

## ORAL MANIFESTATIONS OF HIV INFECTIONS - A REVIEW

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### ABSTRACT

Oral disease is frequently associated with HIV. Factors that predispose to HIV-related oral conditions include CD4+ cell count of less than 200/ $\mu$ L, plasma HIV RNA levels greater than 3000 copies/mL, xerostomia, poor oral hygiene, and smoking. While nearly all oral disorders associated with HIV infection also occur in other conditions characterized by immunosuppression, no other condition is associated with as wide and significant a spectrum of oral disease as is HIV infection. Many HIV-associated oral disorders occur early in HIV infection, not infrequently as the presenting sign or symptom. Thus, early detection of associated oral disease should, in many cases, result in earlier diagnosis of HIV infection. HIV-related oral abnormalities are present in 30% to 80% of HIV-infected individuals, and these abnormalities are often inaccurately described in medical care. Rates of treatment for oral conditions are also very low; findings in 1424 adults in the AIDS Cost and Utilization Study indicated that only 9.1% received treatment for oral manifestations of HIV diseases. Factors predictive of receiving oral care included education beyond a high school level, participation in clinical trials, and utilization of support services such as medical social workers. Likewise, awareness of the variety of oral disorders which can develop throughout the course of HIV infection, and coordination of health care services between physician and dentist, should improve overall health and comfort of the patient. This paper reviews the clinical aspects of HIV-associated oral disorders.

**Key Words:** HIV, oral manifestations, oral diseases

(Bangladesh J Physiol Pharmacol 2007; 23(1&2) : 25-30)

### INTRODUCTION

#### Oral Manifestations of HIV Infections-

Dental expertise is necessary for proper management of oral complications in HIV infection or AIDS. Based on standard classification and diagnostic criteria, common HIV-associated oral disorders can be broadly classified into four categories by pathophysiological process: infection (fungal, viral, bacterial), neoplasm, immune-mediated, and other (xerostomia, pain syndromes, and nutritional) (Table 1). No particular oral lesion is uniquely associated with HIV infection. However, the presence of one or more lesions requires that HIV infection be considered as a possible underlying cause. Some oral lesions, such as oral candidiasis and oral hairy leukoplakia, are so strongly associated with HIV infection that they have been incorporated into the Centers for Disease Control and Prevention clinical classification of HIV disease<sup>1</sup>.

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### Table-I

#### Common HIV-Associated Oral Disorders

##### Infection

Fungal: candidiasis; cryptococcus; histoplasmosis; aspergillosis.

Viral: herpes simplex virus; oral hairy leukoplakia (Epstein-Barr); human papilloma virus; cytomegalovirus.

Bacterial: bacillary angiomatosis (*Rochalimaea henselae*); linear erythematous gingivitis; necrotizing ulcerative periodontitis; syphilis (*Treponema pallidum*).

##### Neoplasm:

Fungal: Kaposi's sarcoma.

Viral: non-Hodgkin's lymphoma.

Immune-Mediated:

Fungal: major aphthous.

Viral: necrotizing stomatitis.

##### Other:

Fungal: xerostomia; parotid disease.

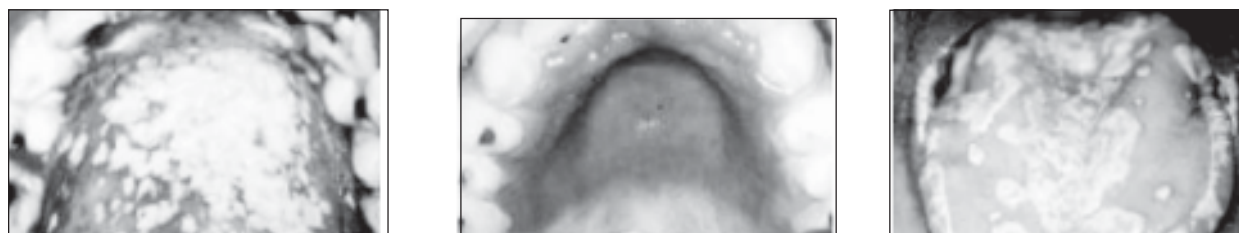
Viral: pain syndromes.

