

Oral Manifestations of HIV Disease

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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 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. 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.

Key Words: HIV, oral manifestations, oral disease.

Introduction

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) (1) (Table 1).

TABLE 1
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.

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 (2). Indeed, the emergence of one or more oral lesions correlates highly with HIV progression. A CD4 lymphocyte count of less than 200/mm³ is a reliable prognosticator of active disease and probability of shortened lifespan (3–8). The spectrum of HIV-associated oral lesions also varies with transmission risk-factor, gender, age, and health-care access (7–13).

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.

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 (13, 14). 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 (9, 15–18). 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 (19).

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. The appearance of each clinical type of candidiasis is summarized in Table 2 and representative photographs are depicted in Fig. 1.

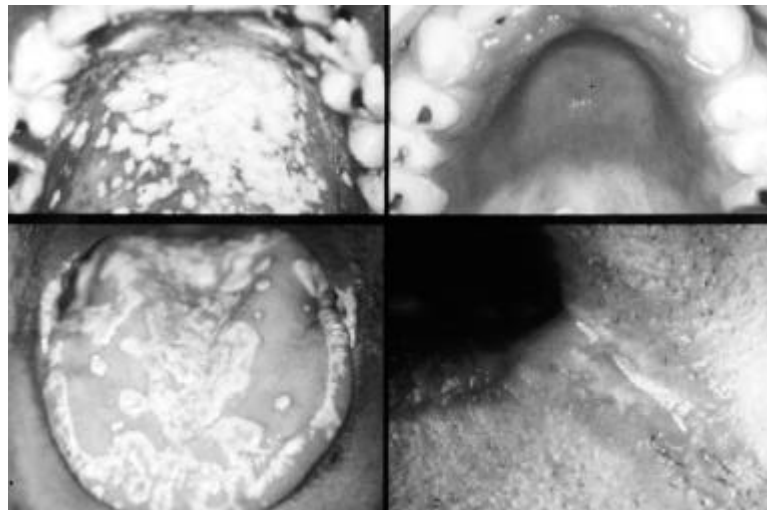


Fig . 1. Clinical spectrum of oral candidiasis. Upper left: pseudomembranous, removable white plaques; upper right: erythematous or atrophic candidiasis; lower left: hyperplastic (non-removable) candidiasis; lower right: angular cheilitis.

TABLE 2
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	white non-removable plaque; may be stained by food; any mucosal surface	associated with severe immune suppression / long-standing disease; may be associated with increased risk for carcinoma.
Angular Cheilitis	radiating fissures from labial commissure, sometimes covered with a pseudomembrane	can occur during all stages of HIV disease; xerostomia may be a contributing factor.

Treatment of oral candidiasis is determined by the clinical type, distribution, and severity of infection (20). 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 of these agents can result in significant dental caries due to the fermentable carbohydrate substrates. Increased risk of caries can be avoided by using nystatin oral suspension (100,000 units/5 ml, rinsing mouth and expectorating 3 times/day). Also clotrimazole vaginal troches can be effective (patient dissolves 1 troche in the mouth 3 times daily). Chlorhexidine 0.12% oral rinses do not contain a cariogenic substrate (21, 22) and may be similarly effective. Topical amphotericin B is also a useful non-cariogenic treatment for resistant candidiasis and can be prepared by dissolving 50 mg in 500 ml of sterile saline (0.1 mg/ml). Regular, gentle mechanical debridement with soft gauze soaked with 10% povidone-iodine or chlorhexidine 0.12% solution is very effective in managing focal, limited candidiasis. Clotrimazole 1% cream, miconazole or ketoconazole 2% cream, nystatin ointment, and Vytone® (hydrocortisone iodoquinol) 1% cream are useful medications for angular cheilitis and for application to a removable denture base when there is candidal infection involving the underlying mucosa. When long-term treatment or prophylactic use is required, systemic antifungal therapy is often required.

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 favorable therapeutic index, making it the preferred systemic antifungal medication. Itraconazole

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(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. Prophylaxis should be reserved only for those patients with demonstrated recurrence who cannot be controlled with topical medication. Treatment strategies and doses for antifungal therapy are summarized in Table 3.

