

# Oral lesions in HIV infected individuals from Ribeirão Preto, Brazil

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## Abstract

**Objectives:** The aim of this study was to diagnosis oral lesions related to HIV infection in individuals followed in the General Hospital of the School of Medicine of Ribeirão Preto, University of São Paulo, Brazil. The presence of oral lesions was correlated with gender, age, smoking habit, levels of CD4 lymphocytes, HIV load, time of HIV seropositivity, AIDS condition, use of removable dental prosthesis, and use of HAART. **Materials and Methods:** 340 HIV infected individuals were selected for this study, all participants of the study were examined by only one practiced dentist which performed anamnesis, peribuccal and oral examination. **Results:** Oral lesions were observed in 113 of 340 (33.2%) HIV infected individuals. These oral lesions included: oral candidiasis (17.7%) of pseudomembranous (10.8%) and of erythematous types (6.9%), angular cheilitis (13.9%), hairy leukoplakia (11.8%), and oral ulcers (2.1%). Oral candidiasis lesions were more frequently observed in women (p.033). Smoking addict participants presented a high frequency of tongue hairy leukoplakia (p.038) and a reduced frequency of oral ulcers (p.018). Hairy leukoplakia and pseudomembranous candidiasis were inversely correlated to CD4+L levels and directly correlated with HIV load, behaving as immune depression markers. Hairy leukoplakia and pseudomembranous candidiasis also showed an inverse correlation with HAART use (p<.0001). Patients using mobile dental prosthesis presented a high frequency of erythematous candidiasis (p.003). **Conclusion:** The inverse correlation with CD4+L level and the direct correlation with HIV load suggest that oral lesions could be used as alternative clinical markers for poor immune condition in HIV infected individuals.

**Key words:** Oral lesions, HIV, AIDS, load viral, CD4+L level, HAART.

## Introduction

HIV is a Lentivirus of the Retroviridae that has lymphocytes and monocytes as target cells (1, 2), and is transmitted by contact with human contaminated fluids (3-5).

HIV, the etiologic agent of AIDS, has caused a huge outbreak with 38.6 million infections and 20 million deaths since the first description in 1981 thru 2003 (6). In Brazil, more than 360 000 AIDS cases were reported until 2004 (7).

Since 1996, the use of highly active antiretroviral therapy (HAART) has reduced fatalities and increased the quality of life of AIDS patients by decreasing the incidence of

opportunistic infections (8). Brazil supplies free antiretroviral therapy to AIDS patients since 1996 and only in 2005, about 170,000 individuals received HAART (9).

Oral lesions, most of them related to opportunistic pathogens, represent an important problem to AIDS patients (10, 11). The aim of this study was to diagnosis oral lesions related to HIV infection in individuals from Ribeirão Preto, SP, Brazil. The presence of oral lesions was correlated with gender, age, smoking habit, levels of CD4 lymphocytes, HIV load, time of HIV seropositivity, AIDS condition, use of removable dental prosthesis, and use of HAART.

## Materials and Methods

A number of 357 HIV infected individuals followed in the General Hospital of the School of Medicine of Ribeirão Preto, University of São Paulo (GH-SMRP-USP), and having more than 18 years old were selected for the study. Seventeen individuals that did not have CD4 lymphocyte counts performed in a period of 3 month before to 3 month after oral examination were excluded of the study. Therefore, 340 HIV infected individuals were selected for this study which was carried out from January 2004 to March 2006.

All participants of the study were examined by only one practiced dentist which performed anamnesis, peribuccal and oral examination as well as palpation of lymphonodes. The oral lesions were identified following the EC-Clearinghouse on Oral Problems Related to HIV Infection and WHO Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus, 1993 (12). Biopsies were performed only for diagnosis of five oral cancer suspected cases.

The protocol of this study was previously approved by the Ethics Committee of the GH-SMRP-USP and the HIV infected patients only participated of the study after learning on the study objectives and signing a consent document.

The prevalence of the distinct oral lesions was correlated to gender, age, smoking habit, time of HIV seropositivity, presence of removable dental prosthesis, CD4+ lymphocyte (CD4+L) levels, HIV load, AIDS condition (13) and regular use of HAART by the participants. Smoking habit was only considered in individuals that used tobacco every day, at any amount.

Only 288 participants were included in the analysis of oral lesions by fungus because 52 individuals were using antifungal drugs and therefore were excluded of the mycological analysis of the study.

