

Review Article**Oral Manifestations of HIV-AIDS: A Diagnostic and Management Dilemma**

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ABSTRACT

Oral disease is frequently associated with HIV. While nearly all oral disorders associated with HIV infection also occur in other conditions characterized by immune-suppression, 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. 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, diagnostic and therapeutic aspects of HIV-associated oral disorders.

Keywords: Oral Manifestations, HIV-AIDS, Dilemma**INTRODUCTION**

The number of people living with HIV in 2004 was estimated at about 40 million, which is the highest level ever. Approximately 4.9 million people were reported to have acquired HIV in 2004 (WHO, 2005). The main signs and symptoms observed in AIDS patients include diarrhoea, generalised multiple lymphadenopathy, weight loss, and other symptoms related to secondary or opportunistic infections, such as fever, cough, and nodular swelling of the skin [1].

Since the beginning of the AIDS epidemic, much has been learned about the clinical oral manifestations of HIV disease, and epidemiologic studies have been conducted by many investigators who reported the prevalence of specific oral lesions in various adult populations [2]. Candidiasis and hairy leukoplakia have consistently been found to be the most common oral lesions seen in adults with HIV disease [3]. A strong association between the occurrence of oral candidiasis and hairy leukoplakia, and a declining CD4 T cell count is demonstrated among adults.² The pattern of occurrence of HIV-related oral mucosal diseases appears to differ in children as compared with adults. The most common oral conditions in HIV infected children are candidiasis (with prevalence higher than in adults) and parotid enlargement, whereas hairy leukoplakia has rarely been

documented [4]. Furthermore, children appear to develop oral candidiasis at a much earlier stage of HIV disease than adults. Adolescents are at the crossroads between childhood and adulthood, the clinical presentation in adolescents is ambiguous and it is unclear whether the pattern of HIV-related oral diseases in this group resembles that of children or that of adults, and the stage of HIV disease at which oral lesions begin to manifest among adolescents [5].

Oral manifestations are often among the first symptoms of HIV/AIDS and thus can be useful in early detection of the disease. [6]. 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) [7].

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. 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 [8].



Fig 1. Pseudomembranous Candidiasis^a

Treatment of oral candidiasis is determined by the clinical type, distribution, and severity of infection. Topical treatment is effective for limited and accessible lesions. Clotrimazole troches, nystatin pastilles, and nystatin oral suspension are effective for mild-to-moderate erythematous and pseudomembranous candidiasis. However, prolonged use can result in significant dental caries due to the fermentable carbohydrate substrates. Systemic treatment for oral candidiasis involves the use of imidazole (ketoconazole) and triazole (fluconazole and itraconazole) antifungal medications. Ketoconazole is hepatotoxic and requires gastric acid for absorption, thereby limiting its usefulness in patients with HIV infection who may also have developed gastric achlorhydria. Fluconazole is an excellent systemic antifungal medication with a favourable therapeutic index, making it the preferred systemic antifungal medication. Itraconazole (100 mg tablet, 1–2 tabs/day) is another excellent systemic antifungal for use alone, or in combination with fluconazole (100 mg tablet, 1–2 tabs/day), for resistant candidiasis. Therapy should be continued for 2 weeks, until clinical infection is eliminated [9].

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 [9].



Fig 2. Hyperplastic Candidiasis^a

Viral Infections

Herpes virus 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) [10].

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. Recurrent intraoral HSV in patients with HIV infection often results in ulceration and pain of longer duration. It occurs 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. Clinical diagnosis can be assisted by culture and examination of a cytologic smear for the virus. Less commonly occurring viral infections involving the oral cavity include cytomegalovirus and human papilloma virus. Intraoral HSV infection responds well to systemic acyclovir, 2 grams daily in divided doses. However, the incidence of acyclovir-resistant HSV has increased among patients with HIV infection. For most of these cases, oral famciclovir and valacyclovir and intravenous foscarnet alone or in combination are effective. Topical acyclovir is approved for genital HSV infections, but has been found to have little therapeutic effect for oral HSV.

Oral Hairy Leukoplakia It appears as an asymptomatic adherent white patch with vertical corrugations, most commonly on the lateral borders of the tongue. 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/mm³.¹¹ While the diagnosis is most often clinical, histological inspection will reveal typical epithelial hyperplasia suggestive of EBV infection. This asymptomatic lesion does not require treatment. However, for cosmetic purposes, some patients may request treatment. Oral acyclovir (3,200 mg daily in divided doses), topical podophyllum resin, retinoids, and surgical removal have all been reported as successful treatments. In most cases, the lesion returns after initial therapy, thus requiring prophylactic treatment with acyclovir 200 mg daily.

Human Papilloma Virus causes a focal epithelial and connective tissue hyperplasia, forming an oral wart. More than 50 strains of HPV exist. The most common genotypes found in the mouth of patients with HIV infection are 2, 6, 11, 13, 16 and 32. Surgical removal, with or without intraoperative irrigation with podophyllum resin, is the treatment of choice.



Fig 3. Human Papilloma Virus ^a

Oral Cytomegalovirus 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. Thus, biopsy and histological inspections are essential for definitive diagnosis. Ganciclovir is the drug of choice.

