Perspective

Oral Manifestations of HIV Disease

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, recurrent aphthous ulcers, and neutropenic ulcers. This article summarizes a presentation on oral manifestations of HIV disease made by David A. Reznik, DDS, at the 8th Annual Clinical Conference for Ryan White CARE Act Clinicians in New Orleans in June 2005.

In 2000, US Surgeon General David Satcher stated, "Those who suffer the worst oral health include poor Americans. Members of racial and ethnic groups also experience a disproportionate level of oral health problems. And people with disabilities and complex health conditions are at greater risk for oral diseases that, in turn, further complicate their health."

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/µL, plasma HIV-RNA 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.

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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 disease (Mascarenhas, *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 1999). 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. African-Americans and Hispanic-Americans were significantly less likely to receive treatment than were white patients. The overall prevalence of oral manifestations of HIV disease has changed since the advent of potent antiretroviral therapy. One study by Patton and colleagues noted a reduction of oral lesions from 47.6% pre-potent antiretroviral therapy to 37.5% during the potent antiretroviral therapy era (*Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 2000). Overall, there appears to be a reduced incidence of candidiasis, Kaposi's sarcoma, oral hairy leukoplakia, and necrotizing ulcerative periodontitis; an increased incidence of salivary gland disease, oral warts, and dental caries in the form of "brittle teeth syndrome;" and a relatively unchanged incidence of oral ulcers.

Some of the oral conditions encountered in HIV-infected individuals are discussed below. A good resource for information on these and other conditions is www.hivdent.org.

Xerostomia

Xerostomia is a major contributing factor in dental decay in HIV-infected individuals. More than 400 medications lead to symptoms of xerostomia. Approximately 30% to 40% of HIV-infected individuals experience moderate to severe xerostomia in association with the effects of medications (eg, didanosine) or the proliferation of CD8+ cells in the major salivary glands. Changes in the quantity and quality of saliva, including diminished antimicrobial properties, lead to rapidly advancing dental decay and periodontal disease (Figure 1).

Use of crystal methamphetamine is associated with increased risk of HIV acquisition, and its use by infected individuals can be associated with rapid dental decay known as "meth mouth" (Figure 2). The primary factor in this condition is probably xerostomia, with contributions from bruxism, poor diet, sugar cravings, and the corrosive constituents of crystal methamphetamine—ie, lithium, muriatic and sulfuric acids, and lye.

Candidiasis

The 3 common presentations of oral candidiasis are angular cheilitis, erythematous candidiasis, and pseudomembranous candidiasis.

Angular cheilitis presents as erythema or fissuring of the corners of the mouth (Figure 3). It can occur with or without erythematous or pseudomembranous candidiasis, and can persist for an extensive period of time if left untreated. Treatment involves the use of a topical antifungal cream

applied directly to the affected areas 4 times a day for the 2-week treatment period.

Erythematous candidiasis may be the most underdiagnosed and misdiagnosed oral manifestation of HIV disease. The condition presents as a red, flat, subtle lesion on the dorsal surface of the tongue or on the hard or soft palates (Figure 4). It may present as a "kissing" lesion—if a lesion is present on the tongue, the palate should be examined for a matching lesion, and vice versa. The condition tends to be symptomatic, with patients complaining of oral burning, most frequently while eating salty or spicy foods or drinking acidic beverages. Clinical diagnosis is based on appearance, as well as on the patient's medical history and virologic status. The presence of fungal hyphae or, more likely, blastospores can be confirmed by performing a potassium hydroxide (KOH) preparation.

Pseudomembranous candidiasis (or thrush) appears as creamy, white, curd-like plaques on the buccal mucosa, tongue, and other oral mucosal surfaces. The plaques can be wiped away, typically leaving a red or bleeding underlying surface. The most common organism involved is *Candida albicans*; however, there are increasing reports of involvement of non-*albicans* species. As with erythematous candidiasis, diagnosis is based on appearance. Figure 5A shows a mild to moderate case; Figure 5B shows more severe disease.