Bacterial: nutritional.

Indeed, the emergence of one or more oral lesions correlates highly with HIV progression. The spectrum of HIV-associated oral lesions also varies with transmission risk-factor, gender, age, and health-care access. Oral health is an important component of overall health status in HIV infection. Even common dental diseases such as caries and periodontal disease have greater impact on patients with HIV infection<sup>2</sup>. Odontogenic pain and non-replacement of missing teeth may limit oral intake of food required for adequate nutrition. Many medications used to treat HIV infection and associated opportunistic infections contribute to increased numbers of caries as a result of decreased salivation and cariogenic fermentable carbohydrate substrates in the presence of several topical oral medications. Painful HIV-associated oral diseases such as necrotizing ulcerative periodontitis and stomatitis, major aphthous ulceration, candidiasis, and Kaposi's sarcoma impair ingestion of food and negatively impact on nutritional health. Therefore, it is essential that the physician and dentist, together, identify and reduce risk factors for oral disease in the patient with HIV infection<sup>3</sup>.

### Fungal Infections

**Candidiasis.** The most common HIV-related oral lesion is candidiasis, predominantly due to *Candida albicans*. While *Candida* can be isolated from 30–50% of the oral cavities of healthy adults, making it a constituent of the normal oral flora, clinical oral candidiasis rarely occurs in healthy patients. In stark contrast, clinical oral candidiasis has been reported to occur in 17–43% of patients with HIV infection and in more than 90% of patients with AIDS. One report found that unexplained oral candidiasis in healthy adults with risk factors for HIV infection predicted the development of clinical signs of AIDS within 3 months<sup>4, 5</sup>. Based on clinical appearance, oral candidiasis can appear as one of four distinct clinical entities: erythematous or atrophic candidiasis, pseudomembranous candidiasis, hyperplastic or chronic candidiasis, and angular cheilitis. In all cases, the infection is superficial. While in most instances the clinical appearance is adequate to arrive at a diagnosis, simple exfoliative cytology will identify the characteristic budding yeast and hyphae when the clinical diagnosis is uncertain<sup>6</sup>. The appearance of each clinical type of candidiasis is summarized in Table 2 and representative photographs are depicted in Fig. 1.



**Fig-1:** Clinical spectrum of oral candidiasis. From left to right: pseudomembranous, removable white plaques; erythematous and hyperplastic (non-removable) candidiasis.

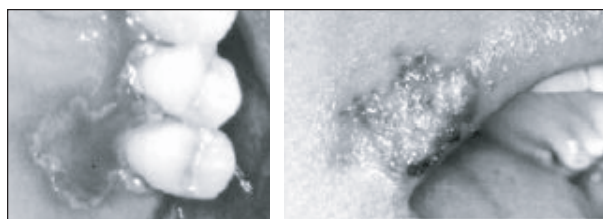
**Table-II**  
Clinical Types of Oral Candidiasis

Type	Appearance	Significance
Erythematous /Atrophic disease	Erythematous or atrophic macular patches on palate, buccal mucosa, and tongue	Associated with early HIV
Pseudomembranous	Yellow-white plaque which can be easily wiped away; any mucosal surface	Associated with initial and progressive immune deterioration; CD4<400
Hyperplastic/chronic with angular chilitis	White non removable plaque; any mucosal surface radiating fissure from labial commissure, sometimes covered with pseudomembrane	Associated with severe immune suppression /long standing HIV diseases- may be associated risk for carcinoma Can occur all stages of HIV diseases; Xerostomia may be a contributory factor

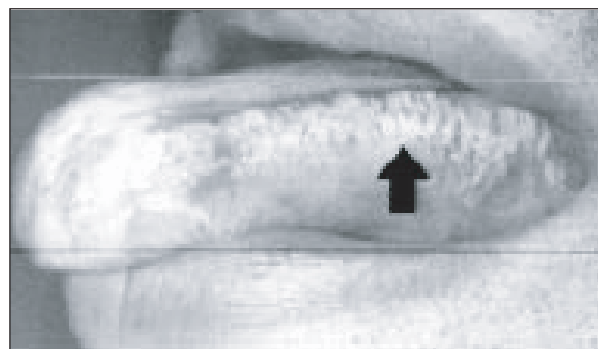
**Deep Fungal Infections.** Unlike the superficial infection of candidiasis, several systemic fungal infections can infrequently lead to single or multiple, deep oral lesions with the potential for considerable local tissue destruction. Cryptococcosis, histoplasmosis, aspergillosis, and mucormycosis are uncommon oral deep fungal infections which require histological diagnosis. Treatment typically requires the use of intravenous antifungal therapy with amphotericin<sup>7</sup>.

