Rev Saúde Pública 2013;47(1):52-9

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Risk factors of HIV-related oral lesions in adults

Fatores de risco de lesões bucais associadas ao HIV em adultos

ABSTRACT

OBJECTIVE: To assess the risk factors in the occurrence of oral lesions in HIV-positive adults.

METHODS: A retrospective analytical-descriptive survey was conducted using the medical/dental records of 534 patients with oral lesions associated with HIV. The data were collected from five referral centers for managing HIV and associated comorbidities in the city of Porto Alegre, Southern Brazil, between 1996 and 2011. Using a standardized form, socio-demographic and clinical data were recorded. Exclusively and definitively diagnosed oral pathologies were included and classified according to ECC criteria on Oral Problems Related to HIV Infection. For data analysis cross-tabulations, Chi-squared tests and logistic regression models were used where appropriate.

RESULTS: CD4+ counts lower than 350 cells/mm³ ($p < 0.001$), alcohol consumption ($p = 0.011$) and female gender ($p = 0.031$) were predisposing factors for oral candidiasis. The occurrence of hairy leukoplakia was independently associated with CD4+ counts below 500 cells/mm³, ($p = 0.029$) a viral load above 5,000 copies/mm³ ($p = 0.003$) and smoking ($p = 0.005$).

CONCLUSIONS: Moderate and severe degrees of immunodeficiency and detectable viral loads were risk factors for the onset of oral lesions. Smoking and alcohol consumption also increased susceptibility to the development of opportunistic infections in HIV-positive adults from Porto Alegre, irrespective of the use of antiretroviral therapy.

DESCRIPTORS: AIDS-Related Opportunistic Infections, epidemiology. Oral Manifestations. Risk Factors. HIV Infections. Acquired Immunodeficiency Syndrome. Cross-Sectional Studies.

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Received: 4/18/2012
Approved: 7/23/2012

Article available from: www.scielo.br/rsp

RESUMO

OBJETIVO: Analisar fatores de risco para a ocorrência de lesões bucais em adultos soropositivos para o HIV.

MÉTODOS: Estudo transversal, descritivo analítico de prontuários médicos/odontológicos de 534 pacientes com lesões bucais associadas ao HIV em Porto Alegre, RS, no período de 1996 a 2011. Os dados foram coletados em cinco centros de referência em saúde para o atendimento de portadores do HIV e comorbidades associadas. Os dados sociodemográficos e clínico-laboratoriais foram coletados em formulários padronizados. Foram incluídos dados exclusivamente de lesões com diagnóstico definitivo e classificadas de acordo com os critérios da *ECC on Oral Problems Related to HIV Infection*. A análise dos dados foi realizada mediante a aplicação de tabulações cruzadas, teste do Qui-quadrado e modelos de regressão logística.

RESULTADOS: Níveis de CD4+ < 350 células/mm³ (p < 0,001), consumo de álcool (p = 0,011) e sexo feminino (p = 0,031) foram predisponentes para candidíase bucal. A ocorrência de leucoplasia pilosa foi associada com contagens de CD4+ < 500 células/mm³ (p = 0,029), cargas virais > 5.000 cópias/mm³ (p = 0,003) e tabagismo (p = 0,005).

CONCLUSÕES: Graus de imunodeficiência moderados e severos e cargas virais detectáveis foram fatores de risco para o desenvolvimento de lesões bucais. O consumo de tabaco e álcool aumentou a suscetibilidade de desenvolver infecções oportunistas em adultos HIV positivos, independentemente do uso de terapia antirretroviral.

DESCRITORES: Infecções Oportunistas Relacionadas com a AIDS, epidemiologia. Manifestações Bucais. Fatores de Risco. Infecções por HIV. Síndrome de Imunodeficiência Adquirida. Estudos Transversais.

