

Oral lesions: A true clinical indicator in human immunodeficiency virus

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Abstract

From the onset of the human immunodeficiency virus (HIV) epidemic over 20 years ago (since the appearance of the first cases of contamination by the HIV virus in the 1980s), more than 60 million people have become infected and more than 20 million people have died. An estimated 15,000 new infections occur each day, with more than 95% of these in developing countries. The distinctive characteristic in the pathogenesis of HIV/acquired immunodeficiency syndrome is that the primary target cell for HIV is immune cells bearing the CD4 marker at their surface, and the CD4 cell count and viral load have been used lately as the most important laboratory parameters to evaluate the evolution of the disease. Oral lesions are common (30–80%) in patients infected by the HIV virus and may indicate an impairment in the patient's general health status and, consequently, a poor prognosis. Oral manifestations can suggest decreased cluster-differentiated (CD4+) T cell count and increased viral load, which might also aid in diagnosis, progression, and prognosis of the disease. At the tertiary level of oral care, a dentist should be available to make definitive diagnoses of oral lesions and provide professional oral services such as prophylaxis, restorations, biopsies, and the prescription of appropriate medication.

Key words: CD4, dental, HIV, oral

INTRODUCTION

HIV: Prevalence and epidemiology

Human immunodeficiency virus (HIV) causes progressive mutilation of the body's cellular immune system, leading to augmented susceptibility to tumors and fatal conditions such as acquired immunodeficiency syndrome (AIDS). The emergence and pandemic spread of AIDS constitute the greatest challenge to the public in modern times.^[1] From the onset of the HIV epidemic over 20 years ago (since the appearance of the first cases of contamination by the HIV virus in the 1980s), more than 60 million people have become infected and more than 20 million people have died. More than 20 years into this HIV-AIDS pandemic, it has stuck almost all the countries and populations in many

ways. No disease has struck with such serious consequences as AIDS. It has devastating social, psychological, and financial ramifications. Currently, it is the fourth-leading cause of mortality worldwide.^[2] AIDS, caused by HIV, is presently considered as one of the most dreadful diseases affecting human kind. An estimated 15,000 new infections occur each day, with more than 95% of these in developing countries. Sub-Saharan Africa currently bears the greatest burden worldwide, with 28.5 million (70%) individuals infected. In South Africa, 5.2 million of the population was estimated to be infected with HIV/AIDS. HIV is transmitted by sexual means, through the exchange of body fluids (especially infected semen during intercourse); by non-sexual means, via the parenteral transfer of infected blood; or through vertical transmission to infants born of infected mothers. The only fluids that have been demonstrated to be associated with transmission of the virus are blood, semen, breast milk, and vaginal secretions. Casual contact (shaking hands, hugging, casual kissing, etc.) has not been shown to transmit HIV. The United Nations Programme on HIV/AIDS estimates that over 40 million people are living with HIV/AIDS globally. An estimated 15,000 new infections occur each day, with more than

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95% of these in developing countries. Sub-Saharan Africa currently bears the greatest burden worldwide, with 28.5 million (70%) individuals infected. In South Africa, 5.2 million of the population was estimated to be infected with HIV/AIDS. Between 60% and 90% of the people with HIV infection will have at least one oral manifestation at some time during the course of their disease. Oral lesions cause significant discomfort and have a major impact on the quality of life. Recognition and management of these oral conditions is therefore important for the health and quality of life of the individual with HIV/AIDS. Despite the increasing number of reports on the prevalence of oral manifestations in HIV-positive/AIDS patients, there is limited information about the impact of these lesions on the quality of life in these patients.

Structure of human immunodeficiency virus

The HIVs are members of the retrovirus family of viruses. The retrovirus family is composed of three subfamilies: oncoviruses, spumaviruses and lentiviruses. Based on the structure, biologic properties, and protein and nucleic acid sequence homology, HIV is classified as lentivirus. A mature extracellular particle of HIV is characteristically 90–130 nm in diameter. HIV has a cylindrical eccentric nucleoid, or core. The nucleoid contains the HIV genome, which is diploid (i.e., composed of two identical single-stranded RNAs). Encoded in the RNA genome are the entire complements of genes of the virus. These genes code for the structural proteins that are used to assemble the virus particles and the regulatory proteins involved in the regulation of viral gene expression. The HIV RNA genome is associated with a basic nucleic acid-binding protein p9 and the reverse transcriptase (RT). The core or capsid antigen p24 encloses the nucleoid components, completing the nucleocapsid structure. The matrix antigen p17 encircles the viral core and lines the inner surface of the envelope of the virus. The surface of the HIV manifests external knob-like structures formed by the envelope glycoprotein gp120. The transmembrane protein (TMP) gp41 spans the viral membrane and has both external and internal domains. The TMP anchors the external gp 120 to the viral envelope. The membrane lipid bilayer is derived from the host cell plasma membrane.^[3]

