

# Oral manifestations of human immunodeficiency virus/acquired immunodeficiency syndrome and their correlation to cluster of differentiation lymphocyte count in population of North-East India in highly active antiretroviral therapy era

SARAT KUMAR NAYAK, BIJAY KUMAR DAS, SURYA NARAYAN DAS, NAMITA MOHAPATRA<sup>1</sup>, SURYAKANTI NAYAK, LIPSA BHUYAN<sup>2</sup>

## Abstract

**Background:** The human immunodeficiency virus (HIV) infection which manifests as acquired immunodeficiency syndrome (AIDS) is a disease involving the defects of the T-lymphocyte arm of the immune system. Certain laboratory parameters such as the cluster of differentiation (CD4) count and clinical parameters have long been used as markers of disease progression. In industrialized countries, many studies show a highly correlation between the incidence of oral lesions and immunosuppression and hence, can be used as a marker of immunosuppression. This might not be applicable to a developing country like India. In this study, efforts have been made to supplement the present knowledge on various aspects of oral manifestations in HIV patients in the Indian subcontinent. **Aims:** To correlate the oral manifestations in HIV/AIDS patients to the level of circulating CD4+ T-lymphocyte count and their effect in anti-retroviral therapy (ART). **Subjects and Methods:** A total of 104 HIV positive patients were examined for oral lesions. The CD4 count estimated on the same day by fluorescent activated cell sort count machine was then correlated with various oral lesions. **Results:** Oral manifestations appeared when CD4 count decreased below 500 cells/mm<sup>3</sup>. Moreover, oral lesions found at different stages showed very strong correlation to their respective CD4 count. Furthermore, there was considerable decline in the incidence of oral manifestations in patients undergoing highly active ART. **Conclusions:** Oral manifestations are highly predictive markers of severe immune deterioration and disease progression in HIV patients.

**Keywords:** Acquired immunodeficiency syndrome, antiretroviral therapy, cluster of differentiation 4, human immunodeficiency virus

## Introduction

The human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) represents a pandemic form of immunodeficiency involving defects of the T-lymphocyte arm of the immune system.<sup>[1]</sup> As the popular phrase says “Mouth is the mirror of systemic diseases” oral lesions in HIV patients occur even before the causative

organism is identified. Certain clinical and laboratory parameters may prove to be useful indicators of disease progression and can be employed by the dental clinicians. One such parameter is cluster of differentiation (CD4+) count which has been long used and still the best surrogate marker for immune function.<sup>[2,3]</sup>

Estimation of CD4+ count requires a blood sample and developed laboratory facilities. However, the identification of oral manifestations such as oral candidiasis and oral hairy leukoplakia can be made during the routine oral examination. As the development of these oral lesions has high correlation with immunosuppression, the same can be used as markers of immunosuppression. The relevance of using these oral manifestations as markers of immune dysfunction in selected population has been previously studied in industrialized countries.<sup>[4-8]</sup> Data obtained from these studies may not be

*Departments of Oral Pathology and Microbiology and <sup>1</sup>Medicine, SCB Dental College and Hospital, Cuttack, <sup>2</sup>Department of Oral and Maxillofacial Pathology, Kalinga Institute of Dental Sciences, Bhubaneswar, Odisha, India*

**Correspondence:** Dr. Suryakanti Nayak,  
Department of Oral Pathology and Microbiology, SCB Dental  
College and Hospital, Cuttack - 753 007, Odisha, India.  
E-mail: suryakantinayak9@gmail.com

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applicable to developing nations like India. In this study, efforts were made to supplement the present knowledge on various aspects of HIV infection in Indian subcontinent particularly among the northeast population. We hereby aim to correlate the oral manifestations in HIV/AIDS patients to the levels of circulating CD4+ T lymphocyte count and its effect in antiretroviral therapy (ART).

## Subjects and Methods

### Study population

The study was conducted among 104 HIV patients at ART center, SCB Medical College and Hospital, Cuttack, Odisha. These patients were diagnosed positive by enzyme-linked immunosorbent assay for HIV antibody followed by confirmatory test by western blot.

Written informed consent was obtained after explaining the aims of the study, methodology, risks, and benefits of participation. Consent from the treating physician was also obtained. The protocol received approval from the Institutional Ethical Committee, SCB Medical College and Hospital, Cuttack.

### Oral examination and cluster of differentiation count

Information regarding demographic features, high-risk behaviors and the history of HIV infection and duration was obtained from the patients. Each individual was assigned a case number and confidentiality of the records was maintained.

