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Oral manifestations of HIV disease: A review

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SUMMARY

The HIV/AIDS pandemic continues to plague the world. Evaluation of oral health status is important at every stage in the management of HIV disease. Oral health services and professionals can contribute effectively to the control of HIV/AIDS through health education, patient care, infection control and surveillance. Dental professionals have an important task of determining accurate diagnosis of oral manifestations and choosing proper treatment for each case. This review provides information on HIV associated orofacial lesions, their clinical presentation and up to date treatment strategies.

Key words: oral lesions, HIV, AIDS, oral health care.

INTRODUCTION

The HIV/AIDS pandemic has become a human and social disaster, particularly in resource limited settings. Oral health is an important component of the overall health status in HIV infection and essential component of quality of life (1,2). HIV-related oral abnormalities occur in 30 to 80 percent of the affected patient population (3). Policies for strengthening oral health promotion and the care of HIV-infected patients have been issued by WHO (2). Oral health services and professionals can contribute effectively to the control of HIV/AIDS through health education, patient care, infection control and surveillance.

Oral lesions are among the early signs of HIV infection and for individuals with unknown HIV status may suggest possible HIV diagnosis. For persons diagnosed with HIV who are not yeat on therapy, the presence of certain oral manifestations may predict progression to AIDS (4). Furthermore, for patients on highly active antiretroviral therapy (HAART) the presence of certain oral manifestations may serve as surrogate markers for the efficacy of antiretroviral therapy (5,6). Even thought the prevalence of specific oral lesions like candidiasis, hairy leukoplakia and Kaposi's sarcoma has been proven to be lower among patients on HAART (7,8,9,10) other conditions such as oral warts (11,12) and salivary gland disease (11,13) have been found to be more prevalent in this population as part of immune reconstitution resulting from antiretroviral therapy initiation.

CLASSIFICATION

There are two main classifications of oral lessions associated with HIV (HIV-OL). The first is based on the HIV-OLs etiology and according to it, they are classified as bacterial, viral, or fungal infections or as neoplastic lesions or other conditions. In 1993 EC-Clearinghouse on Oral Problems Related to HIV Infection and WHO Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus has reached a consensus on new classification of the oral manifestations of HIV infection. It classifies HIV-OLs into three: lesions strongly associated with HIV infection, those less commonly associated with HIV infection and lesions seen in HIV infection (14). (Table1). The 1993 EC-Clearinghouse classification is still globally used despite controversy on the relevance of periodontal diseases today (15). HIV-OL case definitions were updated in 2009 to facilitate the accuracy of HIV-OL diagnoses by non-dental healthcare workers in large-scale epidemiologic studies and clinical trials (16).

Besides diagnosing, it is essential to choose proper treatment for each case. This review provides

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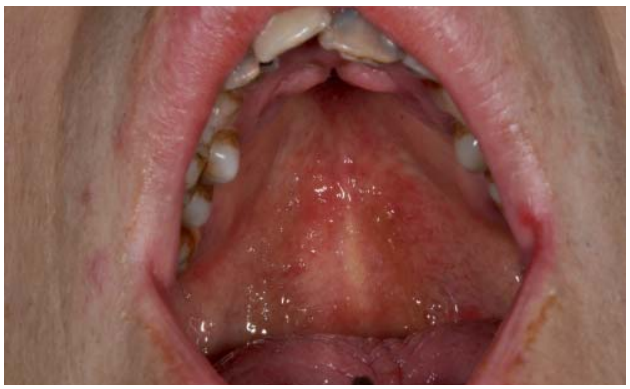

