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ORIGINAL ARTICLE

Oral candidosis and oral hairy leukoplakia as predictors of HAART failure in Brazilian HIV-infected patients

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INTRODUCTION: Oral candidosis (OC) and hairy leukoplakia (OHL) are important markers of Human Immunodeficiency Virus (HIV) infection immune status.
OBJECTIVES: to evaluate if OC and/or OHL should be considered clinical predictors of immune and virologic failure on HIV-infected Brazilian adults undergoing Highly Active Antiretroviral Therapy (HAART).
METHODS: 124 HIV-infected patients who used HAART for a minimum of six months were prospectively evaluated. All of them under-took oral examination and serum $CD4^+$ count and viral load (VL), being divided in two groups, P and A, respectively according to the presence or absence of OC and/or OHL. During a six month period, patients belonging to group A were followed. They were re-examined for new oral lesions. New blood samples were collected and they were subdivided into groups P6 and A6. $CD4^+$ count and VL were compared between groups at baseline and after the six months period. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and relative risk (RR) were obtained in order to assess the accuracy of using OC and OHL as predictors of immune and virologic failure, at baseline and after a six month period.
RESULTS: At baseline and after six months, patients with OC and OHL have mean $CD4^+$ count lower and mean VL higher than patients of group A and A6 ($p < 0.001$). OC had high PPV for immune failure and a moderated PPV for virologic failure. OHL had low PPVs for both measures.
DISCUSSION AND CONCLUSIONS: OC and OHL still indicate low serum $CD4^+$ count and high VL, but OC seems to be a better predictor of immune and virologic failure in patients undergoing HAART than OHL.
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Keywords: HIV; AIDS; Oral candidosis; hairy leukoplakia; antiretroviral therapy; HAART

Introduction

Oral lesions (OL), oral candidosis (OC) and oral hairy leukoplakia (OHL) are important prognostic factors of human immunodeficiency virus (HIV) infection (Patton *et al*, 1998). The presence of these lesions suggest HIV infection and may be one of the first signs of evolution to the acquired immune deficiency syndrome (AIDS) (Ditchtel, 1992).

Besides, OC and OHL have been associated with immunologic dysfunction and reduced amounts of serum $CD4^+$ T-lymphocytes. These are clinical predictors of AIDS progression and usually are associated with $CD4^+$ T-lymphocytes count < 200 cells mm^{-3} and high viral load (VL) levels (Ravina *et al*, 1996; Margiotta *et al*, 1999; Ramirez-Amador *et al*, 2001; Campo *et al*, 2002).

The introduction of protease inhibitors in the mid-1990s produced important therapeutic effects and dramatic changes in the clinical prospect of HIV infection. Although related data are sparing, it has also been suggested that the presence of OL related to HIV infection could be a clinical predictor of highly active antiretroviral therapy (HAART) failure (Tappuni and Fleming, 2001). In a recent study, Gaitán-Cepeda *et al* (2005) concluded that OC should be considered a clinical predictor of immune failure in patients with HIV/AIDS undergoing HAART.

Therefore, this study aims to evaluate if OC and/or OHL should be considered clinical predictors of immune failure ($CD4^+$ count < 200 cells mm^{-3}) or virologic failure (VL $\geq 20\,000$ copies ml^{-1}) in Brazilian HIV-infected adults undergoing HAART.

Casuistic and methods

From January to December 2004, a successive sample of 124 HIV-infected patients, with or without AIDS, were

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treated in accordance with the criteria of the Centers for Disease Control and Prevention (1992, 1998). Brazilian adults attending the AIDS Group of the Otorhinolaringologic Division from Hospital das Clínicas, São Paulo University Medical School, due to ENT problems were enrolled prospectively in this study.

All patients gave informed consent and the study protocol was approved by the ethics committee of the hospital. Demographic data, medications in use and clinical immunodeficiency status were registered for each patient.

Only patients undergoing HAART – two nucleoside reverse transcriptase inhibitor (NRTI) plus a protease inhibitor (PI) of HIV-1 or a nucleoside and a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus a protease inhibitor of HIV-1) – for at least 6 months were included in the protocol. None of the patients were receiving antifungal medication.

Oral lesion diagnosis was performed by the same physician (IDM), according to the classification and diagnostic criteria for oral lesions in HIV infection (Anonymous, 1993). OC diagnosis was based on clinical and symptomatic characteristics, later confirmed by positive culture to *Candida* species and/or morphologic microscopic observation. OHL diagnosis was based on clinical and symptomatic characteristics, after a lack of response to anti-fungal treatment by 2 weeks.