Oral examination was carried out with sterile gloves and mouth mask in a conventional dental chair with artificial illumination using a sterile mouth mirror and probe. Oral lesions were diagnosed clinically, according to the presumptive diagnostic criteria established by the European Economic Community Clearinghouse on oral problems related to HIV infection in August 1990 and September 1992.<sup>[9-11]</sup> CD4 cell counts were estimated using a nonlysis method on a fluorescent activated cell sort count flow cytometer (Becton Dickinson, USA), at ART Plus center SCB Medical College Cuttack, Odisha.

### Statistical analysis

Association between subject variable and each type of oral lesion were analyzed using Chi-square test. Odds ratio and 95% of confidence interval were used in logistic regression analysis for association between oral manifestations and CD4 count within the groups. The value of  $P < 0.05$  was taken to be statistically significant.

## Results

Oral manifestations were observed in 40.39% of the patients. Of which, 46% were males and 29% were females [Table 1].

The most prevalent lesion was oral candidiasis (39.5%) among which pseudomembranous subtype was most frequent followed by erythematous subtype [Table 2]. The incidence of oral manifestation increases significantly when CD4 count falls below 200 cells/mm<sup>3</sup> irrespective of ART [Table 3]. Nearly 74% of patients showed oral manifestation with ART in comparison to 92% in the absence of ART [Table 4].

## Discussion

Patients in our study group belonged to the age group of 21–40 years. The male to female ratio was 2:1 with mean age of 36 years and 32 years for males and females, respectively. In this study, of 104 patients, 42 revealed oral manifestations with a prevalence rate of 40.4% [Table 1] which is in consonance with the study by Barone *et al.* where the prevalence rate was 41% in a group of 217 patients.<sup>[12]</sup> The higher prevalence rate of oral lesions was seen at Mexican and Spanish population, that is, 75% and 99.5%, respectively.<sup>[13,14]</sup> These substantial differences in the rate of prevalence of HIV/AIDS-related oral lesions could be explained by factors such as lifestyle and access to healthcare. The preinfective condition of the oral cavity may play a major role in influencing the development of oral lesions in persons with HIV infection as reported by Lamster *et al.*<sup>[15]</sup>

The association between progression of HIV disease and CD4+ depletion is well established. Oral manifestations have been reported to appear more frequently below a CD4+ count of 200 cells/mm<sup>3</sup>. Accordingly, in this study, the mean CD4+ count was 142 cells/mm<sup>3</sup> in the presence of oral lesion when compared to 414 cells/mm<sup>3</sup> where no oral lesions were reported. Similar observations were reported in a study population of 606 patients by Patton and Chapel Hill of North Carolina. The mean CD4 count for any lesion present was 243 cells/mm<sup>3</sup> as compared to 416 cells/mm<sup>3</sup> while lesion absent in homosexual men and 332 cells/mm<sup>3</sup> as compared to 411 cells/mm<sup>3</sup> among intravenous drug users.<sup>[8,13]</sup>

In this study, the most frequent lesion was oral candidiasis with a frequency of 39.5%, with pseudomembranous subtype being the most frequent, followed by erythematous subtype [Figures 1 and 2]. These findings were consistent with other clinical studies where pseudomembranous and erythematous candidiasis were predominantly present [Table 2].<sup>[12,16,17]</sup>

The mean CD4 count of 143.95 cells/mm<sup>3</sup> in patients with oral candidiasis was approximately similar to studies reported

**Table 1: Mean CD4 count in patients with and without the presence of oral manifestation**

Oral manifestation	No	Mean CD4 count±SD	t	P	Inference
Present	42	142.05±92.58	8.9876 df=102	<0.0001	significant
Absent	62	414.016±180.488			

**Table 2: Frequency and mean CD4+count of particular oral manifestation**

Type of lesion	Frequency No of patients)	Range of CD4 count	Mean CD4 count	S.D
Periodontitis	2	402-444	423	29.69
Linear gingival erythema	4	240-276	259	15.099
Oral and perioral pigmentation	2	190-256	223	46.66
Erythematous candidiasis	5	60-276	199.6	85.69
Pseudo membranous candidiasis	6	60-271	151	90.58
Herpes Simplex	3	112-186	139	40.85
Generalised pseudo membranous candidiasis	8	49-160	103.62	43.98
Angular cheilitis	6	64-123	91.6	28.2
Necrotising ulcerative periodontitis	8	59-179	87	38.26
Kaposi sarcoma	1	75	75	-
Apthous ulcer	3	4-95	37.66	49.9

