JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 32, no. 2 (S1), 51-59 (2018)

EDITORIAL

PREVALENCE OF HIV-RELATED ORAL MANIFESTATIONS AND THEIR ASSOCIATION WITH HAART AND CD4+ T CELL COUNT: A REVIEW

L. OTTRIA[1*], D. LAURITANO[2*], L. OBERTI[2], V. CANDOTTO[3], F. CURA[4], A. TAGLIABUE[5**] and L. TETTAMANTI[5**]

[1]Dental School, Tor Vergata University, Rome, Italy; [2]Department of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy; [3]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy; [4]Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [5]Department of Medicine and Surgery, University of Insubria, Varese, Italy

*these authors contributed equally to this work and they are co-first authors
**these authors contributed equally to this work and they are co-last authors

HIV infection is one of the major health problem of the last decades. This disease causes a chronic infection that can lead to acquired immunodeficiency syndrome (AIDS). According to the Global AIDS update, released in 2016 by HIV department of World Health Organization (WHO) and by the Joint United Nations Program on HIV/AIDS (UNAIDS), at the end of 2015, 36.7 million people were infected by HIV: 34.9 million of these were adults and 1.8 million were children under 15 years of age. The same report shows that during 2015, 2.1 million of new infection cases have occurred all over the world and about 1.1 million people have died for HIV. The aim of this short review is to up-date of the main HIV-related oral manifestations and their correlation with HAART (Highly Active Antiretroviral Therapy) and CD4+ T-cell count. Despite that more than 20 years have elapsed, this classification still remains valid: even today, group 1 lesions are found in the majority of HIV-positive patients with oral manifestations. Group 1 includes the following conditions: oral candidiasis (*pseudomembranous candidiasis, erythematous candidiasis, angle cheilitis*), oral hairy leukoplakia, periodontal diseases (necrotizing gingivitis, necrotizing periodontitis, linear gingival erythema), Kaposi's sarcoma, and non-Hodgkin's lymphoma. Melanotic hyperpigmentation, HSV infection and HPV infection, which are included in group 2, are also common. Oral candidiasis, oral hairy leukoplakia, Kaposi's sarcoma and HSV infection are the lesions that have seen the major drop in their incidence after the HAART introduction. The increase in CD4+ T-cell count is not significantly correlated to the decrease of every type of oral lesions, but it is statistically significant only in relation to oral *candidiasis* (p-value <0.001). Oral lesions are an important sign of immunodepression and with the introduction of HAART their incidence has strongly decreased, particularly in urban areas. Nevertheless, developing countries still have a high prevalence of these manifestations because of the persistence of many risk factors, like the difficulty to access treatment, poor oral hygiene, low socioeconomic status and late diagnosis.

HIV infection is one of the major health problem of the last decades. This disease causes a chronic infection that can lead to acquired immunodeficiency syndrome (AIDS). According to the Global AIDS update, released in 2016 by HIV department of World Health Organization (WHO) and by the Joint United

Key words: HIV, AIDS, HIV-related oral manifestations, HAART, CD4

Mailing address:
Prof. Angelo Tagliabue,
Department of Medicine and Surgery,
University of Insubria,
Via Piatti 10, 21100 Varese, Italy
Tel.: +39.0332-825625 - Fax: +39.0332-825655
e.mail: angelo.tagliabue@uninsubria.it

0393-974X (2018)

Nations Programme on HIV/AIDS (UNAIDS), at the end of 2015, 36.7 million people were infected by HIV; 34.9 million of these were adults and 1.8 million were children under 15 years-of-age. The same report shows that during 2015, 2.1 million of new cases have occurred all over the world and about 1.1 million of people have died from HIV.

In the initial phases, the infection is asymptomatic and it can stay unchanged for years until the first symptoms, due to immunosuppression, show up. This condition is the direct consequence of the destructive effect of HIV on T-helper lymphocytes, which the virus has a strong tropism for and where it completes its replication cycle. The first symptoms, which can be local or systemic, are considered manifestations of opportunistic infections. Among these, oral lesions are one of the most common HIV-related diseases.

In 1981, Gottlieb identified AIDS in a group of young homosexual men and he published a description of the disease, revealing the association between AIDS and oral candidiasis, which represents an important sign of immunodepression (Fig.1). Nowadays it is known that oral candidiasis, as well as other oral manifestations, is not only related to AIDS but it is also a common sign of immunodepression in HIV-positive patients, who have not developed AIDS yet (1).

HIV-related oral manifestations include a large group of lesions, like bacterial, viral or fungal infections, idiopathic lesions, salivary gland diseases and neoplastic diseases (1). These manifestations are often the first symptom of HIV infection (2).

