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Oral lesions associated with HIV infection before and during the antiretroviral therapy era in Ribeirão Preto, Brazil

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Abstract: We estimated the prevalence of oral lesions associated with human immunodeficiency virus (HIV-OLs) before and during the antiretroviral therapy (ART) era. The first period was 1997, when many patients received two types of antiretroviral (ARV) drugs. The second study period was 2004 through 2008, when all patients were treated with ART (a combination of two or three classes of drugs, including protease inhibitors). A total of 148 and 388 seropositive participants were examined in 1997 and 2004-2008, respectively. The evaluation consisted of anamnesis and physical examination. The prevalence of HIV-OLs decreased between 1997 (60.1%) and 2004-2008 (29.9%). The HIV-OL responsible for the greatest reduction in prevalence between the two periods was oral candidiasis, of which erythematous candidiasis was the clinical form that decreased most, followed by pseudomembranous candidiasis. In conclusion, we observed a significant reduction in HIV-OLs, which was closely associated with the use of ART. In addition, among patients with a clinical diagnosis of AIDS, we confirmed a significant reduction in HIV-OL prevalence between 1997 and 2004-2008. (J Oral Sci 53, 379-385, 2011)

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Introduction

Acquired immunodeficiency syndrome (AIDS) is a severe disease and is the late manifestation of human immunodeficiency virus (HIV) infection (1-3). It has been estimated that 33.4 million people are infected by HIV worldwide (4). In Brazil, 544,846 cases were reported from 1980 through 2009 and 217,091 deaths occurred between 1980 and 2008 (5).

In 1986, the capacity of zidovudine (AZT) to inhibit HIV replication was discovered, and the Brazilian government authorized the free distribution of this drug in 1992 (6). In 1996, the efficacy of antiretroviral therapy (ART) in treating HIV was proved. ART, which has been defined as the combination of two or three classes of drugs (7), reduced the number of deaths and significantly increased quality of life among people with AIDS (8, 9). In 1996, the Brazilian government signed a law establishing the free distribution of AZT, which gave HIV-seropositive patients access to antiretroviral (ARV) drugs. Later, and particularly after 2001, the Brazilian government was able to markedly reduce the prices of ARV drugs by means of patent infringement. Such efforts further increased the distribution of these medicines by the public health network. The number of patients receiving free ARV drugs through the public health system was 55,600 in 1997, 73,000 in 1999, and approximately 105,000 in 2001 (7).

Table 1 Characteristics of study participants

Characteristics	1997		2004-2008		*P*
	n	%	*n*	%	
Average age	33		38		0.0001*
Duration of seropositivity	2.8		6		0.0001*
Men	93	62.8%	239	61.6%	0.7915
Women	55	37.2%	149	38.4%	0.7915
$CD4^+L$ count	193		323		0.0001*
Smoker	115	77.7%	169	43.6%	0.0001*
Use of ARV	47	31.7%	0	0%	0.0001*
Use of ART	18	12.2%	310	79.9%	0.0001*
No ARV/ART	83	56.1%	78	20.1%	0.0001*
No. of participants	148		388		

ARV: antiretroviral, ART: antiretroviral therapy, *statistically significant

In the Clinical Hospital of the School of Medicine of Ribeirão Preto, University of São Paulo, Brazil (CH-SMRP-USP), where this study was conducted, ARV drugs started to be freely and efficiently distributed in 1996. In that year, with the advent of ART, only those patients who were not having good results with one or two ARVs were switched to ART, whereas therapy was unchanged for patients who remained stable on a regimen of one or two ARV drugs. Gradually, the number of patients on ART increased and encompassed nearly all patients receiving ARVs by 2004.

Oral lesions are associated with HIV progression and were described in the first cases of HIV infection (10,11). HIV-associated oral lesions (HIV-OLs) result from reduced immunity among infected individuals, which permits the development of diseases deriving from opportunistic pathogens (12). Sometimes they present as the initial manifestations of AIDS and can precede systemic diseases (13,14). HIV-OLs can also exacerbate systemic symptoms, such as weight loss and diarrhea, that are common among individuals with HIV (12,15-18). Because many HIV-OLs are easily visualized and diagnosed on the basis of their clinical characteristics, they are excellent indicators of an individual's immune status and permit evaluation of the extent of immunologic involvement (18-21).

