ABSTRACT:
People with human immunodeficiency virus, the virus that causes acquired immunodeficiency syndrome, are at special risk for oral health problems. Many of these problems arise because the person's immune system is weakened and less able to fight off infections. Human immunodeficiency virus-related oral conditions occur in a large proportion of patients, and frequently are misdiagnosed or inadequately treated. Dental expertise is necessary for appropriate management, but many patients do not receive adequate dental care. Oral manifestations include oral lesions and novel presentations of previously known opportunistic diseases. Careful history taking and detailed examination of the patient's oral cavity are important parts of the physical examination, and diagnosis requires appropriate investigative techniques. Early recognition, diagnosis, and treatment of human immunodeficiency virus-associated oral lesions may reduce morbidity. Likewise, awareness of the variety of oral disorders which can develop throughout the course of human immunodeficiency virus infection, and coordination of health care services between physician and dentist, should improve overall health and comfort of the patient.

Key words: Human immunodeficiency virus, Acquired immunodeficiency syndrome, oral health, oral manifestations.

INTRODUCTION
Emerging and re-emerging diseases are having a profound worldwide impact on society and on the delivery of medical and oral health care. The acquired immunodeficiency syndrome (AIDS) pandemic, caused by infection with human immunodeficiency virus (HIV) dramatically illustrates the awesome transmission capabilities of disease. Spread by blood borne and sexual contact HIV has infected over 36.1 million people in the world and according to joint UNAIDS (United Nations Programme on HIV/AIDS) and WHO, 1600 new cases are coming up every day.\(^1\) The 2006 Political Declaration on HIV/AIDS recognized the urgent need to achieve universal access to HIV treatment, prevention, care and support.\(^2\)

Globally, an estimated 35.3 (32.2-38.8) million people were living with HIV in 2012. There were 2.3 (1.9-2.7) million new HIV infections globally, showing a 33% decline in the number of new infections from 3.4 (3.1-3.7) million in 2001. At the same time the number of AIDS deaths is also declining with 1.6 (1.4-1.9)
In 2012, there were 1.46 million AIDS deaths, down from 2.3 million in 2005.3

Undiagnosed or untreated infection with HIV results in progressive loss of immune function marked by depletion of the CD4+ T lymphocytes (CD4), leading to opportunistic infections and malignancies characteristic of Acquired Immunodeficiency Syndrome (AIDS).4

Oral manifestations of HIV are common and have been important in identification of patients harbouring the HIV virus and in predicting the decline in their immune system. Early recognition, diagnosis, and treatment of HIV-associated oral lesions may reduce morbidity. Oral manifestations of HIV disease are common and include oral lesions and novel presentations of previously known opportunistic diseases.5 Careful history taking and detailed examination of the patient’s oral cavity are important parts of the physical examination, and diagnosis requires appropriate investigative techniques.

Oral lesions are an important component of the spectrum of disease seen in HIV infection. There are almost forty different lesions reported in association with HIV disease. Presence of any of these lesions may be an early diagnostic indicator of immunodeficiency and HIV infection. Some oral lesions are also indicators of the disease’s progression. Current classification of many oral lesions of HIV disease is based on their strength of association with HIV infection:8

**Lesions Strongly Associated with HIV Infection:**
1. Fungal Infections:
   - Pseudomembranous Candidiasis
   - Erythematous Candidiasis
   - Candidal Angular Cheilitis
2. Hairy Leukoplakia
3. Linear Gingival Erythema
4. Necrotising Ulcerative Gingivitis
5. Necrotising Ulcerative Periodontitis
6. Necrotising Ulcerative Stomatitis
7. Kaposi’s Sarcoma
8. Non-Hodgkin’s Lymphoma

**Lesions Less Commonly Associated with HIV Infection:**
1. Viral Infections:
   - Herpes Simplex
   - Herpes Zoster
   - Condyloma Acuminata
   - Verruca Vulgaris
2. Salivary Gland Disease:
   - Xerostomia
   - Salivary Gland Swelling
3. Thrombocytopenic Purpura
4. Recurrent Aphthous Ulcers
5. Melanotic Hyperpigmentation
6. Cryptococcosis
7. Histoplasmosis

