Clin Oral Invest (2009) 13:141–148
DOI 10.1007/s00784-008-0210-z

ORIGINAL ARTICLE

Oral manifestations as predictors of immune suppression in a HIV-/AIDS-infected population in south India

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Received: 16 December 2007 / Accepted: 12 June 2008 / Published online: 31 July 2008

Abstract The objectives of the study are to evaluate the relationship between common HIV-related oral lesions and absolute CD4+ count, age, gender, and medication used and to assess the sensitivity, specificity, positive and negative predictive value of oral manifestations for low absolute CD4+ counts. HIV-positive patients, 200, from south India were selected, whose absolute CD4+ counts were determined within 2 weeks of oral examination. Sociodemographic data was obtained using a structured questionnaire. Oral manifestations were diagnosed according to presumptive criteria of EEC-clearinghouse classification (1993). Four or more concurrent oral lesions were statistically significant with low CD4+ counts <200 cells/mm3 (P= 0.005). The highest and lowest mean CD4+ cell counts were seen in individuals with linear gingival erythema (LGE; 172.5 cells/mm^3) and pseudomembranous candidiasis (PC; 87 cells/mm^3), respectively. Smoking, age (<35 years), and males had a positive association with oral hairy leukoplakia (OHL; P<0.05). Patients with CD4+ counts<200 cells/mm^3 were associated with 15 times greater risk of PC and four times at greater risk for occurrence of any oral manifestation. Concurrent oral manifestations (≥4) were good predictors (80–100%) of severe immune suppression. In most resource poor countries where facilities for undertaking CD4+ counts are not available, the presence of concurrent oral manifestations may be used as an indicator of deteriorating immune status.

Keywords HIV · AIDS · Oral manifestations · India · CD4 count

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Introduction

Approximately 5.2 million people in India are infected with HIV/AIDS, accounting for more than two thirds of HIV-infected population in Asia [36]. Absolute CD4+ counts are widely used as laboratory marker for immunosuppression in HIV infection. Specific common oral lesions have been documented to be related with immune suppression as indicated by CD4+ counts that have been widely studied and reported in the developed countries [10, 15, 20, 21]. However, the documentation of relationship of oral manifestations with CD4 counts with oral manifestations from Asian countries, especially India, have been sparse [18, 30, 35]. Hence, this cross-sectional study was undertaken among HIV-infected population in southern India with objectives to (1) analyze the relationship between oral manifestations and absolute CD4+ count, (2) assess the sensitivity, specificity, positive predictive values and nega-

tive predictive values of HIV-associated oral manifestations for identifying immune suppression, and (3) evaluate association of oral diseases with age, gender, smoking, alcohol, and medications used.

Subjects and methods

Three hundred HIV-positive patients were screened during this cross-sectional study which was conducted over 1-year period between July 2004 and June 2005 under the approval of Institutional research ethical committee. Written informed consents were obtained from participants (patients). Patients were included in the study only if their absolute CD4+ counts were available within 2 weeks of oral examination (either prior or later), thus establishing a final study sample of 200 patients. The patients were selected from out-patient departments of infectious diseases units at Attavar hospital, Mangalore and hospitalized patients of Kasturba hospital, Manipal. In both these centers, patients were diagnosed as HIV-antibody-positive by enzyme-linked immunosorbent assay (ELISA)—HIV. Three separate positive ELISA tests were considered confirmatory, and absolute CD4+ lymphocyte counts were performed using flow cytometry (SRL, Ranbaxy Laboratories, Mumbai). Clinical history was obtained from patient's medical records. HIV viral load was not performed because of the financial constraints. Sociodemographic data was obtained using a structured questionnaire.

Medications used by the patients were categorized into four different groups: antiretroviral therapy (ART), antitubercular drugs (ATT), antifungals, and others (anti hypertensive, vitamins, antidepressants and corticosteroids). The stage of HIV infection was categorized into three different stages: asymptomatic, symptomatic, and AIDS, in accordance with CDC clinical staging [11]. Patients were categorized with AIDS only if they were having absolute CD4+ counts below 200 cells/mm^3 or were having any of the AIDS-defining diseases (ADD). Patients according to CD4+ counts were clustered into three groups: 0–200 cells/mm^3, 201–500 cells/mm^3, and more than 500 cells/mm^3. Oral lesions were diagnosed according to presumptive criteria of EEC Clearinghouse Classification [14]. A single examiner (G.S) trained in oral diagnosis, examined and recorded all oromucosal lesions.

