



## CASE STUDY

### ORAL MANIFESTATIONS OF HIV INFECTION

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#### ABSTRACT

HIV-related oral conditions occur in a large proportion of patients, and frequently are misdiagnosed or inadequately treated. Dental expertise is necessary for appropriate management of oral manifestations of HIV infection or AIDS, but many patients do not receive adequate dental care. Common or notable HIV-related oral conditions include xerostomia, candidiasis, oral hairy leukoplakia, periodontal diseases such as linear gingival erythema and necrotizing ulcerative periodontitis, Kaposi's sarcoma, human papilloma virus-associated warts, and ulcerative conditions including herpes simplex virus lesions and recurrent aphthous ulcers. This article summarizes a presentation on oral manifestations of HIV disease and its clinical presentation.

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## INTRODUCTION

Studies have estimated that more than 90% of persons with human immunodeficiency virus (HIV) infection will have at least one oral manifestation at some time during the course of their disease (McCarthy, 1992; Greenspan *et al.*, 1990). A summary of these studies has shown that the frequency and type of oral lesion varies with the patient's stage of disease and degree of immunosuppression (Greenspan *et al.*, 1990). The studies often contradict each other about when a particular manifestation may first appear and about the relative frequency of a given lesion; the discrepancies seem to be a function of the populations studied. All, however, agree that the risk for oral complications increases as further immunologic impairment develops (Kirby *et al.*, 1994; Glick *et al.*, 1994; Nielsen *et al.*, 1994; Kolokotronis *et al.*, 1994; Glick *et al.*, 1994; Lifson *et al.*, 1994; Royce *et al.*, 1991). Data also identify oral diseases as a marker for deteriorating immune function independent of CD4<sup>+</sup> lymphocyte count. The identification of such lesions may, therefore, have prognostic significance for the

development of the acquired immunodeficiency syndrome (AIDS) in affected patients (Katz *et al.*, 1992; Nielsen *et al.*, 1994; Feigal *et al.*, 1991; Maden *et al.*, 1994). Severely compromised oral health has serious implications for the general health of patients with HIV infection. Left untreated, oral disease can result in odynophagia and dysphagia, which may interfere with talking, chewing, and swallowing. Persons with severe pain reduce their oral intake of nutrients, resulting in weight loss, dehydration, malnutrition, and the HIV wasting syndrome. Prevention and treatment of oral disease are important in maintaining quality of life and preventing more serious complications. Thus, it is important that physicians recognize the earliest signs of the most common oral diseases so that they can diagnose and treat the disease and provide appropriate dental referrals.

#### Classification of Orofacial Lesions Associated with HIV

There are two main classification systems of oral lesions associated with HIV infection. The first is based on the etiology of the oral lesions. According to this system, orofacial lesions are classified as bacterial, viral, or fungal infections or as neoplastic lesions or other conditions. The second, more widely used, system—recommended by the EC (European

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Community) Clearinghouse on Oral Problems Related to HIV Infection and WHO Collaborating Centre on Oral Manifestations of the Human Immunodeficiency Virus—

classifies orofacial lesions into three groups according to the degree of their association with HIV infection. Tables 1 and 2 show this classification of orofacial lesions associated with HIV/AIDS in adults and children, respectively.