The majority of studies on this issue concern a population of HIV-positive patients, living in developing countries with a large diffusion of HIV, in particular Sub-Saharan Africa, where about the 65% of the global HIV-infected people live and where 5.5% of inhabitants are HIV-positive; The Caribbean, where 1.1% of population is HIV-infected and South-East Asia/India, where 15% of global seropositive population live (3). On the contrary, the prevalence of these lesions in the urban areas is less, probably because of rapid diagnosis and easier access to treatment (3).

Despite the amount of information that can be collected, it is difficult to find the exact prevalence of oral manifestations in the HIV-infected population, due to many variable factors that can affect this datum. Studies in heterogeneous seropositive populations show discordant prevalences of HIV-related oral lesions: according to Gaurav et al., the prevalence is 80.6% in South India (4), whereas the study conducted by Lourenço et al. reports a prevalence of 29.9% in a HIV-positive Brazilian population (5). In any case, we can presume that HIV-related oral manifestations prevalence is between 30% and 80% (2). This value increases in presence of adverse factors such as diagnosis of AIDS, low CD4+ T-cell count (<200 cell/mm^3) and high viral load (>20,000 copies/mL); while it decreases in patients undergoing HAART (Highly Active Antiretroviral

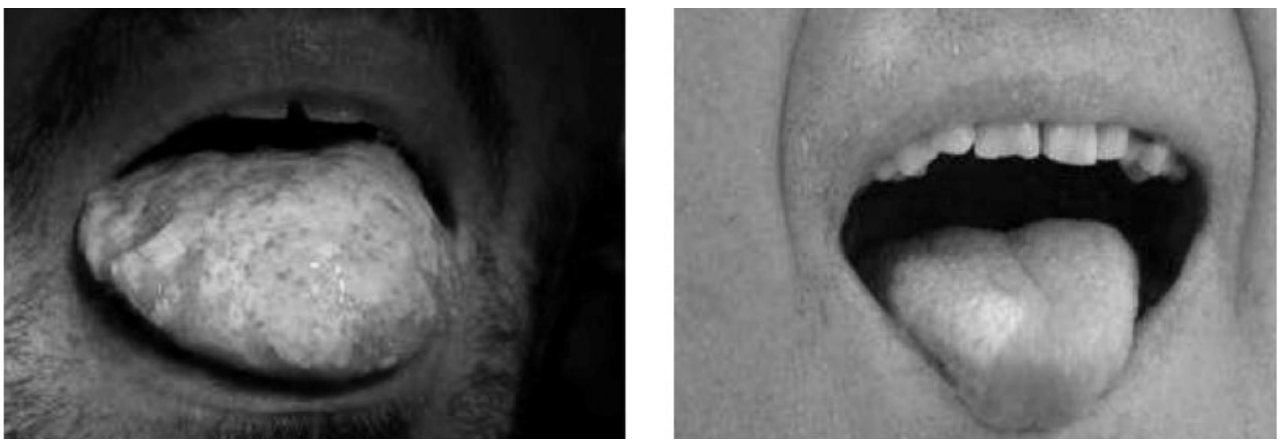

Fig. 1. *Pseudomenbranous oral candidiasis of tongue in young patients with AIDS.*

Therapy), with high CD4+ T-cell count and low viral load. These are the main factors influencing the appearance of oral manifestation in HIV-positive people.

Major HIV-related oral manifestations

In 1993 the EC-Clearinghouse on oral problems related to HIV infection and WHO collaborating center on oral manifestations of the immunodeficiency virus produced a classification of HIV-related oral manifestations (6).

No oral lesion is unique to HIV; nevertheless, three groups were established, sorted by the frequency of association with HIV infection: strongly associated lesions, less commonly associated lesions, possible associated lesions.

Despite more than 20 years have elapsed, this classification still remains adequate: even today, group 1 lesions are found in the majority of HIV-positive patients with oral manifestations (7).

Group 1 includes the following conditions: oral candidiasis (*pseudomembranous candidiasis, erythematous candidiasis, angle cheilitis*), oral hairy leukoplakia, periodontal diseases (necrotizing gingivitis, necrotizing periodontitis, linear gingival erythema), Kaposi's sarcoma (8-11), and non-Hodgkin's lymphoma (7). Melanotic hyperpigmentation, HSV infection and HPV infection (12-19), which are included in group 2, are also common.

Fig. 2: *Pseudomemebranes of candida on soft palate and pharynx in a patient with AIDS.*

The majority of studies conducted around the world agree that candidiasis (OC) is the most common HIV-related oral lesion, both in patients undergoing HAART and in untreated ones (1). In studies by Bodhade et al. and Sontakke et al., oral candidiasis is the main HIV-related oral manifestations, with a 39.3% and 32.3% prevalence respectively (20, 21). These findings are confirmed in the study by Kumar et al. where 36.5% of subjects suffer from OC (22), and in that of Nanteza et al. where this value is 24.9% (23). Gaurav et al. and Da Silva et al. also come to the same conclusion, indicating HIV-related candidiasis as the most common lesion with a 38.8% and 9.3% prevalence respectively (4, 24) (Fig. 2).

