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Gender differences in oral manifestations among HIV-infected Brazilian adults

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Aim: The purpose of this study was to compare gender differences in the prevalence of oral lesions in HIV-infected Brazilian adults. **Methodology:** A retrospective study was conducted of medical records from HIV/AIDS patients from 1993 to 2004. Oral lesions were only included in this study if definitively diagnosed through microscopic analysis, therapeutic test or according to EC-Clearinghouse criteria. **Results:** A total of 750 men and 237 women were included in the study. Statistically significant differences were observed only for oral hairy leukoplakia, Kaposi sarcoma and lymphadenopathy ($P < 0.01$). However, a model of logistic regression showed that only oral hairy leukoplakia presented a significant association with gender and males had a significantly likelihood (four times higher than females) of presenting with this oral manifestation [OR 4.3 (95% CI: 1.39–13.36)]. **Conclusion:** These data shows that oral manifestations are less prevalent in females than in males, particularly oral hairy leukoplakia.

Key words: *HIV-infections, oral manifestations, women*

INTRODUCTION

Recently, a growing trend of women infected with human immunodeficiency virus (HIV) worldwide has been observed. In 2008, it was reported that about 15.7 million adult women were living with the virus – about 1.6 million more than in 2001[1]. This situation is more alarming in sub-Saharan Africa, which has more women than men living with HIV. Latin America, Asia and Eastern Europe have presented a slower growth[1]. In Brazil, data have indicated that the number of infected women has also showed an increasing trend in recent years, particularly in poorer populations[2]. This trend was similarly reported by Ferreira *et al.*[3] in a study on oral manifestations in Brazilian HIV-infected individuals.

Oral lesions are frequently observed in HIV-infected patients and are considered to be markers of disease progression and immunosuppression[4–7]. Candidiasis and oral hairy leukoplakia are among the most prevalent oral lesions associated with HIV infection, especially among patients not receiving highly active antiretroviral therapy (HAART) and with low absolute TCD4+ counts[3,5]. Gender differences also influence the prevalence of oral manifestations of HIV/acquired immune deficiency syndrome (AIDS). Some studies have shown a higher prevalence of oral hairy leukoplakia and Kaposi sarcoma in men, while linear gingival erythema and aphthous ulcers were more frequently identified in women[3,4,8]. However, despite there being an increasing prevalence of HIV-infected women in the world, a lower incidence of oral lesions is observed in this group of patients. Thus, the purpose of this study was to compare gender differences in the prevalence of oral lesions in a referral centre for the dental treatment of patients with HIV in Rio de Janeiro, Brazil.

MATERIALS AND METHODS

The study protocol was submitted to the Ethical Research Committee of the University Hospital Clementino Fraga Filho/Federal University of Rio de Janeiro (HUCFF/UFRJ) and approved by document CEP MEMO/HUCFF no 692/04. The research was conducted in full accordance with the World Medical Association Declaration of Helsinki.

A retrospective study was conducted of medical records of HIV/AIDS patients who attended the

University Hospital Clementino Fraga Filho and the Dental School of the Federal University of Rio de Janeiro from 1993 to 2004. All subjects were informed about the aims, risks and benefits of the study and signed a consent form. Written consent was obtained from the parents of minors involved. Data were obtained from an anamnesis questionnaire, the patient's medical record and by oral examination during two visits. This information included: gender, mode of HIV transmission, history of AIDS-defining opportunistic infections, monthly familial income, level of education, socio-economic status, tobacco, alcohol and drug use (recreational and injecting drug), type of antiretroviral therapy, TCD4 counts, viral load and presence, site and type of HIV-associated oral lesions. All patients with HIV/AIDS older than 13 years of age were included in the study. Patients were excluded if the medical record contained insufficient data on HIV status, gender, pregnancy or oral manifestations.

Oral examinations were conducted in a dental chair by a dental oral pathology specialist under halogen lighting, using a dental mirror, gauze and tongue depressors. Oral lesions were only included in this study if definitively diagnosed through cytopathology, histopathology analysis, therapeutic tests or according to EC-Clearinghouse and World Health Organisation (WHO) criteria[9]. Immunological laboratory values were considered only if obtained from blood work performed 3 months before or 1 month after the oral examination.