Statistical analysis

Associations between subject variable and each type of oral lesion were analyzed using chi- square test. Odds ratio and 95% confidence interval were used in logistic regression analysis for association between oral manifestations and variables such as age, gender, smoking, ART, and low CD4+ (<200 cells/ mm^3) counts. Partial correlation coefficient was used between presence of oral manifestation and antiretroviral therapy after controlling absolute CD4 counts. Mann–Whitney U test was used for differences between mean values of groups of patients. Mean, sensitivity, specificity, positive predictive and negative predictive values of individual oral manifestations for low CD4+ counts (<200 cells/mm^3) were calculated. Sensitivity for any oral lesion is the probability for that lesion to be present when the person has CD4+ count <200 cells/mm^3, and specificity for oral lesion is the probability that lesion is not present when the person has CD4+ count >200 cells/mm^3. The probability that the patient had CD4+ counts <200 cells/mm^3 when a specific oral lesion is present is reported as positive predictive value (PPV). Similarly, the likelihood that the person's CD4+ count is greater than 200 cells/mm^3 when a specific oral lesion is absent is reported as negative predictive value (NPV). Statistical analysis was managed and analyzed using SPSS version 11 software.

Results

Sociodemographic data and clinical data are summarized in Table 1. The combined mean age for males and females was 38.3 years. Among medications used, 81 (40.5%) HIV-positive subjects were on antiretroviral therapy that included lamivudine/stavudine combination or lamivudine/stavudine/nevirapine combination. Thirteen patients were on antifungals, and 73 patients were on other medications.

Absolute CD4+ counts were categorized in three different groups: group I (0–200 cells/mm^3), group II (201–500 cells/mm^3), and group III (≥501 cells/mm^3). The oral manifestations were common in group I (87.9%), followed by group II (68.5%), and group III (50%), respectively (P<0.001, statistically significant).

Means and percentages of main oral manifestations were calculated. The distribution of all oral manifestations in spectrum of absolute CD4+ counts is shown in Table 2. Erythematous candidiasis (EC; 44%) followed by xerostomia (35.5%), hyperpigmentation (33.5%), oral hairy leukoplakia (OHL; 18.5%), linear gingival erythema (LGE; 11.5%), and pseudomembranous candidiasis (PC) (10.5%) were common oral findings.

Multivariate logistic regression analysis of various variables associated with main oral manifestations (Table 3) showed that low CD4+ counts were significantly associated with EC and PC. Smoking, younger age group (<35 years), and male gender had a positive association with OHL. A reverse effect of antiretroviral therapy on OHL (P=0.016) was also seen. Partial correlation coefficient showed no evidence of correlation between ART and presence of oral

Table 1 Sociodemographic and clinical data of HIV infected patients

Variables	No. of patients
Gender	
Male	151
Female	49
Age group (in years)	
16–24	7
25–34	72
35–44	77
45–54	30
≥55	14
Mode of transmission	
Heterosexual route	196
Homosexual route	3
IDU	1
Education (At least 12 years)	
Educated	99
Uneducated	101
Income (at least Rs. 3000/month)	
Above poverty line	98
Below poverty line	102
Oral habits	
Smokers	66
Nonsmokers	134
Alcohol	93
Nonalcohol	107
Tobacco chewer	70
Nontobacco chewer	130
CDC HIV clinical disease stage	
Stage A (asymptomatic)	10
Stage B (symptomatic)	33
AIDS	157
Absolute CD4 staging	
0–200 cells/mm^3	132
201–500 cells	54
≥501 cells	14
Mean CD4 count±SD	195.11±183.76
Medications used[a]	
Antiretroviral therapy	81
ATT	47
Antifungal therapy	13
Other drugs	73

[a] Some patients were on more than one drug.

manifestation (P=0.843) after controlling absolute CD4 counts.

Patients, 161 (80.5%), had some type of oral manifestation. Males were more likely to have oral lesions as CD4+ counts declined (P=0.001). OHL was found in a significant association with AIDS (P=0.007). The percentage of patients having AIDS was 78.5%(157 patients).

A decreased prevalence of individual oral manifestations of patients receiving ART (81 patients/40.5%) compared to patients not receiving ART (119 patients) was observed with the exception of melanotic hyperpigmentation and LGE (Table 4). Bivariate correlation for ART showed an association between ART and OHL (P<0.05).The three most common individual oral manifestations observed in patients on ATT were EC (51.1%), melanotic hyperpigmentation (34.0%), and OHL (34.0%).

