

Oral Manifestations of HIV

Rachana V Prabhu^{1*}, Vishnudas Prabhu², Laxmikanth Chatra¹ and Prashant Shenai¹

¹Department of Oral Medicine and Radiology, Yenepoya Dental College, Yenepoya University, Mangalore, India

²Department of Oral and Maxillofacial Pathology, Yenepoya Dental College, Yenepoya University, Mangalore, India

Abstract

Oral manifestations of HIV are common and have been important in identification of patients harboring the HIV virus and in predicting the decline in their immune system.

Careful history taking and detailed examination of the patient's oral cavity are important parts of the physical examination. Early recognition, diagnosis, and treatment of HIV-associated oral lesions may reduce morbidity. Orofacial manifestations are among the earliest and most common clinical signs of pediatric HIV disease too. Early diagnosis of perinatally exposed infants and children is especially important because the intervals between infection, development of AIDS, and death are compressed in pediatric patients. Early diagnosis allows prompt institution of both multi-drug therapy, which appears to be most effective when instituted early, and prophylactic therapy to forestall life-threatening opportunistic infections. The present paper discusses in detail the oral manifestations of HIV and their diagnostic criteria in adults as well as in pediatric patients.

Keywords: HIV; AIDS; Oral manifestation; Oral lesions

Introduction

Emerging and re-emerging diseases are having a profound worldwide impact on society and on the delivery of medical and oral health care. The acquired immunodeficiency syndrome (AIDS) pandemic, caused by infection with human immunodeficiency virus (HIV) dramatically illustrates the awesome transmission capabilities of disease. Spread by blood borne and sexual contact HIV has infected over 36.1 million people in the world and according to joint UNAIDS (United Nations Programme on HIV/AIDS) and WHO, 1600 new cases are coming up every day [1]. By the end of 2005, an estimated 40.3 million people were alive with HIV infection in the world, the vast majority of who were resident in low-income countries [2].

The estimated number of persons living with HIV worldwide in 2007 is now assumed to be 33.2 million [30.6–36.1 million], a reduction of 16% compared with the estimate published in 2006 (39.5 million [34.7–47.1 million]) [3]. In developing countries in 2007, an estimated 330,000 children younger than the 15 years of age died of AIDS, and more children younger than the age of 5 years die from AIDS now than from any other cause [4]. HIV infection leading to AIDS has been a major cause of illness and death among children, teens, and young adults worldwide. In 2007 alone, 420,000 infants and children were newly infected with HIV in developing countries, more than 1,150 every day. An estimated 330,000 children died from HIV and AIDS during 2007, joining more than 4 million children already claimed by the epidemic [4].

HIV infection can be transmitted through unprotected sexual intercourse with an infected partner. It can be transmitted through unprotected oral sex, both from fellatio and cunnilingus [5]. Other transmission routes are injection or transfusion of contaminated blood or blood products (infection through artificial insemination, skin grafts, and organ transplants is also possible) [6], sharing unsterilized injection equipment that was previously used by an infected person [7] and maternal-fetal transmission (during pregnancy, at birth, and through breastfeeding) [8,9]. Occupational HIV infections of healthcare or laboratory workers may occur, but this mode of infection is not frequent [10]. Transmission of HIV from an infected patient to a health-care worker has been documented after parenteral or mucous-membrane exposure to blood. However, this risk is less than 1%, is

limited to exposure to blood, and can be further minimized through the availability of more effective Antiretroviral Therapy (ART) [11]. There remains little evidence that supports transmission of HIV via oral fluids. However, saliva seems to play an important role in an individual's protection from HIV infections [12,13]. The risk of transmission of HIV from a patient to a dental health care worker remains very low. Transmission of HIV from an infected dental health care worker is also rare, although possible [14,15]. Although hundreds of millions of research dollars have been spent seeking successful treatment and eradication of HIV from infected individuals, that goal has yet to be achieved. A Preventive HIV vaccine is very technically challenging to construct, largely due to a high rate of spontaneous mutation and HIV strain variation and, therefore is not available [16].

Undiagnosed or untreated infection with HIV, results in progressive loss of immune function marked by depletion of the CD4⁺ T lymphocytes (CD4), leading to opportunistic infections and malignancies characteristic of Acquired Immunodeficiency Syndrome (AIDS) [16]. Oral manifestations of HIV are common and have been important in identification of patients harboring the HIV virus and in predicting the decline in their immune system. Early recognition, diagnosis, and treatment of HIV-associated oral lesions may reduce morbidity. Orofacial manifestations are among the earliest and most common clinical signs of pediatric HIV disease too. Early diagnosis of perinatally exposed infants and children is especially important because the intervals between infection, development of AIDS, and death are compressed in pediatric patients. Early diagnosis allows prompt institution of both multi-drug therapy, which appears to be most effective when instituted early, and prophylactic therapy to forestall life-threatening opportunistic infections. The present paper discusses

***Corresponding author:** Rachana V Prabhu, Department of Oral Medicine and Radiology, Yenepoya Dental College, Yenepoya University, Mangalore, India, Tel: +91 8147020203; E-mail: drachanaacharya@rediffmail.com

Received July 12, 2013; Accepted July 24, 2013; Published July 26, 2013

Citation: Prabhu RV, Prabhu V, Chatra L, Shenai P (2013) Oral Manifestations of HIV. J Trop Dis 1: 111. doi:10.4172/2329-891X.1000111

Copyright: © 2013 Prabhu RV, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

in detail the oral manifestations of HIV and their diagnostic criteria in adults as well as in pediatric patients.