Statistical analysis

All of the statistical tests were carried out using the SPSS package (SPSS, Statistical Package for the Social Sciences, release 17.0; SPSS, Inc., Chicago, IL, USA). Descriptive analyses of the sociodemographic and laboratory data were performed. Statistically significant differences were sought using the chi-square test and Fisher exact test. Multivariate logistic regression analyses (backward stepwise method) were performed to assess the association between gender and each systemic and oral manifestation adjusted for potential confounders. In the logistic regression analyses, the variables that presented statistically significant differences between males and females were used. The statistical significance level established was 5% for all analyses.

RESULTS

Socio-demographic data

A total of 987 patients were included in the study: 750 men (76%) and 237 women (24%). *Table 1* shows the sociodemographic data between males and females ($P < 0.05$, χ^2). There were statistically significant differences between males and females for all variables. Most male (91.7%) and female (92.8%) individuals were 20–49 years of age. In 163 (16.5%) cases, there were no data regarding the educational levels of patients. Among the remaining 824 individuals (83.5%), a higher prevalence of subjects had completed secondary education (30%), with 50 (25.8%) females and 197 (31.3%) males having achieved this level. A significant difference was observed between genders regarding level of education, with 57.5% of males having completed secondary education and either completed or not completed third-level education, while only 39.7% of females had similar levels of education ($P = 0.0003$). Information regarding monthly family income was lacking in 653 (66.2%) patients. The remaining 174 (52.1%) received two minimum wages (MW) or lower (59 females and 115 males).

Information about tobacco use was missing from 263 (26.6%) records. Four hundred and eighteen

Table 1 Sociodemographic data of the study population by gender

Variable	Male *n* (%)	Female *n* (%)	*P*
Patients	750 (76)	237 (24)	
Age (years)			
13–19	3 (0.4)	5 (2.1)	0.037
20–29	184 (24.5)	70 (29.5)	
30–39	334 (44.5)	96 (40.5)	
40–49	170 (22.7)	54 (22.8)	
Above 50	59 (7.9)	12 (5.1)	
Monthly family income(MW)*			
2	115 (48.9)	59 (59.6)	0.048
3–4	65 (27.7)	27 (27.3)	
5–9	39 (16.6)	8 (8.1)	
10–19	14 (0.6)	2 (2.0)	
≥20	2 (0.9)	3 (3.0)	
Education levels†			
Illiterate	9 (1.4)	6 (3.1)	<0.001
Incomplete primary level	97 (15.4)	44 (22.7)	
Complete primary level	111 (17.6)	50 (25.8)	
Incomplete secondary level	51 (8.1)	17 (8.8)	
Complete secondary level	197 (31.3)	50 (25.8)	
Incomplete/complete third level	165 (26.2)	27 (13.9)	
Tobacco use‡			
Non-smoker	304 (55.7)	114 (64.0)	0.042
1–10 cigarettes/day	138 (25.3)	49 (27.5)	
11–20 cigarettes/day	67 (12.3)	9 (5.1)	
>20 cigarettes/day	37 (6.8)	6 (3.4)	
Alcohol consumption§			
Never	277 (56.3)	122 (74.8)	<0.001
1–2 dose/week	189 (38.4)	39 (23.9)	
3–4 dose/week	4 (0.8)	0 (0)	
≥5 dose/week	22 (4.5)	2 (1.2)	

P values refer to Fisher's exact test.
*Data available for 334 individuals.
†Data available for 824 individuals.
‡Data available for 724 individuals.
§Data available for 655 individuals.

individuals were non-smokers (304 male and 114 female), while 43 smoked more than 20 cigarettes per day (37 male and 6 female). The data on alcohol consumption were absent from 332 (33.6%) records. Among the remaining 655 individuals, 256 (39.1%; 41 female and 215 male) reported alcoholism.