**Table 1. Orofacial lesions associated with HIV/AIDS in adults**

Lesions strongly associated with HIV infection	
1	<ul style="list-style-type: none"> <li>● Candidiasis               <ul style="list-style-type: none"> <li>– Erythematous</li> <li>– Pseudomembranous</li> </ul> </li> <li>● Hairy leukoplakia</li> <li>● Kaposi's sarcoma</li> </ul>
	<ul style="list-style-type: none"> <li>● Non-Hodgkin's lymphoma</li> <li>● Periodontal disease               <ul style="list-style-type: none"> <li>– Linear gingival erythema</li> <li>– Necrotizing (ulcerative) gingivitis</li> <li>– Necrotizing (ulcerative) periodontitis</li> </ul> </li> </ul>
Lesions less commonly associated with HIV infection	
2	<ul style="list-style-type: none"> <li>● Bacterial infections               <ul style="list-style-type: none"> <li>– Mycobacterium avium-intracellulare</li> <li>– Mycobacterium tuberculosis</li> </ul> </li> <li>● Melanotic hyperpigmentation</li> <li>● Necrotizing (ulcerative) stomatitis</li> <li>● Salivary gland disease               <ul style="list-style-type: none"> <li>– Dry mouth due to decreased salivary flow rate</li> <li>– Unilateral or bilateral swelling of the major salivary glands</li> </ul> </li> <li>● Thrombocytopenic purpura</li> <li>● Ulceration NOS (not otherwise specified)</li> </ul>
	<ul style="list-style-type: none"> <li>● Viral infections               <ul style="list-style-type: none"> <li>– Herpes simplex virus</li> <li>– Human papillomavirus (wart-like lesions)                   <ul style="list-style-type: none"> <li>– Condyloma acuminatum</li> <li>– Focal epithelial hyperplasia</li> </ul> </li> <li>– Verruca vulgaris</li> <li>– Varicella zoster virus</li> <li>– Herpes zoster</li> <li>– Varicella</li> </ul> </li> </ul>
Lesions seen in HIV infection	
3	<ul style="list-style-type: none"> <li>● Bacterial infections               <ul style="list-style-type: none"> <li>– Actinomyces israeli</li> <li>– Escherichia coli</li> <li>– Klebsiella pneumoniae</li> </ul> </li> <li>● Cat-scratch disease</li> <li>● Drug reactions (ulcerative, erythema multiforme, lichenoid, toxic epidermolysis)</li> <li>● Epithelioid (bacillary) angiomatosis</li> <li>● Neurologic disturbances               <ul style="list-style-type: none"> <li>– Facial palsy</li> <li>– Trigeminal neuralgia</li> </ul> </li> </ul>
	<ul style="list-style-type: none"> <li>● Fungal infection other than candidiasis               <ul style="list-style-type: none"> <li>– Cryptococcus neoformans</li> <li>– Geotrichum candidum</li> <li>– Histoplasma capsulatum</li> <li>– Mucoraceae (mucormycosis/ zygomycosis)</li> <li>– Aspergillus flavus</li> </ul> </li> <li>● Recurrent aphthous stomatitis</li> <li>● Viral infections               <ul style="list-style-type: none"> <li>– Cytomegalovirus</li> <li>– Molluscum contagiosum</li> </ul> </li> </ul>

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**Table 2. Orofacial lesions associated with pediatric HIV infection**

Lesions commonly associated with pediatric HIV infection	
1	<ul style="list-style-type: none"> <li>● Oral candidiasis               <ul style="list-style-type: none"> <li>– Pseudomembranous</li> <li>– Erythematous</li> <li>– Angular cheilitis</li> </ul> </li> <li>● Herpes simplex virus infection</li> <li>● Linear gingival erythema</li> </ul>
	<ul style="list-style-type: none"> <li>● Parotid enlargement (swelling of the major salivary glands)</li> <li>● Recurrent aphthous ulcers               <ul style="list-style-type: none"> <li>– Minor</li> <li>– Major</li> <li>– Herpetiform</li> </ul> </li> </ul>
Lesions less commonly associated with pediatric HIV infection	
2	<ul style="list-style-type: none"> <li>● Bacterial infections of oral tissues</li> <li>● Periodontal diseases               <ul style="list-style-type: none"> <li>– Necrotizing ulcerative gingivitis</li> <li>– Necrotizing ulcerative periodontitis</li> <li>– Necrotizing stomatitis</li> </ul> </li> <li>● Xerostomia</li> <li>● Seborrheic dermatitis</li> </ul>
	<ul style="list-style-type: none"> <li>● Viral infections               <ul style="list-style-type: none"> <li>– Cytomegalovirus</li> <li>– Human papillomavirus</li> <li>– Molluscum contagiosum</li> <li>– Varicella zoster virus                   <ul style="list-style-type: none"> <li>– Herpes zoster</li> <li>– Varicella</li> </ul> </li> </ul> </li> </ul>
Lesions strongly associated with HIV infection but rare in children	
3	<ul style="list-style-type: none"> <li>● Neoplasms               <ul style="list-style-type: none"> <li>– Kaposi's sarcoma and non-Hodgkin's lymphoma</li> </ul> </li> <li>● Oral hairy leukoplakia</li> <li>● Tuberculosis-related ulcers</li> </ul>

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## Orofacial manifestation of HIV infection Oral Candidiasis

Oral candidiasis is the most common orofacial manifestation of HIV infection. Its prevalence may depend on study population, diagnostic criteria, study design, and availability of antiretroviral therapy. Reported prevalence rates have varied widely, to as high as 72% in children and 94% in adults. Oral candidiasis is also a significant predictor of HIV disease progression in both adults and children. The median time of survival from its clinical diagnosis to death is 3.4 years among HIV-infected children. The main etiologic factor of oral candidiasis is the fungus *Candida albicans*, although other species of *Candida* may be involved.