Fig. 1. Erythematous candidiasis in 40 year old male with AIDS, CD4 count 74

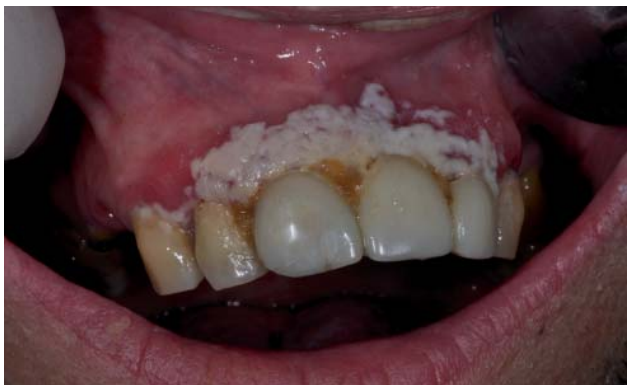

Fig. 2. Pseudomembranous candidiasis in 41 year old male with AIDS, CD4 count 74

information on HIV associated orofacial lesions, their clinical presentaion and treatment strategies (Table 2).

ORAL CANDIDIASIS

Oral cadidiasis (OC) remains the most common HIV-OL (5,7,12). Being strongly associated with a low CD4 count, OC occurred in as many as 90% of patients before introduction of HAART (17). The prevalence of OC among patients who receive antiretroviral treatment is 50% lower compared to the prevalence before HAART era (10). However OC remains common in HIV-infected patients without access to HAART or those for whom antiviral therapy is started late (17).

Candida albicans is the most prominent pathogen (17). Other *Candida* species (particularly *C. krusei*, *C. glabrata, C. dublinensis)* are also associated with oral candidiasis in HIV patients. Emergence of non-albicans *Candida* species might result in reduced azole susceptibility in the oral cavity (17).

OC presents commonly in three forms: erythematous candidiasis, pseudomembranous candidiasis, and angular cheilitis (4).

Erythematous candidiasis (Fig. 1) presents as a red, flat, atrophic lesion on the dorsal surface of the tongue or on the hard or soft palates. The condition tends to be symptomatic, with patients complaining of oral burning, most frequently while eating salty or spicy foods or drinking acidic beverages (2). Erythematous candidiasis form is more prevalent among HIV patiens than in general population (18).

Pseudomembranous candidiasis (Fig. 2) presents as painless creamy white plaque-like lesions on the tongue, palate, buccal mucosa, or oropharynx and is frequently asymptomatic (18).

Table 1. Classification of orofacial lesions associated with HIV/AIDS in adults

Lesions strongly associated with HIV infection	
• Candidiasis – Erythematous – Pseudomembranous • Hairy leukoplakia • Kaposi's sarcoma	• NonHodgkin's lymphoma • Periodontal disease – Linear gingival erythema – Necrotizing (ulcerative) gingivitis – Necrotizing (ulcerative) periodontitis
Lesions less commonly associated with HIV infection	
• Bacterial infections – Mycobacterium aviumintracellulare – Mycobacterium tuberculosis • Melanotic hyperpigmentation • Necrotizing (ulcerative) stomatitis • Salivary gland disease – Dry mouth due to decreased salivary flow rate • Unilateral or bilateral swelling of the majorsalivary glands • Thrombocytopenic purpura • Ulceration NOS (not otherwise specified)	• Viral infections – Herpes simplex virus – Human papillomavirus (wartlike lesions) – Condyloma acuminatum – Focal epithelial hyperplasia – Verruca vulgaris – Varicella zoster virus – Herpes zoster – Varicella
Lesions seen in HIV infection	
• Bacterial infections – Actinomyces Israel – Escherichia coli – Klebsiella pneumoniae • Catscratch disease • Drug reactions (ulcerative, erythema multiforme,lichenoid, toxic epidermolysis) • Epithelioid (bacillary) angiomatosis • Neurologic disturbances – Facial palsy – Trigeminal neuralgia	• Fungal infection other than candidiasis – Cryptococcus neoformans – Geotrichum candidum – Histoplasma capsulatum – Mucoraceae (mucormycosis/ zygomycosis) – Aspergillus flavus • Recurrent aphthous stomatitis • Viral infections – Cytomegalovirus – Molluscum contagiosum