**Table 3: Oral manifestations among patients with CD4 count <200 cells/mm<sup>3</sup>**

	Patient with ART	Patient without ART	Total
Present	11 (74%)	23 (92%)	34 (85%)
Absent	4 (26%)	2 (8%)	6 (15%)
Total	15 (100%)	25 (100%)	40 (100%)

$\chi^2=2.562$ ,  $df=1$ ,  $P=0.1095$  (Not Significant)

**Table 4: Distribution of oral manifestation group among different CD4 categories**

Oral manifestation	CD4 Count			Total
	<200	200-500	>500	
No of patients (%)	34 (81%)	8 (19%)	0	42 (100%)

by Glick *et al.*<sup>[18]</sup> The mean CD4+ count of patients with pseudomembranous candidiasis and erythematous candidiasis was 151 cells/mm<sup>3</sup> and 199 cells/mm<sup>3</sup>, respectively [Table 2]. Nielsen *et al.*<sup>[16]</sup> from Copenhagen reported the mean CD4+ count of patients with pseudomembranous and erythematous candidiasis to be 220 cells/mm<sup>3</sup> and 320 cells/mm<sup>3</sup>, respectively.

Angular cheilitis was present in 12.5% of oral lesion, and the mean CD4+ count of patients with angular cheilitis was 91.6 [Table 2]. The frequency observed is similar to that seen in other series by Laskaris *et al.*<sup>[19]</sup> (11%) and Moniaci *et al.*<sup>[20]</sup> (13.8%). A higher prevalence was noted by Aguirre-Urizar in a Spanish population.<sup>[12]</sup>

The prevalence of HIV-associated periodontal conditions in our study population was 4.17%. However, the prevalence of periodontitis in HIV-infected patients as reported in the literature varies between 5% and 17%.<sup>[21,22]</sup> We observed 4 cases of linear gingival erythema with mean CD4+ count 259 cells/mm<sup>3</sup>.

The prevalence rate of necrotizing ulcerative periodontitis (NUP) was 16.6%, and the mean CD4+ count of patients with NUP was 87 cells/mm<sup>3</sup>. Glick *et al.*<sup>[23]</sup> have investigated the association between NUP diagnosis and CD4 count below 200 cells/mm<sup>3</sup>. The prevalence of NUP as reported by them was 6.3%, and the mean CD4 count was 51.8 cells/mm<sup>3</sup>. They also suggested that NUP should be considered to be included as a clinical marker for the staging of HIV disease and AIDS.

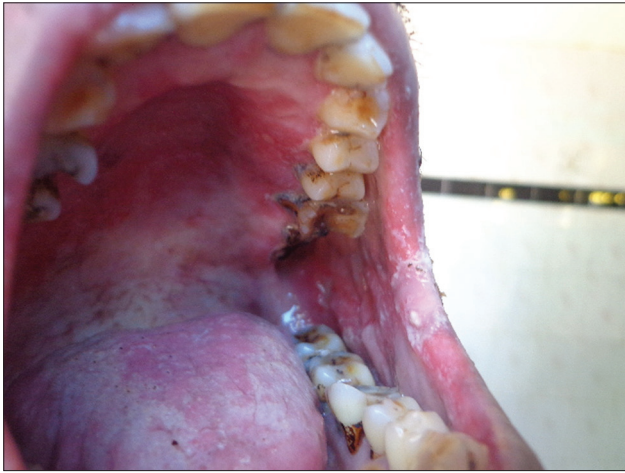
A prevalence of 5.1% and CD4+ cell count of <100/mm<sup>3</sup> has been reported by Glick *et al.*<sup>[18]</sup> for herpes simplex lesion. However, in our study, 6.25% of patients had herpes simplex with a mean CD4+ count of 139 cells/mm<sup>3</sup> [Figure 3].

Altered pigmentation of the skin, nails, and mucous membranes has been observed in HIV-infected patients. Drugs (e.g., clofazamine, ketoconazole, pyrimethamine, and zidovudine), adrenocortical destruction and inflammation caused by immune mediators or infectious agents have been considered possible etiological agents.<sup>[24]</sup> In this study, hyperpigmentation and depigmentation was observed in one case each [Figure 4].

The lesion wise CD4 count in our study showed that oral manifestation in the form of periodontitis had the mean CD4 count 423 cells/mm<sup>3</sup>, whereas Kaposi's sarcoma and apthous ulcer showed 75 cells/mm<sup>3</sup> and 37 cells/mm<sup>3</sup> CD4 count, respectively. Hence, it could be concluded that each type of oral lesion has a different bearing of CD4 count and therefore can be considered a predictor of the disease status and can contribute to plan accurate therapeutic requirement.