Two forms of OC are mainly observed: *pseudomembranous candidiasis* (PC) and *erythematous candidiasis* (EC). A third form, the angular *cheilitis*, is also common in HIV-positive patients.

Khatibi et al. have found that pseudomembranous candidiasis is the most common variant (25). The same conclusion comes from studies by Sontakke et al. and Nanteza et al. that find a prevalence of PC of 20.1% and 12.1% respectively, instead of an 8.1% and a 8.4% prevalence of EC (21, 23). Even Moodley and Wood affirm that this form is the most observed (3%) (26).

However, there are several studies showing the opposite: Gaurav et al. (2011) report a prevalence of erythematous candidiasis of 38.8%, significantly higher than the 8.7% prevalence of pseudomembranous candidiasis (4). According to Bodhade et al. (2011) EC is the most common form (30.6% compared to 12.3% prevalence of PC) (20).

This difference is due to 3 main factors that may influence the onset of one form instead of another: smoking habits of patients, different geographical area of origin and the use of different antibiotic therapies, which are common in HIV-positive patients for eradicating any opportunistic infection (20). It is not clearly defined which is the most common form of candidiasis, however the pseudomembranous form is considered to be the most frequent.

Another common HIV-related oral manifestation is the oral hairy leukoplakia, a lesion caused by EBV. It is frequently observed in many studies (4, 20, 21,

23, 25-27) and it represents on average 6-7% of all HIV-related oral lesions, with a higher prevalence in Western countries (26) and in the homosexual male population (28). According to Nittayananta et al. OHL might also be due to the increased susceptibility to EBV by the epithelium of oral mucosa in HIV-positive patients (29).

Periodontal disease is another relevant HIV-related oral manifestation. This disease, caused by the alteration of the oral microbiota in seropositive patients, includes linear gingival erythema (LGE), necrotizing gingivitis (NUG) and necrotizing periodontitis (NUP).

The periodontal manifestation with the higher prevalence is LGE. This lesion seems to have fungal aetiology: recent studies have shown the role of *Candida albicans* in its pathogenesis (30). The prevalence emerged in many studies is significantly high: Khatibi et al. have found that 22% of patients were affected by LGE (14), while according to Gaurav et al. and Bodhade et al. this percentage decreases to 13.6% and to 10.3% respectively (4, 20).

Sometimes LGE could evolve in NUG and NUG could predispose to the development of NUP (30). The analyzed studies report variable prevalence of these lesions, due to the difficulty in making a diagnosis with universally valid evaluation criteria and due also to the interference of many other factors related to the development of periodontal disease (smoking habits, oral hygiene, systemic diseases etc.) (30). However the average preva lence is between 3% and 8%.

The role of HIV is still unclear in the onset of chronic periodontitis: nevertheless it has been reported that the risk of periodontal attachment loss is 6 times higher in seropositive patients with a CD4+ T-cell count less than 200 cell/mm^3 and over 35 years of age (30).

Kaposi's sarcoma is the HIV-related neoplasia with the highest prevalence (28). It predominantly affects palate, oropharynx and gum (31), and its average prevalence varies between 0.5% and 3.5%. Homosexuality represents an important risk factor (20). Non-Hodgkin's lymphoma is also an important HIV-related neoplasia with an average prevalence of 0.5-1.5%.

In addition to all the lesions of group 1 (EC-Clearinghouse classification) there are many other common manifestations, like melanotic hyperpigmentations. According to the study by Denny et al. their prevalence is 42.6% (31), while Satyakiran et al. report a 32.8% prevalence (32). This disease is caused by the increased release of α-MSH (melanocyte-stimulating hormone), due to immunological changes in HIV-positive patient and due to the effects of some antiviral and antifungal drugs (4, 20).

Ulcers, HSV infection and xerostomia could occur in HIV-positive patients. The prevalence of ulcerative lesions in the examined studies varies between 1.5% (Nanteza et al.) and 12% (20). The majority of herpetic lesions are caused by HSV, while those caused by VZV are less common. HSV-related lesions are found in 1-3% of seropositive patients. In the study of Mwangosi and Tyllia, HSV lesions are even the HIV-related oral manifestations with the highest prevalence (11.5%) (27). Finally, xerostomia has a prevalence of 1-4%, even though Gaurav et al. reported a 32% prevalence (4).

While the use of HAART has reduced the prevalence of the most common HIV-related oral lesions, the prevalence of HPV infections has not decreased (8). Many studies have shown a significant increase in the incidence of these manifestations between 1990 and 2000. This phenomenon is caused by the introduction of HAART, which happened exactly in the same years (7). HPV could be considered a manifestation of immune reconstitution inflammatory syndrome (IRIS), an atypical inflammatory response due to a viral load decrease and to the improvement of immune system activity (33). HPV infections may also evolve into malignancy (7). The risk of developing HPV-related oropharyngeal cancer is 2-6 times higher in HIV-positive individuals compared with the general population.