Table 2. Treatment of HIV associated oral lesions

	Systemic treatment		Local treatment
Oral Candidiasis (OC) (1,15,17,27, 31)	Preferred therapy: Fluconazole 100 mg PO QD for 7-14 days Alternative therapy: Itraconazole oral solution 200 mg PO QD for 7-14 days, or Posaconazole oral solution 400 mg PO BID once, then 400 mg daily	**Fluconazole-refractory OC** Itraconazole oral solution ≥ 200 mg PO QD, or Posaconazole 400 mg BID, or Voriconazole 200 mg BID	Preferred therapy: Clotrimazole troches 10 mg PO 5 times daily, or Miconazole mucoadhesive buccal tablet 50 mg QD for 5d. Alternative therapy: Nystatin suspension 4-6 ml QID or 1-2 flavored pastilles 4-5 times daily; Chlorhexidine 0.12% oral rinses
Oral Hairy Leukoplakia (OHL) (15,27)	There is a paucity of evidence on OHL treatment. Acyclovir or other systemic antiviral treatments such as valacyclovir, ganciclovir, foscarnet, famciclovir, and valganciclovir. Lesions recur when treatment is discontinued.		Possible efficacy of podophyllin resin 25% application, or podophyllin resin 25% and acyclovir 5% cream, or surgery and topical tretinoin (retinoic acid, vitamin A)
Non-Hodgkin's lymphoma (1,21)	Acyclovir inhibits viral DNA synthesis in lytic infection but not latent infection. Complex cytokine or cytotoxic therapies oncological treatment. Prognosis is poor, with mean survival time of less than 1 year, despite treatment with multidrug chemotherapy.		
Kaposi's sarcoma (KS) (1,27, 31)	Mild-to-moderate KS: initiation or optimization of antiretroviral therapy (ART); Advanced KS: chemotherapy + ART		Intralesional vinblastine and sodium tetradecyl sulfate 3%; Radiation therapy (800–2,000 cGy), laser therapy
Periodontal diseases Linear gingival erythema (1,21,27)	If Candida is identified, antifungal drugs (see oral candidiasis)		Improved oral hygiene, Chlorhexidine 0.12% oral rinses Periodontal debridement
Necrotising ulcerative disease (1,2,27)	Metronidazole (250 mg orally 4 times daily for 10 days), or other systemic antibiotics, such as tetracycline, clindamycin, amoxicillin, and amoxicillin-clavulanate potassium Adequate pain management		Chlorhexidine 0.12% oral rinses Periodontal debridement
Significant bacterial infections (TB) (21)	Management is systemic in the hands of a specialist physician.		
Melanotic pigmentation (29)			Depigmentation might be treated with surgery, cryosurgery, electrosurgery, or different types of laser surgery
Salivary gland disease (1)	Adequate ART, systemic corticosteroids		Repeated aspiration, or rarely a radical removal of large cysts; drinking more water, chewing sugar free gum
Trombocytopaenic purpura (30)	Plasmapheresis, fresh plasma, corticosteroids (not recommended in very immunosuppressed patients) ART even with stable numbers of CD4 cells or viral load		
Recurrent aphthous-like ulcerations (1,27)	Thalidomide (200 mg/d for 4-6 weeks) has strict requirements for use, but is the most effective. Systemic steroids in same doses and duration as those used for HIV-negative patients with recurrent aphthous ulcerations (prednisone 1 mg/kg), or dapsone 50–100 mg daily for 4 weeks		Topical steroids in same doses and duration as those used for HIV-negative patients with recurrent aphthous ulcerations Chlorhexidine 0.12% oral rinses
Herpes simplex infection (31)	Valacyclovir 1 g PO BID, or Famciclovir 500 mg PO BID, or Acyclovir 400 mg PO TID for 5 to 10 days		
Herpes zoster (31)	Valacyclovir 1g PO BID, or Famciclovir 500 mg PO BID, or Acyclovir 800 mg PO 5 times daily for 7-10 days		
Human papillomavirus (1,2,27,31) Oral warts Condyloma acuminatum			There is no consensus on optimal treatments of oral warts. Treatment may involve surgery, laser surgery, or cryotherapy with or without intraoperative irrigation with podophyllum resin