In this study, of 104 patients, 65 of the patients were under ART, and 39 patients were without ART as they were diagnosed cases recently. Out of the above 65 patients, those were under ART, 17 (40%) patients exhibit oral manifestations, whereas of 39 patients who were without ART, 25 patients (60%) exhibit





**Figure 1:** Pseudomembranous candidiasis of tongue and buccal mucosa



**Figure 2:** Erythematous candidiasis of tongue



**Figure 3:** Herpes labialis on lower lip



**Figure 4:** Hyperpigmentation of tongue

oral manifestation which suggest that ART may have direct or indirect role in controlling oral manifestation [Table 3].

Forty patients had CD4 count below 200 cells/mm<sup>3</sup> and out of them 34 patients (85%) exhibited various types of oral manifestations which suggested that incidence of oral manifestation significantly increases when CD4 count falls below 200 cells/mm<sup>3</sup> whether under ART or not [Table 3].

Nearly 81% of the oral manifestations occurred in patients with a CD4+ count of <200 cells/mm<sup>3</sup>. Nearly 19% of the oral manifestations occurred with patients having a CD4+ count of 200–500 cells/mm<sup>3</sup>. Oral manifestations were absent in patients when CD4+ count of >500 cells/mm<sup>3</sup> [Table 4]. Tappuni and Flemming<sup>[25]</sup> showed that subjects with CD4+ count of <200 cells/mm<sup>3</sup> and viral load >3000 copies/ml, whether on ART or not, were significantly more likely to experience oral manifestations of HIV than the other patients with CD4+ count of >200 cells/mm<sup>3</sup>. 11 patients who received ART and 23 who did not receive ART exhibited various types of oral manifestations which suggest declining state of oral

manifestation in highly ART (HAART) era even though CD4 count was below 200 cells/mm<sup>3</sup>.<sup>[24-26]</sup>

The oral manifestations have been correlated with the CD4+ counts. This reliance on the CD4+ cell count as the sole measure of immune status implies that immune function and ultimately disease progression are mediated by this factor alone. Clearly, this assumption may be room for bias. Many researchers have also noted the shortcomings inherent in the measurement of CD4 count including the diurnal variation and laboratory variability. Although CD4+ count is the principal laboratory marker, comparisons with other laboratory parameters such as viral load, p24 antigen,  $\beta$ 2 microglobulin, and the clinical sign of oral manifestations as evident from our study may be taken as a reliable tool in determining the progression of disease in future studies.

## Conclusion

Various types of oral manifestations were found at different stages of HIV/AIDS patients which have a very strong correlation to their CD4 count. This observation can also help

us to predict the CD4 count and disease severity by the profile of the particular type of oral manifestation to determine the disease severity in those areas where CD4 recording is difficult. A considerable decline in the incidence of oral manifestation is seen in the patients in the era of HAART.

Oral manifestations are highly predictive markers of severe immune deterioration and disease progression. Oral examinations are an essential component for early recognition of disease progression and comprehensive evaluation of HIV-infected patients.

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### Conflicts of interest

There are no conflicts of interest.