INTRODUCTION

Porto Alegre, in Southern Brazil, is the city which has the highest incidence of AIDS in Brazil (99.8:100,000 inhabitants) since 2006.[a] Around 21,000 cases of this syndrome had been reported reported by 2010 and occurred mostly in adults (98.5%) with a 38.7% mortality rate. HIV/AIDS remains a major public health problem in this city, attributed principally to diagnosis in late stages of the disease, delayed commencement of highly active antiretroviral therapy (HAART) and poor treatment compliment.[b]

HIV causes the infected host to become susceptible to a wide spectrum of life-threatening secondary infections, malignant neoplasms and other disorders.[1] The development of oral tissue lesions associated with HIV is a frequent clinical finding in Brazil.[21] Despite the use of HAART, more than 50% of HIV/AIDS carriers present opportunistic infections in the oral cavity.[10] Especially oral candidiasis (OC) and hairy leukoplakia (HL) which are considered to be of the utmost importance in the diagnosis and prognosis of HIV infection as well as in predicting therapy failure.[11,14] An increased risk of developing HIV-associated oral manifestations in Brazilian samples has been associated with low CD4 counts, high viral load (VL) levels, low income and schooling and addiction to tobacco and alcohol.[6,15] However, variations may be expected due to the heterogeneity of studied populations and the dynamic spread of HIV infection.

It is pertinent to determine the risk factors that lead to the onset of oral pathologies. This knowledge will allow a better understanding of the course of HIV infection and consequently, allow identification of subjects that are at risk of developing oral affections and contributing to prevention and patient management.

Despite the elevated incidence of AIDS in adults from Porto Alegre, there are few studies available that evaluate risk factors for oral affections in HIV-positive

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adults, especially with regard to VL.[21] This study aimed to assess the risk factors for the occurrence of oral lesions in HIV-positive adults.

METHODS

The survey methodology was based on guidelines for the epidemiological study of oral lesions associated with HIV infection provided by the World Health Organization (WHO).[9] We retrospectively reviewed the records of 534 HIV-positive adults who received medical or dental treatment at five referral health centers in Porto Alegre city, Southern Brazil, between 1996 and 2011. Only the records of subjects that matched predetermined inclusion criteria were sampled: aged 15 or over, an HIV-positive exam independently confirmed by two enzyme-linked immunosorbent assay or western blot tests and the occurrence of any oral lesions at the time of the HIV diagnosis or during the course of the disease progression. The obtainability of sociodemographical, laboratory and clinical data were also considered for inclusion.

The included patients had been previously examined as a part of their routine medical management of HIV or other related illnesses. The oral evaluation of these patients was performed under non standardized physical assets by a non-calibrated infectologists or dentist specialized in oral medicine. The professionals were experienced in the management of HIV seropositive patients and in diagnosing related comorbidities, including oral manifestations of HIV/AIDS. Only the affections that were definitively diagnosed by their clinical features alone or those which were absolutely diagnosed through the completion of additional clinical and laboratory tests, according to the parameters of the WHO[9] were included in the current survey. The data collection was classified according to the criteria of EC-Clearinghouse on Oral Problems Related to HIV Infection.[5]

Sociodemographic (age, gender, race, marital status, occupation and tobacco, alcohol and illegal drug consumption), clinical (HIV-related oral lesions, antiretroviral therapy use) and laboratory (quantitative CD4+ cell count and VL) data were recorded using a standardized form. The considered information was that which was determined closest to the date of the oral lesion appearance with a maximum range of six months before and after.[3,16]

With regard to the risk factors related to an unhealthy lifestyle (use of tobacco, alcohol and illicit drugs), the subjects were classified as users (who reported using legal or illegal substances in a period within six months before the onset of these affections) or non-users (who stopped the consumption of the noxious substances six months before the occurrence of oral lesions), according to data available on medical records.[16]

Categorical variables were described by counts and percentages with a 95% confidence interval (95%CI) and binomial distribution. Quantitative variables with symmetrical distribution were described using mean and standard deviation (sd), and the variables with asymmetrical distributions were described using median and percentiles. Comparisons were analyzed using cross-tabulation, the Chi-square test and a multivariate logistic regression model that was adjusted for confounding factors. $P \leq 0.05$ was determined to be statistically significant.