The mean CD4+ count values of patients having various concurrent oral manifestations was in a diminishing order as concurrent oral manifestations escalate in number (Table 5). The higher the number of concurrent oral lesions (four or more), the stronger was its association with low CD4+ counts (P=0.005).

Mean values of CD4+ cells/mm^3 in groups of patients having individual oral manifestations was compared with groups of patients with absence of these conditions using Mann–Whitney U test (Table 6). It was found that mean absolute CD4+ count of the group of the patients having EC, PC, and OHL was significantly different (P=0.000, P=0.000, and P=0.029 respectively) from the mean absolute CD4+ count of those patients who were not having either EC, PC, or OHL.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of oral manifestations are reported in Table 7 along with their mean CD4+ counts. With respect to oral manifestations, the highest and lowest mean CD4+ cell counts was found for individuals with LGE (172.5±137.03 cells/mm^3) and PC (87±139.62 cells/ mm^3).

Discussion

In this study, we have correlated oral manifestations of HIV-infected patients with their absolute CD4+ counts from a population in south India. Ranganathan et al. had given the odds ratio only for oral candidiasis (1.96) and PC also (2.67) but with no other description of overall oral manifestations with CD4+ counts [30]. Our study in comparison had a higher odds ratio for EC (2.59) and PC (15.46).

Of patients, 75.5% were men, a finding comparable to studies from Thailand (78%) [25] and Cambodia (73.2%) [5] (Table 1). The combined mean age of patients was 38.3 years, a relatively higher figure compared to other Asian studies [19, 25].

In our study, oral manifestations were seen in 80.5% of patients, which is comparable to studies conducted by Khongkunthian et al. (82%) [19], Ramirez et al. (80%) [29], Kerdpon et al. [18], (77% of southern group in Thailand), and Bravo et al. (85%) [8]. The prevalence of oral manifestations varies greatly in literature ranging from 99.5% to 9.5% [10, 23]. These differences in prevalence may be the result of differences in study design and variations in study population such as race, socioeconomic status, sex, drug therapy, genetics, degree of immunosuppression, and variations in diagnostic criteria.

Table 2 Comparison of frequency of oral manifestations in relation to absolute CD4 count

Oral manifestations	Absolute CD4 counts (cells/mm^3)			Total (n=200)
	0–200 (n=132)	201–500 (n=54)	≥501 (n=14)	
Erythematous candidiasis (EC)	67 (50.8%)	20 (37%)	1 (7.1%)	88 (44%)
Pseudomembranous candidiasis (PC)	20 (15.2%)	–	1 (7.1%)	21 (10.5%)
Angular cheilitis	15 (11.9%)	3 (5.6%)	–	18 (9%)
Oral hairy leukoplakia (OHL)	29 (22.0%)	7 (13.0%)	1 (7.3%)	37 (18.5%)
Melanotic hyperpigmentation	49 (37.1%)	13 (24.1%)	5 (35.0%)	67 (33.5%)
Xerostomia	52 (39.4%)	17 (31.5%)	2 (14.2%)	71 (35.5%)
Necrotizing ulcerative gingivitis (NUG)	13 (9.8%)	3 (5.6%)	2 (14.2%)	18 (9%)
Necrotizing ulcerative periodontitis (NUP)	10 (7.6%)	3 (5.6%)	1 (7.1%)	14 (7%)
Linear gingival Erythema (LGE)	17 (12.9%)	6 (11.1%)	–	23 (11.5%)
Apthous ulcers	9 (6.8%)	–	1 (7.1%)	10 (5%)
Herpes labialis	3 (2.2%)	1 (1.8%)	–	4 (2%)
Herpes zoster	1 (0.7%)	1 (1.8%)	–	2 (1%)
Facial palsy	1 (0.7%)	–	–	1 (0.5%)

We found erythematous candidiasis (EC) as the most common (44%) oromucosal manifestation in our cohort. This finding is consistent with other Asian studies [5, 25]. EC was observed to be more common in group I (50.8%; Table 2), which was also statistically significant (P<0.05). The prevalence of EC declined gradually from 37% in group II to 7.1% in patients with CD4+ counts above 500 cells/mm^3.