**Viral Infections**

Herpesvirus accounts for the majority of HIV-related oral viral infections, most frequently as recurrent oral herpes due to herpes simplex virus (HSV) or Epstein-Barr virus (EBV)-induced oral hairy leukoplakia (OHL)<sup>8</sup>. Less commonly occurring viral infections involving the oral cavity include cytomegalovirus and human papilloma virus (fig 4). Figs. 2 and 3 illustrate the common oral viral infections which occur most frequently in patients with HIV infection.



**Fig. 2:** Oral HSV lesions in patients with HIV infection. From left to right-coalesced shallow palatal HSV ulceration, HSV labialis of 4 weeks' duration.

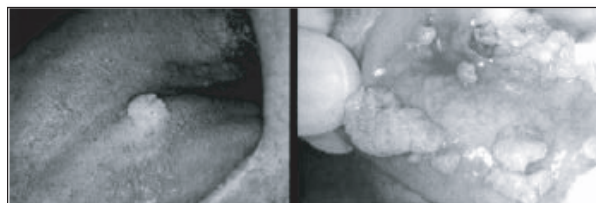


**Fig. 3:** Oral hairy leukoplakia due to Epstein-Barr virus. Adherent white corrugated patches on the lateral tongue.

**Herpes Simplex Virus.** Intraoral herpes in healthy individuals results in multiple, small, shallow ulcerations with irregular raised white borders. Small clusters of lesions usually coalesce to form a larger ulcer, which heals uneventfully in 7–10 days. While the prevalence of seropositive HSV and the rate of reactivation is similar among both HIV-infected and non-infected populations, estimated to be 60% for those older than 30 years of

age, recurrent intraoral HSV in patients with HIV infection often results in ulceration and pain of longer duration. Recurrent intraoral HSV lesions occur more commonly on poorly keratinized tissue like the buccal and labial mucosa, an uncommon site in healthy individuals. The pain associated with persistent herpetic ulceration can result in reduced oral intake of food and significant weight loss<sup>9, 10</sup>.

**Oral Hairy Leukoplakia (OHL).** Although originally postulated to be pathognomonic for HIV infection, this lesion has subsequently been reported in other immune deficiency states as well as in immunocompetent individuals. It appears as an asymptomatic adherent white patch with vertical corrugations, most commonly on the lateral borders of the tongue (Fig. 3). It may infrequently be confused with hypertrophic candidiasis and is predominantly found in homosexual males. Oral hairy leukoplakia has since been shown to be associated with a localized Epstein-Barr virus (EBV) infection and occurs most commonly in individuals whose CD4 lymphocyte count is less than 200/mm<sup>3</sup><sup>11</sup>.



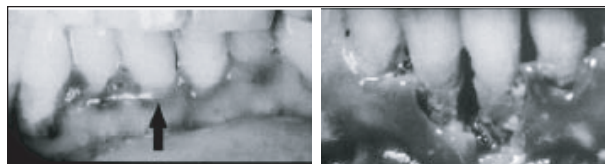
**Fig-4.** Human papilloma virus. Solitary oral wart (left) and multiple, recurrent warts (right).

**Cytomegalovirus (CMV).** It is necessary to recognize oral CMV, which is an uncommon cause of intraoral ulceration in patients with HIV disease. CMV has been detected postmortem in one or more organ systems in as many as 90% of patients with AIDS. Oral CMV infection typically appears as a solitary, chronic deep ulceration most often involving the buccal and labial mucosa. Clinically, it is indistinguishable from other nonspecific ulcerations such as chronic HSV and major aphthous ulceration<sup>12</sup>.