Profile of HIV-infection and laboratory data

Table 2 shows the profile of HIV-infection and laboratory data of the study population separated by gender. There were statistically significant differences only for the variables of drug use ($P = 0.0004$) and antiretroviral therapy ($P = 0.028$). The majority of individuals, of both gender, showed absolute TCD4+ levels between 200 and 500 cells/mm^3, while more than 30% of males and females demonstrated a viral load > 30.000 cp/ml.

Systemic and oral clinical data

Table 3 shows the frequency of systemic manifestations between males and females. These were less prevalent in women than in men (49.4–66.7%; data not shown). Tuberculosis was the most frequently diagnosed systemic condition (22.8%, 229 cases), followed by syphilis (17.7%, 178 cases), *Pneumocystis* pneumonia (16.2% , 162 cases) and *Herpes zoster* (7.4%, 149 cases). When the frequency of each systemic manifestation was compared between male and female patients, statistically significant differences were observed only for syphilis ($P = 0.0001$), Kaposi sarcoma ($P = 0.0001$) and cytomegalovirus ($P = 0.016$), with frequencies among males of 20.4%, 7.0% and 6.1%, respectively, and frequencies among females of 9.5%, 0.8%, and 2.5%, respectively.

The frequencies of oral manifestations are shown in *Table 4*. Oral candidiasis was the most frequently diagnosed oral manifestation (pseudomembranous candidiasis being the most prevalent; 31.9%, 320 cases), followed by hairy leukoplakia (7.8%, 78 cases), necrotising periodontal disease (5.0%, 50 cases) and Kaposi sarcoma (4.4%, 44 cases). In general, males demonstrated a higher frequency of oral manifestations than female individuals (data not shown). However, when we compared the frequency of each oral lesion between males and females, statistically significant differences were observed only for oral hairy leukoplakia ($P = 0.003$), Kaposi sarcoma ($P = 0.001$) and lymphadenopathy ($P = 0.003$), with frequencies among males of 9.1%, 5.5% and 0%, respectively, and frequencies among females of 3.7%, 0.8% and 1.6%, respectively.

Final models of adjusted multivariate logistic regression analyses on the association between gender and systemic and oral manifestations are presented in *Table 5*. This Table shows only data on oral hairy leukoplakia because it was the unique clinical condition that demonstrated statistically significant association with gender after adjusting for age, monthly family income, education levels, tobacco use, alcohol consumption, drug use and antiretroviral therapy. The results of multivariate analysis showed that males had a significantly likelihood (four times higher than females) of presenting with oral hairy leukoplakia.

Table 2 Profile of human immunodeficiency virus (HIV) infection and laboratory data of the study population by gender

Variable	Male *n* (%)	Female *n* (%)	*P*
Drugs user (recreational and injecting drug)*			
No	394 (77.0)	140 (89.7)	0.0004
Yes	118 (23.0)	16 (10.3)	
Antiretroviral therapy			
No therapy	413 (54.3)	128 (52.7)	0.028
Monotherapy	117 (14.4)	22 (9.1)	
Dual therapy	60 (7.9)	25 (10.3)	
HAART	170 (22.4)	68 (28.0)	
TCD4 cell count†			
<200	82 (36.1)	34 (29.8)	0.497
200–500	103 (45.4)	58 (50.9)	
>500	42 (18.5)	22 (19.3)	
Viral load‡			
Undetectable	37 (22.0)	13 (16.5)	0.320
<10,000	62 (36.9)	28 (35.4)	
10,000–30,000	12 (7.1)	11 (13.9)	
>30,000	57 (33.9)	27 (34.2)	

HAART, highly active anti-retroviral therapy.
P values refer to Chi-square test.
*Data available for 668 individuals.
†Data available for 341 individuals (cells/mm^3).
‡Data available for 247 individuals (cp/ml of blood).