**Figure 1: Pseudomembranous Candidiasis**

**Figure 2: Erythematous Candidiasis**
Figure 3: Angular Cheilitis

Figure 4: Hyperplastic Candidiasis

Figure 5: Herpes Simplex Virus

Figure 6: Herpes Zoster Virus (On the Face)

Figure 7: Herpes Zoster Virus

Figure 8: Human Papillomavirus

Figure 9: Cytomegalovirus

Figure 10: Oral Hairy Leukoplakia

Figure 11: Linear Gingival Erythema

Figure 12: Necrotizing Ulcerative Gingivitis

Figure 13: Necrotizing Ulcerative Periodontitis

Figure 14: Necrotizing Ulcerative Stomatitis
Figure 15: BACILLARY ANGIOMATOSIS

Figure 16: SYPHILIS

Figure 17: KAPOSI'S SARCOMA

Figure 18: NON-HODGKIN'S LYMPHOMA

Figure 19: MINOR RECURRENT APHTHOUS ULCER

Figure 20: MINOR RECURRENT ULCER APHTHOUS ULCER

Figure 21: MAJOR RECURRENT APHTHOUS

Figure 22: IDIOPATHIC THROMBOCYTOPENIC PURPURA

Figure 23: CERVICAL CARIES OCCURRING IN ASSOCIATION WITH XEROSTOMIA

Figure 24: PAROTID GLAND ENLARGEMENT

Figure 25: NEUTROPENIC ULCERATIONS

Figure 26: HYPERPIGMENTATION OF THE ORAL MUCOSA/CHEEKS
FUNGAL LESIONS

PSEUDOMEMBRANOUS CANDIDIASIS (THRUSH) (FIGURE 1)

Semi-adherent, whitish yellow, soft and creamy patches that are overgrowth of fungi mixed with inflammatory and desquamated epithelium cells. The white patches can be wiped off with a gauze swab, and underneath will appear a raw, reddish and slightly bleeding surface. Common locations for thrush occurrence are lip/cheeks, tongue, roof of the mouth and gingiva. 9

ERYTHEMATOUS CANDIDIASIS (ATROPHIC CANDIDIASIS) (FIGURE 2)

A red, flat, subtle lesion frequently affecting different areas including the roof of the mouth, dorsum of the tongue, cheeks and can be associated with desquamation and even with some whitish stippling. Unlike thrush, these the white spots cannot be wipe off. Atrophic candidiasis may also present as a “kissing” lesion—if a lesion is present on the tongue, the roof of the mouth should be examined for a matching lesion, and vice versa.10

ANGULAR CHEILITIS (PERLECHE) (FIGURE 3)

A reddish fissuring at one or both corners of the mouth, with or without ulceration, and may be accompanied by subjective symptoms of soreness, tenderness, burning or pain. Often presents with xerostomia (dry mouth) and can also be found in patients with ill-fitting complete dentures.

HYPERPLASTIC CANDIDIASIS (CANDIDAL LEUKOPLAKIA) (FIGURE 4)

White and hyperplastic in some cases whilst others may present as papillary (bubbly) hyperplasia. It is associated with severe immunosuppression.

They can’t be removed by scraping like thrush and are often accompanied by a burning sensation and extreme xerostomia (dry mouth). It can be found in different areas of the mouth including the tongue.11

VIRAL LESIONS

HERPES SIMPLEX VIRUS (HSV 1 & 2) (FIGURE 5)

Herpes simplex causes both primary and secondary or recurrent disease in the oral cavity. Primary herpetic gingivostomatitis commonly occurs in children and young adults and may be followed by frequent recurrences. Following the primary episode, the virus becomes latent in the trigeminal ganglion. Recurrent oral herpes occurs at any age extraorally or intraorally. A single or multiple vesicles (bubbles) typically ruptured causing painful ulcers. This may cluster or stay discrete. Lesions may extend to the labial (and perioral) skin, as well as widespread areas inside the mouth. Recurrent intraoral herpes appears as clusters of painful small vesicles that rupture and ulcerate and usually heal within 1 week to 10 days. We all carry the virus, but it can be activated by immunosuppression, certain foods, UV light, stress, fever, and trauma. Recurrent lesions are common.12,13