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. 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 [9].

Erythematous Gingivitis This entity appears as a 1–3 mm band of marginal gingival erythema, often with petechiae. 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 hyperaemia present. Unlike conventional gingivitis, the erythema often persists following simple dental prophylaxis. Oral rinsing with chlorhexidine gluconate 0.12% often reduces or eliminates the erythema and typically requires prophylactic use to avoid recurrence

Necrotizing Ulcerative Periodontitis 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. 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. 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/mm³ [12]. Treatment consists of rinsing twice daily with chlorhexidine gluconate 0.12%, metronidazole (250 mg orally four times daily for 10 days) and periodontal debridement, which is performed after antibiotic therapy has been initiated.

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



Fig 4. Gingival Erythema^a



Fig 5. Periodontitis^a

of *Treponema pallidum* is diagnostic. Patients with newly diagnosed syphilis should be referred to their physicians for evaluation and treatment; combination treatment with penicillin, erythromycin and tetracycline is the treatment of choice, the dosage and duration of treatment depending on presence or absence of neurosyphilis [13].

Neoplasms 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 [14]. 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 [14]. Definitive diagnosis of KS requires histological examination. There is no cure for KS. Therapy for intraoral KS should be instituted at the earliest sign of the lesion, the goal being local control of the size and number of lesions.

When only one or a few lesions exist and the lesions are small (<1 cm), intralesional chemotherapy with vinblastine sulfate (0.2–0.4 mg/ml per cm² of lesion) or Sclerotherapy with 3% sodium tetradecyl sulfate (0.1–0.2 ml per cm² of lesion) is effective. Radiation therapy (800–2,000 cGy) is effective for larger or multiple lesions

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.



Fig 6. Kaposi's Sarcoma^a

DISCUSSION

Virtually everyone infected with human immunodeficiency virus (HIV) will have oral disease during their illness. Conditions such as oropharyngeal candidiasis, hairy leukoplakia, and oral Kaposi's sarcoma frequently constitute the sentinel event leading to HIV diagnosis. As some oral lesions are independent markers for deteriorating immune function, their prompt identification has prognostic and therapeutic implications [15].

At least 90% of HIV-infected patients will have at least one oral manifestation at some time during the course of their disease [16]. Oral lesions might herald underlying immunodeficiency. Candidiasis involving the oral cavity is rare in immunocompetent patients; however, it is a common feature of HIV infection and occurs in as many as 75% of infected patients. Many studies have confirmed that the risk for oral complications increases as the level of immunodeficiency declines. Certain oral lesions are strongly associated with the degree of disease activity

and might serve as a marker of degree of immunosuppression and viral burden [17] conversely; the implementation of HAART has resulted in a decline in the frequency of oral manifestations, as immune function is reconstituted [18].

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. 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 [19].

Dental expertise is necessary for proper management of oral complications in HIV infection or AIDS. Medical clinicians should be able to recognize HIV-associated oral disease and to provide appropriate care and referral. Factors that predispose to HIV-related oral conditions include CD4+ cell count of less than 200/ μ L, plasma HIVRNA levels greater than 3000 copies/mL, xerostomia, poor oral hygiene, and smoking. For individuals with unknown HIV status, oral manifestations may suggest possible HIV infection, although they are not diagnostic of infection. For persons living with HIV disease who are not yet on therapy, the presence of certain oral manifestations may signal progression of HIV disease. For patients on antiretroviral therapy, the presence of certain oral manifestations may signal an increase in the plasma HIV-1 RNA level [19].

Advances in the management of the human immunodeficiency virus (HIV) infection have resulted in significant changes in the prevalence and incidence of oral diseases found in individuals infected with HIV. In countries where patients have access to effective antiretroviral therapy, people are living with chronic HIV infection for years, although immune suppression and progression due to acquired immune deficiency syndrome (AIDS) may ultimately occur. People with chronic immunosuppression due to HIV face a greater

risk of developing malignant disease. Oral malignancies associated with HIV may reflect local head and neck disease or represent systemic malignant disease. The presence of oral malignancies varies with risk factors for transmission of HIV, including unprotected sexual activity, contact with blood or blood products, and injection drug use (IDU), and differs geographically based on behaviour, viral cofactors, HIV therapy, and genetic variation. Understanding of the pathogenesis of oral malignant disease in HIV and progress in molecular biology has led to improvements in treatment [20].

Combination ART appears to have a critical role in the prevention of oral manifestations of HIV—probably because of its role in the reconstitution of the immune system. The confirmed correlation with CD4 depletion and high level of viral load should promote oral lesions as an adjunct clinical marker for identifying progression of HIV infection, aiding in decisions such as implementation of anti-HIV treatment, and gauging treatment efficacy [21].

CONCLUSION

Oral conditions seen in association with HIV disease are clinically significant and prevalent component of this disease complex. A thorough examination of the oral cavity can easily detect most of the common lesions and good understanding and knowledge of these conditions by an experienced medical/dental professional can herald the treatment in such patients if undiagnosed or may require change in treatment (be more aggressive) of a known patient living with HIV/AIDS. An understanding of the recognition, significance, and treatment of said lesions is essential for long term evaluation and well-being of people living with HIV/AIDS.

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