Oral manifestations of HIV and their correlation with HAART

There are many factors that can influence the appearance of these lesions. The majority of the studies published in the last years affirm that use of

HAART, CD4+ T-cell count and viral load are the main factors affecting the number and the type of lesions. Other factors include poor oral hygiene (25), low socioeconomic status (3, 22, 34) and alcohol abuse (25).

The introduction of HAART has led to a significant decrease in the prevalence of HIV-related oral lesions (7, 25, 28, 30) (26, 29). In a prospective study by Ortega et al. a cohort of patients were followed from 1989 to 2006, and an important reduction in the incidence of HIV-related oral manifestations was observed (35). This reduction was noted in two specific periods: 2000, right after the introduction of protease inhibitors (HAART-PIs), and 2006, when the first non-nucleoside reverse transcriptase inhibitors (HAART-NNRTIs) were diffused (35).

It is estimated that at the end of 2015, about 17 million people living with HIV/AIDS were receiving HAART: this number is still growing compared to 2010 when subjects undergoing HAART were only 7.5 million.

The main goal of this therapy is to reduce viral load and increase CD4+ T-cell count (31). Moreover, HAART seems to alter oral innate immunity, causing an increase in the number of Langerhans cells, neutrophils and monocytes, but also determining a reduction of salivary flow rates in the long term; as a result the risk of chronic opportunistic infections and of malignant transformation increases. Because of that, it is possible to affirm that short-term HAART is the only therapy strengthening oral innate immunity, while long-term adversely affects this immunity (29).

Oral candidiasis, oral hairy leukoplakia, Kaposi's sarcoma and HSV infection are the lesions which have seen the major drop in their incidence after the HAART introduction (26).

Lourenço et al. conducted a study on patients receiving antiretroviral drugs (except protease inhibitors) in 1997 and on subjects undergoing HAART in 2004-2008. This study shows that the prevalence of oral manifestations is of 60.1% in the first group and 29.9% in the second one (p-value <0.0001) (5). An analysis of scientific literature reveals that the majority of studies agree that only two kinds of lesions have seen a statistically significant decrease of their incidence after the introduction of HAART: oral candidiasis and periodontitis. Patil et al. found that 32% of seropositive individuals with oral lesions receive HAART, while 56% of them are not in therapy: this difference is statistically significant (p-value <0.05) (36). The same study also shows that the use of HAART induces a decrease in the prevalence of oral candidiasis and periodontitis from 8% to 2% and from 14% to 2% respectively (36). The study by Rao et al. had the same result, reporting a 24.4% prevalence of oral candidiasis and a 68.8% prevalence of periodontitis before initiating treatment and a 10.3% and a 46.6% prevalence respectively after therapy initiation (p-value: 0.01) (37). Finally, Satyakiran et al. report a direct correlation between the reduction of oral lesions prevalence and the duration of HAART (32).

However, there are some HIV-related oral manifestations, which have seen an increase in their incidence after the introduction of HAART, like hyperpigmentation, xerostomia and salivary gland hypertrophy. This is due to the effects of antiretroviral drugs on melanocyte-stimulating hormone (MSH) and on salivary flow rate (4, 26). The study by Rao et al. show a statistically significant increase in melanotic hyperpigmentations prevalence from 5.3% to 23.8% after initiation of HAART (p-value <0.001) (38). Even Eweka et al. report a similar increase in melanotic hyperpigmentations prevalence from 10.8% before HAART initiation to 66.7% during treatment (33). The same conclusion is drawn by Satyakiran, which indicates a prevalence of hyperpigmentation and xerostomia of 17.6% and 0% respectively in patients with HAART under 4 years duration; a prevalence of 42.3% and 7.6% in patients with HAART between 4 and 8 years duration; a prevalence of 26.3% and 10.5% in patient with HAART for more than 8 years (32).

A notable study conducted by Batavia et al. examined a sample of HAART-naive HIV-positive people with a CD4+ T-cell count between 200 and 350 cell/mm^3 and randomized them into two groups. The first group was immediately subjected to HAART and the second to the same treatment only when the CD4 count was less than 200 cell/mm^3 or with the development of an AIDS-defining condition. The study shows that patients undergoing early treatment have a lower risk in developing HIV-related oral

lesions compared to the other participants (p-value <0.01): there is a statistically significant reduction in the incidence of candidiasis (p-value <0.01), oral hairy leukoplakia (p-value: 0.02) and HSV lesions (p-value: 0.05). The effect of HAART on reducing oral lesions prevalence is also confirmed by comparing oral candidiasis before and after treatment initiation in the delayed group. Finally, the increase of HPV-related oral warts during HAART is also statistically significant It is possible to conclude that the presence of oral lesions in HIV-positive patient is an index of immunosuppression and it represents an important reason for initiating treatment; on the contrary, the presence of HPV-related lesions during HAART is a sign of immune reconstitution (39).