### Clinical appearance

Oral candidiasis is often observed in one of the following four clinical forms: *erythematous (atrophic) candidiasis*, *pseudomembranous candidiasis*, *hyperplastic candidiasis*, and *angular cheilitis*. Erythematous (atrophic) candidiasis appears clinically as multiple small or large patches, most often localized on the tongue and/or palate (Figure 1). Pseudomembranous candidiasis (oral thrush) is characterized by the presence of multiple superficial, creamy white plaques that can be easily wiped off, revealing an erythematous base (Figure 2). They are usually located on the buccal mucosa, oropharynx, and/or dorsal face of the tongue. Hyperplastic candidiasis lesions appear white and 3. hyperplastic and cannot be removed by scraping. This form of oral candidiasis is rare in HIV-infected individuals.

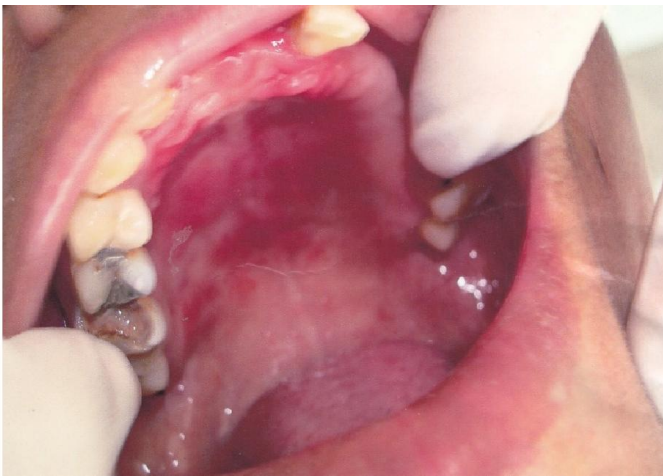


Figure 1. Erythematous candidiasis



Figure 2. Pseudomembranous candidiasis

## Oral Hairy Leukoplakia

Oral hairy leukoplakia (OHL) is more common among HIV-infected adults than among HIV-infected children. The reported prevalence of OHL in adults is about 20%-25%, increasing as the CD4+ lymphocyte count decreases, whereas in children the prevalence is about 2%-3%. The presence of OHL is a sign of severe immunosuppression. OHL is a significant predictor of HIV disease progression in adults. Although its etiology is not clear, OHL seems to be caused by Epstein-Barr virus infection.

### Clinical appearance

OHL presents as white, thick patches that do not wipe away and that may exhibit vertical corrugations with a hairlike appearance (Figure 3). The lesions usually start on the lateral margins of the tongue and sometimes inside the cheeks and lower lip. They may be unilateral or bilateral, and they are asymptomatic. OHL is often associated with oral candidiasis.

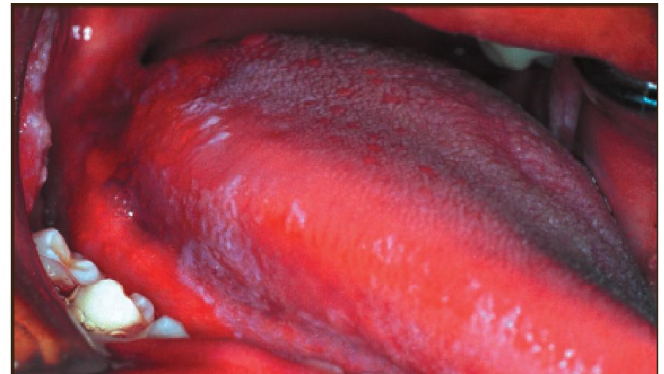


Figure 3. Oral hairy leukoplakia

## Kaposi sarcoma

Kaposi's sarcoma is a multicentric proliferation of vascular and spindle cell components, which was first described in 1872 by Moritz Kaposi. Kaposi sarcoma is a low-grade vascular neoplasm associated with Human Herpesvirus-8 (HHV8) infection. Although India has a large HIV infected population, Kaposi's sarcoma is rare and only 12 cases of AIDS related Kaposi's sarcoma from India have been reported in the published literature to our knowledge. The 50% of total cases in India has been reported from Mumbai. The incidence of AIDS related Kaposi's sarcoma is increasing as more than 50% of the cases are reported in 2008 to 2010. (Joshi *et al* AIDS Related Kaposi's Sarcoma presenting with Palatal and Eyelid Nodule)