Classification of Oral Lesions in HIV Infection in Adults

In 1986, the European Economic Community generated a list of 30 diseases representing those lesions known to be associated with the HIV infection which was then revised by J Pindborg in 1989 [17]. In 1990 a group of oral AIDS clinicians, epidemiologists, and pathologists proposed a set of definitions and diagnostic criteria for the common oral lesions seen in association with the HIV infection [18]. On August 30-31, 1990, based on the discussions during a 2-day EC-sponsored workshop held in Amsterdam, a revised classification was proposed in which three groups of lesions were recognized. Group 1 consisting of lesions strongly associated with HIV infection, Group 2 of lesions less commonly associated with HIV infection and Group 3 were those lesions only possibly associated with HIV infection (Table 1). A fourth group consisting of lesions associated with the use of drugs was

GROUP I	Lesions strongly associated with HIV infection
	a) Candidiasis – Erythematous, Pseudomembranous
	b) Hairy leukoplakia
	c) Kaposi's sarcoma
	d) Non-Hodgkin's lymphoma
	e) Periodontal disease
	Linear gingival erythema
	Necrotizing (ulcerative) gingivitis
	Necrotizing (ulcerative) Periodontitis
GROUP II	Lesions less commonly associated with HIV infection
	a) Bacterial infections
	Mycobacterium avium intracellulare
	Mycobacterium tuberculosis
	b) Melanotic hyperpigmentation
	c) Necrotizing (ulcerative) stomatitis
	d) Salivary gland disease
	Dry mouth due to decreased salivary flow rate
	Unilateral or Bilateral swelling of major salivary glands
	e) Thrombocytopenic purpura
	f) Ulceration NOS (not otherwise specific)
	g) Viral infections
	Herpes simplex virus
	Human papilloma virus (wart-like lesions)
	-Condyloma acuminatum
	-Focal epithelial hyperplasia
	-Verucca vulgaris
	Varicella – Zoster virus
	-Herpes zoster
	-Varicella
GROUP III	Lesions seen in HIV infection
	a) Bacterial infection
	Actinomyces israelii
	Escherichia coli

	Klebsiella pneumoniae
	b) Cat – scratch disease
	c) Drug reactions (Ulceration, Erythema multiforme, Lichenoid, Toxic epidermolysis)
	d) Fungal infections other than candidiasis
	Cryptococcus neoformans
	Geotrichum candidum
	Histoplasma capsulatum
	Mucoraceae (Mucormycosis/Zygomycosis)
	Aspergillus flavus
	e) Neurologic disturbances
	Facial palsy
	Trigeminal neuralgia
	f) Recurrent aphthous stomatitis
	g) Viral infections
	Cytomegalovirus Molluscum contagiosum

Table 1: Revised classification of oral lesions associated with HIV infection in adults.

GROUP I	Seven cardinal lesions that are strongly associated with HIV infection
	Oral candidosis
	Hairy leukoplakia
	Kaposi sarcoma
	Linear gingival erythema,
	Necrotizing ulcerative gingivitis
	Necrotizing ulcerative periodontitis
	Non-Hodgkin lymphoma
GROUP II	Atypical Ulcers
	Salivary glands diseases
	Viral infection such as cytomegalovirus (CMV), herpes simplex virus (HSV), papillomavirus (HPV), and herpes zoster virus (HZV).
GROUP III	Lesion rarer than those on groups 1 and 2
	Diffuse osteomyelitis
	Squamous cell carcinoma

Table 2: Classification of oral lesions associated with HIV infection based on intensity and features.

considered, but definitely accepted. Furthermore, an attempt was made to define the clinical diagnostic criteria of the lesions and conditions listed in Group 1 [19]. On September 17-18, 1992 the previously published classifications of the oral manifestations of HIV infections and their diagnostic criteria were reviewed [18,19]. Table 1 Revised classification of oral lesions associated with HIV infection in adults (1992) [20,21]. Based on the intensity and features, three groups of oral manifestations of AIDS are defined (Table 2) [22,23].

Classification of Oral Lesions in HIV Infected Pediatric Patients

As of June 1998, the World Health Organization (WHO) estimated that 2 million children worldwide had been infected with HIV, representing 7% of the estimated total infected population of almost 30 million. In the United States as of December 31, 1997, 8,086 (1%)

of 641,086 reported cases of AIDS were in children under 13 years of age [24]. HIV-infected infants can be diagnosed presumptively within 1 month after birth by culture of blood mononuclear cells, polymerase chain reaction (PCR), or p24 antigen assay; the diagnosis should be confirmed by a second test 3-6 months later. CD4 lymphocyte counts have been the primary routine measure of immune status and HIV disease progression, but they are less reliable in children than in adults. Most of the HIV-infected children during the first year of life, show normal (high) CD4 counts and symptom free for the first 3-6 months despite high levels of viral replication as demonstrated by PCR. Early diagnosis of perinatally exposed infants and children is especially important because the intervals between infection, development of AIDS, and death are compressed in pediatric patients. Prior to the widespread use of combination drug therapy, approximately one-half of HIV-infected children became clinically symptomatic within the first year of life. Current estimates have decreased to one-quarter, and the rest remain asymptomatic for an unknown number of years. Early diagnosis allows prompt institution of both multi-drug therapy (anti-retrovirals and protease inhibitors), which appears to be most effective when instituted early, and prophylactic therapy to forestall life-threatening opportunistic infections [24].

Orofacial manifestations are among the earliest and most common clinical signs of pediatric HIV disease. In March 1994 and May 1995, the Collaborative Workgroup on the Oral Manifestations of Pediatric HIV Infection met to develop guidelines for the diagnosis and management of HIV-related oral diseases in children [5]. The framework was adapted from the classification system of the European Collaborative Clearinghouse on Oral Problems Related to HIV Infection and the World Health Organization (WHO) Collaborating Centre on Oral Manifestations of the Human Immunodeficiency Virus [20]. The proposed guidelines, are put forth to facilitate early diagnosis of pediatric HIV infection and effective intervention by dental and medical professionals worldwide. The classification of HIV-associated orofacial lesions in children is organized into three groups based on clinical experience and clinical studies limited to the pediatric age group and on the frequency of association of these lesions with HIV infection. Group 1 comprises those lesions commonly associated with pediatric HIV infection; Group 2 includes lesions less commonly associated with pediatric HIV infection; and Group 3 consists of those lesions strongly associated with HIV infection but rare in children (Table 3). Both presumptive and definitive criteria for diagnosis of those lesions are presented. The criteria, listed below, represent the consensus opinion of the Collaborative Workgroup on the Oral Manifestations of Pediatric HIV Infection [21,24].

Current Aspects of the Oral Manifestations of Aids

Since the advent of highly active antiretroviral therapy (HAART), clinical and epidemiological observations have shown a considerable decline in the mortality and morbidity of HIV-positive patients, which can be attributed to a reduction of HIV viral load and the recovery of immune function in previously ill subjects [25]. Patients are protected to some extent against several oral lesion, i.e., candidiasis, salivary gland disease, sarcoma, Kaposi's sarcoma, and oral hairy leukoplakia [26]. The prevalence of all oral lesions has decreased by more than 30% since the introduction of HAART [27].