Oral manifestations of HIV and their correlation with CD4+ T-cell count

The effect of HAART in reducing the incidence of HIV-related oral lesions is to be found not only in increasing the CD4 count, but also in the direct effect that therapy has on every kind of lesion. The increase in CD4+ T-cell count is not significantly correlated to the incidence decrease of every kind of oral lesions, but it is statistically significant only in relation to oral candidiasis (p-value <0.001) (23).

Sontakke et al. reported that pseudomembranous candidiasis was found in 27.4% of patients with a CD4 count <200 cell/mm^3, in 8.1% of those with a CD4 count between 200 and 500 cell/mm^3, and in 1.6% of those with CD4 count >500 cell/mm^3: this correlation is statistically significant (p-value <0.05) (21). A similar result was obtained in the study by Bodhade et al. which analyzed the CD4 count of patients with and without oral candidiasis: the difference indicate a strong association between the lesion and the presence of a CD4+ T-cell count <200 cell/mm^3 (p-value <0.0001) (20). Finally, this significant correlation has also been shown by Saini (2), Da Silva et al. (24), Satyakiran et al. (32), Moodley and Wood (26) and Gaurav et al. (4).

For this reason, it is possible to affirm that oral candidiasis could be a valuable index of a low CD4 T-cell count and therefore also of immunosuppression (PPV: 68%) (23).

Finally, some studies analyzed the correlation

Fig. 2: *Pseudomemebranes of candida on soft palate and pharynx in a patient with AIDS.*

ReferenceN. of subjects N. of subjects	*HAART (%)*	*Any OL (%)*	*OC (%)*	*OHL (%)*	*NUG (%)*	*NUP (%)*	*LGE (%)*	*Neoplasm (%)*	*Others (%)*	*Comments*	
Lourenço *et al.* (2011), Brazil	388	79.9	29.9	EC 6.4 PC 9.3	10.3	ND	ND	ND	KS 0.5 NHL 0.3	AC 11.9 Ulcers 1.8 HSV 0.8	Cross-sectional study comparing 2 periods (1997, 2004-2008). These results correspond to 2004-2008. Diagnosis followed established criteria (EC-Clearinghouse, 1993). HAART duration was described.
Khatibi *et al.* (2011), Iran	200	68.0	74.5	16.5	3.0	4.0	1.5	22.0	NHL 1.5 KS 1.0	PIG 5.5 Ulcers 2.5	Cross-sectional study. Diagnosis based on clinical appearance (except for KS e NHL whose diagnosis was histophatologically confirmed). The study evaluated other possible oral lesions-related factors (drugs and alcohol abuse, smoking habits, oral hygiene, educational status, stage of infection, transmission path).
Gaurav *et al.* (2011), India	103	40.8	80.6	EC 38.8 PC 8.7	17.5	9.7	3.9	13.6	ND	PIG 35.9 Xerost. 32.0 AC 5.8 Ulcers 4.9 VZV 1.9	Cross-sectional study. Diagnosis followed established criteria (EC-Clearinghouse, 1993). The study evaluated CD4/CD8 ratio, types and PPV of the most common lesions, correlation between HAART, viral load and HIV-related oral lesions.
Bodhade *et al.* (2011), India	399	0.0	76.7	39.3 EC 30.6 PC 12.3	11.5	8.5	5.3	10.3	NHL 0.8	PIG 19.5 Ulcers 11.8 AC 4.3 HSV 2.0 VZV 0.3 Xerost. 0.3	Cross-sectional study. Diagnosis followed established criteria (EC-Clearinghouse, 1993). Cytology for candidiasis and biopsy for unknown lesions are included. The study analyzed the prevalence of other opportunistic infections (tubercolosis, zoster, molluscum contagiosum…) and the correlation between CD4+ T-cell count and oral lesions.
Sontakke *et al.* (2011), India	124	ND	71.0	32.3 EC 8.1 PC 20.1	4.1	1.6	5.6	2.4	ND	PIG 30.6 Xerost. 16.1 Ulcers 3.2 HSV 1.6	Cross-sectional study. Diagnosis based on clinical appearance. It was not described the number of patients undergoing HAART. Evaluation of correlation between CD4 T-cell count and oral lesions was included.
Mwangosi e Tyllia (2012), Tanzania	200	100	29.0	7.5	4.0	0.5	ND	ND	KS 3.5	HSV 11.5 Xerost. 1.5 AC 0.5	Cross-sectional study. Diagnosis based on clinical appearance.
Kumar *et al.* (2014), India	126	80.0	74.6	36.5	ND	ND	ND	ND	4.8	Ulcers 11.9 Leuk. 9.8 LP 5.5	Cross-sectional study, comparing HIV-positive patients with a control group (532 subjects). Diagnosis followed WHO 1997 criteria. The study included DMFT score of patients.
Nanteza *et al.* (2014), Uganda	346	0.0	48.6	24.9 EC 8.4 PC 12.1	5.5	ND	ND	2.0	KS 9.3	PIG 17.3 SGS 3.8 HSV 1.7 Ulcers 1.5	Cross-sectional study. Diagnosis followed established criteria (EC-Clearinghouse, 1993). The study included an evaluation of the correlation between CD4+ T-cell count and prevalence of oral candidiasis.

between the incidence of HIV-related oral lesions and viral load (HIV-RNA). In this case, there was also a statistically significant correlation: a high viral load (>20.000 copies/ml) increases the risk of developing HIV-related oral manifestations (4, 26). Different studies about HIV and oral manifestation are reported in Table I.