**Bacterial Infections**

Although isolated cases of oral infection with *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Actinomyces israelii*, *Escherichia coli*, and *Mycobacterium avium intracellulare* have been reported in patients with HIV infection, the most common oral lesions associated with bacterial infection are linear erythematous gingivitis, necrotizing ulcerative periodontitis, and, much less commonly, bacillary epithelioid angiomatosis and syphilis<sup>13</sup>. In the case of the periodontal infections, the bacterial flora is no different from that of a healthy individual with periodontal disease. Thus, the clinical lesion is a manifestation of the altered immune response to the pathogens.

**Linear Erythematous Gingivitis.** This entity appears as a 1–3 mm band of marginal gingival erythema, often with petechiae (Fig. 5). It is typically associated with no symptoms or only mild gingival bleeding and mild pain. Histological examination fails to reveal any significant inflammatory response, suggesting that the lesions represent an incomplete (aborted) inflammatory response, principally with only hyperemia present<sup>14</sup>.



**Fig.5** Periodontal disease in HIV infection. left to right: Linear erythematous gingivitis; Necrotizing ulcerative periodontitis.

**Necrotizing Ulcerative Periodontitis (NUP).** This unique periodontal lesion is characterized by generalized deep osseous pain, significant erythema that is often associated with spontaneous bleeding, and rapidly progressive destruction of the periodontal attachment and bone (Fig. 5). The destruction is not self-limiting and can result in loss of the entire alveolar process in the involved area. This very painful associated lesion adversely affects oral intake of food, resulting in significant and rapid weight loss<sup>15</sup>. Because the periodontal microflora is no different from that seen in healthy patients, the lesion probably results from the altered immune response in HIV infection. More than 95% of patients with NUP have a CD4 lymphocyte count of less than 200/mm<sup>3</sup>.

**Bacillary Epithelioid Angiomatosis (BEA).** This recently described lesion appears to be unique to HIV infection and is often clinically indistinguishable from oral Kaposi's sarcoma (KS). Since both may present as an erythematous, soft mass which may bleed upon gentle manipulation, biopsy and histological examination are required to distinguish BEA from KS. The presumed etiological pathogen, *Rochalimaea henselae*, can be identified using Warthin Starrystaining. Both KS and BEA are histologically characterized by atypical vascular

channels, extravasated red blood cells, and inflammatory cells. However, prominent spindle cells and mitotic figures occur only in KS.<sup>15</sup>

**Syphilis.** While the prevalence of syphilis infection has risen significantly over the past decade, it is an uncommon cause of intraoral ulceration, even in HIV infection. Its appearance is no different from that observed in healthy individuals; it is a chronic, nonhealing, deep, solitary ulceration; often clinically indistinguishable from that due to tuberculosis, deep fungal infection, or malignancy. Dark field examination may demonstrate treponema. Positive reactive plasma reagin (RPR) and histological demonstration of *Treponema pallidum* is diagnostic.

## NEOPLASMS

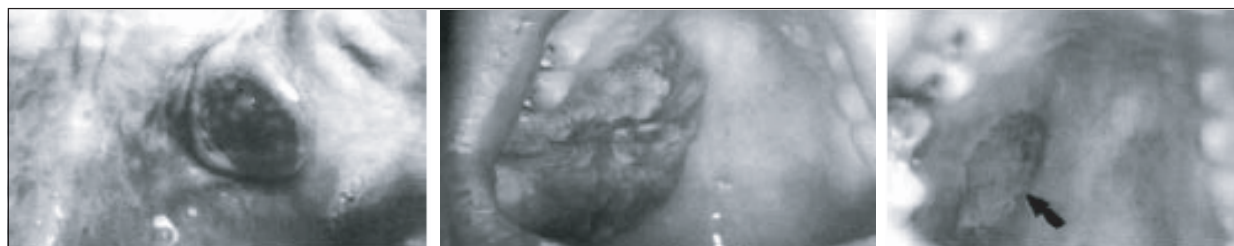
**Kaposi's sarcoma**-Kaposi's sarcoma is the most common intraoral malignancy associated with HIV infection. Recognition of the lesion is essential, since oral KS is often the first manifestation of the disease and is a diagnostic criterion for AIDS. The lesion may appear as a red-purple macule, an ulcer, or as a nodule or mass. Intraoral KS occurs on the heavily keratinized mucosa, the palate being the site in more than 90% of reported cases (Fig. 6).