On the same day of oral evaluation, all patients underwent laboratory assays for the determination of serum $CD4^+$ count and quantitative VL measurements. The serum $CD4^+$ lymphocyte count was performed by flow cytometry, using a FACS Calibulur (Becton-Dickinson, San Jose, CA, USA) machine, and quantitative HIV-RNA determination was performed by PCR technique (Roche Diagnostic Systems). In this technique, the lowest detection level aims for <50 copies ml^{-1}. In such cases of undetectable RNA, we assumed VL value as being 0 (zero).

After the first medical evaluation, patients were divided into two groups: those presenting OC and/or OHL (identified as group 'P') and those with absence of these lesions (identified as group 'A').

During a 6-month follow-up period, patients of group A underwent periodical oral examination. The same physician evaluated each patient to determine the incidence of new OC and/or OHL. New laboratory assays (serum $CD4^+$ T-lymphocyte count and quantitative VL) were performed at the time of diagnosis of the new oral lesion, or after completion of the 6-month period. At this time, patients of group A were subdivided into two new groups, according to the absence (called group A6) or presence (called group P6) of newly diagnosed OC and/or OHL.

Statistical analysis was performed using the Statistical Package for Social Sciences Software (SPSS 10.0 for Windows 10.0; SPSS Inc., Chicago, IL, USA). The Student's *t*-test was used to compare age between groups. Chi-squared or Fisher's exact test was used to compare differences in proportions of categorical variables between groups. The non-parametric Mann-Whitney *U*-test was used to compare mean serum $CD4^+$ T-lymphocyte count and quantitative VL between groups P and A at baseline, and between groups A6 and P6 after 6 months. $P < 0.05$ was considered statistically significant.

Ability of OC and OHL to predict HAART failure

Sensitivity, specificity, positive and negative predictive values (PPV and NPV) were obtained in order to assess the accuracy of using OC and OHL as predictors of serum $CD4^+$ T-lymphocyte count <200 cells mm^{-3} and VL $\geq 20\,000$ copies ml^{-1}. Relative risk (RR) and 95% confidence interval (CI) for the association of OL with the categorical laboratory markers ($CD4^+$ cells count and VL) were reported.

$CD4^+$ count <200 cells mm^{-3} and virologic failure when VL $\geq 20\,000$ copies ml^{-1} were considered as denoting immune failure. The 20 000 copies ml^{-1} cutpoint for HIV-RNA was selected for its clinical relevance, based on its incorporation into the indications for the initiation of the antiretroviral therapy in asymptomatic patients, in the 1998 CDC Guidelines for the Use of Antiretroviral Therapy in HIV-infected Adults and Adolescents.

Results

Baseline

Horizontal transmission by sexual contact was the most common mode of HIV transmission (90.0% in males and 94.2% in females). Forty-one (33.1%) patients corresponded to A3, B3 and C categories and 83 (66.9%) corresponded to A1, A2, B1 and B2 categories. Sixty-three (50.8%) patients were using 2 NRTI + 1 PI, 48 (38.7%) were using 1NRTI + 1 NNRTI + 1 PI, and 13 (10.4%) were using 1 NRTI + 1 NNRTI + 2 PI.

Table 1 Age, sex distribution, serum $CD4^+$ T-lymphocyte count and viral load according to the presence of oral candidosis or oral hairy leukoplakia (group P) and non-affected (group A) patients at baseline

	Group			
	P (n = 43)	*A (n = 81)*	*P*	*Total (n = 124)*
Age (years)	34.1 ± 10.2	33.5 ± 11.4	0.77	33.7 ± 10.9
Male sex	28 (65.1%)	44 (54.3%)	0.25	72 (58.1%)
Mean $CD4^+$ count (cells mm^{-3})	191.9 ± 101.8	389.9 ± 153.2	<0.001	321.3 ± 166.6
Mean VL (copies ml^{-1})	122 223 ± 143 903	16 286 ± 43 503	<0.001	53 022 ± 103 763

VL, viral load.

Table 2 Mean serum $CD4^+$ T-lymphocyte count and viral load according to the presence of oral candidosis (OC) or oral hairy leukoplakia (OHL) at baseline

	Group		
	OC (n = 28)	*OHL (n = 15)*	*P*
Mean $CD4^+$ count (cells mm^{-3})	159.9 ± 93.7	251.5 ± 91.3	< 0.001
VL (copies ml^{-1})	173 653 ± 154 068	26 222 ± 17 920	< 0.001

VL, viral load.