Another topic is implant dentistry in HIV patients. In fact, since many HIV positive patients have a very long life expectancy, they require implant prosthetic rehabilitation. Problems related to survival rate of implants in positive HIV patients are a topic that requires further insights (40-46).

CONCLUSION

Oral lesions are an important sign of immunodepression and with the introduction of HAART their incidence has strongly decreased, particularly in urban areas. Nevertheless, developing countries still have a high prevalence of these manifestations because of the persistence of many risk factors, such as difficulty in accessing treatment, poor oral hygiene, low socioeconomic status and late diagnosis.

Dental surgeons may have a potential role, not only in the treatment of HIV-related oral manifestations, but also in monitoring the evolution of HIV infection, because of the strong correlation between the presence of oral lesions and a low CD4+ T-cell count (<200 cell/mm^3) (7, 47).

For these reasons, an oral examination might help in the early diagnosis and in the prognosis of HIV infection, as already happens with oral cancer (2, 48-53).

REFERENCES

1. Patton L. Progress in understanding oral health and HIV/AIDS. Oral Dis 2014; 20(3):223-5.
2. Saini R. Oral lesions: A true clinical indicator in human immunodeficiency virus. J Nat Sci Biol Med 2011; 2(2):145-50.
3. Challacombe SJ. Global oral inequalities in HIV infection. Oral Dis 2016; 22(S1):35-41.
4. Gaurav S, Keerthilatha PM, Archna N. Prevalence of oral manifestations and their association with CD4/CD8 ratio and HIV viral load in South India. Int J Dent 2011; 2011:964278.
5. Lourenco AG, Motta AC, Figueiredo LT, Machado AA, Komesu MC. Oral lesions associated with HIV infection before and during the antiretroviral therapy era in Ribeirao Preto, Brazil. J Oral Sci 2011; 53(3):379-85.
6. Classification and diagnostic criteria for oral lesions in HIV infection. EC-Clearinghouse on Oral Problems Related to HIV Infection and WHO Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus. J Oral Pathol Med 1993; 22(7):289-91.
7. Patton LL, Ramirez-Amador V, Anaya-Saavedra G, Nittayananta W, Carrozzo M, Ranganathan K. Urban legends series: oral manifestations of HIV infection. Oral Dis 2013; 19(6):533-50.
8. Sollazzo V, Galasso M, Volinia S, Carinci F. Prion proteins (PRNP and PRND) are over-expressed in osteosarcoma. Journal of Orthopaedic Research 2012; 30(6):1004-12.
9. Palmieri A, Pezzetti F, Brunelli G, Ilaria Z, Carinci F. A comparison between genetic portraits of normal osteoblasts and osteosarcoma cell lines. Indian Journal of Dental Research 2009; 20(1):52-59.
10. Bodo M, Lilli C, Bellucci C, Carinci P, Calvitti M, Pezzetti F, Stabellini G, Bellocchio S, Balducci C, Carinci F, Baroni T. Basic fibroblast growth factor autocrine loop controls human osteosarcoma phenotyping and differentiation. Molecular Medicine 2002; 8(7):393-404.
11. Blotta P, Carinci F, Pelucchi S, Cavazzini L, Martini A. Chondrosarcoma of the nasal septum. Annals of Otology, Rhinology and Laryngology 2001; 110(2):202-04.
12. Lauritano D, Lucchese A, Contaldo M, Serpico R, Muzio LLO, Biolcati F, Carinci F. Oral squamous cell carcinoma: diagnostic markers and prognostic indicators. J Biol Regul Homeost Agents 2016; 30(2):169-76.
13. Palmieri A, Carinci F, Martinelli M, Pezzetti F, Girardi A, Cura F, Rubini C, Scapoli L. Role of the MIR146A polymorphism in the origin and progression of oral squamous cell carcinoma. Eur J Oral Sci 2014; 122(3):198-201.
14. Paderni C, Compilato D, Carinci F, et al. Direct