The objective of the present study was to compare the prevalence of HIV-OLs during two time periods at CH-SMRP-USP. The first period was 1997, when many of the patients followed at the CH-SMRP-USP received two kinds of ARV drugs and only the most severe cases received ART. The second period was 2004 through 2008, when all patients receiving ARV drugs were treated with ART.

Subjects and Methods

An epidemiologic study was performed during two time periods to determine the prevalence of HIV-OLs among HIV-seropositive patients that were followed-up at the CH-SMRP-USP. A total of 148 and 388 seropositive participants were examined in 1997 and 2004-2008, respectively, and the participants evaluated in 2004-2008 were not necessarily those who were seen in 1997. The other inclusion criteria were age older than 18 years and data on recent T CD4 lymphocyte counts (CD4+L) 3 months before and 3 months after an oral exam.

The same methodology and same criteria for classification of HIV-OLs were used during both time periods. Evaluation of the participants comprised anamnesis, lymph node palpation, perioral examination, and oral examination. HIV-OLs were identified according to the criteria of the EC-Clearinghouse on Oral Problems Related to HIV Infection and the WHO Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus, 1993 (22). The protocols of these studies were previously approved by the Ethics Committee of CH-SMRP-USP, and all patients gave written informed consent to participate.

Treatment that included one or more antiretroviral agents including nucleosides but excluding protease inhibitors was defined as antiretroviral (ARV) drug treatment, and treatment that included one or more antiretroviral agents plus protease inhibitors was defined as ART.

The software packages GraphPad 3.01 (GraphPad Software Inc., San Diego, CA, USA) and GraphPad Prism 4.00 were used for the statistical analysis. Variables such as age, duration of seropositivity time, and $CD4^+L$ count were analyzed using the Student t-test, and data normality was verified using histograms constructed

Table 2 Numbers of patients with oral lesions in 1997 and 2004-2008

Oral lesions	1997		2004-2008		*P*	OR	95% CI
	n	%	*n*	%			
Erythematous candidiasis	38	25.7%	25	6.4%	0.0001*	5.016	(2.900-8.677)
Pseudomembranous candidiasis	27	18.2%	36	9.3%	0.004*	2.182	(1.271-3.745)
Angular cheilitis	15	10.1%	46	11.9%	0.6828	0.8385	(0.4527-1.553)
Hairy leukoplakia	19	12.8%	40	10.3%	0.4953	1.281	(0.7157-2.294)
Herpes simplex	4	2.7%	3	0.8%	0.1823	3.565	(0.7879-16.129)
Oral ulcers	4	2.7%	7	1.8%	0.7525	1.512	(0.4359-5.244)
Oral Kaposi's sarcoma	0	0.0%	2	0.5%	0.9340	0.5205	(0.02483-10.915)
Swelling of salivary glands	1	0,7%	0	0.0%	0.6162	7.902	(0.3198-195.21)
Multifocal epithelial hyperplasia	0	0.0%	1	0.3%	0.5365	0.8698	(0.03521-21.488)
Oral lymphoma	0	0.0%	1	0.3%	0.5365	0.8698	(0.03521-21.488)
Oral condyloma	0	0.0%	1	0.3%	0.5365	0.8698	(0.03521-21.488)
No. of participants with HIV-OLs**	89	60.1%	116	29.9%	0.0001*	3.865	(2.585-5.777)
No. of participants	148		388				

OR: odds ratio, CI: confidence interval

* statistically significant, **Some participants had more than one type of HIV-OL

with the Microsoft Excel program (Microsoft Office Excel 2007, Redmond, WA, USA). Variables such as smoking, sex, ARV/ART use, and presence of HIV-OLs were analyzed using the chi-square test, which was also used to compare HIV-OL prevalence in the two study periods. To measure the correlation between HIV-OLs and different ARV schemes in 1997, we used the chi-square test for independent samples. A *P* value of 0.05 or less was considered to indicate statistical significance.