Topical treatments for mild to moderate cases of both erythematous and pseudomembranous candidiasis include clotrimazole troches, nystatin oral suspension, and nystatin pastilles (Table 1). It should be noted that the common nystatin oral suspension contains 50% sucrose, which is cariogenic; this is less of a potential problem if fluoride is prescribed along with the nystatin. The clotrimazole oral treatment is formulated with fructose, which is less cariogenic. Systemic agents for moderate to severe disease consist of fluconazole, the most widely used drug; itraconazole; and voriconazole, the latter of which should be reserved for cases of fluconazole resistance (Table 1). Figure 6A shows disease with fluconazole-resistant *Candida albicans*; its attachment to tissue is stronger, and it is more difficult to wipe away than azole-susceptible candidiasis. Figure 6B shows disease due to *Candida glabrata*, which is intrinsically azole-resistant. Factors associated with azole-resistant disease include prior exposure to azoles, low CD4+ cell count, and presence of non-*albicans* species.

Table **1.** Topical and Systemic Agents for Oral Candidiasis

Topical agents (mild to moderate oral candidiasis)	
Clotrimazole troches	10 mg: Dispense 70, dissolve 1 troche in mouth 5 times a day for 14 days
Nystatin oral suspension	500,000 units: Swish 5 mL in mouth as long as possible then swallow (optional), 4 times a day for 14 days
Nystatin pastilles	100,000 units: Dispense 56, dissolve 1 in mouth 4 times a day for 14 days
Systemic agents	
Fluconazole	100 mg: Dispense 15 tablets, take 2 tablets on day 1, followed by 1 tablet a day for the remainder of the 14-day treatment period
Itraconazole oral suspension	10 mg/10 mL: Dispense 140 mL, swish and swallow 10 mL per day for 7 to 14 days. Take medication without food
Voriconazole	200 mg: Dispense 14 tablets, take 1 tablet twice daily for 2 weeks or at least 7 days following resolution of symptoms
Drug interactions	
Contraindications: rifampin, rifabutin, ritonavir, and efavirenz (all are potent CYP450 inducers). Drug interactions are most significant with voriconazole and present with itraconazole oral suspension, but less critical with fluconazole	

The primary lesson to be learned in the treatment of any candidiasis—whether it be with a topical agent for mild to moderate disease or a systemic agent for more severe disease—is that treatment must be continued for at least 2 weeks in order to reduce organism colony-forming units to levels low enough to prevent recurrence.

Oral Hairy Leukoplakia

Oral hairy leukoplakia, which is caused by Epstein-Barr virus, presents as a white, corrugated lesion on the lateral borders of the tongue; the lesion cannot be wiped away (Figure 7). There has been a marked decrease in the incidence of oral hairy leukoplakia in the potent antiretroviral era. This condition is normally asymptomatic and does not require therapy unless there are cosmetic concerns. However, it is important to note that the condition is observed with immune deterioration and that patients presenting with it while on antiretroviral therapy may thus be experiencing failure of their current regimen.

Periodontal Disease

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 8). 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 petechia-like 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." However, antifungals typically are not needed for treatment. Treatment includes debridement by a dental professional, twice-daily rinses with a 0.12% chlorhexidine gluconate suspension for 2 weeks, and improved home oral hygiene.

Necrotizing Ulcerative Periodontitis

Although necrotizing gingivitis and necrotizing periodontitis may reflect the same disease entity, they are differentiated by the rapid destruction of soft tissue in the former condition and hard tissue in the latter. Necrotizing ulcerative periodontitis is a marker of severe immune suppression. The condition is characterized by severe pain, loosening of teeth, bleeding, fetid odor, ulcerated gingival papillae, and rapid loss of bone and soft tissue (Figure 9). Patients often refer to the pain as "deep jaw pain." Treatment includes removal of dental plaque, calculus, and necrotic soft tissues utilizing a 0.12% chlorhexidine gluconate or 10% povidone-iodine lavage, and institution of antibiotic therapy (Table 2). Pain management is crucial, as is attention to nutrition in these patients. Timely referral to primary care is indicated to rule out other systemic opportunistic infections.

Kaposi's Sarcoma

Kaposi's sarcoma is still the most frequent HIV-associated oral malignancy, although its incidence has dramatically decreased in the potent antiretroviral therapy era. Kaposi's sarcoma-associated herpesvirus (KSHV) has been identified as the etiologic agent.