visualization of oral-cavity tissue fluorescence as novel aid for early oral cancer diagnosis and potentially malignant disorders monitoring. Int J Immunopathol Pharmacol 2011; 24(2S):121-8.
15. Colella G, Izzo G, Carinci F, et al. Expression of sexual hormones receptors in oral squamous cell carcinoma. Int J Immunopathol Pharmacol 2011; 24(2S):129-32.
16. Pannone G, Santoro A, Carinci F, et al. Double demonstration of oncogenic high risk human papilloma virus DNA and HPV-E7 protein in oral cancers. Int J Immunopathol Pharmacol 2011; 24(2S):95-101.
17. Santarelli A, Di Fede O, Carinci F, et al. Reciprocal altered expression of E-cadherin and P-cadherin in mucous membrane pemphigoid. International Journal of Immunopathology and Pharmacology 2011; 24:103-06.
18. Campisi G, Calvino F, Carinci F, et al. Peri-tumoral inflammatory cell infiltration in OSCC: a reliable marker of local recurrence and prognosis? An investigation using artificial neural networks. Int J Immunopathol Pharmacol 2011; 24(2S):113-20.
19. Carinci F, Lessiani G, Spinas E, Kritas SK, Ronconi G, Caraffa A, Conti P. Mast cell and cancer with special emphasis on il-37 an anti-inflammatory and inhibitor of innate immunity: new frontiers. J Biol Regul Homeost Agents 2016; 30:945-50.
20. Bodhade AS, Sindhu MG, Hazarey VK. Oral manifestations of HIV and their correlation with CD4 count. J Oral Sci 2011; 53(203-11.
21. Sontakke SA, Umarji HR, Karjodkar F. Comparison of oral manifestation with CD4+ count in HIV-infected patients. Indian J Dent Res 2011; 22:732.
22. Kumar S, Mishra P, Warhekar S, Airen B, Jain D, Godha S. Oral Health Status and Oromucosal Lesions in Patients Living with HIV/AIDS in India: A Comparative Study. AIDS Res Treat 2014; 2014:480247.
23. Nanteza M, Tusiime JB, Kalyango J, Kasangaki A. Association between oral candidiasis and low CD4+ count among HIV positive patients in Hoima Regional Referral Hospital. BMC Oral Health 2014; 14:143.
24. Silva DC, Lourenco AG, Ribeiro AE, Machado AA, Komesu MC, Motta AC. Oral health management of 97 patients living with HIV/AIDS in Ribeirao Preto, Sao Paulo, Brazil. Braz Oral Res 2015; 29:1-6.
25. Khatibi M, Moshari AA, Jahromi ZM, Ramezankhani A. Prevalence of oral mucosal lesions and related factors in 200 HIV+/AIDS Iranian patients. J Oral Pathol Med 2011; 40(8):659-64.
26. Moodley A, Wood NH. HIV-associated oral lesions in HIV-seropositive patients at an HIV-treatment clinic in South Africa. J AIDS Clin Res 2015; 6:422.
27. Mwangosi IE, Tillya J. Oral lesions associated with HIV/AIDS in HIV-seropositive patients attending a counselling and treatment centre in Dar es Salaam. Int Dent J 2012; 62(4):197-202.
28. Jha R, Kaur T, Sharma A. Oral manifestations of HIV-AIDS: a diagnostic and management dilemma. J Res Med Dent Sci 2014; 2:96-101.
29. Nittayananta W, Tao R, Jiang L, Peng Y, Huang Y. Oral innate immunity in HIV infection in HAART era. J Oral Pathol Med 2016; 45(1):3-8.
30. Goncalves LS, Goncalves BM, Fontes TV. Periodontal disease in HIV-infected adults in the HAART era: Clinical, immunological, and microbiological aspects. Arch Oral Biol 2013; 58(10):1385-96.
31. Denny CE, Ramapuram J, Bastian TS, Ongole R, Binnal A, Natarajan S, Ahmed J. Oral lesions in HIV/AIDS patients on a higly active antiretroviral therapy. World J Dent 2016; 7:95-99.
32. Satyakiran GV, Bavle RM, Alexander G, Rao S, Venugopal R, Hosthor SS. A relationship between CD4 count and oral manifestations of human immunodeficiency virus-infected patients on highly active antiretroviral therapy in urban population. J Oral Maxillofac Pathol 2016; 20(3):419-26.
33. Anaya-Saavedra G, Flores-Moreno B, Garcia-Carranca A, Irigoyen-Camacho E, Guido-Jimenez M, Ramirez-Amador V. HPV oral lesions in HIV-infected patients: the impact of long-term HAART. J Oral Pathol Med 2013; 42(6):443-9.
34. Koyio L, Ranganathan K, Kattappagari KK, Williams DM, Robinson PG. Oral health needs assessment world-wide in relation to HIV. Themes: Oral health needs and inequalities, oral health promotion, co-ordinating research and enhancing dissemination in relation to HIV- a workshop report. Oral Dis 2016; 22:(S1)199-205.
35. Ortega KL, Vale DA, Magalhaes MH. Impact of PI and NNRTI HAART-based therapy on oral lesions of Brazilian HIV-infected patients. J Oral Pathol Med 2009; 38(6):489-94.