Table 3 Frequency of systemic manifestations between males and females of the study population

Systemic manifestations	*n* (%)	Male *n* (%)	Female *n* (%)	*P*
Tuberculosis*	229 (22.8)	182 (23.9)	47 (19.3)	0.137
Syphilis*	178 (17.7)	155 (20.4)	23 (9.5)	<0.001
Pneumocystis pneumonia *	162 (16.2)	132 (17.4)	30 (12.3)	0.064
*Herpes zoster**	149 (7.4)	122 (16.1)	27 (11.1)	0.059
*Herpes simplex**	124 (12.4)	91 (12.0)	33 (13.6)	0.508
Toxoplasmosis*	101 (10.1)	75 (9.9)	26 (10.7)	0.708
Kaposi Sarcoma†	55 (5.5)	53 (7.0)	2 (0.8)	<0.001
Cytomegalovirus†	52 (5.2)	46 (6.1)	6 (2.5)	0.016
Cryptococcosis†	21 (2.1)	13 (1.7)	8 (3.3)	0.194
Primary lymphoma of the CNS†	19 (1.9)	13 (1.7)	6 (2.5)	0.426

CNS, central nervous system.
*Chi-square test.
†Fisher's exact test.

Table 4 Frequency of oral manifestations between males and females of the study population

Oral manifestation	*n* (%)	Male *n* (%)	Female *n* (%)	*P*
Candidiasis	320 (31.9)	250 (32.9)	70 (28.8)	
Pseudomembranous*	201 (20)	159 (20.9)	42 (17.3)	0.218
Erythematous*	151 (15.1)	115 (15.1)	36 (14.8)	0.904
Angular cheilitis*	74 (7.4)	55 (7.2)	19 (7.8)	0.763
Oral hairy leukoplakia*	78 (7.8)	69 (9.1)	9 (3.7)	0.003
Necrotising periodontal disease	50 (5.0)	39 (5.1)	11 (4.5)	
Necrotising gingivitis†	15 (1.5)	11 (1.4)	4 (1.6)	0.824
Necrotising periodontitis†	16 (1.6)	13 (1.7)	3 (1.2)	0.606
Gingival linear erythema†	25 (2.5)	21 (2.8)	4 (1.6)	0.478
Kaposi sarcoma†	44 (4.4)	42 (5.5)	2 (0.8)	0.001
Recurrent aphthous ulcers*	40 (4.0)	29 (3.8)	11 (4.5)	0.622
Unspecific ulcers†	24 (2.4)	19 (2.5)	5 (2.1)	0.813
Herpes virus infection	19 (1.9)	15 (2.0)	4 (1.6)	
Labial herpes†	13 (1.3)	10 (1.3)	3 (1.2)	0.922
Herpetic stomatitis†	6 (0.6)	5 (0.7)	1 (0.4)	0.665
Papillomatous lesions†	8 (0.8)	7 (0.9)	1 (0.4)	0.688
Lymphadenopathy†	4 (0.4)	0 (0.0)	4 (1.6)	0.003

*Chi-square test.
†Fisher's exact test.

Table 5 Final model of multivariate logistic regression analyses (backward stepwise method) the association between gender and oral hairy leukoplakia adjusted for potential confounders

Variable	Oral hairy leukoplakia		*P* value	Adjusted OR (CI 95%)
	Yes	No		
Gender*				
Female	9 (11.5)	228 (25.1)	0.003	1
Male	69 (88.5)	681 (74.9)		4.3 (1.39–13.36)
Age (years)†				
13–19	0 (0)	8 (0.9)	0.880	1
20–29	29 (23.6)	225 (25.9)		1.13 (0.68–1.88)
30–39	27 (49.1)	403 (43.2)		0.95 (0.54–1.70)
40–49	18 (20.0)	206 (22.9)		0.95 (0.42–2.12)
Above 50	4 (7.3)	67 (7.1)		0.95 (0.37–2.41)
Education levels†‡				
Illiterate	5 (7.1)	10 (1.3)	0.040	1
Incomplete primary level	11 (15.7)	130 (17.2)		0.55 (0.84–3.61)
Complete primary level	9 (12.9)	152 (20.2)		0.06 (0.01–0.87)
Incomplete secondary level	8 (11.4)	60 (8.0)		0.95 (0.133–6.81)
Complete secondary level	21 (30.0)	226 (30.0)		0.45 (0.06–3.08)
Incomplete/complete third level	16 (22.9)	176 (23.3)		1.07 (0.14–7.84)

*Chi-square test.
†Fisher's exact test.
‡Data available for 824 individuals.