Table **2.** Management of Necrotizing Ulcerative Periodontitis

Initial visit

- Prescribe narrow spectrum antibiotics such as metronidazole 500 mg, dispense 14 to 20 tablets, take 1 tablet twice daily for 7 to 10 days. Other antibiotic options include clindamycin and amoxicillin
- Pain management is extremely important
- Nutritional supplementation or counseling may be necessary

Follow-up visits

- Detailed periodontal care, such as scaling and root planing

Kaposi's sarcoma can be macular, nodular, or raised and ulcerated, with color ranging from red to purple (Figure 10); early lesions tend to be flat, red, and asymptomatic, with the color becoming darker as the lesion ages. Diagnosis is frequently missed in African-American patients due to lesion coloration. Progressing lesions can interfere with the normal functions of the oral cavity and become symptomatic secondary to trauma or infection. Definitive diagnosis requires biopsy. Treatment ranges from localized injections of chemotherapeutic agents, such as vinblastine sulfate, to surgical removal. Oral hygiene must be stressed. Systemic chemotherapy may be the treatment of choice for patients with extraoral and intraoral Kaposi's sarcoma.

Oral Warts—Human Papilloma Virus

The incidence of oral warts due to human papillomavirus (HPV) has dramatically increased in the potent antiretroviral therapy era. Studies at the author's institution indicate that the risk of HPV-associated oral warts is associated with a 1-$\log_{10}$ or greater decrease in plasma HIV RNA level within the 6 months prior to oral HPV diagnosis, suggesting that the development of warts may be related to immune reconstitution. The warts may be cauliflower-like, spiked, or raised with a flat surface (Figure 11). Treatment may involve surgery, laser surgery, or cryotherapy. It should be noted that HPV survives in aerosol. Topical 5-fluorouracil treatment has been used on external lesions, but should be avoided in African-American patients since it can cause hyperpigmentation. It should be noted, however, that this is a specialized treatment and should only be used by those experienced with the use of this topical medication. Lesions tend to recur after treatment.

Ulcerative Diseases

Herpes simplex virus

Herpes simplex virus (HSV)-1 infection is widespread and oral lesions are common. Recurrent intraoral HSV outbreaks start as a small crop of vesicles that rupture to produce small, painful ulcerations that may coalesce. Lesions on the lip are fairly easy to recognize. In the mouth, lesions on keratinized, or fixed, tissues, including the hard palate and gums, should prompt suspicion of HSV infection (Figure 12). Herpetic ulcerations are often self-limiting, although the use of an antiviral medication such as acyclovir is sometimes necessary to control the outbreak.

Aphthous ulcerations

Recurrent aphthous ulcerations appear on non-keratinized, or non-fixed, tissues, such as the labial or buccal mucosa, floor of the mouth, ventral surface of the tongue, posterior oropharynx, and maxillary and mandibular vestibules (Figure 13). Their cause is unknown. The lesions are characterized by a halo of inflammation and a yellow-gray pseudomembranous covering. They are very painful, especially during consumption of salty, spicy, or acidic foods and beverages, or hard or rough foods. In immunocompromised patients, these lesions tend

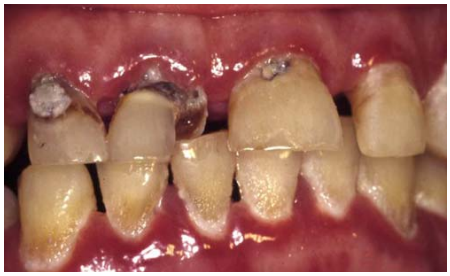

Figure **1**. Cervical caries occurring in association with xerostomia.

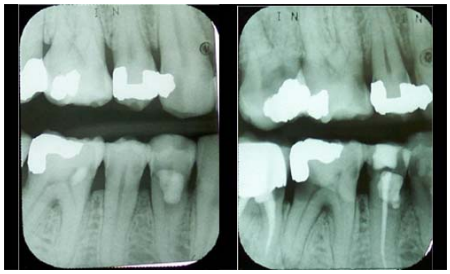

Figure **2**. Dental decay in less than 1 year (from left to right) with "meth mouth."