Results

The relevant demographic and clinical characteristics of the seropositive patients, i.e., age, $CD4^+$L count, smoking status, and ARV use, differed between the two study periods; the ratio of men to women was similar (Table 1). The mean age of participants increased from 33 years in 1997 to 38 years in 2004-2008 ($P < 0.0001$). We also observed a significant increase in the time of HIV seropositivity, from 2.8 years in 1997 to 6 years in 2004-2008 ($P < 0.0001$). Average CD4+L count also increased, from 193 cells/mm^3 in 1997 to 323 cells/mm^3 in 2004-2008 ($P < 0.0001$).

In 1997, among the 148 patients studied, 93 (62.8%) were men and 55 (37.2%) were women, and the proportions were similar in 2004-2008, when 239 (61.6%) of the 388 patients studied were men and 149 (38.4%) were women ($P = 0.7915$; OR, 1.054; 95% CI, 0.7128-1.559). We also observed a significant reduction in the number of patients who smoked, from 115/148 (77.7%) in 1997 to 169/388 (43.6%) in 2004-2008 ($P < 0.0001$; OR, 4.516; 95% CI, 2.920-6.984). In 1997, 83/148 (56.1%) of participants did not receive ARV or ART, 47/148 (31.7%) received ARVs, and only 18/148 participants (12.2%) received ART. In 2004-2008, 310/388 (79.9%) participants received ART and 78/388 (20.1%) did not.

We observed a significant reduction in the prevalence of HIV-OLs between 1997 and 2004-2008. In 1997, HIV-OL prevalence was 89/148 (60.1%); in 2004-2008, it was 116/388 (29.9%; $P < 0.0001$; OR, 3.865; 95% CI, 2.585 – 5.777) (Table 2). The most important HIV-OLs detected during both 1997 and 2004-2008 were pseudomembranous candidiasis (PC), erythematous candidiasis (EC), angular cheilitis (AC), hairy leukoplakia (HL), and oral ulcers (OU; Table 2). Oral candidiasis (OC) was the HIV-OL with the greatest reduction in prevalence between the two study periods. Regarding the clinical forms of OC, EC had the greatest reduction in prevalence, from 38/148 (25.7%) in 1997 to 25/388 (6.4%) in 2004-2008 ($P < 0.0001$; OR, 5.016; 95% CI, 2.900 – 8.677), followed by PC, the prevalence of which decreased from 27/148 (18.2%) in 1997 to 36/388 (9.3%) in 2004-2008 ($P = 0.004$; OR, 2.182; 95% CI, 1.271 – 3.745). AC did not decrease between periods, with 15/148 cases (10.1%) in 1997 and 46/388 (11.9%) in 2004-2008 ($P = 0.6828$; OR, 0.8385; 95% CI, 0.4527 – 1.553).

Although we observed an improvement in patient immunity between 1997 and 2004-2008, HL prevalence did not significantly decrease between periods, with

Table 3 ARV use and HIV-OLs

Antiretroviral regimen	Total no. of patients	HIV-OLs (no.)	HIV-OLs	*P*
1997				
ARVs	47	36	76.6%	0.0011*
ART	18	14	77.8%	
No ARV/ART	83	39	47.0%	
2004-2008				
ARVs	0	0	0%	
ART	310	76	24.5%	<0.0001*
No ART	78	40	51.3%	

ARV: antiretroviral, ART: antiretroviral therapy, * statistically significant

Table 4 AIDS status and HIV-OLs

	No. of participants	HIV-OLs (no.)	HIV-OLs	*P*	OR	95% CI
No AIDS						
1997	15	2	13.3%	0.4561	0.5385	(0.1038 -2.794)
2004-2008	45	10	22.2%			
AIDS						
1997	133	87	65.4%	<0.0001*	3.701	(2.428 - 5.642)
2004-2008	343	116	33.8%			

OR: odds ratio, CI: confidence interval, * statistically significant

19/148 cases (12.8%) in 1997 and 40/388 (10.3%) in 2004-2008 (P = 0.4953; OR, 1.281; 95% CI, 0.7157 – 2.294). The prevalences of other HIV-OLs were similar in 1997 and 2004-2008.