In a study conducted by Tukuruku et al. [28] the prevalence of Necrotizing Ulcerative Gingivitis (NUG) and Necrotizing Ulcerative Periodontitis (NUP) before HAART was 17%, and 16% of all lesions included these bacterial infections; nowadays the rates are lower at 10%

GROUP I	Lesions commonly associated with pediatric HIV infection
	a) Candidiasis
	Pseudomembranous Erythematous
	Angular cheilitis
	b) Herpes simplex virus infection
	c) Linear gingival erythema
	d) Parotid enlargement
	e) Recurrent aphthous ulcers
	Minor
	Major
	Herpetiform
GROUP II	Lesions less commonly associated with pediatric HIV infection
	a) Bacterial infections of oral tissues
	b) Periodontal diseases
	Necrotizing (ulcerative) gingivitis
	Necrotizing (ulcerative) stomatitis
	Necrotizing stomatitis
	c) Seborrheic dermatitis
	d) Viral infections
	Cytomegalovirus
	Human papilloma virus
	Molluscum contagiosum
	Varicella – Zoster virus
	-Herpes zoster
	-Varicella
	e) Xerostomia
GROUP III	Lesions strongly associated with HIV infection but rare in children
	a) Neoplasms
	Kaposi's sarcoma
	Non-Hodgkin's lymphoma
	b) Oral hairy leukoplakia
	c) Tuberculosis – related ulcers

Table 3: Consensus classification of orofacial lesions associated with pediatric HIV infection.

for NUG and 5% for NUP [29]. However, the prevalence of some oral lesions has nevertheless increased, such as HIV salivary gland disease, or remained the same, such as oral candidiasis, aphtous ulcers, and Kaposi's sarcoma [30].

The frequency and presentation of some oral lesions associated with HIV infection will, and do, vary with the geography [31]. Patients who do not receive ART are likely to still have the common oral features of HIV disease: candidiasis (typically acute pseudomembranous candidiasis), hairy leukoplakia, Kaposi's sarcoma, and perhaps periodontal disease [32]. Tuberculosis is more likely in persons residing in or migrating from the developing world, while periodontal disease and other oral lesions due to the use of antiretroviral drugs seem to be most commonly reported in individuals in the developed world [21].

Diagnostic Criteria for Oral Lesions in Adults

These criteria assume a working knowledge of oral mucosal disease. They have been divided into presumptive and definitive criteria. Presumptive criteria are diagnostic features applied during the clinical assessment of a patient, including the clinical characteristics of a lesion, such as its appearance, color, texture, location, size, and reported symptomatology [19]. They may not be perfect, because other diseases may present with similar appearances.

Definitive criteria include the application of presumptive criteria and a reasonable differential diagnosis, as well as invasive or investigative laboratory tests to confirm the diagnosis. In general, it is recommended that a definitive diagnosis be obtained for many of these orofacial manifestations, especially when the HIV status of a patient is not known [24].

Candidiasis

Candida albicans is the predominant yeast that colonizes the oral cavity of both healthy subjects and HIV-infected individuals in the developed and developing world. However, oral pseudomembranous candidiasis still remains the most common fungal infection of HIV disease; it has been associated with more frequent progression of HIV to AIDS and has been also used as a clinical marker to define the severity of HIV infection [33], with pseudomembranous candidiasis usually followed by erythematous candidiasis.

Candidal infection has been reported in adults, with a prevalence varying from 1.5 to 56%, 65 with the higher prevalence rates in the developing world [34]. The wide variability in the prevalence of oral candidiasis may be attributed to a variety of factors including the socio-demographic and clinical characteristics of the study group and the diagnostic methods employed [35]. Pseudomembranous candidiasis (PC) is the most common clinical presentation of all candidal infections (ranging from 55.8 to 69.7%), followed by erythematous candidiasis (EC) (25.7-50%), angular cheilitis (13.7-27.1%), and hyperplastic candidiasis (0-1.7%) [36,37].

Erythematous candidiasis

Presumptive criteria: Red areas located on the palate and dorsum of the tongue but occasionally on the buccal mucosa. White spots and plaques may be seen but not conspicuous [20].

Definitive criteria: No definitive criteria.

Detection of *Candida albicans* and/or response to anti fungal therapy may help to establish the diagnosis [20].

Pseudomembranous candidiasis

Presumptive criteria: White or yellow spots or plaques located in any part of the oral cavity and can be wiped off to reveal an erythematous surface which may bleed.

Definitive criteria: Response of the lesions to anti fungal therapy & tests (smears or cultures) for the presence of *Candida albicans* [20].

Notes: Angular cheilitis associated with *Candida albicans*, Denture induced stomatitis due to *Candida albicans* may be seen in patients with HIV infection. Different types of candidiasis may coexist in the same patient.

Hairy Leukoplakia

Oral Hairy Leukoplakia (OHL) is a clinical manifestation of

Epstein-Barr virus (EBV) infection almost exclusively found in patients with untreated advanced HIV disease and typically occurs on the lateral border of the tongue of HIV-infected individuals and other groups of immunocompromised individuals [38]. The prevalence of OHL in recent studies of HIV-infected adults varies from 0.42 to 38% in both developed and developing countries [39-41]. The increased prevalence of OHL might be related to a higher exposure to EBV, a lower CD4+ count, and a higher HIV viral load [42,43].

Because OHL is asymptomatic and has no malignant potential, it rarely requires treatment. Nevertheless, acyclovir, and more recently valacyclovir, has been used for the treatment of OHL; unfortunately, acyclovir resistance can prevent the clinical resolution of OHL. Some studies have observed that the frequency of OHL falls with HAART, thus further adding to the rationale that there is little if any need for active intervention in OHL [44].

Presumptive criteria: Bilateral whitish/grey lesions on the lateral margins of the tongue which are not removable and may exhibit vertical corrugations. Lesions may extend onto the ventral and dorsal surfaces of the tongue, where they are usually flat and rarely occur on the buccal mucosa [20].

Definitive criteria: Demonstration of EBV in the lesions. In the absence of facilities to demonstrate the presence of EBV, a lack of response to anti-fungal treatment or the demonstration of an immunodeficient status will add weight to the presumptive diagnosis [20].