However, lesions have also been reported on the gingivae, tongue, and buccal mucosa. The skin should also be examined for lesions whenever oral lesions are discovered. KS is especially common among homosexual and bisexual males and is rarely found in HIV-infected women<sup>16</sup>. A new human herpes virus (HHV8) has recently been demonstrated to be an important cofactor in the development of KS.

**Non-Hodgkin's Lymphoma (NHL).** NHL is the most common lymphoma associated with HIV infection and is usually seen in late stages with CD4 lymphocyte counts of less than 100/mm<sup>3</sup>. It appears as a rapidly enlarging mass, less commonly as an ulcer or plaque, and most commonly on the palate or gingivae. NHL may be indistinguishable from masses caused by KS or other diseases in HIV-infected patients.

## IMMUNE-MEDIATED ORAL LESION

While HIV infection and progression is characterized by progressive immune deterioration, it is equally well

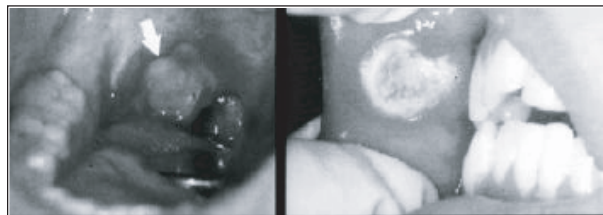


**Fig. 6.** Intraoral Kaposi's sarcoma. Variety of appearance: from left to right –plaque, ulcer and mass.



characterized by an abnormally activated immune system. In other words, the immune system activation itself leads to tissue injury and the worsening health of the patient.

**Major aphthous ulceration** is the most common immune-mediated HIV-related oral disorder, with a prevalence of approximately 2–3%. The large solitary or multiple, chronic, deep, painful ulcerations of major aphthae appear identical to those in non-infected patients, but they often last much longer and are less responsive to therapy<sup>17</sup>. (Fig 7)



**Fig. 7.** Major aphthous ulceration form left to right- palatal and buccal mucosa

**Necrotizing stomatitis** is an uncommon acute, painful ulceration which often exposes underlying bone and leads to considerable tissue destruction. This lesion may be a variant of major aphthous ulceration, but occurs in areas overlying bone and is associated with severe immune deterioration. Unlike necrotizing ulcerative periodontitis, the lesion may occur in edentulous areas.

#### XEROSTOMIA

Xerostomia is common in HIV disease, most often as a side effect of antiviral medications or of the other antihypertensive, antidepressant, anxiolytic or analgesic medications commonly prescribed for patients with HIV infection. The oral dryness presents a significant risk factor for caries and can lead to rapid dental deterioration. Xerostomia also contributes to oral candidiasis, mucosal injury and dysphagia, and is often associated with pain and reduced oral intake of food. Although several saliva substitutes exist, compliance is often poor and relief inadequate<sup>18</sup>.

#### PAROTID GLAND DISEASE

HIV infection is associated with parotid gland disease, characterized clinically by gland enlargement and diminished flow, and histologically by lymphoepithelial infiltration and benign cyst formation<sup>19</sup>. The enlargement typically involves the tail of the parotid gland or, less commonly, the submandibular gland, and it may present uni- or bi-laterally with periods of increased or decreased size.

#### PAIN SYNDROMES

Pain is a common symptom experienced by patients with HIV infection. Pain may result from a wide variety of disease processes, including direct effects of HIV on the

central or peripheral nervous system, infection, malignancy, and antiretroviral therapy. Headache is a common symptom, occurring in approximately 46% of patients with HIV infection and accounting for approximately 17% of all pains in patients with HIV infection<sup>19</sup>. Neuropathic pain is common among patients with HIV infection (19%), the most common diagnosis being painful peripheral sensory neuropathy.

#### CONCLUSION

Oral conditions seen in association with HIV infections 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.

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