36. Patil N, Chaurasia VR, Babaji P, Ramesh D, Jhamb K, Sharma AM. The effect of highly active antiretroviral therapy on the prevalence of oral manifestation in human immunodeficiency virus-infected patients in Karnataka, India. Eur J Dent 2015; 9(1):47-52.
37. Rao W, Benzi R. Single mandibular first molar implants with flapless guided surgery and immediate function: preliminary clinical and radiographic results of a prospective study. J Prosthet Dent 2007; 97(6S):S3-S14.
38. Rao KV, Chitturi RT, Kattappagari KK, Kantheti LP, Poosarla C, Baddam VR. Impact of highly active antiretroviral therapy on oral manifestations of patients with human immunodeficiency virus/acquired immuno deficiency syndrome in South India. Indian J Sex Transm Dis 2015; 36(1):35-9.
39. Batavia AS, Secours R, Espinosa P, Jean Juste MA, Severe P, Pape JW, Fitzgerald DW. Diagnosis of HIV-Associated Oral Lesions in Relation to Early versus Delayed Antiretroviral Therapy: Results from the CIPRA HT001 Trial. PLoS One 2016; 11(3):e0150656.
40. Lauritano D, Bignozzi CA, Pazzi D, Cura F, Carinci F. Efficacy of a new coating of implantabutment connections in reducing bacterial loading: An in vitro study. ORAL and Implantology 2017; 10(1):1-10.
41. Lauritano D, Muzio LL, Gaudio RM, Russo LL, Mucchi D, Nardi GM, Martinelli M. Why should patients with systemic disease and tobacco smokers go to the dentist? J Biol Regul Homeost Agents 2016; 30(2):135-41.
42. Baj A, Muzio LL, Lauritano D, Candotto V, Mancini GE, Gianni AB. Success of immediate versus standard loaded implants: A short literature review. J Biol Regul Homeost Agents 2016; 30(2):183-88.
43. Lauritano D, Muzio LLO, Gaudio RM, Russo LLO, Mucchi D, Nardi GM, Scapoli L. The ecological catastrophe of oral diseases: A possible link between periodontitis and protozoa. J Biol Regul Homeost Agents 2016; 30(2):143-47.
44. Baj A, Sollazzo V, Lauritano D, Candotto V, Mancini GE, Gianni AB. Lights and shadows of bone augumentation in severe resorbed mandible in combination with implant dentistry. J Biol Regul Homeost Agents 2016; 30(2):177-82.
45. Lauritano D, Pazzi D, Iapichino A, Gaudio RM, Di Muzio M, Lo Russo L, Pezzetti F. Evaluation of the efficacy of a new oral gel containing carvacrol and thymol for home oral care in the management of chronic periodontitis using PCR analysis: a microbiological pilot study. J Biol Regul Homeost Agents 2016; 30(2S1):129-34.
46. Lauritano D, Grassi R, Di Stasio D, Lucchese A, Petruzzi M. Successful mandible rehabilitation of lower incisors with one-piece implants. Journal of Medical Case Reports 2014; 8(1):406
47. Bachman SS, Abel SN, Reznik DA. New approaches to oral health care for people living with HIV/AIDS. Public Health Rep 2012; 127:(S2)3-4.
48. Campo J, Cano J, del Romero J, Hernando V, del Amo J, Moreno S. Role of the dental surgeon in the early detection of adults with underlying HIV infection/AIDS. Med Oral Patol Oral Cir Bucal 2012; 17(3):e401-8.
49. Baj A, Ali Youssef D, Monteverdi R, Bianchi B, Combi VA, Giannì AB. Reconstruction of partial maxillary defects with the double-barrel fibula free flap. Acta Otorhinolaryngologica Italica 2010; 30(6):299-302.
50. Baj A, Beltramini GA, Demarchi M, Giannì AB. Extended-pedicle peroneal artery perforator flap in intraoral reconstruction. Acta Otorhinolaryngologica Italica 2013; 33(4):282-85.
51. Baj A, Bellocchio G, Marelli S, Goglio L, Formillo P, Giannì AB. Reconstruction of the anterior floor of the mouth using a peroneal perforator free flap. A case report. Acta Otorhinolaryngologica Italica 2010; 30(1):47-51.
52. Baj A, Spotti S, Marelli S, Beltramini GA, GiAnnì AB. Use of porous polyethylene for correcting defects of temporal region following transposition of temporalis myofascial flap. Acta Otorhinolaryngologica Italica 2009; 29(5):265-69.
53. Lauritano D, Lucchese A, Contaldo M, Serpico R, Muzio LLO, Biolcati F, Carinci F. Moral squamous cell carcinoma: Diagnostic markers and prognostic indicators. J Biol Regul Homeost Agents 2016; 30(2):169-76.