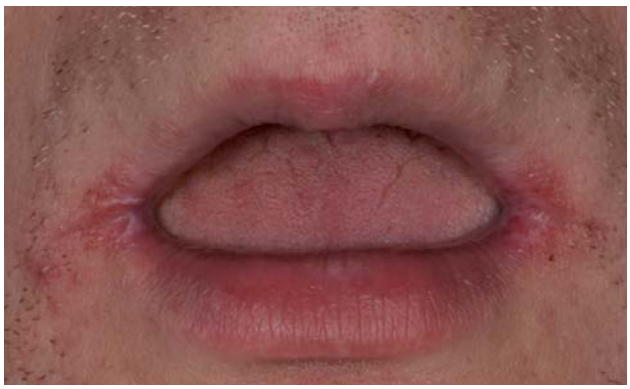

Fig. 3. Angular cheilitis in 33 year old HIV-infected male, CD4 count 480.

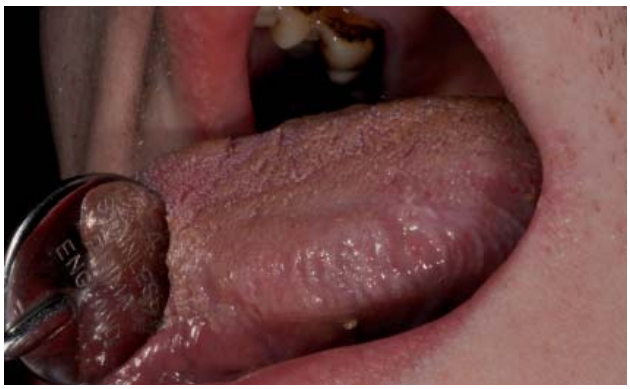

Fig. 4. Oral hairy leukoplakia in 62 year old male with AIDS, CD4 count 110

Angular cheilitis (Fig. 3) can occur with or without erytematous or pseudomembranous candidiasis. It presents as painful erythema, fissuring or erosion of the corners of the mouth covered with fine scale (19).

ORAL HAIRY LEUKOPLAKIA

Oral hairy leucoplakia (OHL) is another reliable indicator of low CD4 count (5,7). It is a benign epithelial hyperplasia on the lateral borders of the tongue, more prevalent in males (Fig. 4) (20). OHL is caused by latent Epstein-Barr virus (EBV) reactivation (4). OHL appears as white, corrugated lesion on the lateral borders of the tongue, that can not be wiped away (2,21). OHL might be unilateral or bilateral.

NON-HODGKIN'S LYMPHOMA

EBV drives a range of malignancies of the lymphatic system, associated with B-cell non-Hodgkin's lymphomas (NHL) (21). Non-Hodgkin's lymphomas (NHL) are 60 times more common in HIV-infected patients, compared to general population (23). Around 25% of all the extranodal NHLs are located in oral cavity (23). Clinically oral NHL presents as growth and ulceration (19). It commonly affects gingival, palatal, and alveolar mucosa and may mimic dental infections (4,21).

KAPOSI'S SARCOMA

Kaposis's sarcoma (KS) is the most frequent HIV-associated oral malignancy (2). KS is caused by human herpesvirus-8 (HHV-8), also called Kaposi sarcoma-associated virus (1,4). HHV-8 infection drives endothelial cells to a form of neoplastic hyperproliferation (21).

Early KS lesions commonly present in mouth, especially palate and gingiva. Clinically colour of lesions may vary from purple or red to brown, or yellow – brown. Lesions of KS can grow to a very considerable size and in advanced AIDS are likely to be multiple. Sometimes lesions may ulcerate. Lesions of greater size show greater risk of complications such as haemorrhage, secondary infection, destruction of bone and periodontium and are a serious aesthetic and functional problem (19).