DISCUSSION

An increasing number of studies have been published showing a worrying increase in HIV-infected women in Sub-Saharan African countries. This trend can be attributed to several causes, for example gender inequality in different societies can lead women to assume a submissive position with a sexual partner and thus accept refusal by a sexual partner to use condoms. In addition, sexual violence, prejudice, low socio-economic status and lack of perception to the risks of infection can also explain this increasing prevalence in women[10,11].

In the current study, 987 individuals were analysed, 750 of which were male and 237 female. These numbers are in accord with several studies that found a higher prevalence of men among HIV-infected individuals[4,12–21]. Although this study presents a lower prevalence for women than for men, when evaluating the frequency over the years a trend towards an increasing number of women and a declining number of infected men from the early 1990s was observed.

Patients aged between 30 years and 39 years had the the greatest prevalence of HIV infection in both genders. This result is similar to the majority of previous studies[14,16,18,22–24]. It was also observed that

there was a slight increase of younger women patients in comparison with men. Some studies describe a higher prevalence of HIV-infected women of 20–30 years of age[4,10,13,25]. This can be explained by the fact that in these studies the majority of the younger women were infected through intravenous drug use. In the present study, the main route of exposure was sexual.

Overall, lower educational levels were expected in this study population, but it was demonstrated that the majority of both men and women had completed secondary education and either completed or did not complete third level education. However, there was a significant difference between males and females with regard to education, with females having a lower level of education. Of the 987 individuals in the present study, it was possible to obtain information about monthly family income for 334. Of both men and women, the majority had a monthly family income of 0–2 minimum wages. Ranganathan *et al.*[4] reported that most women (75%) were domestic, and a study by Sharma *et al.*[8] reported that most patients were poor and illiterate. Combining these data gives clues to the impoverishment of AIDS, which has been reported by the Brazilian Ministry of Health[10]. This also reflects spread of HIV infection to rural areas, thus reaching a population with little resources, poorer education and lower employment and, therefore, with a much lower income than residents of large urban centres[10].

The habits of these individuals was assessed and it was observed that male patients smoked ($P = 0.011$) and consumed alcohol ($P = 0.001$) significantly more than women; these findings are in agreement with studies by Bendick *et al.*[14] The frequency of drug users was 20.1% and male use was significantly higher than use by women (23% *vs.* 10.3%; $P = 0.0004$), which is similar to the results of Souza *et al.*[13]

A history of systemic manifestations was observed in 62.5% of the individuals and was less frequent in women than in men (49.4–66.7%; data not shown), which is in agreement with findings by Bendick *et al.*[14] and Ranganathan *et al.*[4] Tuberculosis, for example, has been described as the most frequent AIDS-defining illness[4,14,26]. In the current study, tuberculosis was also the most prevalent condition, representing 22.8% (229 cases). Nevertheless, of all systemic manifestations documented, only syphilis, Kaposi sarcoma and cytomegalovirus were significantly more prevalent in men than women. However, this was not observed after the multivariate logistic regression adjusted for potential confounders.

Regional differences may also influence a higher frequency of certain systemic manifestations related to AIDS in different studies; for example, in African countries, Kaposi sarcoma is more common[16,27,28]. Another important issue to be considered is the availability of antiretroviral drugs. In Brazil, these drugs are available and distributed for HIV-infected patients, while for many countries this represents a major difficulty, particularly in other developing countries[29–32]. As antiretroviral therapy is very important for controlling opportunistic infections, this is a factor that needs to be considered in the prevalence of systemic manifestations in HIV-infected individuals[33].