Table 3 Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and relative risk (RR) of the presence of oral hairy leukoplakia (OHL) or oral candidosis (OC) as predictors of immune and virologic failure at baseline

	Sensitivity (%)	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*RR (95% CI)*
Immune failure[a]					
OC	85.7	85.4	63.2	95.3	5.9 (3.5–9.8)
OHL	53.3	72.5	21.1	91.9	1.9 (1.1–3.4)
Virologic failure[b]					
OC	100	74.0	52.8	100	3.8 (2.7–5.4)
OHL	60.0	59.6	17.0	91.5	1.5 (0.9–2.4)

[a]CD4 < 200 cells mm^{-3}.
[b]Viral load ≥20 000 copies ml^{-1}.

At baseline, we observed 28 (19.3%) patients with OC and 15 (12.0%) with OHL (group P = 43 patients). We did not observe any patient bearing simultaneously OC and OHL. Thus, group A consisted of 81 patients without OC and/or OHL. As can be seen in Table 1, there is no statistical difference between groups related to mean age and sex distribution.

Sixteen patients had non-detectable VL, all pertaining to group A. The mean count of serum $CD4^+$ T-lymphocytes and VL of groups P and A at baseline are also shown in Table 1. The differences in mean $CD4^+$ cells count and VL between groups P and A were statistically significant ($P < 0.001$).

The mean $CD4^+$ cell count and VL of patients bearing OC and OHL are shown in Table 2. Patients with OC had lower mean $CD4^+$ cells count and higher mean VL than patients with OHL ($P < 0.001$).

Table 3 presents sensitivity, specificity, PPV, NPV and RR of OC and OHL as predictors of immune and virologic failure. Patients with OC presented higher PPV (63.2% *vs* 21.1%) and RR (5.9 *vs* 1.9) than patients with OHL for the outcome of $CD4^+$ cell count < 200 cells mm^{-3}. Patients with OC also presented higher PPV and RR than patients with OHL for the outcome of VL ≥20 000 copies ml^{-1}.

After 6 months

During the 6-month period after baseline, 16 (19.8%) patients of group A were lost to follow-up. Of the remaining 65 patients, 10 (15.4%) developed OC and seven (10.6%) developed OHL. Once again, no patient had OC and OHL simultaneously. P6 group consisted of 17 patients, and the A6 group, 48 patients.

Mean counts of serum $CD4^+$ T-lymphocytes and VL of groups P6 and A6 after the 6-month period are shown in Table 4. The differences in mean $CD4^+$ cell count and VL between groups P6 and A6 were statistically significant ($P < 0.001$).

Table 5 presents sensitivity, specificity, PPV and NPV of OC and OHL as predictors of immune and virologic failure after the 6-month period. Again, patients with OC presented higher PPV (66.7% *vs* 16.7%) and RR (11 *vs* 1.6) than patients with OHL for the outcome of $CD4^+$ cell count < 200 cells mm^{-3} and also presented higher PPV and RR for the outcome of VL ≥20 000 copies ml^{-1}.

Patients with OC had mean serum $CD4^+$ T-lymphocyte count below mean count of OHL patients and mean VL above mean VL of OHL patients; however, the differences were not statistically significant ($P > 0.05$; Table 6).

Discussion

All patients included in the present study were receiving medications for HIV treatment. A program of the Brazilian government allows free distribution of antiretrovirals to all HIV-infected patients since the end of the 1990s. Thus, patients in the present study who developed OC and OHL, with low serum $CD4^+$ T-lymphocyte count and high VL, were under HAART.

High VL, as noted in several patients of our cohort, is indicative of ineffective or failing therapy (Eyeson *et al*, 2002). Thus it is important to point out that there were not any other factors (related to duration of HAART or non-adherence to treatment) influencing the immunosuppressive status of OC and OHL carriers in our series.

Table 4 Mean serum $CD4^+$ T-lymphocyte count and viral load (VL) according to the incidence of newly diagnosed oral candidosis or oral hairy leukoplakia (group P6) and non-affected (group A6) after a 6-month period

	Group			
	P6 (n = 17)	*A6 (n = 48)*	*P*	*Total (n = 65)*
Age (years)	29.2 ± 7.3	34.7 ± 12.7	0.19	33.3 ± 11.7
Male sex	8 (47.1%)	31 (64.6%)	0.21	39 (60%)
Mean $CD4^+$ count (cells mm^{-3})	191.1 ± 100.5	463.3 ± 121.3	< 0.001	392.1 ± 166.9
VL (copies ml^{-1})	35 076 ± 34 345	7208 ± 24 401	< 0.001	14 496 ± 29 740

VL, viral load.