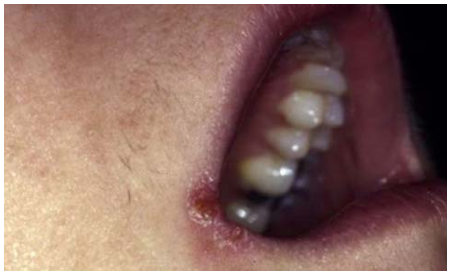

Figure **3**. Angular cheilitis.

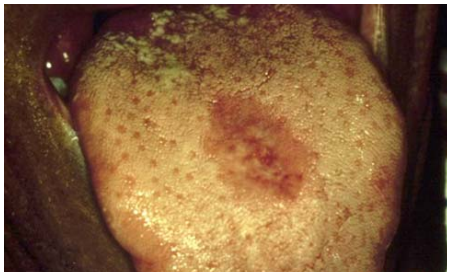

Figure **4a**. Erythematous candidiasis.

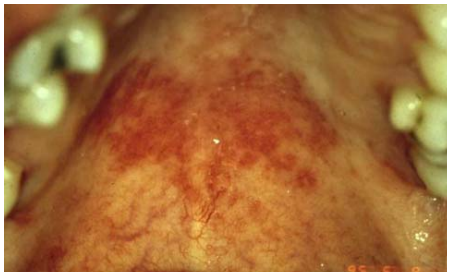

Figure **4b**. Erythematous candidiasis.

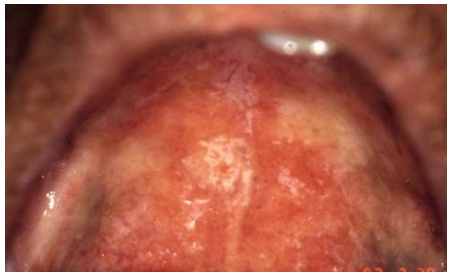

Figure **5a**. Pseudomembranous candidiasis—mild or moderate disease.

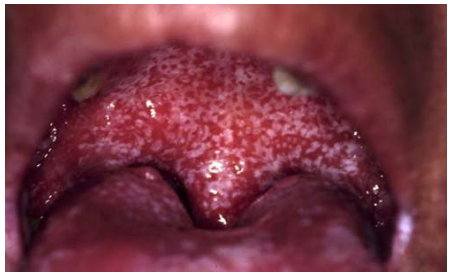

Figure **5b**. Pseudomembranous candidiasis—more severe disease.

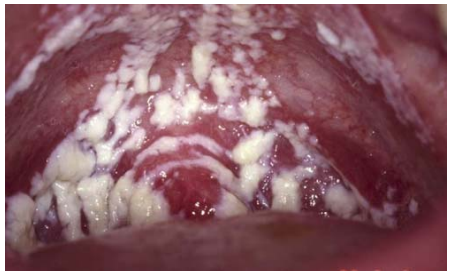

Figure **6a**. Oral candidiasis due to fluconazole-resistant *Candida albicans*.

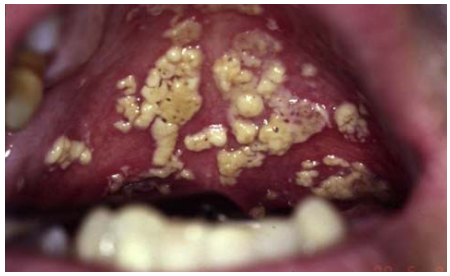

Figure **6b**. Oral candidiasis due to fluconazole-resistant *Candida glabrata*.

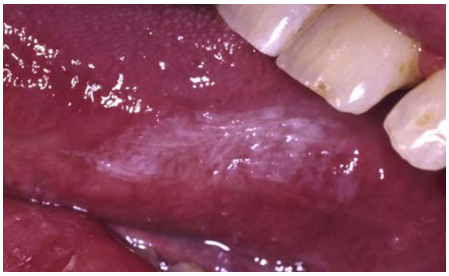

Figure **7**. Oral hairy leukoplakia.