### Clinical appearance

They are typically found on the skin, but spread elsewhere is common, especially the mouth, gastrointestinal tract and respiratory tract. Most common oral sites of Kaposi sarcoma are palate and gingival mucosa. Early oral mucosal sarcomas are flat and slightly blue, red or purple plaques either focal or diffused, may be completely asymptomatic and easily overlooked with time, lesion become more deeply discolored and surface papules and soft nodules develop or may become exophytic and ulcerated and may bleed, usually measuring less than 2cm in size. Individual lesions may coalesce



**Figure 4. Kaposi sarcoma**

### HIV-Associated Periodontal Disease

Periodontal (gum) disease is common among HIV-infected patients. It is characterized by bleeding gums, bad breath, pain/discomfort, mobile teeth, and sometimes sores. Its reported prevalence ranges widely, between 0% and 50%. Left untreated, HIV-associated periodontal disease may progress to life-threatening infections, such as Ludwig's angina and noma (cancrum oris).

### Clinical appearance

Four forms of HIV-associated periodontal disease have been described: linear gingival erythema, necrotizing ulcerative gingivitis (NUG), necrotizing ulcerative periodontitis (NUP), and necrotizing stomatitis.

### Linear gingival erythema

Linear gingival erythema, or "red band gingivitis," presents as a red band along the gingival margin and may or may not be accompanied by occasional bleeding and discomfort (Figure 4). It is seen most frequently in association with anterior teeth, but commonly extends to the posterior teeth. It can also present on attached and non-attached gingiva as petechialike patches. Some data indicate a relationship between sub-gingival colonization of *Candida* species and HIV-related periodontal conditions including linear gingival erythema. The most recent American Academy of Periodontology classification of periodontal diseases groups linear gingival erythema under "gingival disease of fungal origin."



**Figure 5. Linear gingival erythema**

NUG is more common in adults than in children. It is characterized by the presence of ulceration, sloughing, and

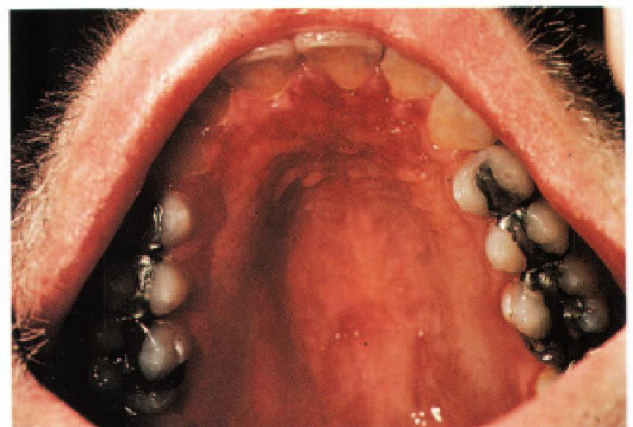
necrosis of one or more interdental papillae, accompanied by pain, bleeding, and fetid halitosis. NUP is characterized by the extensive and rapid loss of soft tissue and teeth. Necrotizing stomatitis is thought to be a consequence of severe, untreated NUP. It is characterized by acute and painful ulceronecrotic lesions on the oral mucosa that expose underlying alveolar bone.

### Herpes Simplex Virus Infection

Herpes simplex virus (HSV) infection may be either primary (herpetic gingivostomatitis) or secondary (herpes labialis). The prevalence of oral HSV infection varies between 10% and 35% in HIV-infected adults and children. The presence of HSV infection for more than 1 month constitutes an AIDS-defining condition.

### Clinical appearance

HSV infection appears as a crop of vesicles usually localized on the keratinized mucosa (hard palate, gingiva) and/or vermillion borders of the lips and perioral skin (Figure 5). The vesicles rupture and form irregular painful ulcers. They may interfere with mastication and swallowing, resulting in decreased oral intake and dehydration.