TABLE 3
Treatment Strategies and Doses for Antifungal Therapy

Drug	Route	Indication	Dose	Notes
clotrimazole troche	topical	erythematous and pseudomembranous	10 mg troche, 1 troche 5 times daily	cariogenic
nystatin pastille	topical	erythematous and pseudomembranous	200,000 U, 1 pastille 4–5 times daily	cariogenic
nystatin suspension	topical	erythematous and pseudomembranous	500,000 U/5 cc, 1 tsp rinse and swallow 4 times daily	cariogenic
nystatin vaginal troche	topical	erythematous and pseudomembranous	100,000 U, 1 troche 5–6 times daily	non-cariogenic
chlorhexidine 0.12%	topical	erythematous and pseudomembranous	1 tsp rinse and spit out 3 times daily; debridement with soaked gauze	
clotrimazole 1% cream miconazole 2% cream ketoconazole 2% cream hydrocortisone-iodoquinol 1% cream	topical	erythematous and pseudomembranous; angular cheilitis	apply to affected area 4 times daily	
ketoconazole	systemic, oral	erythematous and pseudomembranous	200 mg tab, 2 stat, 1 tab daily	hepatotoxic, take after meals
fluconazole	systemic, oral	all intra-oral types	100 mg tab, 2 stat, 1 tab 1–2 times daily	
itraconazole	systemic, oral	fluconazole resistance	100 mg cap, 2 caps once daily after a full meal	
amphotericin B	topical, systemic IV	fluconazole and itraconazole resistant	50 mg in 500 cc DW, rinse and spit out 3 times daily	

Deep Fungal Infections. Unlike the superficial infection of candidiasis, several systemic fungal

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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.

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) (23). Less commonly occurring viral infections involving the oral cavity include cytomegalovirus and human papilloma virus. Figs. 2 and 3 illustrate the common oral viral infections which occur most frequently in patients with HIV infection.

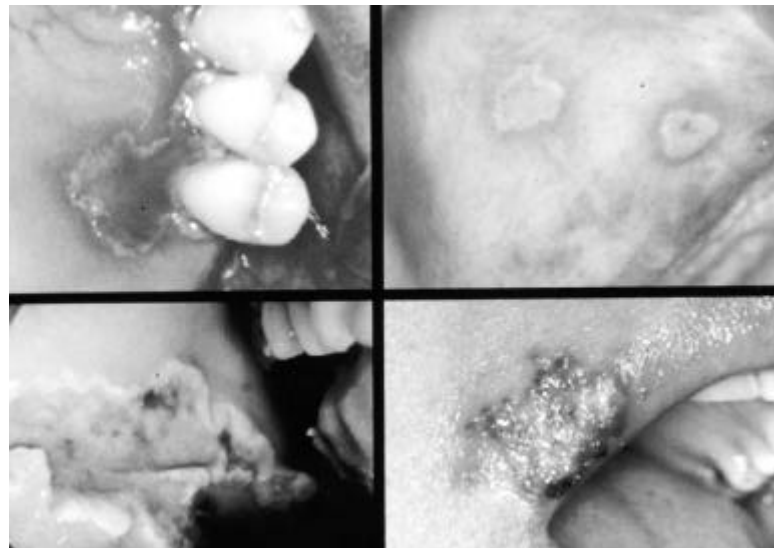


Fig. 2. Oral HSV lesions in patients with HIV infection. Upper left, right: coalesced shallow palatal HSV ulceration; lower left: extensive chronic HSV on the buccal mucosa; lower right: HSV labialis of 4 weeks' duration.

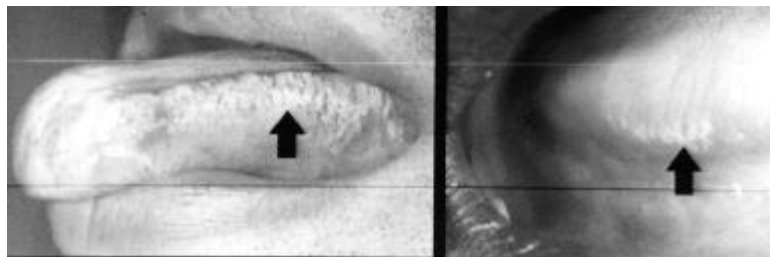


Fig. 3. Oral hairy leukoplakia due to Epstein-Barr virus. Adherent white corrugated patches on the lateral tongue.

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 (24–27). 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. Clinical diagnosis can be assisted by culture and examination of a cytologic smear for the virus. Culture results should be interpreted with caution due to the high HSV seropositivity and the potential for false negative results due to silent shedding of HSV.