Of our study cohort, 10.5% presented with PC, which is comparable to another study conducted in India (11%) [35]. The presence of PC was found to be highly significant with absolute CD4+ count below 200 cells/mm^3 (P=0.002; chi square test). Comparing EC and PC, it was found that PC had a greater correlation with progression of HIV infection [Table 3; PC—(OR=15.46; CI 1.928–124.214; P=0.010) and EC—(OR=2.5; CI 1.334–5.037; P=0.005)]. This finding is similar to studies done in Italy, Thailand, and United Kingdom [9, 18, 31]. However, Dodd et al. and Nielsen et al. observed contradictory findings showing similar prognostic significance of both EC and PC [13, 24]. Prognostic significance of two forms of candidiasis needs to be reappraised in larger longitudinal studies.

Similar to other studies, our statistics show a weak association between OHL and low CD4+ counts [15, 18, 26, 28]. OHL was found to be more common (OR=3.7; P< 0.05) in males (Table 3). This finding was also observed in other studies from Asia [18, 25, 30]. Higher prevalence among men is a major point of contention in the literature with no comprehensible explanations. Coinfections with other microorganisms may alter the oral environment and promote OHL expression.

No other oral manifestations were significantly associated with low CD4+ counts. However, it was found using multivariate logistic regression analysis that patients having

Table 3 Logistic regression analysis showing association of common oral manifestations with various variables

Lesions	Variable	Odds ratio (OR)	95% CI	P value
Any oral manifestation	CD4 (0–200 cells/mm^3)	4.076	1.535–10.822	0.005
	Age group (<35 yrs)	0.396	0.182–0.858	0.019
Erythematous candidiasis	CD4 (0–200 cells/mm^3)	2.592	1.334–5.037	0.005
	Age group (<35 years)	0.435	0.238–0.794	0.007
	Alcohol	2.176	0.977–4.850	0.057
	Tobacco chewer	0.481	0.236–0.979	0.043
Oral hairy leukoplakia	Antiretroviral therapy	0.340	0.141–0.819	0.016
	Gender (Male)	3.772	1.079–13.185	0.030
	Age group (<35 year)	2.335	1.045–5.214	0.039
	Smokers	3.131	1.452–10.643	0.007
	Alcohol	0.364	0.315–0.980	0.046
Pseudomembranous candidiasis	CD4 (0–200 cells /mm^3)	15.46	1.928–124.214	0.010
Presence of 3 or more lesions	CD4 (0–200 cells /mm^3)	2.264	1.198–4.280	0.012

All P values statistically significant
CI Confidence interval

Table 4 Comparison of oral manifestations of patients on specific medication and not receiving medication

Oral manifestation (OM)	Patients with OM on medication		Patients with OM *not* receiving medication	*P* value
	Medication	Number (percentage)	Number-percentage	
EC	ART (81 patients/40.5%)	35 (43.2%)	53 (44.5%)	0.934[a]
PC		6 (7.4%)	15 (12.6%)	0.257[a]
Hyperpigmentation		33 (40.7%)	34 (28.6%)	0.062[a]
Xerostomia		26 (32.1%)	45 (37.8%)	0.460[a]
OHL		9 (11.1%)	28 (23.5%)	0.030[b]
LGE		7 (8.6%)	16 (3.4%)	0.316[a]
NUP		5 (6.2%)	9 (7.6%)	0.730[a]
EC	ATT (47 patients/23.5%)	24 (51.1%)	64 (41.8%)	0.239[a]
PC		7 (14.9%)	14 (9.2%)	0.251[a]
Hyperpigmentation		16 (34.0%)	51 (33.3%)	0.885[a]
Xerostomia		15 (31.9%)	56 (36.6%)	0.598[a]
OHL		16 (34.0%)	21 (13.7%)	0.001[b]
LGE		6 (12.8%)	17 (11.1%)	0.735[a]
NUP		6 (12.8%)	8 (5.2%)	0.073[a]

[a] *P* value>0.05 (not significant)
[b] *P* value<0.05 (statistically significant)

CD4+ counts below 200 cells/mm^3 would be at four times higher risk for development of any oral manifestation (Table 3).

Smoking in HIV-positive infected individuals is considered as a significant copromoter for oral candidiasis and OHL [28]. Salivary alterations caused due to smoking may modify infectivity of Epstein Barr virus (EBV) in some unknown way. In our study, OHL was significantly associated with smoking, with smokers being three times at greater risk for OHL compared to nonsmokers [2, 12, 27, 33]. In our study, we could not find an association between oral candidiasis and smoking. This finding is compatible with the findings in a similar study by Nittyananta et al. [25]. However, some studies have showed a positive correlation of candidiasis with smoking [12, 22, 27]. These findings may suggest that differences in tobacco product might be responsible for variable findings [25].