Looking for a correlation between oral lesions with CD4 lymphocyte levels, it was used the t unpaired test. For the correlation of oral lesions with HIV load it was used the Mann-Whitney test. For other correlations of oral lesions, with gender, AIDS condition, use of removable dental prosthesis and use of HAART, chi squared and Fisher tests including Odds Ratio (OR) were used. For the correlation between oral lesions with age and time of HIV seropositivity, it was used the chi-squared test for trend. All statistical tests were considered significant when having a higher than 95% significance level ( $p < .05$ ). GraphPad 3.01 and GraphPad Prism 4.00 softwares (InStat, EUA) were used for this statistical analysis.

## Results

The 340 HIV infected individuals that participated of the study included 217 males (63.8%) and 123 females (36.1%), ranging from 18 to 77 years (median of 38 years). Two hundred seventy one participants (79.7%) referred a

regular use of HAART. Smoking habit was referred by 152 participants (44.7%). Three hundred participants (88.3%) had AIDS and, among them, opportunistic infections were referred by 285 (95 %). One hundred twenty three participants (36.2%) had removable dental prosthesis. These data are shown in Table 1.

Oral lesions were observed in 113 participants (33.2% positivity) and included angular cheilitis (AC), hairy leukoplakia (HL), pseudomembranous candidiasis (PC), erythematous candidiasis (EC) and oral ulcers (OU), as shown in Table 2

Women showed more oral candidiasis (26/109, 23.8%) than men (25/179, 14%) ( $p = .033$ ; OR: 1.93; confidential interval (CI): 1.048 – 3.553). Oral lesions occurred in participants at any age. OU was only observed in non-smoking participants (7/188, 3.72%,  $p = .018$ ). On the opposite, HL was more prevalent among smokers (24/152, 15.8%) than non-smokers (16/188, 8.5%,  $p = .038$ ; OR: 2.02; CI: 1.028 – 3.950).

Participants with oral lesions had 236 CD4+L/mm<sup>3</sup> of blood as average and it was significantly lower than the 352 CD4+L/mm<sup>3</sup> of blood average of those without oral lesions ( $p < .0001$ ; CI: 59.364 – 172.84). HL and PC were observed among participants having as averages 189 CD4+L/mm<sup>3</sup> of blood and 171 CD4+L/mm<sup>3</sup> of blood, respectively. For those that did not have HL or PC, CD4+L averages were 331 and 360 /mm<sup>3</sup> of blood respectively ( $p = .009$ ; IC: 58.655 – 225.750 for HL and  $p < .0001$ ; CI: 94.894 – 283.75 for PC), as shown in Table 3.

Medians of HIV loads in blood were distinct among participants having or not having oral lesions, 12311 virus copies/ml and 75 virus copies/ml ( $p < .0001$ ), respectively. HL and PC were associated to high HIV loads ( $p < .0001$ ) and were more frequent among those having median HIV loads higher than 56000 virus copies/ml of blood. Participants not having HP or PC showed median HIV loads under 110 virus copies/ml of blood, as shown in Table 3. PC was not observed in the 39 participants without AIDS ( $p = .020$ ).

AC was observed in participants having a shorter average time of HIV seropositivity (4.51 years) compared to those not having AC (6.16 years,  $p = .023$ ).

Oral lesions were more prevalent among participants using removable dental prosthesis (51/123, 41.4%) than in those not using this kind of prosthesis (62/217, 28.57%,  $p = .015$ ; OR: 1.77; CI: 1.113 – 2.817). EC was observed in 13.89% of the participants using removable dental prosthesis and in only 2.78% of those not using it ( $p = .0003$ ; OR: 5.64; CI: 1.989 – 16.022).

The prevalence of oral lesions among those participants using HAART (75/271, 27.67%) was significantly lower than this prevalence among those not using HAART (38/69, 55.07%,  $p < .0001$ ; OR: 0.18; CI: 0.181 – 0.537). QA and EC were more prevalent among participants not using HAART compared to those using it but this diffe-

**Table 1.** Data of HIV infected individuals that participated of the study.

Characteristics	Oral lesions				p value
	No.	(%)	Present	Absent	
Gender					0.6978
Male	217	64	70	147	
Female	123	36	43	80	
Age (years)					0.7735
18 – 30	45	13	19	26	
20 – 30	149	44	48	101	
30 – 40	102	30	27	75	
>50	44	13	19	25	
Smoking habit					0.0832
Yes	152	45	58	94	
No	188	55	55	133	
AIDS cases					0.1752
Yes	300	88	104	196	
No	40	12	9	31	
Time of AIDS diagnosis (years)					0.1577
0 – 3	113	33	43	70	
4 – 7	114	33,5	37	77	
8 – 11	73	21,5	22	51	
>12	40	12	11	29	
Use of dental prosthesis					0.0212*
Yes	123	36	51	72	
No	217	64	62	155	
Use of HAART					<0.0001*
yes	271	80	75	196	
No	69	20	38	31	

\* Statistically significant.