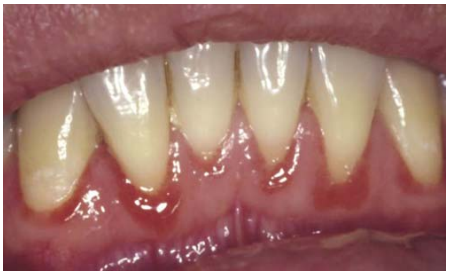

Figure **8**. Linear gingival erythema.

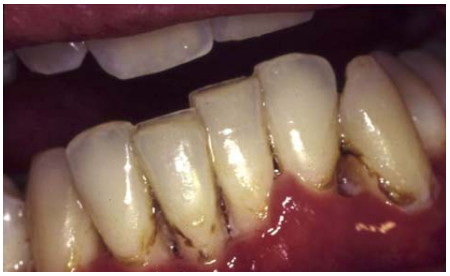

Figure **9**. Necrotizing ulcerative periodontitis.

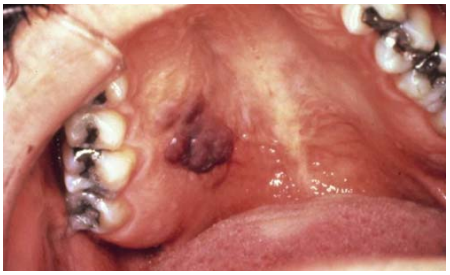

Figure **10a**. Kaposi's sarcoma.

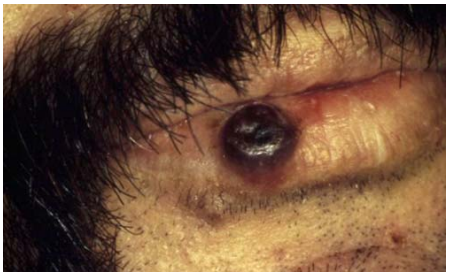

Figure **10b**. Kaposi's sarcoma.

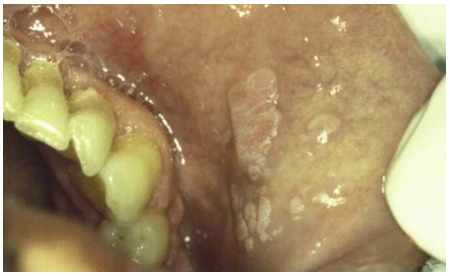

Figure **11a**. HPV-associated warts.

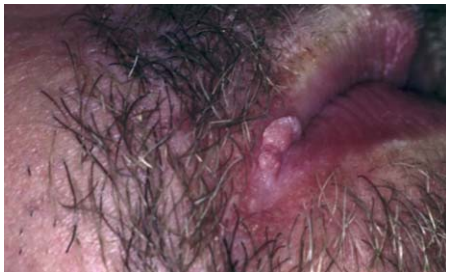

Figure **11b**. HPV-associated warts.

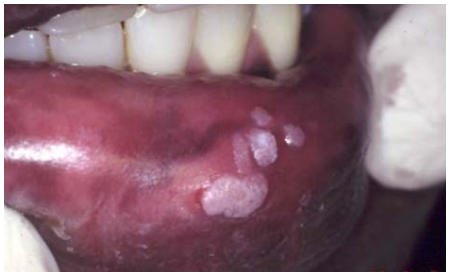

Figure **11c**. HPV-associated warts.

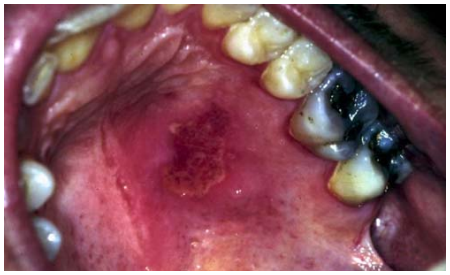

Figure **12a**. HSV-1 lesion.