HERPES ZOSTER VIRUS (SHINGLES) (FIGURE 6,7)

The reactivation of varicella zoster virus (VZV) causes herpes zoster (shingles). The disease occurs in the elderly and the immunosuppressed population. Skin and oral lesions are frequently unilateral and follow the distribution of the maxillary and/or mandibular branches of the trigeminal nerve. The skin lesions form crusts and the oral lesions coalesce to form large ulcers. The ulcers frequently affect the gingiva, so tooth pain may be an early complaint. On the face: unilateral, with skin and mucosa eruption of maculopapular, linear, clustered vesicles that appear along the course of one or more branches of trigeminal nerve of the face. Inside the mouth: present in the form of spread (ephemeral) vesicles, which break up and leave unilateral herpetiform ulcerations that are most commonly found in the roof of the mouth. The lesions can further extend to the bone and cause necrosis.14

HUMAN PAPILLOMAVIRUS (HPV) (FIGURE 8)

Oral warts, papillomas, skin warts, and genital warts are associated with the human papilloma virus (HPV). Lesions caused by HPV are common on the skin and mucous membranes of persons with HIV disease. Anal warts have frequently been reported among homosexual men. They appeared as white or pink warts that are single or multiple, may be cauliflower-like, spiked, or raised with a flat surface anywhere in the oral cavity. Roof of the
mouth, tongue and lips are most common areas affected. Oral warts are uncommon in immunocompetent individuals but are more likely to arise in those with concomitant HIV infection.15

**CYTOMEGALOVIRUS (CMV) (FIGURE 9)**

CMV ulcers in the oral cavity usually occur in individuals with disseminated CMV disease. Therefore, diagnosis of CMV-infected oral ulcers should be followed by examination for the systemic disease. CMV ulcers resolve when ganciclovir is used to treat CMV disease. CMV ulcers are painful, large, sharply demarcated, non-specific and punched out usually on the roof of the mouth or the gums but occasionally on the cheeks, lips, tongue, and pharynx with lack of surrounding swelling (edema). Their size can vary from a few millimetres up to several centimetres.16

**ORAL HAIRY LEUKOPLAKIA (FIGURE 10)**

Oral hairy leukoplakia (HL), which presents as a nonmovable, corrugated or “hairy” white lesion on the lateral margins of the tongue, occurs in all risk groups for HIV infections, although less commonly in children than in adults.

Diagnosis of HL is an indication of both HIV infection and immunodeficiency; it is an indication for a work-up to evaluate and treat HIV disease. HL correlates with a statistical risk for more rapid progression of HIV disease. In an early study, 30% of persons with HL progressed to late-stage HIV disease characterized by CDC-defined AIDS within 36 months. They are present as slightly raised, painless, white, vertically corrugated hyperkeratotic striated lesion on the lateral border of the tongue, sometimes on the dorsal or ventral tongue where it is usually flat and plaque-like, and on the cheeks. It tends to be whitish in colour.18

**BACTERIAL LESIONS
PERIODONTAL DISEASE**

Periodontal disease is a fairly common problem in both asymptomatic and symptomatic HIV-infected patient. It can take two forms: the rapid and severe condition called necrotizing ulcerative periodontitis (NUP) and its associated and possibly precursor condition called linear gingival erythema (LGE). The presenting clinical features of these diseases often differ from those in non-HIV-infected persons.19

**LINEAR GINGIVAL ERYTHEMA (FIGURE 11)**

It appears as a distinct reddish (erythematous) band 2 to 3 mm in width along the gingival margin. There is occasional gingival bleeding, often in the absence of plaque or dental calculus. In LGE, the gingiva may be reddened and edematous. Patients sometimes complain of spontaneous bleeding. In acute-onset ulcerative gingivitis, ulcers occur at the tips of the interdental papilla and along the gingival margins, and often elicit complaints of severe pain. The ulcers heal, leaving the gingival papillae with a characteristic cratered appearance.20

**NECROTIZING ULCERATIVE GINGIVITIS (FIGURE 12)**

It is characterized by very painful, swollen, red, bleeding gums with ulcers and foul mouth odour. Primarily caused by bacteria (gram-negative bacilli) and it is associated with severe immunosuppression. It causes rapid destruction of the gingiva.