Subject age was treated as a quantitative continuous variable and non-parametrically included in the logistic regression models. The sociodemographic characteristics: gender (reference: masculine), race (reference: Caucasian), alcohol, tobacco and illicit drugs use (reference: non user) were equally considered as nominal and dichotomous. The categorical variables: CD4+ count ($\geq$ 500 cells/mm^3, 350 to 500 cells/mm^3, $<$ 350 cells/mm^3), VL level ($>$ 20,000 copies/mm^3, 5,001 to 20,000 copies/mm^3, 51 to 5,000 copies/mm^3, $\leq$ 50 copies/mm^3) and HAART use (compliant, noncompliant, not prescribed) were parametrically included in the regression models.

The data analyses were performed using the Statistical Package for the Social Sciences (SPSS®, Chicago, IL, USA) version 18.0 software program for Windows.

The study was conducted in compliance with the principles of the Helsinski Declaration and in agreement with the Brazilian-specific normative for research involving human subjects nº 196/96. It was also approved by the institutional review board of each participating institution *Serviço de Estomatologia e Prevenção do Câncer Bucomaxilofacial e Serviço de Infectologia do Hospital São Lucas*, Process nº 0092/2010, approved on November 17th, 2010; *Centro de Especialidades Odontológicas do Hopital Nossa Senhora da Conceição*, Process nº 11/011, approved on March 16th, 2011, *Centro de Saúde Vila dos Comerciários*, Process nº 0010003281116, approved on February 8th, 2011 and *Centro de Testagem e Aconselhamento do Hospital Sanatório Partenon,* approved on April 8th, 2011; CAAE- 0392.0.002.164-11).

RESULTS

Of the 534 medical records, 51.7% of the patients were male, which resulted in a 1.1:1 male-to-female ratio. The mean age was 42.9 (sd = 11) years old, 68% of the subjects were Caucasian, 61.5% were single and 35.0% did not have any job connections. The demographic characteristics of the evaluated subjects were not statistically different in gender ($p = 0.328$), age ($p = 0.069$), race ($p = 0.295$), marital status ($p = 0.099$) or occupation ($p = 0.182$), although they came from five different health centers.

Most of the oral lesions were diagnosed at a routine consultation, while 31.5% were observed during hospitalization. The median of CD4+ counts and VL of the patients sample was 242 cells/mm³ and 4,191 copies/mm³, respectively (Table 1).

The use of HAART was mentioned in the medical records of 61.0% of patients; of those, 69.3% were in compliance with the treatment at the time of oral lesion occurrence. Poor adherence to the HAART was described in 30.7% of the patients' records. However, 38.6% had not previously used antiretroviral drugs. A combination of two nucleoside reverse transcriptase inhibitor plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) (Lamivudine/Zidovudine plus Efavirenz) were used for 50.0% of the treated individuals. Women were more susceptible to OC than men (OR 0.66, 95%CI 0.45;0.96, p = 0.031), and OC was also associated with chronic alcohol consumption (OR 2.38, 95%CI 1.22;4.67, p = 0.011). HL (OR 2.85, 95%CI 1.38;5.88, p = 0.005) was strongly associated with tobacco use. No correlations were observed between the different oral lesions and the proposed risk factors in the logistic regression analysis (Tables 2 and 3).

DISCUSSION

Moderate and severe degrees of immunodeficiency and detectable viral loads were risk factors for the onset of oral lesions, irrespective of the use of HAART in Southern Brazil. Smoking and alcohol consumption contributed to a high susceptibility to the development of these affections in the evaluated subjects.

Table 1. The most prevalent oral lesions with respect to CD4+ and VL ranges. Porto Alegre, Southern Brazil, 2012.

Lesion	CD4+ (cells/mm³) (n = 534)						Viral load (copies/mm³) (n = 534)							
	< 350 (n = 351)		350-500 (n = 82)		> 500 (n = 101)		≤ 50 (n = 158)		51-5,000 (n = 118)		5,001-20,000 (n = 92)		> 20,000 (n = 166)	
	f	%	f	%	f	%	f	%	f	%	f	%	f	%
OC	207	59.0	37	45.1	23	22.8	48	30.4	62	52.5	57	62.0	100	60.2
HL	42	12.0	10	12.2	1	1.0	5	3.2	8	6.8	22	23.9	18	10.8
KS	10	2.8	2	2.4	0	0.0	3	1.9	2	1.7	1	1.1	6	3.6
HSI	24	6.8	3	3.7	18	17.8	15	9.5	12	10.2	6	6.5	12	7.2
AOU	21	6.0	9	11.0	7	6.9	13	8.2	10	8.5	6	6.5	8	4.8
MP	10	2.8	4	4.9	12	11.9	14	8.9	7	5.9	2	2.2	3	1.8
LYM	45	12.8	14	17.1	9	8.9	22	13.9	12	10.2	10	10.9	24	14.5