PERIODONTAL DISEASES

Periodontal diseases are a group of diseases that affect periodontal tissues. Periodontal disease associated with HIV are classified: linear gingival erythema or marginal gingivitis, necrotizing ulcerative disease, and necrotising stomatitis (4,6,21).

LINEAR GINGIVAL ERYTHEMA (LGE)

LGE can be defined as a distinct fiery red band along the margin of the gingiva, most frequently found in anterior teeth, accompanied in some cases by bleeding and discomfort (Fig. 5) (19). The aetiology of this oral disease seems to involve an invasion by *Candida* species of the gingival tissue (9). It manifests in imunocompromised patients with $CD4^+$ T lymphocyte counts <200 cells/mm^3 (4,9).

NECROTISING ULCERATIVE DISEASE

Necrotising ulcerative disease (NUD) is subclasified as necrotising ulcerative gingivitis (NUG) and necrotising ulcerative periodontitis (NUP) that appear to be different stages of the same disease. NUG is characterized by rapid onset and acute painful inflammation of gingiva with rapid destruction of soft tissues. NUP is escorted by bleeding, extremely sharp pain, ulcerated gingival papillae, rapid and extensive soft tissue necrosis and advanced loss of

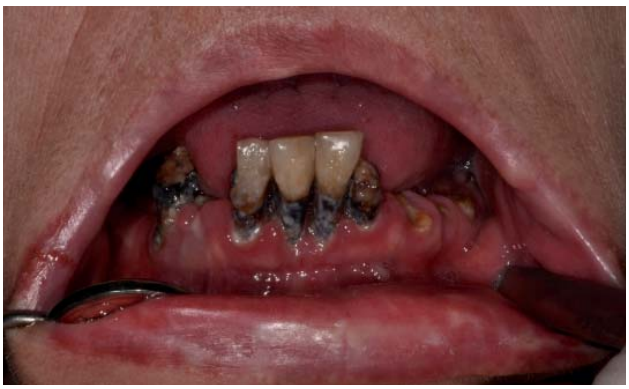

Fig. 5. Linear gingival erythema in 49 year old female with AIDS, CD4 count 115.

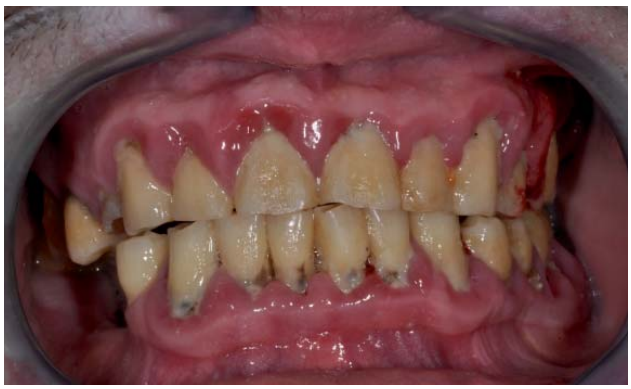

Fig. 6. Necrotising ulcerative disease in 17 year old immunocompetent female

periodontal attachment, frequently leading to bone exposure, and crater-shaped defects, sequestration of a significant piece of alveolar bone (Fig. 6) (19,22). Sometimes necrotizing ulcerative disease may progress to necrotizing stomatitis (9). NUD is ussualy followed by fever, malaise, halitosis and lympthadenopathia (19).

Similarly as in HIV negative patients, microorganisms, associated with necrotic ulcerative periodontal disease include *Porphyromonas gingivalis, Tannerella forsythia, Dialister pneumosintes, Aggregatibacter actinomicetemcomitans* (4).

NUD is more common among immunocompromised patients, particularly if they have psychological/motivational problems, poor nutrition, and use tobacco or other drugs (21). Sometimes NUD might develop as a symptom of immune reconstitution disease after innitiation of HAART (9).

BACTERIAL INFECTIONS

As imunosuppression of HIV infected patient progresesses, extra-pulmonary tuberculosis (TB) becomes more common and affects many internal body sights. Occasionally mycobacteria caused lesions might occur in mouth.

