study all patients were infected by vertical transmission. However, it was difficult to conclude the exact way by which the infection were transmitted as approximately 94 % patients in our study were also breast fed. It has been reported that the risk of transmission of HIV from mother to child is 15-25% for non-breast feeding mothers and 25-45% for breast-feeding mothers [25]. Thus, in our study, breast-feeding may have contributed to the mode of vertical transmission.

Some oral lesions occur early in HIV infection, whereas others occur later, and thus the appearance of these lesions signifies the progress of HIV/AIDS with or without treatment [26]. In our study, a total of 56% patients (63.8%

in the HAART group and 49.1% in the non- HAART group) had at least one oral manifestation. This observation is relatively higher than the prevalence reported from Brazil [27], Thailand [28] and USA [29]. The prevalence rates of oral lesions in these studies were 52.6%, 48.9% and 45% respectively. This could be attributed to the low sample size in their study which was 38 patients, 45 patients and 60 patients respectively. Except for the prevalence of recurrent aphthous ulcers, we found no significant difference in the prevalence of oral lesions between children on HAART and those not on HAART. All lesions were examined and diagnosed based on clinical descriptions according to the classification and diagnosis for oro-facial lesions in HIV infected children proposed by Ramos-Gomez and coworkers [20]. This classification criteria used in our study is in accordance with those used in previous studies [28, 30, 31].

In our study, the most common oral lesion reported was oral candidiasis (33% patients) and this finding was consistent with the reports of a Indian study where OC was observed in 36.4% patients [32]. However, their sample size was less (27 patients) compared to our sample of 100 patients. The OC prevalence of 33% in our study was not consistent with the results of other studies reported from USA [33] and South Africa [6] where it was 67% and 63% respectively. The increased prevalence of OC in the pediatric cohorts from South Africa may be attributed to the fact that about 42% of patients were hospitalized, where by the patients may be more symptomatic and the immune status may be very low, making them prone to opportunistic infections like fungal diseases. In the same study, the prevalence of OC (63%) was recorded in hospitalized patients alone. However, our study was structured on out patients who reported for their regular checkups and on institution based children.

It has been documented that the prevalence of OC in HIV patients ranged from 20% to 76% [34]. This large range can possibly be explained by the sample size, diagnostic criteria (clinical *vs* laboratory) and examiner variability. Reporting of OC in the literature is inconsistent. Some studies report individual variants of OC, whilst others combine the variants and report a composite value for OC. Furthermore, not all studies defined angular cheilitis as a variant of OC or they have grouped PC and EC together with AC [29]. In this study, a diagnosis of OC was made if one or more of the following lesions were observed: pseudomembranous candidiasis, erythematous candidiasis, hyperplastic candidiasis, and angular cheilitis. The prevalence was taken if any one of the clinical types of candidiasis were present and if more than one variety were present in a single patient, it was still considered to be a single case of candidiasis. We observed all variants of OC, except hyperplastic candidiasis, in both HAART and non-HAART groups. In our study, the occurrence of OC was higher in the non- HAART group than in the HAART group. This is in accordance with a Brazilian study where it was reported that the absence of HAART significantly increased the candida colonization in children [35].

The distribution of various clinical variants of OC in our study showed that the percentage of EC was higher than those with PC, both in the HAART and non- HAART groups. This higher prevalence of EC in our study is consistent with that reported from Greece, where out of 15 pediatric cohorts examined, EC was seen in 7 patients compared to 2 patients with PC [36]. This may be attributed to the difference in variable clinical criteria for the diagnosis of OC, in conjunction with the different stages of HIV disease in the study group. It has been also suggested that PC is a precursor of the more serious EC type [37]. In our study there were only 4 cases which showed both EC and PC together, but it would be difficult to analyze which lesion would have occurred initially as this is a point prevalence study. The prevalence of AC in our study is consistent with that reported from Thailand [30].