Kaposi's Sarcoma

Kaposi's sarcoma (KS) is a malignant, multifocal systemic disease that originates from the vascular endothelium and has a variable clinical course. KS is caused by human herpes virus 8 (HHV-8), which is transmitted sexually or via blood or saliva. The most frequently involved site is the skin, but mucous membranes, the lymphatic system, and viscera, in particular the lung and gastrointestinal tract, can also be involved. In patients with HIV disease, KS usually arises when the CD4+ T cell count is less than 200 [45,46].

The prevalence of oral Kaposi's sarcoma of the mouth varies from 0 to 12% in Africa and 0 to 38% in US and Europe. However, differences in the frequency of both oral and non-oral KS in HIV disease between the developed and developing world are likely to exist. In the developed world, the incidence of HIV-related KS began to decline from 25.6 cases per 1000 person-years (95% confidence interval [CI], 21.8-29.9) in the early 1990s to an average incidence of 7.5 per 1000 person-years (95% CI, 3.4-16.7) in 1996 and 1997 [47] before HAART became available; this trend became more pronounced thereafter. In contrast, the prevalence of KS has risen alarmingly during this same time period in Africa.88 Since the advent of AIDS, KS has become more frequent in both genders, and the male to female ratio has changed from 19:1 to 1.7:1, particularly in East Africa. Recently, the high prevalence of oral KS was demonstrated by the observation that 18.6% of a group of HIV-infected patients in Zimbabwe and from 6 to 14% of another group of patients in the same region had oral KS [48].

Presumptive criteria: One or more erythematous, slightly bluish or violaceous macules or swellings with or without ulceration, predominantly seen on the palate or gingival [20].

Definitive criteria: Characteristic histological appearance on biopsy [20].

Non-Hodgkin's Lymphoma

Non-Hodgkin's Lymphoma (NHL) is the second most common HIV-associated tumor. As with KS, the frequency of this tumor has fallen with the introduction of ART; however, it is still a very common tumor of HIV-infected individuals in the developing world. A variety of NHLs can arise in the mouth in HIV disease; in fact, a rare type called plasmablastic lymphoma seems to nearly always arise exclusively in the mouth [49].

Presumptive criteria: A firm, elastic, often somewhat reddish or purplish swelling, with or without ulceration. The gingiva, palatal mucosa and fauces are sites predilection.

Definitive criteria: Characteristic histological appearance on biopsy, supported by appropriate immunocytochemical or molecular biological investigations.

Periodontal Disease

Gingival and periodontal disease is common in HIV infection, particularly in individuals residing in or who have migrated from the developing world.

In reviewing the previous classification of HIV-related periodontal disease the following changes were made by the EC Clearinghouse [20]:

1. HIV-gingivitis was renamed as Linear gingival erythema
2. HIV-necrotising gingivitis was renamed as Necrotising (ulcerative) gingivitis (NUG)
3. HIV-periodontitis was renamed as Necrotising (ulcerative) periodontitis (NUP)

"Chronic" periodontal disease has been described to be more common and/or more aggressive in HIV-infected patients. The possible occurrence of HIV-specific periodontal disease has been observed in some but not all groups of HIV-infected patients, suggesting that HIV infection alone does not predispose patients to pocketing, attachment loss, or bleeding on probing [50].

The reported prevalence of HIV-related gingival and periodontal disease (excluding opportunistic infections and malignancy) varies from 0 to 47% in adults [105] and from 0 to 20% in children; NUG and NUP are less prevalent, varying from 2.2 to 5% [106]. Although aspects of HIV-induced immunosuppression have been proposed as the likely cause of HIV-related gingival and periodontal disease, HIV-infected patients often have other relevant risk factors, such as tobacco smoking and poor oral hygiene, and these factors alone can explain the increased prevalence of the disease [51].

Linear gingival erythema

Presumptive criteria: A distinct fiery red band along the margin of the gingiva. The amount of erythema is disproportionately intense for the amount of plaque seen. No ulceration is present and no evidence of pocketing or attachment loss [20].

Definitive criteria: This is at present a clinical diagnosis without definitive Criteria. However, a feature of the lesion is that it does not respond well to oral hygiene measures, and the removal of dental plaque and calculus [20].

Necrotising (ulcerative) gingivitis

Presumptive criteria: Destruction of one or more interdental papillae. In the acute stage of the process, ulceration, necrosis and

sloughing may be seen, ready hemorrhage and characteristic fetor [20].

Definitive criteria: This is a clinical diagnosis without definitive criteria [20].

Necrotising (ulcerative) periodontitis

Presumptive criteria: Periodontitis characterized by soft tissue as a result of ulceration or necrosis. Exposure, destruction or sequestration of bone may be seen, and the teeth may become loosened. Pain may be a prominent feature [20].

Definitive criteria: This is a clinical diagnosis without definitive criteria [20].

Changes to the Classification of Group 2 and 3 Lesions

GROUP 2 Lesions less commonly associated with HIV infection [20]

Among the changes made to this part of the classification, cytomegalovirus infections have been moved from Group 2 to Group 3 while melanotic pigmentation has been transferred from Group 3 to Group 2. Bacterial infections caused by *Mycobacterium avium-intracellulare* or *Mycobacterium tuberculosis* has also been transferred from Group 3 to Group 2. Necrotising (ulcerative) stomatitis has been added to the Group 2 list and its criteria are described below. Atypical ulceration is removed from the list and replaced with the term Ulceration NOS (not otherwise specified), the criteria for which are described below.

Necrotizing (ulcerative) stomatitis

Presumptive criteria: Localised acute, painful ulcero-necrotic lesion of the oral mucosa that exposes underlying bone or penetrates or extends into contiguous tissues. These lesions may extend from areas of necrotising periodontitis [20].

Definitive criteria: Histological features are those of non-specific ulceration. Microbiological studies fail to identify a specific aetiological agent [20].

Ulceration NOS (not otherwise specified)

Presumptive criteria: Ulceration with a predilection for a pharynx and palate which does not correspond to any of the recognized patterns of Recurrent Aphthous Stomatitis (RAS).

Definitive criteria: Histological features are those of non-specific ulceration. Viral or bacterial cultures fail to identify a specific aetiological agent [20].

GROUP 3 Lesions seen in HIV Infection. This group was previously entitled "Lesions possibly associated with HIV". Several conditions in this group have been removed from the classification completely. They include: Bacterial infections caused by *Enterobacter cloacae*, exacerbation of apical periodontitis, osteomyelitis, sinusitis, submandibular cellulitis and, perhaps most notably, squamous cell carcinoma. Melanotic hyperpigmentation has been transferred from Group 3 to Group 2. A new section for viral lesions has been introduced into Group 3 to include cytomegalovirus-associated lesions (moved from Group 2) and molluscum contagiosum. Finally, recurrent aphthous stomatitis (RAS) has been added to Group 3. Although the overall incidence of RAS may not be greater in HIV-positive individuals, the incidence of the major or herpetiform types or RAS is increased [20].