**NECROTIZING ULCERATIVE PERIODONTITIS (NUP) (FIGURE 13)**

NUP may present as rapid loss of supporting bone and soft tissue. Typically, these losses occur simultaneously with no formation of gingival pockets, sometimes involving only isolated areas of the mouth. Teeth may loosen and eventually fall out, but uninvolved sites can appear healthy. Necrotizing stomatitis may develop, and areas of necrotic bone may appear along the gingival margin. The bone may eventually sequestrate. Patients with NUP and necrotizing stomatitis frequently complain of extreme pain and spontaneous bleeding.21

Severe deep-aching jaw pain can be one of the hallmarks. “Punched-out” dental papilla, soft tissue and bone necrosis, spontaneous bleeding, deep seated pain, mouth odour, reddish in appearance, spontaneous exfoliation of teeth, necrosis of the bone, and swelling are common.22

**DIFFERENT COURSE IN HIV INFECTION**

The microbiology of periodontal disease in HIV-infected patients has not been fully described. Oral flora associated with LGE and NUP appear to be similar to those associated with periodontal disease seen in non-HIV-infected persons. Recurrences of acute episodes are common and response to conventional treatment may be poor. However, therapeutic strategies and frequent recall
appointments can produce effective local treatment of LGE and NUP. There is as yet no known relationship between these conditions and the progression of HIV disease.23

**NECROTIZING ULCERATIVE STOMATITIS (FIGURE 14)**

It is characterized by a localized, acute, rapid, extensive, painful tissue destruction and necrosis from gums to adjacent mucosal and osseous tissues with foul mouth odour. Underlying bone may be exposed, or the lesion may penetrate or extend into adjoining tissues.

**BACILLARY ANGIOMATOSIS (FIGURE 15)**

Oral lesions resemble Kaposi’s sarcoma with painless, reddish, and slightly elevated soft tissue plaque or nodule. Roof of the mouth, cheeks, gums and tongue are the most common sites of this disease. This disease is also commonly found on skin as purplish red papules, plaques, and nodules as well.24

**MYCOBACTERIUM AVIUM-INTRACELLULARE**

One report describes a case of Mycobacterium avium-intracellulare that presented as palatal and gingival granulomatous masses in the oral cavity. A diagnosis of acid-fast bacilli (AFB) was made from a specially stained (acid-fast) biopsy specimen. The AFB cultured from blood and sputum were Mycobacterium avium-intracellulare.25

**SYPHILIS (FIGURE 16)**

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.26

**NEOPLASTIC LESIONS KAPOSI’S SARCOMA (FIGURE 17)**

Kaposi’s sarcoma (KS) may occur intraorally, either alone or in association with skin and disseminated lesions. Intraoral lesions have been reported at other sites and may be the first manifestation of late-stage HIV disease (AIDS). KS occurs most commonly in men but also has been observed in women. Blue, red, or purple macules, papules, or patches on the palate (most commonly the roof of the mouth, hard and soft palates), gums, cheeks, and/or tongue that may not blanch with applied pressure. Lesions are usually painless, but as they progress into unilocular or multifocal vascular soft tissue nodules and increase in size, patients may experience pain due to secondary trauma and ulceration. Oral KS lesions may enlarge, ulcerate, and become infected. Good oral hygiene is essential to minimize these complications.

**SQUAMOUS CELL CARCINOMA (CANCER)**

Oral neoplasia has been associated with chewing of tobacco with betel quid (BQ) in India and other Asian countries, whereas in western countries, cigarette smoking and heavy alcohol consumption are the main risk factors. The International Agency For Research on Cancer (IARC) confirmed that smoking of various forms of tobacco (e.g., bidis, pipes, cigars and cigarettes) is carcinogenic in humans.27 The pathogenesis of oral squamous cell carcinoma in patients with HIV includes increased cell growth and proliferation caused by viral interference with tumour suppressor proteins (p53, Rb) and activity of the HIV transactivator of transcription protein and HPV. They are most commonly found in the gingiva and lips, as well as any other area.28