The second predominant lesion recorded in our study was linear gingival erythema observed in 16% of patients. Linear gingival erythema and oral hyper-pigmentation were distributed equally among the HAART and the non- HAART groups. Unlike conventional gingivitis, linear gingival erythema usually do not respond to routine oral hygiene measures and it was the most predominant finding of an Iranian study [38]. Oral macular pigmentation present mainly on the buccal mucosa, palate and tongue were seen in 8% of patients, but the cause for pigmentation seen clinically could not be ascertained. The manifestation of pigmentation in HIV positive pediatric children is rare and further studies are required to find out the exact cause of pigmentation in these children. Oral ulcerations formed the other important group of lesions seen in the HIV positive pediatric cohorts in our study. It included primary recurrent aphthous ulcers and herpes simplex virus infection and was found to be higher among the HAART group than the non- HAART group. The occurrence of aphthous ulcers have been reported secondary to the administration of various HAART regimen throughout the course of treatment [39]. In our study, we observed OHL in 6.4% in the HAART group and only 1.9% in the non-HAART group. This may be justified by the slow response of OHL to HAART which was evident in a Nigerian study [40].

In a previous Indian study among pediatric HIV patients, the most prevalent oral manifestation was pseudomembraneous candidiasis and the most prevalent systemic manifestations were lymphadenopathy and pruritic eruptions [17]. This is in contrast with our study, where the most prevalent oral lesion was erythematous candidiasis and the most prevalent systemic manifestations were lymphadenopathy and upper respiratory tract infection.

In our study, approximately 82 patients out of 100 had at least one or more systemic lesions and the remaining 18 patients were clinically normal; excluding the clinical findings of lymphadenopathy which was present in about 85% of patients. Apart from the lymphadenopathy, we noticed a higher prevalence of upper respiratory tract infection in the HAART group ($p=<0.001$). Similarly, there was significant association in the prevalence of pulmonary tuberculosis and otitis media in the HAART and non-HAART groups ($p<0.05$). Consequently, this may be attributed to the common prevalence of these systemic opportunistic infections in immunosuppressed children leading to poor general health. Although seborrheic dermatitis is less commonly associated with paediatric HIV infection [20], we noticed 29.8% in the HAART group compared to 11.3 % in the non- HAART group ($p=0.02$).

The other skin related lesions noticed in our cohort were papular pruritic eruptions, petechaie and molluscum contagiosum which is consistent with previous studies [31, 41]. In our study, parotid enlargement was observed in 17% in the non- HAART group compared to 8.5% in the HAART group. Salivary gland enlargement had been reported to have increased with the initiation of HAART regimen [39], while some studies had reported no change of the same during treatment with HAART [42, 43]. These conflicting findings may be due to the use of different HAART regimens and different treatment durations. In our study, epistaxis was seen in 2% patients, particularly in the non- HAART group. Further studies are required to determine whether epistaxis is another associated finding in HIV infection in pediatric children. In contrast to the report where oral diseases was significantly associated with low CD4 lymphocyte counts [44], the present study showed no influence of CD4 count on the occurrence of oral lesions in the HAART and non-HAART groups.

CONCLUSION

This study of oral and systemic lesions in pediatric HIV patients with and without HAART, to our knowledge, is the first report from India. The prevalence of oral and systemic manifestations is a persistent feature associated with pediatric HIV, though of moderate intensity in those using HAART and may vary according to individual immune status. Erythematous candidiasis and linear gingival erythema were the most predominant oral findings whereas; lymphadenopathy and upper respiratory tract infection were the most predominant systemic findings in our cohort. Within the limitation of this study, a valuable baseline information with regard to HAART and non- HAART pediatric HIV patients and their oral and systemic manifestations has been provided. Further research has to be done on a larger sample size and an investigation like CD4 counts has to be done at the same time the lesions are recorded.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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PATIENT CONSENT

Declared none.

HUMAN/ANIMAL RIGHTS

Declared none.

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