Table 5 Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and relative risk (RR) of the presence of oral hairy leukoplakia (OHL) or oral candidosis (OC) as predictors of immune and virologic failure after the 6-month period in 81 patients

	Sensitivity (%)	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*RR (95% CI)*
Immune failure[a]					
OC	80.0	92.7	66.7	96.2	11 (4.1–29.7)
OHL	28.6	82.8	16.7	90.6	1.6 (0.5–6.1)
Virologic failure[b]					
OC	50	87.3	41.7	90.6	3.9 (1.6–9.9)
OHL	42.9	84.5	25.0	92.5	2.8 (0.9–7.9)

[a]CD4 < 200 cells mm^{-3}.
[b]Viral load $\geq 20\,000$ copies ml^{-1}.

Table 6 Mean serum $CD4^+$ T-lymphocyte count and viral load according to the presence of oral candidosis (OC) or oral hairy leukoplakia (OHL) after the 6-month period

	Group		
	OC ($n = 10$)	*OHL ($n = 7$)*	*P*
Mean $CD4^+$ count (cells mm^{-3})	162.9 ± 75.0	231.4 ± 123.6	0.15
VL (copies ml^{-1})	42 841 ± 40 982	23 983 ± 19 548	0.46

VL, viral load.

Prevalence of OC and OHL

The prevalence of OC and OHL in patients undergoing HAART in the present study was 19.3% and 12.0%, respectively, and it is partially in accordance with previous data: Nicolatou-Galitis *et al* (2004), 19.4% and 9.1%; Ramirez-Amador *et al* (2003), 23.7% and 16.3% and Diz-Dios *et al* (2000) 17.1% and 2.8%.

Patton *et al* (2000) found similar results. In their series, the prevalence of OHL fell from 25.8% to 11.4% after HAART introduction, while OC fell slightly from 20.3% to 16.7%, although this was not statistically significant.

In our study, after the 6-month follow-up period, the incidence of OC and OHL in A group was 15.4% and 10.6%, respectively.

Host defenses to *Candida* species in OC and Epstein–Baar virus (EBV) in OHL are partially immune mediated. The decrease in the prevalence of OC and OHL in our series suggests that HAART can increase serum $CD4^+$ T-lymphocyte count, and consequently improve host defenses, as reported by other authors (Diz-Dios *et al*, 2000; Patton *et al*, 2000; Ramirez-Amador *et al*, 2003; Nicolatou-Galitis *et al*, 2004).

We did not observe any patient with OC and OHL concurrently. Despite the association of low serum $CD4^+$ T-lymphocyte count with the appearance of these lesions, it is unusual that they occur simultaneously. It suggests that there are distinct host immune disabilities associated with each pathologic lesion. Probably, in HIV-infected subjects, susceptibility to OC is mostly immune based, while susceptibility to OHL could be more associated with other factors than mucosal immune function (Leigh *et al*, 2004).

Ability of OC and OHL to predict immune failure

The effect of antiretroviral therapy on the ability of any oral candidiasis and OHL to predict $CD4^+$ cell count below 200 cells mm^{-3} was also studied by Patton (2000). The author found that sensitivities were relatively low, specificities were high, and PPVs for $CD4^+$ cell count < 200 cells mm^{-3} were 73.8% for any OC alone and 61.4% for OHL alone.

During the pre-HAART era, in a cohort of 454 patients, Glick *et al* (1994) reported sensitivities for OC (77.2%) and OHL (22.6%), and PPVs for OC (69.9%) and OHL (70.1%). In a smaller cohort, Begg *et al* (1996) reported that individual OL had low sensitivity, high specificity, and moderate PPVs for prediction of $CD4^+$ cell count < 200 cells mm^{-3}. Among homosexual men and injection drug users, respectively, PPVs varied for OC (50.0%; 42.9%) and OHL (55.6%; 55.6%).

In our study, at baseline, sensitivities were high for OC and relatively low for OHL. Specificities were high for both lesions, and PPV for OC (63.2%) was moderate and for OHL (21.1%) it was low. Both values were lower than PPVs showed by Patton (2000) and Glick *et al* (1994). The relative risk that related lesion presence to immune suppression ($CD4^+$ cell count < 200 cells mm^{-3}) in our study was high for OC (5.9) and low for OHL (1.9).