**Table 2.** Oral lesions observed in the HIV infected individuals that participated of the study.

Type of oral lesion	Number of patients having the lesion	Frequency (%)
Angular cheilitis*	40	13.9%
Hairy leukoplakia	40	11.8%
Pseudomembranous candidiasis *	31	10.8%
Erythematous candidiasis *	20	6.9%
Oral ulcerations	7	2.1%
Herpes simplex	3	0.9%
Kaposi's sarcoma	2	0.6%
Multifocal epithelial hyperplasia	1	0.3%
Pseudo-epithelial hyperplasia	1	0.3%
Melanic hiperpigmentation	1	0.3%
Lymphoma	1	0.3%
Median rombic glossitis	1	0.3%
Total of lesions/ total of participants**	148/340	

\* Only 288 individuals participated of this analysis. \*\*More than one type of oral lesion was found in some participants.

**Table 3.** Frequency of oral lesion in HIV-infected participants according to average CD4+L and median HIV load in blood.

Type of oral lesions*	Participants presenting oral lesion			Participants not presenting oral lesion		
	Average of CD4+L/mm <sup>3</sup>	Median of virus copies/ml	n°	Average of CD4+L/mm <sup>3</sup>	Median of virus copies/ml	n°
Angular cheilitis	303	455	40	345	159	248
Hairy leukoplakia**	189	56831	40	331	108	300
Pseud. candidíases**	171	58025	31	360	69	257
Erythem candidíases	330	383	20	340	207,5	268
Oral ulcerations	300	50	7	314	350	333
Herpes simplex	85	3136330	3	314	350	337
Kaposi's sarcoma	32	307593	2	316	326.50	338
Multifocal epithelial hyperplasia	124	50	1	315	350	339
Pseudo-epitelial hyperplasia	201	88908	1	314	350	339
Melanic hiperpigmentation	251	50	1	314	350	339
Lymphoma	353	20575	1	314	350	339
Median rombic glossite	211	116	1	316	350	339

\*More than one type of oral lesion was found in some participants. \*\* Statistically significant (p<0,009).

**Table 4.** Frequency of oral lesions in HIV-infected participants including use of HAART.

Type of oral lesions*	With HAART		Without HAART		p
	Present	Absent	Present	Absent	
Angular cheilitis	28	205	12	43	0.0587
Hairy leukoplakia	22	249	18	51	<0.0001**
Pseudomembranous candidiasis	17	216	14	41	<0.0001**
Erythematous candidiasis	13	220	7	48	0.0607
Oral ulcerations	6	265	1	68	1.00
Herpes simplex	1	270	2	67	0.1060
Kaposi's sarcoma	1	270	1	68	0.1060
Multifocal epithelial hyperplasia	1	37	0	43	0.4726
Pseudo-epitelial hiperplasia	1	270	0	69	1.00
Melanic hiperpigmentation	1	270	0	69	1.00
Lymphoma	0	271	1	68	0.2053
Median rombic glossite	1	270	0	69	1.00

\* More than one type of oral lesion was found in some participants. \*\* Statistically significant.

rence was not statistically significant (p.058 and p.060). HL and CP were less prevalent among participants using HAART compared to those not using it (p< .0001; OR 0.25; CI: 0.1253 – 0.5001 for HL and p<.0001; OR 0.23; CI: 0.105 – 0.504 for CP). The frequency of each oral lesion also including the association with use of HAART, is shown in Table 4.

**Discussion**

About 80% of the participants of the study were using HAART regularly. This high frequency of HAART use is probably stimulated by the offer of free antiretroviral medication by the Brazilian Ministry of Health. This is

different of what happens in other third world countries such as Cambodia where patients have to purchase the anti-retroviral drugs and only 8.9% of them used HAART (14). However, despite of HAART use, systemic opportunistic infections were observed in 84% of the participants of the present study and it could be explained by the characteristics of this HIV infected population, which had relevant health problems. That is the reason they were forwarded into the GH-SMRP-USP, a hospital that offers tertiary level assistance. Unfortunately, it was not possible to discriminate types and time of use of antiretroviral drugs by the participants of the present study. Oral lesions were observed in 33.2% of the participants.