**Figure 6. Herpes Simplex Virus Infection**

### Recurrent Aphthous Ulcers

Recurrent aphthous ulcers (RAUs) occur in about 1%-7% of HIV-infected patients. They are painful ulcers on the nonkeratinized oral mucosa, such as labial and buccal mucosa, soft palate, and ventral aspect of the tongue. Severe recurrent aphthous lesions usually occur when the CD4+ lymphocyte count is less than 100 cells/ $\mu$ L. This result may be suggestive of HIV disease progression. The etiology of RAUs is not well known.

### Clinical appearance

RAUs may present as minor, major, or herpetiform aphthae. Minor aphthous ulcers are ulcers less than 5 mm in diameter covered by pseudomembrane and surrounded by an erythematous halo. They usually heal spontaneously without scarring (Figure 6). Major aphthous ulcers resemble minor aphthous ulcers, but they are fewer and larger in diameter (1-3 cm), are more painful, and may persist longer. Their presence interferes with mastication, swallowing, and speaking. Healing

occurs over 2-6 weeks. Scarring is common. Herpetiformaphthous ulcers occur as a crop of many small lesions (1-2 mm) disseminated on the soft palate, tonsils, tongue, and/or buccal mucosa.



Figure 7a. Recurrent Aphthous Ulcers



Figure 7b. Recurrent Aphthous Ulcer

### Parotid Enlargement and Xerostomia

Parotid enlargement is commonly associated with HIV infection in children (10%-30%) and less commonly in adults. It occurs in the late course of HIV infection and is associated with a slower rate of HIV disease progression. The median time from its diagnosis to death has been reported to be 5.4 years among HIV-infected children. Lymphocytic infiltration of the salivary glands may be an etiologic factor.

### Clinical appearance

Parotid enlargement occurs as unilateral or bilateral swelling of the parotid glands. It is usually asymptomatic and may be accompanied by decreased salivary flow (xerostomia or dry mouth). Problems with dry mouth in HIV-infected patients are often caused by medications that interfere with salivary secretion, such as antihistamines, antianxiety medications, antidepressants, and some antiretroviral drugs (didanosine and zalcitabine).

### Human Papillomavirus Infection (Oral Warts)

The incidence of oral warts due to human papillomavirus infection has increased dramatically since the era of HAART.

The lesions are more prevalent in adults (1%-4% of cases) than in children.

### Clinical appearance

Oral warts may appear cauliflower-like, spiked, or raised with a flat surface. They are asymptomatic. The most common location is the labial and buccal mucosa. The most common clinical presentation is multifocal flat lesions resembling focal epithelial hyperplasia (Heck's disease).

### Common HPV serotypes

Category	Examples	Common HPV Serotypes
Nongenital Cutaneous	common warts, flat warts, plantar warts	1, 2, 3, 4, 7, 10, 63
Anogenital/Mucosal	anogenital cancer: high risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
	anogenital cancer: probable high risk	26, 53, 66, 68, 73, 72
	oropharyngeal cancer	16, 18, 31, 33, 35
Epidermodyplasia verruciformes		5, 8, 9, 10, 12, 14, 17, 20

### Summary

Oral conditions seen in association with HIV disease are still quite prevalent and clinically significant. A thorough examination of the oral cavity can easily detect most of the common lesions. An understanding of the recognition, significance, and treatment of said lesions by primary health care providers is essential for the health and well-being of people living with HIV disease. HIV prevalence is increasing worldwide because people on antiretroviral therapy are living longer, although new infections decreased from 3.3 million in 2002, to 2.3 million in 2012. Global AIDS-related deaths peaked at 2.3 million in 2005, and decreased to 1.6 million by 2012. An estimated 9.7 million people in low-income and middle-income countries had started antiretroviral therapy by 2012. New insights into the mechanisms of latent infection and the importance of reservoirs of infection might eventually lead to a cure. The role of immune activation in the pathogenesis of non-AIDS clinical events (major causes of morbidity and mortality in people on antiretroviral therapy) is receiving increased recognition. Breakthroughs in the prevention of HIV important to public health include male medical circumcision, antiretrovirals to prevent mother-to-child transmission, antiretroviral therapy in people with HIV to prevent transmission, and antiretrovirals for pre-exposure prophylaxis. Research into other prevention interventions, notably vaccines and vaginal microbicides, is in progress. (HIV infection: epidemiology, pathogenesis, treatment, and prevention)

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