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 (28–31). Although penciclovir was recently released as the first topical antiviral medication indicated for treatment of herpes simplex labialis, it reduced time to healing by only 0.7 days in healthy individuals compared to vehicle placebo, and no data on its use in patients with HIV infection are available (32).

Oral Hairy Leukoplakia (OHL). Although originally postulated to be pathognomonic for HIV infection (33), this lesion has subsequently been reported in other immune deficiency states as well as in immunocompetent individuals (34, 35). 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/mm³ (5). 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 (36–38).

Human Papilloma Virus (HPV). In some patients with HIV infection, HPV causes a focal epithelial and connective tissue hyperplasia, forming an oral wart (Fig. 4). 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.

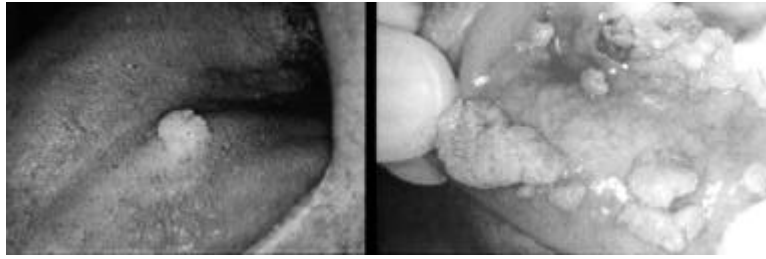


Fig. 4. Human papilloma virus. Solitary oral wart (left) and multiple, recurrent warts (right).

Cytomegalovirus (CMV). It is necessary to recognize oral CMV, which is an uncommon cause of intraoral ulceration in patients with HIV disease. Such a lesion may represent an early sign of disseminated CMV infection (39). Disseminated CMV infection must be diagnosed as early as possible because of the serious nature of its sequelae, including retinitis and meningitis. CMV has been detected postmortem in one or more organ systems in as many as 90% of patients with AIDS (40). 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. Thus, biopsy and histological inspections are essential for definitive diagnosis. Ganciclovir is the drug of choice, now available in a tablet formulation. Many patients with a history of CMV are placed on a prophylactic regimen (1.0 g ganciclovir, 3 times daily with food).

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.

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. There is no evidence to suggest that this entity will proceed to the far more destructive necrotizing periodontitis. 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.

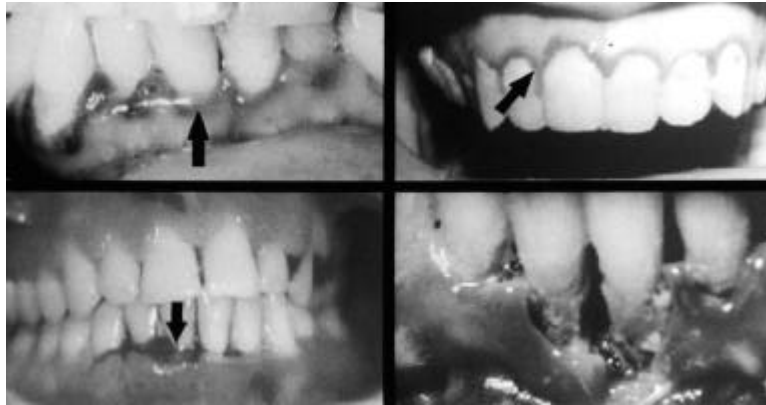


Fig. 5. Periodontal disease in HIV infection. Upper left, right: Linear erythematous gingivitis; lower left, right: Necrotizing ulcerative periodontitis.

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. 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 $200/\text{mm}^3$ (41, 42). 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. Within 36–48 hours of antibiotic therapy, relief of pain associated with NUP is obtained.

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) (43, 44). 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-Starry staining. 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. Erythromycin (erythromycin estolate, 500 mg 4 times daily for at least 10 days) is the treatment of choice for BEA.

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. 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 (56).

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 (2). 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).