The oral lesions more frequently observed were AC, HL, PC and EC. Other authors also reported a high frequency of oral candidiasis in HIV infected individuals. Ramirez-Amador et al (15), in Mexico, found high frequencies of EC and PC. Anteyi et al (16), in Nigeria, detected more frequently PC and AC.

Candidiasis lesions are usually caused by *Candida albicans*, and are described as a precocious manifestation of AIDS (17, 18). In the present study, oral candidiasis was more prevalent in females (23.85%) than in males (13.97%,  $p=0.033$ ) as previously reported by Campisi et al (19) in Italy, where 34.8% of women and 12.2% of men presented these lesions. The authors suggest that the occurrence of oral candidiasis could be gender-related. HL was more frequent among men (12.9%) than in women, but this difference was not statistically significant. Patton et al (20) observed that HL was significantly more frequent among men. The high prevalence of HL, as reported by Ammatuna et al (21), should be related to a possible higher specificity of Epstein-Barr virus to oral epithelium of males.

Oral lesions were observed in HIV infected participants at all ages without predominance, as previously reported in England by Eyeson et al (22). However, Sharma et al (23), in India, observed a higher risk of HL among individuals under 35 years old.

AC was the most prevalent oral lesion (13.9%) in the present study and it was associated to a short time of HIV seropositivity ( $p=0.023$ ), as previously reported by Bendick et al (14), in Cambodia. Nevertheless, reasons for this association are unknown.

The total oral lesions were more frequently observed among smoker participants (38.16%) than among non-smokers (26.25%), but without statistical significance ( $p=0.08$ ). However, HL was positively related to smoking habit ( $p=0.038$ ). On the opposite OU was only observed in non-smokers ( $p=0.018$ ). Bendick et al (14), in Cambodia, also reported OU in non-smokers only. Muzyka and Glick (24) pointed that smokers have a large keratin layer at oral mucosa and it could protect to OU. Palacio et al, in 1997 (25), reported that the smoking habit increased the frequency of oral lesions, especially oral candidiasis and oral warts.

Oral lesions, especially EC, were more frequent among those participants using removable dental prosthesis ( $p=0.021$  for oral lesions and  $p=0.0003$  for EC). These lesions are probably caused by *Candida* sheltered in the irregular surface of the prosthesis (26), especially, in those that do not hygienize it properly (27).

The prevalence of oral lesions was inversely correlated with CD4+L levels of the participants, especially for HL and PC ( $p<0.0001$  for PC and  $p=0.009$  for HL). Therefore, the occurrence of HL and PC could alert for immune depression of HIV infected patients as previously observed by Miziara et al in 2006 (28), and Ramirez-Amador et

al in 2001 (29). The last authors reported HL and PC as reliable clinical markers of immune depression.

In the present study, the presence of oral lesions and specially HL and PC, were correlated to high HIV load ( $p<0.0001$ ). Adurogbangba et al (30) in Nigeria, Ramirez-Amador et al (15) in Mexico, and Bravo et al (31) in Venezuela also reported the same association. In the present study, PC was only observed in AIDS patients ( $p=0.019$ ). AIDS participants at C3 and B3 stage levels (13), had their oral lesions positively correlated with high HIV viremia and immune depression, both occurring in severe forms of the disease. Some authors reported oral lesions appearing early in the disease and behaving as precocious indicators of the immune depression of AIDS (32,33). Therefore, the incidence of oral lesions in HIV infected patients could be an useful tool to evaluate AIDS progression into a severe disease, especially in places where CD4+L count and HIV load exams are not available (34-36).

A reduction on the prevalence of oral lesions has been reported in AIDS patients using HAART (22, 34, 36, 37). In the present study, the regular use of HAART, probably, reduced the prevalence of oral lesions and specially, reduced HL and PC, which were significantly less frequent in these participants. The reduction of oral lesions is related to the immunity recovery obtained by the use of HAART (22, 34). Moura et al in 2006 (38) in Brazil, also reported that the regular use of HAART protected AIDS patients of HL. A similar report was also made by Nicolatou-Galitis et al in 2004 (39) in Greece, which reinforced the importance of HIV protease-inhibitor drugs on reducing oral lesions.

In short, we show that oral lesions are common in Brazilian HIV infected individuals and that these lesions are related to different individual characteristics. It is also shown that the regular use of HAART reduces the prevalence of oral lesions, and that oral lesions behave as immune depression markers which could be helpful for the management of AIDS patients.

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