Diagnostic Criteria of Oral Lesions in HIV Infected Pediatric Patients Candidiasis

Oral candidiasis is the most common oral lesion in children infected with HIV and is the first clinically observable manifestation of the disease. Studies [52,53] indicate that oral candidiasis occurs in up to 72% of all cases of pediatric HIV infection. Furthermore, candidiasis may be of significant value in predicting the development of AIDS in infected children [54]. Three presentations of oral candidiasis have been documented in HIV-infected pediatric patients and are described below. Among children in the developed and developing world, rates of oral candidiasis have been described as varying from 22.5 to 83.3%. PC infection seems to be the most prevalent form in children followed by EC, and then angular cheilitis as the third most prevalent. However, EC has been occasionally reported to be more prevalent than PC [55].

Pseudomembranous candidiasis

Presumptive criteria: Multifocal, nonadherent creamy white papules or plaques that can be wiped off with minimal pressure, leaving an erythematous surface. Pinpoint or petechial bleeding may be observed occasionally after removal of the superficial white coating. In general, these lesions are widespread and may be located anywhere in the oropharyngeal area [24].

Definitive criteria: The patient's response to antifungal therapy is the principal defining criterion for diagnosis. However, cytologic smear or culture tests for the presence of *Candida* spp. may be helpful, particularly if the patient does not respond to antifungal treatment due to potential resistance [24].

Erythematous candidiasis

Presumptive criteria: Multiple, flat, red patches of varying intensity, most commonly located on the palate and the dorsum of the tongue. Nonadherent, filmy white-to-creamy plaques may be seen concurrently with this form of candidiasis. Median rhomboid glossitis, which is usually a red, smooth, depapillated patch on the mid-dorsal tongue, is a variant of this form of candidiasis. Tenderness or a burning sensation may be experienced [24].

Definitive criteria: Definitive diagnosis may be assisted by detection of *Candida* spp. in culture or cytologic smear or by the patient's response to antifungal treatment [24].

Angular cheilitis

Presumptive criteria: Linear red or ulcerated fissures radiating from the corners of the mouth. Typically the lesions are bilateral, and multiple red papules may be found when the adjacent perioral skin is involved. Concurrent intraoral candidal involvement is a common clinical finding. These lesions are usually tender and slow to heal because of repeated manipulation from opening the mouth [24].

Definitive criteria: Definitive diagnosis may be assisted by detection of intraoral *Candida* spp. in culture or cytologic smear or by the patient's response to antifungal therapies. A staphylococcal or streptococcal coinfection may be present in some cases [24].

Herpes Simplex Virus infection

Herpes simplex virus (HSV) infection is a common childhood infection that is not specifically related to HIV status. The primary disease, referred to as primary gingivostomatitis, and the secondary disease, referred to as recurrent HSV infection, may develop in children with HIV infection. Most studies do not distinguish between the two

forms of the disease. The reported prevalence for HSV infections in HIV-infected children ranges from 1.7% to 24% [56,57].

Presumptive criteria: Patients will exhibit fever and malaise, swollen and tender cervical lymph nodes, and intraoral and perioral lesions on the gingiva, hard palate, and vermilion border of the lips. However, any mucosal site may be involved. Initially present as vesicles, these lesions rupture to become painful, irregular ulcers.

Definitive criteria: Confirmation of a diagnosis of herpetic infection by laboratory methods is available but rarely used. The virus may be isolated in tissue culture. Intact intraoral vesicles are rare. Cytologic examination reveals ballooning degeneration of infected epithelial cells and nuclear inclusion bodies, but it does not permit viral identification. Therefore, DNA hybridization is necessary for a definitive diagnosis [24].

Linear gingival erythema

Linear gingival erythema, which was formerly referred to as HIV gingivitis, is the most common form of HIV-associated periodontal disease in HIV infected children. The prevalence of this type of gingivitis varies widely in different studies, ranging from 0% to 48% [53,57]. The frequency of this particular lesion in children is not known but appears to differ among study populations.

Presumptive criteria: A fiery red, linear band 2 to 3 mm wide on the marginal gingiva accompanied by petechiae-like or diffuse red lesions on the attached gingiva and oral mucosa. The amount of erythema is disproportionately intense given the amount of plaque present. The erythema may be accompanied by bleeding during brushing and, in severe cases, by spontaneous bleeding. It is most notable on the buccal surfaces from cuspid to cuspid. Pain is rarely associated with linear gingival erythema [19].

Definitive criteria: There are currently no known criteria for obtaining a definitive diagnosis of linear gingival erythema. However, linear gingival erythema resists conventional plaque removal therapies and oral, hygiene measures. A similar clinical presentation occurs in neutropenia. Thus, clinicians should review results of a recent complete blood count and differential analysis of the white blood cells [24].

Parotid enlargement

Parotid swelling occurs in 10% to 30% of HIV infected children, although a study [11] of 99 infected children found the condition in nearly half of all subjects. The condition generally occurs late in the course of HIV disease. HIV testing is recommended for pediatric patients with parotid swelling who are not known to be HIV positive. Parotid swelling has been associated with slower progression to AIDS; the median time to death has been reported as 3.4 years among patients with oral candidiasis and 5.4 years among those with parotid swelling [58].

Presumptive criteria: Unilateral or bilateral diffuse soft-tissue swelling resulting in facial disfigurement. May be accompanied by pain, and may be associated with lymphoid interstitial pneumonitis [24].

Definitive criteria: No criteria have been established for the definitive diagnosis of parotid swelling.

Recurrent Aphthous Ulcers

Recurrent aphthous ulcers occur in approximately 2% to 6% of the adult HIV-infected population and are more common among HIV-infected children, especially due to drugs such as ddI that may induce

lesions. Recurrent aphthous ulcers occur in several different clinical forms, usually described as minor, major, and herpetiform, based on the size, number, and duration of lesions present.

Minor recurrent aphthous ulcers

Presumptive criteria: A small ulcer less than 5 mm in diameter covered with a pseudomembrane and surrounded by an erythematous halo.