After 6 months, sensitivities and specificities in our cohort remained high for OC, but sensitivity was very low for OHL (28.6%). The relative risk was very high for OC (11.0) but low for OHL (1.6). PPVs for OC (66.7%) was moderate and for OHL (16.7%) it was very low. Both values remained lower than PPVs showed by Patton (2000) and Glick *et al* (1994). In comparison with the study of Begg *et al* (1996), our PPVs were higher for OC and lower for OHL.

Although the PPV of OL for advanced immune suppression is dependent on the level of immune suppression in the study population (Patton, 2000), low PPVs for OHL in our cohort, compared with HIV/AIDS population of Patton (2000) and Glick *et al* (1994), may be due to the small number of patients of our cohort and not as a result of less severe immune suppression in the current population with OHL.

Ability of OC and OHL to predict virologic failure

Patton *et al* (1999), using a multivariate logistic regression model, demonstrated that individuals with OHL and OC were, respectively, 2.0 and 1.5 times more likely to have VLs $\geq 20\,000$ copies ml^{-1} than individuals without OL, independently of serum $CD4^+$ T-lymphocyte count and antiretroviral therapy.

Inversely, in our study, at baseline, relative risk for VLs $\geq 20\,000$ copies ml^{-1} was 3.8 for OC and 1.5 for OHL. After 6 months, RR was 3.9 for OC and 2.8 for OHL.

The PPVs for the ability of OL to identify patients having a VL $\geq 20\,000$ copies ml^{-1} were, at baseline and after 6 months respectively, higher for OC

(52,8%;41.7%) than OHL (17%;25%). Besides, at baseline, OC bearers had mean VL higher than mean VL of patients with OHL.

A possible explanation lies in the fact that in our series most of OC bearers were in greater immunosuppressive status ($CD4^+$ T-lymphocyte count < 200 cells mm^{-3}), supporting intense viral replication. However, after 6 months, there was no statistical difference between mean VL in patients with OC and with OHL, again possibly due to the small sample (only 18 patients).

Final considerations

Our results suggest that individuals included in the present study who presented OC or OHL may have experienced considerable immunosuppressive status and have not achieved immune reconstitution by HAART, after, at least, 6 months of therapy (P group) or 1 year of therapy (P6 group), because they have lower mean $CD4^+$ T-lymphocyte count and higher mean VL than A and A6 groups. The strong association between OC or OHL and low serum $CD4^+$ T-lymphocyte counts and high VL in the pre-HAART era has been already demonstrated (Moniaci *et al*, 1990).

In addition to this, the high specificities of OC and OHL in our cohort of patients undergoing HAART and the differences in $CD4^+$ cell count and VL between groups A, P, A6 and P6, suggest that these OL still provide some value in 'ruling in' good immune function and attainment or maintenance of viral suppression when OL are not present.

Thus we partially disagree with the conclusions of Gaitán-Cepeda *et al* (2005). They examined a similar sample (151 HIV-infected patients) and established a relationship between immunologic and virologic failure in the presence of OC, but not in the presence of OHL. Our results suggest a slight association between OHL and immunologic and virologic failure in patients receiving HAART.

In fact, our results should be interpreted with caution. First, our study did not consider the occurrence of viral resistance to HAART. Second, differences verified between the groups do not imply causality. Besides, further studies are necessary to access HIV-infected groups who use other combinations of antiretroviral therapy.

Anyway, the simplicity of diagnosing OC and OHL for an experienced otorrhinolaringologist, dentist, or clinician, without considerable expenses makes it an invaluable resource in underdeveloped countries where the lack of resources and remoteness from urban centers (as in Brazil) do not allow laboratorial routine tests in most HIV-infected subjects.

Conclusion

Oral manifestations of HIV, particularly OC, have important predictive value for immune suppression defined as $CD4^+$ cell count < 200 cells mm^{-3}, and moderate predictive value for viral suppression defined as VL $\geq 20\,000$ copies ml^{-1}, in this Brazilian adult cohort undergoing HAART.

Otherwise, OHL has low predictive value for both measures, but perhaps it still has utility in screening examinations for identifying individuals with immune suppression and substantial viral replication.

References

Anonymous (1993). EC-Clearinghouse on Oral Problems Related to HIV Infection and WHO Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus. Classification and diagnostic criteria for oral lesions in HIV infection. *J Oral Pathol Med* **22:** 289–291.