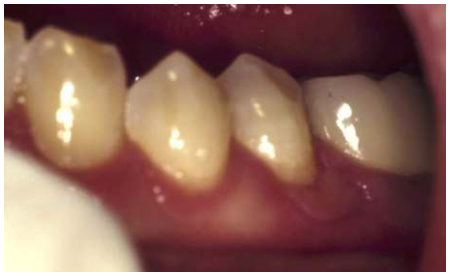

Figure **12b**. HSV-1 lesion.

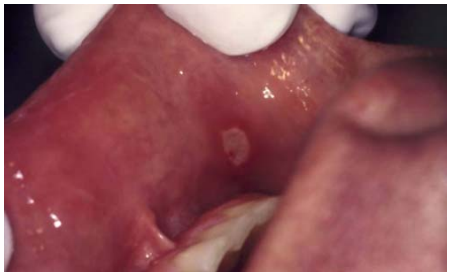

Figure **13a**. Aphthous ulceration.

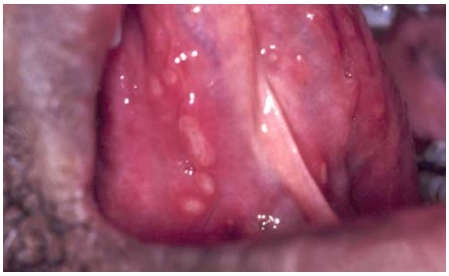

Figure **13b**. Aphthous ulceration.

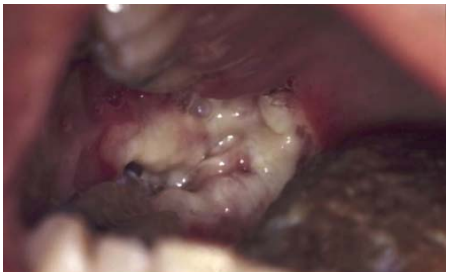

Figure **14a**. Neutropenic ulcerations in a patient before therapy.

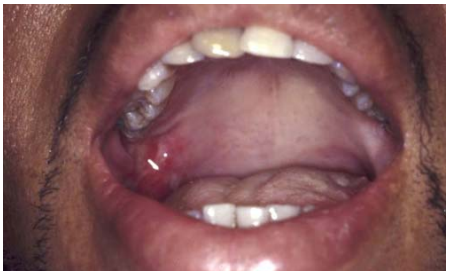

Figure **14b**. Neutropenic ulcerations in the patient shown in Figure 14a after therapy.

to persist for longer than the 7- to 14-day period observed in immunocompetent individuals. Treatment for milder cases involves the use of topical corticosteroids such as dexamethasone elixir (0.5 mg/5 mL) 5 mL swished for 1 minute and then expectorated, 2 to 3 times daily until symptoms resolve. For more severe occurrences, systemic corticosteroids such as prednisone are used.

Neutropenic ulcerations

Neutropenic ulcerations are very painful ulcerations that can appear on both keratinized and non-keratinized tissues, and are associated with absolute granulocyte counts of less than 800/µL (Figure 14). These lesions are being found with increasing frequency in the HIV-infected population, although the cause of this increase in frequency remains unknown. Large, unusual-looking, or fulminant ulcers in the oral cavity that cannot otherwise be identified or explained should prompt suspicion of this condition. Patients should receive granulocyte colony-stimulating factor treatment prior to systemic or topical steroid treatment, depending on the size and location of the lesion.

Pain in ulcerative disease

Pain management is a crucial component of treating ulcerative oral diseases. Pain usually is treated with topical anesthetics or systemic analgesics. However, relief provided by topical anesthetics is usually of short duration. Furthermore, anesthetic mouth rinses numb the taste buds, resulting in a decreased desire to eat, and diminished nutritional intake can have a significant negative impact on overall well-being for many patients. Systemic analgesics are also somewhat effective, but do not specifically address localized pain. One product that has been found to be effective in ulcer pain control is a rinse composed of polyvinylpyrrolidone, hyaluronic acid, and glycyrrhetinic acid. If other topical treatments are to be used (eg, topical steroids), they should be applied prior to use of this rinse, since the barrier formed by the product will prevent penetration of the other topical medications.

Conclusion

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.

Presented by David A. Reznik, DDS, in June 2005. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Reznik in November 2005.

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Suggested Reading

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