Definitive criteria: A prompt response to steroid treatment confirms the diagnosis of recurrent aphthous ulcers [24].

Major recurrent aphthous ulcers

Presumptive criteria - Similar to those for minor recurrent aphthous ulceration; however, the mucosal lesions are much larger-sometimes 1 to 2 cm in diameter -and may persist for weeks at a time. Major recurrent aphthous ulcers are painful and may interfere with mastication and swallowing. They tend to occur on the soft palate, buccal mucosa, tonsillar area, and tongue.

Definitive criteria - Response to treatment with steroid agents.

Herpetiform recurrent aphthous ulcers

Presumptive criteria: Herpetiform lesions appear as clusters or crops of tiny recurrent aphthous ulcers, 1 to 2 mm in diameter, which may coalesce. Like major recurrent aphthous ulcers, herpetiform lesions tend to occur in locations where they hinder eating and speaking, such as the soft palate, buccal mucosa, tonsillar area, and tongue.

Definitive criteria: Response to treatment with steroid agents.

Bacterial Infections of Oral Tissues

HIV-infected children are more susceptible than adults to bacterial infections, especially those involving polysaccharide-encapsulated organisms (e.g., *Streptococcus pneumoniae*). Bacterial infections in immunocompromised children are frequently severe, deep seated, and difficult to treat. Sinusitis and otitis media occur in children almost universally.

Periodontal Diseases

Moreover, although HIV-associated periodontal diseases have been thought to appear less frequently in children than in adults, recent studies indicate that this assessment may be premature. A study of one cohort of 67 HIV infected children in Newark, New Jersey, showed a periodontal disease prevalence of 37% [59], and a study of 84 HIV-infected children in Rwanda reported periodontal disease as the most common oral manifestation [58].

Necrotizing ulcerative gingivitis (NUG)

Presumptive criteria: The destruction of one or more interdental papillae accompanied by necrosis, ulceration, and/or sloughing. Destruction is limited to the marginal gingival tissues. In the acute stage (i.e., acute necrotizing ulcerative gingivitis, or ANUG), the gingival tissues appear fiery-red and swollen, and are accompanied by yellowish-gray necrotic tissue that bleeds easily. Patients experience symptoms such as bleeding while brushing, pain, and a characteristic halitosis [24].

Definitive criteria: There are at present no definitive criteria for either NUG or ANUG. Diagnosis must be determined clinically. Responds to systemic antibiotic treatment and local debridement.

Necrotizing ulcerative periodontitis (NUP)

Presumptive criteria: Severe soft-tissue necrosis along with destruction of the periodontal attachment and bone over a short period of time. Patients often experience spontaneous gingival bleeding or bleeding when brushing and severe, deep, aching pain in the jaw bone. In the most severe cases, the jawbone may be exposed. The final stage of necrotizing ulcerative periodontitis is marked by severe gingival recession resulting from rapid bone loss and soft-tissue necrosis.

Definitive criteria: There are at present no definitive criteria for the diagnosis of necrotizing ulcerative periodontitis.

Necrotizing Stomatitis (NS)

Presumptive criteria: Acute and painful ulceronecrotic lesion on the oral mucosa. Underlying bone may be exposed, or the lesion may penetrate or extend into adjoining tissues.

Definitive criteria: Histologic examination reveals the features of nonspecific ulceration. No specific microbial organism has been identified as the cause of necrotizing stomatitis.

Seborrheic dermatitis

Presumptive criteria - Erythema and scaling of the scalp, skin behind the ears, and nasolabial folds are particularly characteristic.

Definitive criteria

No definitive criteria.

Viral Infections

Cytomegalovirus

Presumptive criteria: Lesions associated with cytomegalovirus may mimic a number of persistent oral ulcers, including aphthous ulcers, recurrent herpes simplex virus infection, necrotizing stomatitis, and ulceration NOS. Occasionally this infection may present as a brightly erythematous gingivitis.

Definitive criteria: A definitive diagnosis can be made through culture and biopsy.

Human papillomavirus (HPV)

Presumptive criteria: Raised, irregular, flesh-colored lesions (warts).

Definitive criteria: Excisional biopsy. However, diagnosis is generally based on clinical appearance.

Molluscum contagiosum

Presumptive criteria: A virally induced lesion of the skin, mucus membranes, and, rarely, the oral cavity. Lesions are small, discrete and dome-shaped. Their color ranges from pearly white to skin color. In HIV-infected patients, the lesions may number in the hundreds.

Definitive criteria: When the core of the lesion is expressed and stained, molluscum bodies, which are virally transformed epithelial cells, can be seen.

Varicella Zoster Virus

Herpes zoster

Presumptive criteria: Secondary disease or reactivation of latent varicella-zoster virus. Herpes zoster is primarily a condition that affects older adults and those who are immunocompromised. Pain or

paresthesia is a prodromal symptom. A well-delineated unilateral maculopapular rash that becomes pustular and ulcerated follows.

Definitive criteria: Cytologic examination reveals virus-infected epithelial cells. Commonly confused with recurrent herpes simplex virus infections, herpes zoster can be definitively diagnosed through virus antigen typing with laboratory immunologic tests [24].

Varicella

Presumptive criteria: Primary infection with the varicella-zoster virus, one of the herpes viruses. A rash involving the head, neck and trunk may be accompanied by fever, chills, malaise and headache. The rash becomes vesicular, pustular and, finally, ulcerated. With successive waves of viremia, successive crops of new lesions appear. When the oral mucus membranes are involved, evanescent vesicles precede multiple shallow ulcers.

Definitive criteria: Careful attention to history of exposure and type and distribution of lesions usually leads to clinical diagnosis.

Xerostomia

Presumptive criteria - Dry mouth and severely reduced salivary flow rates.

Definitive criteria - No definitive criteria exist for xerostomia.

Kaposi's Sarcoma and Non-Hodgkin's Lymphoma

HIV-associated cancers such as Kaposi's sarcoma and non-Hodgkin's lymphoma are far less common in children than in adults. The incidence of HIV-associated cancers in symptomatic children is less than 2%. Recent research indicates that Kaposi's sarcoma may in fact be caused by a herpes virus; however, the significance of this finding for HIV-infected pediatric patients has yet to be determined.

Oral hairy leukoplakia

Presumptive criteria: White, nonremovable lesions with corrugated surface appearing bilaterally on the lateral border of the tongue. These lesions may appear on the ventral and dorsal surfaces of the tongue and, more rarely, on the buccal mucosa.