In the present study, 54.8% of the patients did not use any type of antiretroviral therapy, with about the same proportion among men and women. Similar results were found by Khongkunthian *et al.*[22] and Sharma *et al.*[8], while Lourenço & Figueiredo[21] found a higher proportion (79.7%) of patients undergoing HAART. For most of these individuals, no antiretroviral therapy was administered during the first study period, from 1993 to 1995. In the same period, 100% of women received no therapy and over the remaining periods assessed the prevalence of women receiving no therapy was higher than that of men. The use of HAART in this sample has only been observed from 1997 onwards. Before this time these patients were not undergoing antiretroviral therapy, or were receiving monotherapy or dual therapy, as HAART was not yet available in the centre where this study was conducted. Therefore, only 24.1% of patients have benefited from HAART, with protease inhibitors (PI) being the most widely used by both men and women.

No statistically significant difference was observed between men and women regarding viral load and absolute TCD4 levels. Laboratory results were not determinants when the frequency of oral manifestations between men and women was compared. The data for viral load were available during the same period as when the patient started HAART but, unlike this study, no other study was found that compared both oral manifestations and viral load between men and women[4,12,14,22,23].

Few studies have described the prevalence of oral manifestations in HIV-infected women[22]. Of the 987 individuals studied, 458 (47.4%) patients had oral lesions and, of these, men formed the majority (48.4% men, 37% women). This trend was observed in several studies, which showed that women were less affected by oral manifestations than were men[4,13,15,16,21,34,35]. This can be explained by the fact that oral manifestations in women are diagnosed at an earlier stage of HIV infection and women have a greater concern with adherence to medications, their health and personal hygiene, especially oral care. In addition, some HIV-associated lesions have a lower predisposition in women, such as Kaposi sarcoma, which has been related to hormonal protection in females[25]. In this study, men showed a higher

prevalence of oral lesions than women, particularly oral hairy leukoplakia ($P = 0.003$) and Kaposi sarcoma ($P = 0.001$). This is in agreement with a study by Patton *et al.*[34] In contrast, lymphadenopathy was observed only in women ($P = 0.003$). A model of logistic regression was performed and these findings were not totally confirmed. In fact, only oral hairy leukoplakia presented a significant association with gender and males had a significantly greater likelihood (four times higher than females) of presenting this condition (OR 4.3, 95% CI 1.39–13.36). This oral manifestation was the second most prevalent lesion observed in this study (7.8% of patients). A higher prevalence of this lesion has been observed among smokers[8,21,36,37] and drinkers[17]. However, in the present study, the variables tobacco use and alcohol consumption did not contribute to the outcome of oral hairy leukoplakia in the logistic regression model (*Table 5*).

Oral candidiasis has been shown to be the most prevalent oral lesion in HIV-infected individuals[13,21–23]. Similar findings were observed in the present study, with a prevalence of 31.9%. Males were affected more than females, although other studies have reported a higher prevalence of this lesion among women[21,38]. Pseudomembranous candidiasis has been frequently more detected than other(s) forms of candidiasis (erythematous and angular cheilitis)[4,23]. The present study found similar results, but they were not significantly more prevalent in males than in females. In addition, the three forms of oral candidiasis were associated with the absence of antiretroviral therapy, absolute TCD4+ lymphocytes $< 200/mm^3$ and high levels of viral load in both genders (data not shown), as observed in others studies[39,40].

Several studies have demonstrated a change in the clinical behaviour of oral manifestations in HIV patients with the introduction of HAART. This initiated a reduction in lesions strongly associated with AIDS[26,41–43], and the emergence of new forms of the *Human papilloma virus* (HPV) lesions that some authors consider to be the result or side-effect of HAART[15] or a form of immune reconstitution syndrome[44,45]. In the current study, although we observed eight cases of papillomatous lesions, it would be unwise to say that these are a result of the above, as they were present in both the period before and the period after HAART and should be explored further to prove their relation to HIV infection.

The similarities and differences of the data found in this study regarding the international literature may have a large number of complex explanations. Often the comparison of data here was made difficult because of the differing variables for each study. Thereby prospective studies are needed to confirm these findings.

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Conflicts of interest

None declared.

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