**LYMPHOMAS NON-HODGKIN’S LYMPHOMA (FIGURE 18)**

HIV attacks T-cell lymphocytes called CD4 cells, which help the immune system response to infections. This makes people with the virus more prone to developing serious infections and different types of cancer, including lymphoma. Lymphoma can develop at any time, but it is more common when the number of CD4 cells (the CD4 count) is low. Diffuse, undifferentiated non-Hodgkin’s lymphoma (NHL) is frequent HIV-associated malignancy. Most are of B cell origin, and Epstein-Barr virus occurs in cells from several cases.
Lymphoma can occur anywhere in the oral cavity, and there may be soft tissue involvement with or without involvement of underlying bone. The lesion may present as firm, painless swelling that may be ulcerated. Some oral lesions may appear as shallow ulcerations. Oral NHL may appear as solitary lesions with no evidence of disseminated disease. Ulcerations or masses those are painful, firm, elastic, often reddish or purplish. They enlarge rapidly with the most common areas involved being the gums of the back teeth, the roof of the mouth (soft palate), back molar area, tonsils areas and tongue. Such masses may be discrete (shallow) or large and multifocal.

OTHER ORAL LESIONS ASSOCIATED WITH HIV DISEASE ORAL ULCERATION (FIGURE 19, 20, 21)

Oral ulcers resembling recurrent aphthous ulcers (RAUs) in HIV-infected persons are reported with increasing frequency. The cause of these ulcers is unknown. Proposed causes include stress and unidentified infectious agents. In HIV-infected patients, the ulcers are well circumscribed with erythematous margins. The ulcers of the minor RAU type may appear as solitary lesions of about 0.5 to 1.0 cm. The herpetiform type appear as clusters of small ulcers (1 to 2 mm), usually on the soft palate and oropharynx. The major RAU type appears as extremely large (2 to 4 cm) necrotic ulcers. The major RAUs are very painful and may persist for several weeks.

IDIOPATHIC THROMBOCYTOPENIC PURPURA (FIGURE 22)

Reports have described idiopathic thrombocytopenic purpura (ITP) in HIV-infected patients. Oral lesions may be the first manifestation of this condition. Petechiae, ecchymoses, and hematoma can occur anywhere on the oral mucosa. Spontaneous bleeding from the gingiva can occur, and patients may report finding blood in their mouths on waking.

SALIVARY GLAND DISEASE (SGD) AND XEROSTOMIA (DRY MOUTH) (FIGURE 23,24)

Salivary gland disease associated with HIV infection (HIV-SGD) can present as xerostomia with or without salivary gland enlargement. Reports describe salivary gland enlargement in children and adults with HIV infection usually involving the parotid gland. The enlarged salivary glands are soft but not fluctuant. In some cases, enlarged salivary glands may be due to lymphoepithelial cysts. At the initial stages of HIV infection, even without immunosuppression, the parotid glands (in front of the ear) can grow with no apparent cause. It is painless bilateral parotid gland enlargement without signs of infection. This might cause facial disfiguration. Patients living with HIV have higher rates of salivary flow reduction, which can lead to xerostomia (sensation of dry mouth). With low and no saliva, the mouth has lower capacity to fight off the acids produced by bacteria and patients might be at higher risk to develop tooth decay.

NEUTROPENIC ULCERATIONS (FIGURE 25)

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. Very painful ulcerations that can appear on both keratinized and non-keratinized mucosa tissues (cheeks and gums). They are large and unusual-looking, or fulminant ulcers in the oral cavity that cannot otherwise be identified or explained as any other condition.

HYPERPIGMENTATION OF THE ORAL MUCOSA/CHEEKS (FIGURE 26)

Appear as flat, brown or blue mucosal (cheeks) lesions. It can appear as a patchy pigmentation of the oral mucosa, which is a common finding in dark skinned races.

CONCLUSION & RECOMMENDATION

As the oral manifestations are among the earliest and most important indicators of HIV infection, a better understanding of these manifestations in both adults and children is a must for all dental health care workers. Early recognition, diagnosis, and treatment of HIV-associated oral lesions may reduce morbidity of the adults. The knowledge of the epidemiology of the spread of HIV, the biology of the virus and the sociology of the affected persons must be utilized to explore relevant research directions. The prevention, diagnosis, treatment, and control of these oral manifestations should be part of the objectives of every dental health professional.
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