Definitive criteria: Presence of Epstein-Barr virus in the lesions, to be determined by laboratory histopathology and in situ DNA hybridization. If these studies cannot be performed, the lack of response to antifungal therapy may reinforce a presumptive diagnosis of hairy leukoplakia.

Tuberculosis-related ulcers

Presumptive criteria: Painless, non-healing ulceration of the buccal mucosa, hard palate, gingivae and/or tongue. Occasionally TB may present with tongue involvement manifested as macroglossia or a mass in the cheeks. In most cases the mucosal lesions are difficult to recognize, but enlarged regional lymph nodes may call attention to the process.

Definitive criteria: A chest X-ray and a PPD test with appropriate controls should be obtained when the disease is suspected. The diagnosis is usually confirmed with acid-fast stains and cultures obtained from suspicious lesions and other sources (sputum, tracheal aspirates, bronchoalveolar lavages, gastric aspirates, lymph nodes, or tissue biopsies) [59].

Conclusion

As the Oral manifestations are among the earliest and most

important indicators of HIV infection, a better understanding these manifestations in both adults and children is a must for all dental health care workers. Early recognition, diagnosis, and treatment of HIV-associated oral lesions may reduce morbidity of the adults. Early diagnosis of perinatally exposed infants and children allows prompt institution of both multi-drug therapy, which appears to be most effective when instituted early, and prophylactic therapy to forestall life-threatening opportunistic infections.

The prevention, diagnosis, treatment, and control of these oral manifestations should be part of the objectives of every dental health professional.