### References

- Gottlieb MS, Groopman JE, Weinstein WM, Fahey JL, Detels R. The acquired immunodeficiency syndrome. *Ann Intern Med* 1983;99:208-20.
- Mehrotra V, Devi P, Thimmarase VR, Bhuvan J. Mouth as a mirror of systemic diseases. *Gomal J Med Sci* 2010;8:235-41.
- Hengel RL, Kovacs JA. Surrogate markers of immune function in human immunodeficiency virus-infected patients: What are they surrogates for? *J Infect Dis* 2003;188:1791-3.
- Ravina A, Ficarra G, Chiodo M, Mazzetti M, Romagnani S. Relationship of circulating CD4+T-lymphocytes and p24 antigenemia to the risk of developing AIDS in HIV-infected subjects with oral hairy leukoplakia. *J Oral Pathol Med* 1996;25:108-11.
- Begg MD, Panageas KS, Mitchell-Lewis D, Bucklan RS, Phelan JA, Lamster IB. Oral lesions as markers of severe immunosuppression in HIV-infected homosexual men and injection drug users. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996;82:276-83.
- Schuman P, Ohmit SE, Sobel JD, Mayer KH, Greene V, Rompalo A, *et al.* Oral lesions among women living with or at risk for HIV infection. HIV epidemiology research study (HERS) group. *Am J Med* 1998;104:559-64.
- Margiotta V, Campisi G, Mancuso S, Accurso V, Abbadessa V. HIV infection: Oral lesions, CD4+ cell count and viral load in an Italian study population. *J Oral Pathol Med* 1999;28:173-7.
- Patton LL. Sensitivity, specificity, and positive predictive value of oral opportunistic infections in adults with HIV/AIDS as markers of immune suppression and viral burden. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000;90:182-8.
- Axell T, Baert AE, Brcherious C, Challacombe S, Greenspan D, Ten Kate RW, *et al.* An update of the classification and diagnostic criteria of oral lesions in HIV infection. *J Oral Pathol Med* 1991; 20:97-100.
- Greenspan JS, Barr CE, Sciubba JJ, Winkler JR. Oral manifestations of HIV infection. Definitions, diagnostic criteria, and principles of therapy. The U.S.A. Oral AIDS Collaborative Group. *Oral Surg Oral Med Oral Pathol* 1992;73:142-4.
- Axell T, Azul AM, Challacombe SJ, Ficarra G, Greenspan D, Greenspan J, *et al.* Classification and diagnostic criteria of oral lesions in HIV infection. *J Oral Pathol Med* 1993;22:289-91.
- Barone R, Ficarra G, Gaglioti D, Orsi A, Mazzotta F. Prevalence of oral lesions among HIV-infected intravenous drug abusers and other risk groups. *Oral Surg Oral Med Oral Pathol* 1990;69:169-73.
- Ramirez-Amador V, Esquivel-Pedraza L, Sierra-Madero J, Ponce-de-Leon S, Ponce-de-Leon S. Oral manifestations of HIV infection by gender and transmission category in Mexico City. *J Oral Pathol Med* 1998;27:135-40.
- Ceballos-Salobreña A, Aguirre-Urizar JM, Bagan-Sebastian JV. Oral manifestations associated with human immunodeficiency virus infection in a Spanish population. *J Oral Pathol Med* 1996;25:523-6.
- Lamster IB, Begg MD, Mitchell-Lewis D, Fine JB, Grbic JT, Todak GG, *et al.* Oral manifestations of HIV infection in homosexual men and intravenous drug users. Study design and relationship of epidemiologic, clinical, and immunologic parameters to oral lesions. *Oral Surg Oral Med Oral Pathol* 1994;78:163-74.
- Nielsen H, Bentsen KD, Højtvéd L, Willemoes EH, Scheutz F, Schiødt M, *et al.* Oral candidiasis and immune status of HIV-infected patients. *J Oral Pathol Med* 1994;23:140-3.
- Phelan JA, Saltzman BR, Friedland GH, Klein RS. Oral findings in patients with acquired immunodeficiency syndrome. *Oral Surg Oral Med Oral Pathol* 1987;64:50-6.
- Glick M, Muzyka BC, Lurie D, Salkin LM. Oral manifestations associated with HIV-related disease as markers for immune suppression and AIDS. *Oral Surg Oral Med Oral Pathol* 1994;77:344-9.
- Laskaris G, Hadjivassiliou M, Stratigos J. Oral signs and symptoms in 160 Greek HIV-infected patients. *J Oral Pathol Med* 1992;21:120-3.
- Moniaci D, Greco D, Flecchia G, Raiteri R, Sinicco A. Epidemiology, clinical features and prognostic value of HIV-1 related oral lesions. *J Oral Pathol Med* 1990;19:477-81.
- Robinson P. Periodontal diseases and HIV infection. A review of the literature. *J Clin Periodontol* 1992;19(9 Pt 1):609-14.
- Holmstrup P, Westergaard J. Periodontal diseases in HIV-infected patients. *J Clin Periodontol* 1994;21:270-80.
- Glick M, Muzyka BC, Salkin LM, Lurie D. Necrotizing ulcerative periodontitis: A marker for immune deterioration and a predictor for the diagnosis of AIDS. *J Periodontol* 1994;65:393-7.
- Sivapathasundharam B, Gururaj N, Ranganathan K. Viral infection of oral cavity. In: Rajendran R, Sivapathasundaram B, (Editors). *Shafer's Textbook of Oral Pathology*, 5<sup>th</sup> ed. New Delhi: Elsevier; 2006. p. 495.
- Tappuni AR, Fleming GJ. The effect of antiretroviral therapy on the prevalence of oral manifestations in HIV-infected patients: A UK study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001;92:623-8.
- Greenspan D, Gange SJ, Phelan JA, Navazesh M, Alves ME, MacPhail LA, *et al.* Incidence of oral lesions in HIV-1-infected women: Reduction with HAART. *J Dent Res* 2004;83:145-50.