In a study in Kenia it was noticed, that there is a link between TB and oral candidiasis and they suggest that especially in high-incidence communities, TB diagnosis must be sought when a patient presents with oral candidiasis (21).

MELANOTIC PIGMENTATION

Melanotic pigmentation can be found in patients with long HIV history. Some of the reasons that have been advanced to explain such intra-oral pigmentation include: increased release of α melanocyte-stimulating hormone caused by deregulation of cytokines in HIV disease; use of melanocyte-stimulating drugs; antiretrovirals, antifungals and Addison's disease (24,25).

SALIVARY GLAND DISEASE

HIV infection is associated with salivary gland disease (SGD) which clinically results in gland enlargement and diminished flow of secretions (4,19). The enlargement typically involves the tail of the parotid gland or, less commonly, the submandibular gland, and it may present uni- or bilaterally with periods of increased or decreased size (1). Patients suffer from redused salivary flow and mouth dryness (Fig. 7). It is more frequent among men (4). Histologically, there may be lymphoepithelial infiltration and benign cyst formation (1).

TROMBOCYTOPAENIC PURPURA

HIV infection can cause a marked thrombocytopaenia, particularly in the acute or initial phase. This can present to dental clinicians as intramucosal haemorrhages (21).

ORAL ULCERATION AND RECURRENT APHTHOUS STOMATITIS

Atypical ulceration, including recurrent aphthous ulcer, is found in 3-13% HIV-infected patients (25). According to size, number and duration of ulcers recurrent aphthous stomatitis is classified as minor, major and herpetiform. Unlike in immunocompetent patients, they persist for more than 2 weeks and their presence is indicative of immunosupression (4).

HERPES SIMPLEX INFECTION

Recurrent herpes simplex (usually HSV-1, occasionally HSV-2) oral infection is prevalent

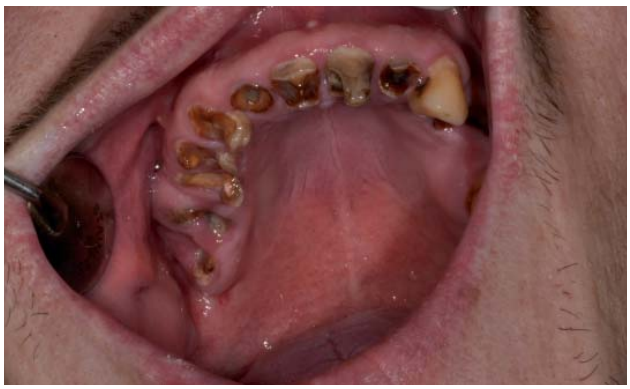

Fig. 7. Extensive caries lesions in HIV-infected 30 year old male due to xerostomia and methamphetamine drug abuse, CD4 count 450

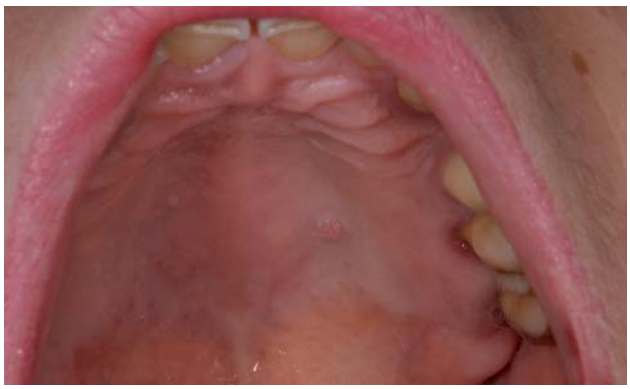

Fig. 8. Oral wart on palate in 51 year old HIV-infected female, CD4 count 586

among HIV infected patients. It might manifest as herpes labialis or primary herpetic gingivostomatitis (21). Oral manifestations, represented by diffuse mucosal ulcerations, are usualy accompanied by fever, malaise, and cervical lymphadenopathy (1). Recurrent intraoral HSV outbreaks start as a small crop of vesicles that rupture to produce small, painful ulcerations that may coalesce. Lesions usually erupt on lips and keratinized tissues, including the hard palate and gums (2). Ulcers might persist for more than 1 month and their presence is indicative of immunosuppression (25). Persisting painful lesions can result in reduced intake of food and weight loss, which worsen the morbid condition (26).