In 1997, patients who were not receiving ARV/ART had a lower prevalence of HIV-OLs than did those who were (P = 0.0011; Table 3). In 1997, 39/83 (47%) of patients not receiving ARV drugs developed HIV-OLs, whereas the prevalence of HIV-OLs was higher among patients receiving ART: 77.8% (14/18). We observed HIV-OLs in 76.6% (36/47) of patients receiving ARVs. In contrast, in 2004-2008, the prevalence of HIV-OLs was higher in patients not receiving ARV or ART (P < 0.0001; OR, 3.241; 95% CI, 1.938 – 5.419). Forty (51.3%) of the 78 patients not receiving ART developed HIV-OLs, and 76 (24.5%) of the 310 participants receiving ART developed HIV-OLs. It is important to mention that the prevalence of HIV-OLs among patients who did not receive ARVs did not change between study periods. In 1997, 39/83 (47%) patients not receiving ARVs developed HIV-OLs, and a similar prevalence was noted in 2004-2008, when 40/78 (51.3%) of those not receiving ARVs developed HIV-OLs (P = 0.5860; OR, 0.8420; 95% CI, 0.4534 – 1.564). Regarding the relation between HIV-OL occurrence and a clinical diagnosis of AIDS, we observed that patients without a clinical diagnosis of AIDS had a similar prevalence of HIV-OLs in both study periods (P = 0.4561; OR, 0.5385; 95% CI, 0.1038 – 2.794). In 1997, 2 (13.3%) of the 15 participants without a clinical diagnosis of AIDS developed an HIV-OL, and in 2004-2008, 10 (22.2%) of 45 participants without a clinical diagnosis of AIDS developed HIV-OLs. Patients with a clinical diagnosis of AIDS in 1997 had a higher prevalence of HIV-OLs than did those studied in 2004-2008 (P < 0.0001; OR, 3.701; 95% CI, 2.428 – 5.642). In 1997, 87 (65.4%) of the 133 participants with a clinical diagnosis of AIDS developed HIV-OLs, whereas in 2004-2008, the prevalence of HIV-OLs was 116 (33.8%) of 343 participants (Table 4).

Discussion

The prevalence of HIV-OLs differs by country. The AIDS epidemic has been discussed in relation to its medical context (15,23-28) and epidemiologic and socio-economic characteristics (29-31); however, few studies have described the prevalence of HIV-OL in Brazil, especially with regard to changes in the prevalence of HIV-OL that occurred with the advent of ART era (32).

Since 1992, and to a greater extent since 1996, the Ministry of Health has guaranteed free access to ARVs

for people with AIDS living in Brazil (7,33). In 2001, the Brazilian government infringed patents to obtain a large reduction in the cost of ARVs, from US $303 million in 2000 to US $232 million in 2001 (7).

ART, which began in 1996 after the discovery of new classes of ARVs, eg, protease inhibitors, was the beginning of a new phase in AIDS treatment. It radically changed the quality of life of seropositive patients, because treatment now controlled viral load while drastically decreasing the resistance of HIV to ARVs (34).

In CH-SMRP-USP, the site of the present study, patients started to receive ARVs free of charge in 1996, which was the same year that some patients began ART. However, only patients who did not respond to the use of one or two ARVs received ART. Gradually, ART was provided to all patients who used ARVs. In 1997, most patients on ARVs received a combination of two nucleoside reverse transcriptase inhibitors (NRTIs)—comprising mainly AZT, dideoxyinosine (DDI), and dideoxycytidine (DDC). In 2004-2008, all patients on ARVs received a combination of drugs—an NRTI; a non-nucleoside reverse transcriptase inhibitor (NNRTI), mainly efavirenz and nevirapine; and protease inhibitors (PI), mainly saquinavir, indinavir, ritonavir, nelfinavir, and lopinavir. The quality of life of patients greatly improved with ART, as indicated by the increase in average age from 33 years in 1997 to 38 years in 2004-2008 and by the increase in the duration of HIV-1 seropositivity, from 2.8 years in 1997 to 6 years in 2004-2008. We also observed an increase in patient immunity: CD4+L count increased from 193 cells/mm^3 in 1997 to 323 cells/mm^3 in 2004-2008. Smoking reduction policies also succeeded in reducing the number of smoking patients from 77.7% in 1997 to 43.6% in 2004-2008. The male/female ratio was stable between study periods.