Begg MD, Panageas KS, Mitchell-Lewis D, Bucklan RS, Phelan JA, Lamster IB (1996). Oral lesions as markers of severe immune suppression in HIV-infected homosexual men and injection drug users. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **82:** 276–283.

Campo J, Del Romero J, Castilha J, Garcia S, Rodriguez C, Bascones 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.

Centers for Disease Control and Prevention (1992). 1993 revised classification and expanded surveillance case definition for aids among adolescents and adults. *Mor Mortal Wkly Rep* **41:** 1–19.

Centers for Disease Control and Prevention (1998). Report of the NIH panel to define principles of therapy of HIV infection and guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. *Mor Mortal Wkly Rep* **47** (RR-5)**:** 1–82.

Ditchtel WJ (1992). Oral manifestations of human immunodeficiency virus infection. *Otolaryngol Clin North Am* **25:** 1211–1225.

Diz-Dios P, Ocampo A, Miralles C, Simeres J, Thomas I (2000). Changing prevalence of human immunodeficiency virus-associated oral lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **90:** 403 (letter).

Eyeson JD, Tenant-Flowers M, Cooper DJ, Johnson NW, Warnakulasuriya KAAS (2002). Oral manifestations of an HIV positive cohort in the era of highly active antiretroviral therapy (HAART) in South London. *J Oral Pathol Med* **31:** 169–174.

Gaitán-Cepeda LA, Martínez-González MM, Ceballos-Salobreña A (2005). Oral candidosis as a clinical marker of immune failure in patients with HIV/AIDS on HAART. *AIDS Patient Care STDS* **19:** 70–77.

Glick M, Muzika BC, Lurie D, Salkin LM (1994). Oral manifestations associated with HIV-related disease as markers for immune suppression and AIDS. *Oral Surg Oral Med Oral Pathol* **77:** 344–349.

Leigh JE, Shetty K, Fidel PL (2004). Oral opportunistic infections in HIV-positive individuals: review and role of mucosal immunity. *AIDS Patient Care STDS* **18:** 443–456.

Margiotta V, Campisi G, Mancuso S, Accurso V, Abbadessa V (1999). HIV infection: oral lesions, CD4+ cells count and viral load in na Italian study population. *J Oral Pathol Med* **28:** 173–177.

Moniaci D, Greco D, Flecchia G, Raiteri R, Sinicco A (1990). Epidemiology: clinical features and prognostic value of HIV-1 related oral lesion. *J Oral Pathol Med* **19:** 477–481.

Nicolatou-Galitis O, Velegraki A, Paikos S *et al* (2004). Effect of PI-HAART on the prevalence of oral lesions in HIV-1 infected patients. A Greek study. *Oral Dis* **10:** 145–150.

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* **90:** 182–188.

Patton LL, McKaig RG, Rogers D, Strauss RP, Eron JJ Jr (1998). The role oral manifestations of HIV and body signs in suspicion of possible HIV infection. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **85:** 416.

Patton LL, McKaig RG, Strauss RP, Lawrence HP, Eron JJ Jr (1999). Oral hairy leukoplakia and oral candidiasis as predictors of HIV viral load. *AIDS* **13:** 2174–2176.

Patton LL, McKaig R, Strauss R, Rogers D, Eron JJ Jr (2000). Changing prevalence of oral manifestations of human immunodeficiency virus in the era of protease inhibitor therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **89:** 299–304.

Ramirez-Amador V, Esquivel-Pedraza L, Sierra-Madero J *et al* (2001). Oral clinical markers and viral load in a prospective cohort of Mexican HIV-infected patients. *AIDS* **15:** 1910–1911.

Ramirez-Amador V, Esquivel-Pedraza L, Sierra-Madero J, Anaya-Saavedra G, González-Ramírez I, Ponce-de-Leon S (2003). The changing clinical spectrum of human immunodeficiency virus (HIV)-related oral lesions in 1,000 consecutive patients. A 12-year study in a referral center in Mexico. *Medicine* **82:** 39–50.

Ravina A, Ficarra G, Chiodo M, Mazzetti M, Romagnani S (1996). Relationship of circulating CD4+ T-Lymphocytes and p24 antigenemia to the risk of developing AIDS in HIV-infected subjects with oral leukoplakia. *J Oral Pathol Med* **25:** 108–111.

Tappuni AR, Fleming GJ (2001). The effect of antiretroviral therapy on the prevalence of oral manifestations in HIV-infected patients: a UK study. *Oral Surg Oral Med Oral Pathol* **92:** 623–628.