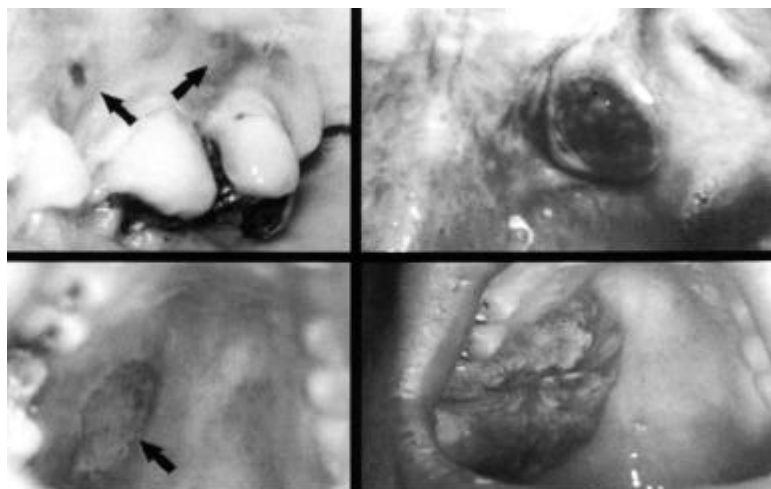


Fig. 6. Intraoral Kaposi's sarcoma. Variety of appearance: macule (upper left), plaque (upper right), ulcer (lower left), and mass (lower right).

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 (9, 10, 45). A new human herpes virus (HHV8) has recently been demonstrated to be an important cofactor in the development of KS, and prophylaxis with foscarnet and ganciclovir, but not acyclovir, has been shown to reduce the incidence of KS in a large at-risk cohort (46, 47).

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; stomatitis and glossitis are common side effect of radiation, but xerostomia is not.

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/mm³. 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. Histological examination is essential for diagnosis and staging. Prognosis is poor, with mean survival time of less than one year, despite treatment with multi-drug chemotherapy (57).

Immune-Mediated Oral Lesion

While HIV infection and progression is characterized by progressive immune deterioration, it is equally well 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% (48, 49). The large solitary or multiple, chronic, deep, painful ulcerations of major apthae appear identical to those in non-infected patients, but they often last much longer and are less responsive to therapy (Fig. 7).



Fig. 7. Major aphthous ulceration of the palate (upper left) and buccal mucosa (upper right). Major aphthous ulceration of the lip before (lower left) and one week after (lower right) treatment with topical clobetasol ointment.

The diagnosis must include the possibility of a primarily infectious entity which can be determined by histological examination of biopsy material. Treatment requires the use of a potent topical steroid such as clobetasol (0.05% ointment applied for 45 seconds 3 times daily) when the lesion is accessible or dexamethasone oral rinse (0.5 mg/5 ml dexamethasone elixir 3 times daily, rinse for 45 seconds and expectorate) when inaccessible. When multiple ulcers are present or response to topical treatment is incomplete, systemic glucocorticosteroid therapy is required (prednisone 1 mg/kg). Since lesions often return after discontinuing medication, the use of prophylactic medication is not uncommon. Major

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aphthae are associated with advanced HIV infection (typically with CD4 lymphocyte counts of less than $50/\text{mm}^3$). Long-term use of systemic prednisone may lead to complications such as oral candidiasis, reactivation of tuberculosis, or worsening of Kaposi's sarcoma. Alternative therapies such as dapsone 50–100 mg daily (58) and thalidomide 200 mg daily for 4 weeks (59) should be considered. When immunosuppressant or modulating drugs are used, concurrent antifungal medications such as fluconazole 100 mg tablet 1–2 daily, itraconazole 100 mg tablet 1–2 times daily, and antibacterial medications such as chlorhexidine gluconate oral rinse 0.12% 3 times daily, may be required to prevent superinfection or opportunistic overgrowth.

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. As in major aphthous ulceration, systemic corticosteroid medication or topical steroid rinse is the treatment of choice.

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. For patients with residual salivary gland function, determined by gustatory challenge, oral pilocarpine (5 mg up to 3 times daily) often provides improved salivary flow and consistency. Oral hygiene instruction, regular maintenance, and the use of prescription-strength, fluoridated dentifrice (Prevident 5000 Plus[®]) is essential.

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 (50). 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 (Fig. 8). While the appearance may raise suspicion of malignancy (salivary gland or lymphoma) or infection, aspiration of a yellow mucinous secretion supports the diagnosis of HIV-related salivary gland disease, thus avoiding unnecessary biopsy or imaging diagnostics (51). Occasional swelling can be managed simply by repeated aspiration and rarely is radical removal of the gland necessary. The pathophysiological mechanism is not known, though cytomegalovirus has been suggested to play a role (52).



Fig. 8. HIV-related parotid gland disease. Gland can vary in size over time.

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 (53). Neuropathic pain is common among patients with HIV infection (19%), the most common diagnosis being painful peripheral sensory neuropathy. A complete discussion of pain syndromes in HIV infection is found elsewhere (53–55).

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