OC: oral candidiasis (all types); HL: hairy leukoplakia; KS: Kaposi's sarcoma; HSI: herpes simplex infection; AOU: atypical oral ulceration; MP: melanocytic pigmentation; LYM: lymphadenitis

Table 2. Logistic regression models for oral candidiasis. Porto Alegre, Southern Brazil, 2012.

Variable		Univariate analysis			Multivariate analysis		
	n	OR	95%CI	p	OR	95%CI	p
CD4+ (cells/mm³)							
> 500 (reference)	23	1			1		
350 to 500	37	2.79	1.47;5.27	0.002	2.47	1.26;4.84	0.009
< 350	207	4.88	2.92;8.13	< 0.001	3.82	2.16;6.77	< 0.001
VL (copies/mm³)							
≤ 50 (reference)	48	1			1		
51-5,000	62	2.54	1.55;4.16	< 0.001	1.63	0.88;3.03	0.124
5,001-20,000	57	3.73	2.17;6.41	< 0.001	1.99	0.90;4.37	0.089
> 20,000	100	3.47	2.19;5.50	< 0.001	1.53	0.70;3.36	0.290
HAART							
Compliant (reference)	66	1			1		
Noncompliant	120	3.11	1.91;5.07	< 0.001	1.74	0.86;3.50	0.124
Not prescribed	81	2.70	1.83;3.99	< 0.001	1.70	0.90;3.20	0.103

OR: odds ratio obtained in a logistic regression model including the following terms: age, gender (male), race (Caucasian), smoking habit, alcohol consumption, illegaldrug use. Confidence interval; p ≤ 0.05: statistical significance

Table 3. Logistic regression models for hairy leukoplakia. Porto Alegre, Southern Brazil, 2012.

Variable		Univariate analysis			Multivariate analysis		
	n	OR	95%CI	p	OR	95%CI	p
CD4+ (cells/mm³)							
> 500 (reference)	1	1			1		
350 to 500	10	13.89	1.73;110.9	0.013	10.57	1.27;87.92	0.029
< 350	42	13.59	1.84;100.0	0.010	8.48	1.10;65.54	0.040
VL (copies/mm³)							
≤ 50 (reference)	5	1			1		
51-5,000	8	2.22	0.71;6.99	0.170	1.97	0.56;6.99	0.293
5,001-20,000	22	9.62	3.50;26.44	<0.001	8.02	2.04;31.52	0.003
> 20,000	18	3.72	1.35;10.28	0.011	3.29	0.78;13.93	0.105
HAART							
Compliant (reference)	13	1			1		
Noncompliant	10	1.82	0.77;4.30	0.172	0.58	0.19;1.83	0.353
Not prescribed	30	2.79	1.41;5.52	0.003	1.05	0.38;2.87	0.928

OR: odds ratio obtained in a logistic regression model including the following terms: age, gender (male), race (Caucasian), smoking habit, alcohol consumption, illegaldrug use. Confidence interval; $p \leq 0.05$: statistical significance

No previous studies which evaluated a sample with similar characteristics or with the same scope had been conducted previously in this city, which has the greatest incidence of AIDS in Brazil.[a] One report evaluated the associations among HIV-associated oral lesions and CD4+ counts in 42 adults, inpatients, carriers of HIV and tuberculosis from Porto Alegre.[21] The literature on this subject is scarce in the state.[6,10]

OC and HL have been associated with HIV since the beginning of the epidemic, but their prevalence has decreased after HAART began to be used. This fact is attributed to immune reconstitution accomplishment after viral replication cessation due to the use of HAART.[14] Our data indicate that OC and HL were the most common opportunistic infections, even among treated patients. These results confirm previous estimates obtained in surveys from Porto Alegre[21] and other Brazilian reports.[14,15]