Table 5 Prevalence and predictive values of concurrent oral manifestations

Concurrent oral manifestations	No of patients per concurrent oral manifestation	Prevalence (%)	Mean CD_4 counts (cells/mm^3)±SD	PPV[a] (%)
0	39	19.5	308.07±218.6	39
1	42	21	210.11±184.8	61.9
2	43	21.5	178.98±189.3	74.4
3	36	18	154.28±152.4	69.4
4	25	12.5	129.12±103.3	80
5	11	5.5	114.73±71.0	81.8
6 or more	4	2	88.33±24.0	100

PPV Positive predictive value
[a] Percentage of patients with actual CD4 counts below 200 cell/mm^3

Alcohol has been shown to be a negative factor for the development of OHL [7, 25]; this, perhaps, reflects the knowledge that expression of the epithelium EBV receptor depends upon the extent of mucosal differentiation [34]. A similar finding was seen in our study (Table 3). However, alcohol was found to be a significant risk factor for EC. This may be attributed to atrophy of oral mucosa [37], and alcohol also has the ability to dissolve the extra cellular lipids present in the oral mucosa, thus increasing its permeability [6], which facilitates the adhesion of *Candida albicans*. These findings are similar to the findings of Nittyananta et al. [25].

Multivariate regression analysis (Table 3) showed that EC is more common in older age group (>35 years), and patients younger than 35 years have a 2.3 times greater chance of having OHL compared to patients more than 35 years. Similar findings were found in studies done by McCarthy et al. [22] and Hilton et al. [16], though Campo et al. [9] found a significant association between candidiasis and patients younger than 35 years, and Scheifele et al. [32] observed peak occurrence of OHL to be at 40–49 years.

Various types of medications may influence the prevalence of oral manifestations [26]. Medications, other than ART, did not correlate significantly with any oral manifestations. Of the patients on ART, 11.1% had OHL compared to 23.5% of patients not on ART. In the present study, we found that ART reduced the risk of having OHL ($P<0.05$), and a trend of reduced number of oral manifestations was found (Table 4).

The number of different concurrent oral manifestations increased with progressively declining CD4+ counts as is documented in Table 5. The more number of concurrent oral manifestations increased the predictive values, with 4,

Table 6 Absolute CD4 counts and their association with presence or absence of oral manifestation

Mann–Whitney *U* test		
Oral manifestations	*Z*	*P* value
EC	4.128	0.000[a]
OHL	2.181	0.029[a]
Xerostomia	2.143	0.032[a]
PC	4.241	0.000[a]
Hyperpigmentation	1.124	0.203[b]
NUP	1.036	0.300[b]
LGE	0.021	0.983[b]

[a] Difference Statistically significant
[b] Difference NS (not significant)

5, and 6 or more concurrent oral manifestations having high predictive values of 80.0%, 81.8%, and 100%, respectively, for low CD4 counts (<200 cells/mm^3). Glick et al., though, found that patients with three or more concurrent oral manifestations had predictive values ranging from 75.0% to 100% [15].

For diagnostic utility of oral manifestations, earlier studies reported in literature were primarily composed of homosexual men and intravenous drug users (IDUs) [3, 4, 15, 26,]. Nevertheless, for heterosexual mode of transmission, as it is found in most African and Asian countries, reported data regarding diagnostic utility is negligible and is absent from Asian countries [17]. To the best of our knowledge, our study is the first Asian study to give sensitivity, specificity, PPVs, and NPVs of oral manifestations to immune suppression.

In this study, sensitivities were relatively low, and specificities were high. These findings are similar to other studies done [3, 26]. High specificities(70% for EC, 98.6% for PC, and 88.6% for OHL), which were seen in all oral manifestations, inferring that attainment of relatively better immune function is seen in the absence of any oral manifestation. In the study done by Glick et al., sensitivity for OC was higher (77.2%) compared to our study (EC; 50.4%), but for OHL, sensitivity was exactly similar (22.6%) [15].