HERPES ZOSTER INFECTION

Contact with the varicella-zoster virus (VZV) may result in varicella (chicken pox) as a primary infection and herpes zoster (shingles) as a reactivated infection. Herpes zoster infection of the oropharyrngeal regions results from reactivation of latent VZV, harbored in the trigeminal nerve, in response to immune deterioration (27). Multiple dermatomes might be involved or herpetic lesions might get secondarily infected. The lesions are usually associated with severe postherpetic neuralgia (2).

HUMAN PAPILLOMAVIRUS

There are over 100 types of human papillomavirus (HPV) (19). In some patients with HIV infection, HPV causes a focal epithelial and connective tissue hyperplasia, forming an oral wart. HPV infection might also result in formation of condyloma acuminatum (28). Oral warts have a papillomatous appearance, either pedunculated or sessile, and are mainly located on the palate, buccal mucosa, and labial commissure (Fig. 8). The most common genotypes of HPV found in the mouth of patients with HIV infection are 2, 6, 11, 13, 16, and 32 (1).

An increase in oral warts was noticed among patients on HAART (11). Development of warts may be related to immune reconstitution (2,4). Warts are often extensive and progressive and recur after removal. Thus they cause substantial discomfort and aesthetic problems (11).

CONDYLOMA ACUMINATUM

Condyloma acuminatum is a contagious HPV-related lesion which usually appears in anogenital area. It is associated with HPV 6, 11, 16, 18, 31 genotypes. Occationally condyloma acuminatum might develop in orofacial area. Clinically eruptions are painless, cauliflower shaped, pink (Fig. 9). As imunosuppresion progresesses, multiple lesions or big conglomerats might develop (19).

It is important to recognise and diagnose oral manifestations of HIV infection since these lesions might be the first symptom of the disease as well as might indicate progression of imunodeficiency or effectiveness of HAART. Adequate treatment of oral lesions associated with HIV infection may considerably increase our patient‘s quality of life.

CONCLUSION

Evaluation of oral health status is important at every stage in the management of HIV disease. Oral candidiasis is the most common oral pathology in HIV infected patients, followed by a large spectrum of other oral manifestations. The necessity to identify HIV-related oral lesions behoves all health care professionals – primary health care workers, infectious diseases specialists, oral health and public health professionals – to closely collaborate to provide the best care, health promotion and prevention possibilities for patients infected with HIV. A major

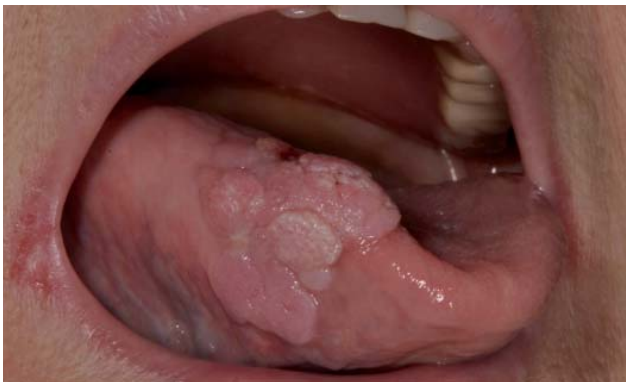

Fig. 9. Condyloma acuminatum in 35 immunocompetent female

challenge lies in the part of HIV- infected persons unaware of their HIV status. Oral health practitioners must take their role in recognizing the potential significance of the oral manifestation of HIV. In the future, the dental office may become a site for rapid testing for HIV.

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All pictures used in this article are from authors' personal archive. Every patient has signed a written consent form to use their pictures for research and publishing.

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