The univariate analyses showed that the subjects with moderate (OR 2.79, 95%CI 1.47;5.27, p = 0.002) and severe (OR 4.88, 95%CI 2.92;8.13, p < 0.001) degrees of immunosuppression were more susceptible to developing OC than those with mild or no immunologic impairment. These associations were also found in the multivariate analyses adjusted for several confounding factors, which demonstrated that patients with CD4+ counts between 350 and 500 cells/mm³ (OR 2.47, 95%CI 1.26;4.84, p = 0.009) and under 350 cells/mm³ (OR 3.83, 95%CI 2.16;6.77, p < 0.001) had a statistically significantly increased risk of developing OC than those with CD4+ counts higher than 500 cells/mm³.

Our data did not support the results of Volkweis et al in relation to the association between OC occurrence and immunosuppression.[21] Similar findings were reported by Aleixo et al[2] and Lourenço & Figueiredo.[8]

A mild immunologic impairment (CD4+ 350 to 500 cells/mm³) was sufficient to increase the risk of developing HL nearly 11-fold (OR 10.57, 95%CI 1.27;87.92, p = 0.029). The multivariate logistic regression model showed that immunologic deficiency could be considered to be an independently associated risk factor for the onset of these lesions, and similar statistics from Brazil confirm this hypothesis.[11,18] Moura et al[12] which assessed the risk factors for HL in HIV-positive adults from Brazil, did not find a relationship between CD4+ counts and this opportunistic infection. Among the 53 carriers of HL observed, one presented CD4+ counts above 500 cells/mm³. The heterogeneous distribution of the sample may be responsible for the high OR values (Table 3).

The univariate model (Table 2) suggested that detectable VL (> 50 copies/mm³) was a risk factor for OC compared with undetectable circulating HIV-RNA. When this association is investigated together with CD4+ counts and use of HAART in a multivariate analysis, detectable VL did not augment the susceptibility of developing this fungal infection. Of the 267 patients who developed OC, 100 presented circulating HIV-RNA levels that were higher than 20,000 copies/mm.³ Despite the absence of significance, the VL range of 5,001 to 20,000 copies/mm³ increased the risk of developing OC nearly 2-fold. Yielded the p (p = 0.089) and the extensive confidence interval (0.90;4.37), the correlation between elevated VL and OC could not be conclusively excluded, despite the sample size and elevated number of adjustment factors.

HL was directly influenced by the progression of the infection. A VL level between 5,001 to 20,000 copies/mm³ was independently associated with an augmented risk of developing HL (OR 8.02, 95%CI 2.04;31.52, p = 0.003) in the multivariate analysis. A longitudinal prospective study from Mexico, which provided the first follow-up evaluation of the association of OC and HL with CD4+ counts and VL levels, showed that the occurrence of these pathologies is preceded by a sustained reduction of lymphocyte counts and an abrupt viral burden.[16]

Individuals with high VL levels may present a complete depletion of mucosal Langerhans cells, and this localized cytopathic effect causes the impairment of mucosal immunologic protection. This cellular event is associated with fungal and viral colonisation events (especially Epstein-Barr) in HIV-positive patients.[5] The salivary levels of HIV-RNA may be higher than the plasma levels if they are enhanced by local inflammatory conditions, which leads to the increased prevalence of oral manifestations.[17]

We acquired data from medical charts and the laboratory index considered included six-month intervals before and after the appearance of oral lesions. It is possible that elevations in VL levels and decreases in CD4+ cell count were not temporally coincident.[3]

The present study did not find that OC and HL were inversely and significantly associated with HAART use. This result is in contrast with other studies, which effectively considered these therapeutic agents as protection factors against oral lesions.[14,16] Most patients who received HAART were treated with a drug combination that contained an NNRTI (Efavirenz). Ortega et al[14] and da Silva et al[18] observed a lower prevalence of oral lesions in patients undergoing HAART with NNRTI than patients who were treated with protease inhibitors. Therapy failure due to ineffectiveness or inadequate compliance, which was elevated among the observed patients, may explain our results.