The PPV of oral manifestations for progressing immunosuppression is dependent on the level of immune suppression in the cohort. The mean CD4+ count from our study for any persons with oral manifestations was 166 cells/mm^3 which was, however, lower compared to mean CD4+ counts reported by other investigators (305 cells/mm^3 for homosexuals, 322 cells/mm^3 for IDUs [3], 252 cells/mm^3 [17], 207 cells/mm^3 [26], 452 cells/mm^3 [1], 306 cells/mm^3 [8], and 410 cells/mm^3 [33]).

The predictive values (probability that patient had CD4+ counts below 200 cells/mm^3) were high for common oral manifestations; PC, 95.2%; EC, 76.1%; OHL, 78.4% and NUP, 71.4%. Comparatively, PPVs in our study in relation to other studies were slightly higher, probably reflecting the advanced immune suppression seen in our cohort. [Glick et al. [15] (oral candidiasis, 69%; OHL, 70.3%; and NUP, 95.1%), Patton [26] (PC, 82.2%; EC, 58.3%; OHL, 66.3%; and NUP, 56.7%), Begg et al. [3] in homosexuals and IDU (oral candidiasis, 50% and 42.9%; OHL, 57.1% and 40%; NUP, 80% and 0%) and Hodgson [17] (PC, 55%; EC, 85.7%; OHL, 60%)].

CD4+ cell counts were lower in our study population, compared to other studies with 134 cells/mm^3 for EC (vs. 186 cells/mm^3—Patton [26]; 185 cells/mm^3—Hodgson [17]), 87 for PC (vs. 116 cells/mm^3—Patton [26]; 191 cells/mm^3—Hodgson [17]; 426 cells/mm^3—Adurogbangba et al. [1]), and 133 for OHL (vs. 155 cells/mm^3—Glick et al. [15]; 171 cells/mm^3—Patton [26]; 171 cells/mm^3—Hodgson [17]). Statistical differences were found for mean of groups of patients with these oral manifestations (Table 6).

These findings suggest that these oral manifestations, especially pseudomembrane candidiasis, are highly predic-

Table 7 Predictive values and mean values of oral manifestations with absolute CD4 counts

Oral manifestations	Mean CD_4 count	SD	PPV[a] (%)	NPV (%)	Sensitivity (%)	Specificity (%)	*P* value
EC	134.17	111.16	76.1	43	50.8	70	0.005[b]
PC	87.24	139.62	95.2	38.1	15.2	98.6	0.002[b]
OHL	133.38	119.61	73.4	37.6	22.0	88.6	0.065[c]
Xerostomia	153.54	135.10	73.2	38.9	39.4	79.2	0.083[c]
NUP	168.57	203.54	71.4	35.1	7.6	94.3	0.620[c]
LGE	172.52	137.03	73.9	35.8	12.9	91.4	0.359[c]
Hyperpigmentation	171.45	177.04	73.1	38.5	37.1	74.3	0.101[c]

SD Standard deviation, *PPV* positive predictive value, *NPV* negative predictive value
[a] Percentage of patients with Abs CD_4 count less than 200 cells/mm^3
[b] Statistically significant (presence in <200 cells/mm^3 when compared to >20 cells/mm^3)
[c] NS (not significant)

tive of severe immune suppression (CD4+ <200 cells/mm^3). In the absence of other clinical or laboratory information and AIDS, especially in relation to Asian context, where CD4+ counts due to financial constraints are not done in every center, this finding assumes clinical implication.

Our study showed the correlation of immune status of patients with oral manifestations in an Indian cohort. Oral manifestations act as harbinger for the development of AIDS (CD4+ counts <200 cells/mm^3), thus, implicating the need for careful oral examination for the benefit of the patient who is not only immunocompromised but also possibly psychologically devastated. The accessibility of oral cavity and the clinical relevance of oral HIV lesions cannot be overlooked.

With a massive HIV population burden, AIDS has, had, and will continue to have an impact on India, especially health care. Without an effective vaccine or completely curative treatment, HIV infection will continue to spread and will cause havoc for the financially deprived. The global response to AIDS must be transformed from an episodic, crisis-management approach to a strategic response that recognizes the need for long-term commitment for HIV epidemic to cease.

The prevalence and correlation of oral manifestations with CD4+ counts below 200 cells/mm^3 in the current study did not show any striking differences from developed nations. PC was shown to be better than EC for progression to AIDS. Patients with PC were found to be at 15 times greater risk of having CD4+ counts less than 200 cells/mm^3 compared to patients with absence of PC. Males were more likely to have OHL. Persons with CD4+ counts less than 200 cells/mm^3 had four times greater risk of having any oral manifestation. Concurrent oral manifestations (more than three) were good predictors (80.0–100%) for severe immune suppression. PC, EC, and OHL were suitable predictors of advanced immune suppression.