There was a significant reduction in the number of patients with HIV-OLs, from 89/148 (60.1%) in 1997 to 116/388 (29.9%) in 2004-2008, in agreement with other studies (35-39). In 1997, HIV-OLs were present in patients receiving ARVs, probably because these drugs were mainly given to patients with complications of HIV infection and also because most patients were receiving ARVs rather than ART. Of the 65 participants receiving ARV therapy in 1997, 73% were receiving ARVs and only 27% were receiving ART. It is important to mention that the patients receiving ART were those who had not satisfactorily responded to ARVs. Thus, because ART was indicated mainly for the most severe cases, HIV-OLs were predominant in this group in 1997. The opposite situation existed in 2004-2008: all patients receiving ARVs were being treated using the ART scheme. The prevalence of HIV-OLs was 24.5% (76/310) among patients receiving ART and 51.3% (40/78) among those not receiving ART. The prevalence of HIV-OLs was similar among patients not receiving ARV: 47% in 1997 and 51.3% in 2004-2008. We conclude that the reduced prevalence of HIV-OLs was due to ART use.

The populations studied in 1997 and 2004-2008 differed in age and the proportion of smokers. In 1997 average age was 33 years, while in 2004-2008 it was 38 years. The incidence of oral lesions might be associated with age; however, we believe that a 5-year difference in age is too small to result in a significant difference.

A 1997 study by Palacio et al. (40) found that smoking was related to increased prevalence of OC in HIV-seropositive patients; thus, the lower percentage of smokers observed in the present study in 2004-2008 might be associated with the lower prevalence of OC. The oral lesion with the greatest decrease in prevalence was OC, especially the erythematous form (from 25.7% in 1997 to 6.4% in 2004-2008) and pseudomembranous form (from 18.2% in 1997 to 9.3% in 2004-2008). Many studies have observed a decrease in HIV-OLs with ART use (37,39,41,42). In 2009, Ortega et al. (32) noted a reduction in OC prevalence, from 34% 1996 to just 2.2% in 2006 among seropositive patients. In a 2007 cohort case-control study in Mexico City, Ramirez-Amador et al. (43) analyzed 1134 individuals and detected a lower OC prevalence among those who were regularly receiving ART. The authors considered the presence of OC to be an excellent marker of virologic failure in patients receiving ART. Lourenço and Figueiredo in 2008 (23) and Miziara and Weber in 2006 (41) showed that OC was more prevalent among patients with a low CD4+L count and high viral loads.

We found no reduction in HL prevalence between the two study periods. HL prevalence was 12.8% in 1997 and 10.3% in 2004- 2008 ($P = 0.4953$; OR, 1.281; 95% CI, 0.7157 – 2.294), in contrasts to the findings of Ortega et al. (2009) (32), who noted a reduction in HL, from 16.3% in 1996 to 0% in 2004-2008. We also observed no difference in the prevalence of AC between 1997 and 2004-2008. AC was observed in 15 (10.1%) of 148 participants in 1997 and 46 (11.9%) of 388 participants in 2004-2008. Although AC is an HIV-OL, other factors such as tooth loss and loss of vertical dimension might have contributed to the persistence of this HIV-OL (44).

In 1997, 65.4% of participants with a clinical diagnosis of AIDS developed HIV-OLs; in 2004-2008, this number decreased to 33.8% ($P < 0.0001$), which shows the efficacy of ART in decreasing the incidence of HIV-OLs, even among patients with HIV-related complications.

In summary, we observed a significant reduction in

HIV-OLs, which was closely related to the use of ART. The oral lesion with the greatest decrease in prevalence was oral candidiasis, especially the erythematous and pseudomembranous forms. In addition, we observed a significant reduction in the prevalence of oral lesions in patients with a clinical diagnosis of AIDS.

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