The chronic consumption of alcoholic drinks was considered to be a risk factor for OC occurrence (OR = 2.38; CI = 1.22 to 4.67; p = 0.011), and the patients who smoked had the highest risk of developing HL (OR = 2.85; CI = 1.38 to 5.88; p = 0.005), which was independent of their CD4+ counts and VL levels.

Candida albicans oxidizes salivary ethanol, which leads to a high level of acetaldehyde production. This product affects the oral mucosa by augmenting its permeability, causing atrophic areas on the surface of the epithelia that became poor in extracellular lipids due to alcohol use. Glucose concentrations of 18 g/dL easily obtained from drinks increase biofilm formation and *C.albicans* adhesion, which facilitates OC occurrence.[20]

The components of cigarette smoke may induce chronic inflammation on the oral mucosae, cause damage to the innate immunity mechanisms against pathogens and inhibit cell growth by apoptosis mechanisms. These effects of smoking reduce the production of salivary enzymes and immunoglobulins and affect the production of lymphocytes, resulting in an imbalance of the oral microflora. These modifications probably encourage EBV infectivity, promoting the occurrence of HL.[7]

Female gender was associated with OC occurrence. Lourenço & Figueiredo[8] described the same finding in Brazilian patients. The relationship between feminine sexual hormones and oral flora remains unclear. Down-regulated levels of oestrogen would predispose the oral mucosae to *C.albicans* colonization. This hormone acted as a protection factor for vaginal candidiasis,[13] possibly in lower levels of oestrogen both tissues, oral and vaginal remain more susceptible to fungal infections.

A wide spectrum of oral diseases have been associated with HIV/AIDS since the beginning of the epidemic.[5] The onset of certain affections can provide valuable clinical information on HIV progression.[8] Several of these manifestations can be accurately diagnosed based exclusively on their clinical features.[5,9] Oral examination is an inexpensive and simple procedure and should be mandatory for HIV carriers, especially in low-income settings.[19]

The limitations of our study are inherent to data collection from medical records not explicitly designed to explore HIV-associated oral lesions. Oral lesions may be under-reported, leading to a sub-estimation of prevalence. Both HIV carriers and AIDS patients were included. This fact would have also influenced the prevalence of some oral affections. Some conditions have a stronger association with HIV-infection and a few are definitively AIDS defining, possibly due to local and systemic immune variations.[4,17] Symptomatic individuals are most at risk of being affected by other systemic opportunistic diseases, which possibly enhanced the risk of developing certain oral affections.[18] Furthermore, we reported data from a single evaluation.

The retrospective analyses made comparison of our results with those presented in prospective surveys difficult. Although the accessible data carefully collected may reflect reliable and relevant information on risk factors for oral lesion development in the observed HIV-carriers, they cannot be inferred for the whole population.

Longitudinal studies are needed to explore the dynamics of the relationship between the VL levels and CD4+ counts preceding the onset of HIV-related oral lesions, especially OC and HL, such as the ability of these pathologies to predict changes in these laboratory indices. These results will emphasize the potential

use of oral opportunistic infections as early clinical markers of disease progression and HAART failure. This validation is of great importance in countries with limited resources, and there are limited data available from the developing world.

The results suggest that elevated VL levels and low CD4+ counts are risk factors for HL. Moderate to severe degrees of immunologic impairment increased the susceptibility of developing OC and HL in adult carriers of HIV. It is necessary to improve prevention, early diagnosis and the management of these pathologies in symptomatic patients, who are more susceptible to opportunistic diseases. Alcohol and tobacco are modifiable habits that should be discontinued since they have been shown to be predisposing factors for OC and HL. We did not obtain sufficient information on substance abuse to make this a reliable independent variable in evaluating its effects on oral health. More studies are necessary in this field, especially applying a more precise measurement of drug abuse. Case-control studies including HIV-positive subjects under HAART and healthy controls are required to clarify the true contribution of alcohol and tobacco to the onset of HIV-related oral lesions.

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Master degree's thesis presented on March 9th, 2012 at Programa de Pós-Graduação em Odontologia – Pontifícia Universidade Católica do Rio Grande do Sul.
The authors declare that there are no conflicts of interest.