References

- National AIDS Control Organization (2003) Prevention of HIV Transmission in health care Settings. In: Training Module on HIV Infection & AIDS for Medical Officers 3-16.
- Health protection agency (2006) Evidence of continuing increase in the HIV prevalence among injecting drug users in England and Wales. *CDR Weekly* 16: 51.
- UNAIDS (2007) Report on the Global AIDS epidemic. WHO.
- UNAIDS (2008) UNAIDS and the Joint United Nations Programme on HIV/AIDS. Children and AIDS: Second stocktaking report. Actions and progress.
- Rothenberg RB, Scarlett M, del Rio C, Reznik D, O'Daniels C (1998) Oral transmission of HIV. *AIDS* 12: 2095-2105.
- Najjoulah F, Barlet V, Renaudier P, Guitton C, Crova P, et al. (2004) Failure and success of HIV tests for the prevention of HIV-1 transmission by blood and tissue donations. *J Med Virol* 73: 347-349.
- Metsch LR, Pereyra M, Purcell DW, Latkin CA, Malow R, et al. (2007) Correlates of lending needles/syringes among HIV-seropositive injection drug users. *J Acquir Immune Defic Syndr* 46: S72-S79.
- Salvatori F, De Martino M, Galli L, Vierucci A, Chieco-Bianchi L, et al. (1998) Horizontal transmission of human immunodeficiency virus type 1 from father to child. *AIDS Res Hum Retroviruses* 14: 1679-1685.
- French MA, Herring BL, Kaldor JM, Sayer DC, Fumer V, et al. (2003) Intrafamilial transmission of HIV-1 infection from individuals with unrecognized HIV-1 infection. *AIDS* 17: 1977-1981.
- Fraser VJ, Powderly WG (1995) Risks of HIV infection in the health care setting. *Annu Rev Med* 46: 203-211.
- Marcus R, Kay K, Mann JM (1989) Transmission of human immunodeficiency virus (HIV) in health-care settings worldwide. *Bull World Health Organ* 67: 577-582.
- Scully C, Porter S (2000) HIV topic update: oro-genital transmission of HIV. *Oral Dis* 6: 92-98.
- Campo J, Perea MA, del Romero J, Cano J, Hernando V, et al. (2006) Oral transmission of HIV, reality or fiction? An update. *Oral Dis* 12: 219-228.
- Scully C, Greenspan JS (2006) Human immunodeficiency virus (HIV) transmission in dentistry. *J Dent Res* 85: 794-800.
- [No authors listed] (1992) Risk of HIV transmission during dental treatment. *Lancet* 340: 1259-1260.
- Patton LL (2003) HIV disease. *Dent Clin North Am* 47: 467-492.
- Pindborg JJ (1989) Classification of oral lesions associated with HIV infection. *Oral Surg Oral Med Oral Pathol* 67: 292-295.
- Greenspan JS, Barr CE, Sciubba JJ, Winkler JR (1992) Oral manifestations of HIV infection. Definitions, diagnostic criteria, and principles of therapy. The U.S.A. Oral AIDS Collaborative Group. *Oral Surg Oral Med Oral Pathol* 73: 142-144.
- [No authors listed] (1991) An update of the classification and diagnostic criteria of oral lesions in HIV infection. EEC-clearinghouse on Oral Problems Related to HIV Infection and WHO Collaborating Centre on Oral Manifestations of the Human Immunodeficiency Virus. *J Oral Pathol Med* 20: 97-100.
- Classification and diagnostic criteria for oral lesions in HIV infection (1993) 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* 22: 289-291.
21. Patton LL, Phelan JA, Ramos-Gomez FJ, Nittayananta W, Shiboski CH, et al. (2002) Prevalence and classification of HIV-associated oral lesions. *Oral Dis* 8: 98-109.
 22. Coogan MM, Greenspan J, Challacombe SJ (2005) Oral lesions in infection with human immunodeficiency virus. *Bull World Health Organ* 83: 700-706.
 23. Challacombe S (1991) Revised classification of HIV-associated oral lesions. *Br Dent J* 170: 305-306.
 24. Ramos-Gomez FJ, Flaitz C, Catapano P, Murray P, Milnes AR, et al. (1999) Classification, diagnostic criteria, and treatment recommendations for orofacial manifestations in HIV-infected pediatric patients. Collaborative Workgroup on Oral Manifestations of Pediatric HIV Infection. *J Clin Pediatr Dent* 23: 85-96.
 25. Sterne JA, Hernán MA, Ledergerber B, Tilling K, Weber R, et al. (2005) Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. *Lancet* 366: 378-384.
 26. Porter SR, Scully C (1998) HIV topic update: protease inhibitor therapy and oral health care. *Oral Dis* 4: 159-163.
 27. Ceballos-Salobrena A, Gaitan-Cepada LA, Ceballos-Garcia L, Lezema-Del Valle D (2000) Oral lesions in HIV/AIDS patients undergoing highly active antiretroviral treatment including protease inhibitors: a new face of oral AIDS? *AIDS Patients Care STDS* 14: 627-635.
 28. Tukutuku K, Muyembe-Tamfum L, Kayembe K, Odio W, Kandi K, et al. (1990) Oral manifestations of AIDS in a heterosexual population in a Zaire hospital. *J Oral Pathol Med* 19: 232-234.
 29. Reichart PA (2003) Oral manifestations in HIV infection: fungal and bacterial infections, Kaposi's sarcoma. *Med Microbiol Immunol* 192: 165-169.
 30. 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.
 31. Leao JC, Ribeiro CM, Carvalho AA, Frezzini C, Porter S (2009) Oral complications of HIV disease. *Clinics (Sao Paulo)* 64: 459-470.
 32. 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 Oral Radiol Endod* 92: 623-628.
 33. Ranganathan K, Hemalatha R (2006) Oral lesions in HIV infection in developing countries: an overview. *Adv Dent Res* 19: 63-68.
 34. Naidoo S, Chikte U (2004) Oro-facial manifestations in paediatric HIV: a comparative study of institutionalized and hospital outpatients. *Oral Dis* 10: 13-18.
 35. Campo J, Del Romero J, Castilla J, García S, Rodríguez C, et al. (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.
 36. Bendick C, Scheifele C, Reichart PA (2002) Oral manifestations in 101 Cambodians with HIV and AIDS. *J Oral Pathol Med* 31: 1-4.
 37. Chidzonga MM (2003) HIV/AIDS orofacial lesions in 156 Zimbabwean patients at referral oral and maxillofacial surgical clinics. *Oral Dis* 9: 317-322.
 38. Lin HC, Corbet EF, Lo EC (2001) Oral mucosal lesions in adult Chinese. *J Dent Res* 80: 1486-1490.
 39. Arendorf T, Holmes H (2000) Oral manifestations associated with human immunodeficiency virus (HIV) infection in developing countries—are there differences from developed countries? *Oral Dis* 6: 133-135.
 40. Greenspan JS, Greenspan D (2002) The epidemiology of the oral lesions of HIV infection in the developed world. *Oral Dis* 8: 34-39.
 41. 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.
 42. Rahman MA, Kingsley LA, Breinig MK, Ho M, Armstrong JA, et al. (1989) Enhanced antibody responses to Epstein-Barr virus in HIV-infected homosexual men. *J Infect Dis* 159: 472-479.
 43. Eyeson JD, Tenant-Flowers M, Cooper DJ, Johnson NW, Warnakulasuriya KA (2002) Oral manifestations of an HIV positive cohort in the era of highly active anti-retroviral therapy (HAART) in South London. *J Oral Pathol Med* 31: 169-174.
 44. Walling DM, Flaitz CM, Nichols CM (2003) Epstein-Barr virus replication in oral hairy leukoplakia: response, persistence, and resistance to treatment with valacyclovir. *J Infect Dis* 188: 883-890.
 45. Martró E, Esteve A, Schulz TF, Sheldon J, Gambús G, et al. (2007) Risk factors for human Herpesvirus 8 infection and AIDS-associated Kaposi's sarcoma among men who have sex with men in a European multicentre study. *Int J Cancer* 120: 1129-1135.
 46. Leão JC, Hinrichsen SL, de Freitas BL, Porter SR (1999) [Human herpes virus 8 and Kaposi's sarcoma]. *Rev Assoc Med Bras* 45: 55-62.
 47. Jacobson LP, Yamashita TE, Detels R, Margolick JB, Chmiel JS, et al. (1999) Impact of potent antiretroviral therapy on the incidence of Kaposi's sarcoma and non-Hodgkin's lymphomas among HIV-1-infected individuals. Multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr* 21: S34-41.
 48. Thomas JO (2001) Acquired immunodeficiency syndrome-associated cancers in Sub-Saharan Africa. *Semin Oncol* 28: 198-206.
 49. Navarro CM, Shibli JA, Ferrari RB, d'Avila S, Spoto MR (2008) Gingival primary extranodal non-Hodgkin's lymphoma as the first manifestation of acquired immunodeficiency syndrome. *J Periodontol* 79: 562-566.
 50. Narani N, Epstein JB (2001) Classifications of oral lesions in HIV infection. *J Clin Periodontol* 28: 137-145.
 51. Robinson PG, Boulter A, Birnbaum W, Johnson NW (2000) A controlled study of relative periodontal attachment loss in people with HIV infection. *J Clin Periodontol* 27: 273-276.
 52. (1991) Children born to women with HIV-1 infection: natural history and risk of transmission. European Collaborative Study. *Lancet* 337: 253-260.
 53. Ketchum L, Berkowitz RJ, McIlveen L, Forrester D, Rakusan T (1990) Oral findings in HIV-seropositive children. *Pediatr Dent* 12: 143-146.
 54. Ramos-Gomez FJ, Hilton JF, Canchola AJ, Greenspan D, Greenspan JS, et al. (1996) Risk factors for HIV-related orofacial soft-tissue manifestations in children. *Pediatr Dent* 18: 121-126.
 55. Magalhães MG, Bueno DF, Serra E, Gonçalves R (2001) Oral manifestations of HIV positive children. *J Clin Pediatr Dent* 25: 103-106.
 56. Katz MH, Mastrucci MT, Leggott PJ, Westenhouse J, Greenspan JS, et al. (1993) Prognostic significance of oral lesions in children with perinatally acquired human immunodeficiency virus infection. *Am J Dis Child* 147: 45-48.
 57. Moniaci D, Cavallari M, Greco D, Bruatto M, Raiteri R, et al. (1993) Oral lesions in children born to HIV-1 positive women. *J Oral Pathol Med* 22: 8-11.
 58. Soubry R, Taelman H, Banyangiliki V, Ladner J, Van de Perre P (1995) Necrotizing periodontal disease in HIV-1-infected patients: a 4-year study in Kigali, Rwanda. In: Greenspan JS, Greenspan D, eds. Oral manifestations of HIV infection. Proceedings of the Second International Workshop on the Oral Manifestations of HIV Infection. Carol Stream, IL: Quintessence 60-67.
 59. (1990) American Thoracic Society. Diagnostic standards and classification of tuberculosis. *Am Rev Respir Dis* 142: 725-735.