The limitations of our study are that there was lack of randomness of our study sample and cross-sectional nature of our study. However, the data will be useful in developing nations like India where there are financial constraints for absolute CD4+ counts. The diagnostic utility of oral manifestations may be used in conjunction with other clinical signs in monitoring HIV disease in developing nations. Research studies in developing nations should be of longitudinal nature in the future to exactly confirm our findings of oral manifestations as significant predictors. There is a need for a combined approach between medical and dental personnel towards HIV, as still, most of the times it is the treating general physician who performs the intraoral examination. All HIV-infected patients should be evaluated by oral medicine/dental specialist for presence of oral manifestations.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Adurogbanga MI, Aderinokum GA, Odaibo GN, Olaleye OD, Lawoyin TO (2004) Orofacial lesions and CD4+ counts associated with HIV/AIDS in an adult population in Oyo state, Nigeria. Oral Dis 10:319–326
2. Andrea MSM, Priepke F, Bergmann FJ, Reichat PA (2000) Decline in rate of oral opportunistic infections following introduction of highly active antiretroviral therapy. J Oral Pathol Med 29:336–341
3. Begg MD, Panageas MS, Mitchell-lewis D, Bucklan RS, Phelan JA, Lamster IB (1996) 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 82:276–283
4. Begg MD, Lamster IB, Panages MS, Mitchell-Lewis D, Phelan JA, Grbic JT (1997) A prospective study of oral lesions and their predictive value for progression of HIV disease. Oral Dis 3:176–183
5. Bendick C, Scheifele C, Reichart PA (2002) Oral manifestations in 101 Cambodian patients with HIV infection and AIDS. J Oral Pathol Med 31:1–4
6. Blanchaert RH (2000) Epidemiology of oral cancer. In: Ord RA, Blanchaert RH (eds) Oral cancer—the dentist's role in diagnosis, management, rehabilitation, and prevention, 1st edn. Quintessence publishing Co, Illinois, pp 3–8
7. Boulter A, Soltanpoor N, Swan AV (1996) Risk factors associated with Epstein–Barr Virus replication in oral epithelial cells of HIV-infected individuals. AIDS 10:935–940
8. Bravo IM, Correnti M, Escalona L, Perrone M, Brito A, Tovar V, Rivera H (2006) Prevalence of oral lesions in HIV patients related to CD4 cell count and viral load in a Venezuelan population. Med Oral Patol Oral Cir Bucal 11:E33–E39
9. Campo J, Del Romero J, Castilla J, Garcia S, Rodriguez C, Bacones A (2002) Oral candidiasis as a clinical marker related to viral load, CD4 lymphocyte count and CD4 lymphocyte percentage in HIV infected patients. J Oral Pathol Med 31:5–10
10. Ceballos-Salobrena A, Aguirre-Urizar JM, Bagan-Sebastian JV (1996) Oral manifestations associated with human immunodeficiency virus infection in a Spanish population. J Oral Pathol Med 25:523–526
11. Centers for disease control and prevention (CDC) (1992) 1993 revised classification for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 41:1–19
12. Chattopadhyay A, Caplan DJ, Slade GD, Shugars Dictions HC, Patton LL (2005) Incidence of oral candidiasis and oral hairy leukoplakia in HIV-infected adults in North Carolina. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 99:39–47
13. Dodd CL, Greenspan D, Katz MH, Westhausen JL, Feigal DW, Greenspan JS (1991) Oral candidiasis in HIV infection; pseudomembranous and erythematous candidiasis show similar rates of progression to AIDS. AIDS 5:1339–1343
14. EEC-Clearinghouse on oral problems related to HIV infection and WHO collaborating Centre on oral manifestations of the human immunodeficiency virus (1993) Classification and diagnostic criteria for oral lesions in HIV infection. J Oral Pathol Med 22:289–291
15. Glick M, Muzyka CB, Lurie D, Salkin LM, Camden NJ (1994) Oral manifestations associated with HIV-related disease as

markers for immune suppression and AIDS. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 77:344–349
16. Hilton JF, Donegan E, Katz MH et al (1998) Development of oral lesions in human immunodeficiency virus-infected transfusion recipients and hemophiliacs. Am J Epidemiol 145:164–174
17. Hodgson TA (1997) HIV-associated oral lesions: prevalence in Zambia. Oral Dis 3(suppl 1):S46–S50
18. Kerdpon D, Pongsiriwet S, Pangsomboon K, Iamaroon A, Kampoo K, Sretrirutchai S, Geater A, Robison V (2004) Oral manifestations of HIV infection in relation to clinical and CD4 immunological status in northern and southern Thai patients. Oral Dis 10:138–144
19. Khongkunthian P, Grote M, Isaratan W, Piyaworawong S, Reichart PA (2001) Oral manifestations in HIV positive adults from northern Thailand. J Oral Pathol Med 30:220–223
20. MacPhail LA, Komaroff E, Alves ME, Navazesh M, Phelan JA, Redford M (2002) Differences in risk factors among clinical types of oral candidiasis in the women's interagency HIV study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 93:45–55
21. Margiotta V, Campisis G, Mancuso S, Accurso V, Abbadesa V (1999) HIV infection: oral lesions, CD4 cell counts and viral load in an Italian study population. J Oral Pathol Med 28:173–177
22. McCarthy GM, Mackie ID, Koval J, Sandhu HS, Deley TD (1991) Factors associated with increased frequency of HIV-related oral candidiasis. J Oral Pathol Med 20:332–336
23. Muzyka BC, Kamwendo L, Mbewza E, Lopez NB, Glick M, Matheson PB et al (2001) Prevalence of HIV-1 and oral lesions in pregnant women in rural Malawi. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 92:56–61
24. Nielsen H, Bentsen KD, HØjtved L, Willemoes EH, Scheutz F, SchiØdt M et al (1994) Oral candidiasis and immune status of HIV infected patients. J Oral Pathol Med 23:140–143
25. Nittayananta W, Chanowanna N, Sripatanakul S, Winn T (2001) Risk factors associated with oral lesions in HIV infected heterosexual and drug abusers in Thailand. J Oral Pathol Med 30:224–230
26. Patton LL (2000) 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 Aug 90(2):182–188
27. Palacio H, Hilton JF, Canchola AJ, Greenspan D (1997) Effect of cigarette smoking on HIV-related oral lesions. J Acquir Immune Defic 14:338–342
28. Palmer GD, Robinson PG, Challacombe SJ, Birnbaum W, Croser D, Erridge PL et al (1996) Aetiological factors for oral manifestations of HIV. Oral Dis 2:193–197
29. Ramirez V, Gonzalez A, de la Rosa E, Gonzalez M, Rivera I, Hernandez C, Ponce de leon S (1990) Oral lesions in Mexican HIV-infected patients. J Oral Pathol Med 19:482–485
30. Ranganathan K, Umadevi M, Saraswathi TR, Kumaraswamy N, Solomon S, Johnson NW (2004) Oral lesions and conditions associated with human immunodeficiency virus infection in 1000 south Indian patients. Ann Acad Med Singapore 33(Suppl 1):S37–S42
31. Robinson PG, Challacombe SJ, Sheiham A, Zakrzewska JM (1997) Is erythematous candidiasis associated with advanced HIV disease? Oral Dis 3(suppl 1):S116–S118
32. Schiefele C, Reichart PA, Dietrich T (2003) Low prevalence of oral leukoplakia in a representative sample of the US population. Oral oncol 39:619–625
33. Sroussi HY, Villines D, Epstein J, Alves MCF, Alves MEAF (2007) Oral lesions in HIV-positive dental patients-one more argument for tobacco smoking cessation. Oral Dis 13:324–328
34. Talacko AA, Teo CG, Griffin BE, Johnson NW (1991) Epstein Barr virus receptors but not viral DNA are present in normal and malignant oral epithelium. J Oral Pathol Med 20:20–25
35. Umadevi KMR, Ranganathan K, Pavithra, Hemalatha R, Saraswati TR, Kumaraswamy N, Solomon S, Greenspan JS (2007) Oral lesions among persons with HIV disease with and without highly active antiretroviral therapy in southern India. J Oral Pathol Med 36:136–141
36. UNAIDS/WHO (2006) 2006 Report on the global AIDS epidemic: Executive summary. UNAIDS 10th anniversary special edition. WHO, Geneva, Switzerland
37. Valentine JA, Scott J, West ST Jr, Hill CA (1985) A histological analysis of early effects of alcohol and tobacco usage on human lingual epithelium. J Oral Pathol Med 14:654–665