Human immunodeficiency virus and immune system: CD4 target

The distinctive characteristic in the pathogenesis of HIV/AIDS is that the primary target cell for HIV is immune cells bearing the CD4 marker at their surface. With the infection of HIV, there will be gradual decrease of human immune cells bearing CD4 antigen receptor, the most important being T helper cells (CD4 T cells), B lymphocytes, macrophages, and natural killer cells. The CD4 cells coordinate a number of immunological

functions, and as these cells are decrease the risk and severity of opportunistic infections (OI) increasing the death of the patients. It is stated that the absolute number of CD4 lymphocytes fall from a normal level of 800–900 cu/mm to 60–100 per year.^[4] Because the loss of immune containment is associated with declining CD4 counts, the Centre for Disease Classification (CDC) stratifies patients with HIV infection into three categories on the basis of CD4 counts: CD4 counts ≥ 500 cells/mm³, 200–499 cells/mm³ and < 200 cells/mm³. A CD4 count < 200 cells/mm³ is associated with severe immune suppression, and the CDC in 1993 included all HIV-infected persons with such a count as fulfilling an AIDS-defining diagnosis.^[5] The amount of CD4 lymphocyte cells per milliliter and/or the quantity of RNA-HIV-1 copies per milliliter (viral load) are surrogate markers of HIV disease progression. It is known that HIV-positive patients with CD4 lymphocyte cells counts less than 200 per milliliter are severely immune depressed and HIV-positive patients with a viral load greater than 10,000 copies per milliliter show an active viremia.^[6,7] The CD4 cell count and viral load have been used lately as the most important laboratory parameters to evaluate the evolution of the disease.^[8] Although there have been reports of delayed antibody response to HIV1 infection, 95% or more of the infected persons develop detectable antibodies to HIV1 within 3–6 months. The interval between infection and seroconversion or detection of antibodies has been called the window period. The standard screening test for HIV infection is elaborated in Table 1.

Human immunodeficiency virus: Clinical presentation

Symptoms of HIV disease can appear at any time during the course of HIV infection. The spectrum of illness changes as the CD4+ T cell count declines. The more severe and life-threatening complications of HIV infection occur in patients with a CD4+ T cell count $< 200/\mu\text{L}$. A diagnosis of AIDS is made in anyone with HIV infection and a CD4+ T cell count $< 200/\mu\text{L}$ and in anyone with HIV infection who develops one of the HIV-associated diseases considered to be indicative of a severe defect in cell-mediated immunity. While the causative agents of the secondary infections are characteristically opportunistic organisms such as *P. carinii*, atypical mycobacteria, cytomegalo virus (CMV), and other organisms that do not ordinarily cause disease in the absence of a compromised immune system, they also include common bacterial and mycobacterial pathogens. Approximately 60% of the deaths among AIDS patients are as a direct result of an infection other than HIV, with *P. carinii*, viral hepatitis, and non-AIDS defining bacterial infections heading the list. Following the widespread use of combination antiretroviral therapy and implementation of guidelines for the prevention of OIs, the incidence of secondary infections has decreased dramatically. Overall, the clinical spectrum of HIV disease is constantly changing

Table 1: Standard screening test for HIV infection

Laboratory detection test	Scientific features
ELISA (enzyme-linked immunoassay)	Screening test Kit test (rapid results) Not optimal with regard to specificity Confirmatory test to be followed upon
Western blot	Most commonly used confirmatory test A Western blot demonstrating antibodies to products of all three of the major genes of HIV is conclusive evidence of HIV infection
p24 capture assay	Enzyme immunoassay Detects the viral protein p24 in the blood of HIV-infected individuals Screening test for HIV infection p24 antigens are present prior to the development of antibodies
HIV RNA (in plasma)	Diagnostic tool in settings where measurements of anti-HIV antibodies may be misleading In cases of acute infection and neonatal infection It includes reverse transcriptase PCR, branched DNA, and the nucleic acid sequence-based assay

Table 2: Stages of HIV progression

Stages of HIV progression	Clinical manifestations
Acute retroviral syndrome	2–6 weeks following initial infection with HIV Acute flu-like syndrome that may last 10–14 days Syndrome of fever, generalized lymphadenopathy, pharyngitis, headache, myalgia, and arthralgia High levels of viral particles can be detected in the plasma CD4+ T cell count declines Seroconversion occurs
Early chronic infection	Lengthy phase (lasts for a decade or more) CD4+ T cell counts will be normal or slightly decreased Viral loads will be low Asymptomatic phase, but can be associated with intermittent fatigue, headaches, night sweats, low-grade fevers, enlarged lymph nodes, weight loss, oral Candidiasis, malaise, and diarrhea
Intermediate chronic infection	Signals progression of HIV disease CD4+ T cell counts begin to decrease Viral load increases Oral lesions Chronic infection will become more persistent
Late chronic infection (AIDS)	Appearance of symptoms of opportunistic diseases (viral, bacterial, fungal, or protozoal) Increased viral loads Generalized lymphadenopathy, severe weight loss, fatigue, chronic diarrhea, chronic fever, and drenching night sweats CD4+ T cell count drops below 200 cells/mm ³ Opportunistic cancers (Kaposi's sarcoma, cervical carcinoma, Burkitts lymphoma, etc.) Dementia develops Wasting syndrome occurs

as patients live longer and new and better approaches to treatment and prophylaxis are developed. In general, it should be stressed that a key element of the treatment of symptomatic complications of HIV disease, whether they are primary or secondary, is achieving good control of HIV replication through the use of combination antiretroviral therapy and instituting primary and secondary prophylaxis as indicated.^[2] Without treatment, HIV-infected patients will progress through the stages described in Table 2.

Oral lesion in human immunodeficiency virus

Oral lesions are common (30–80%) in patients infected by the HIV virus and may indicate an impairment in the patient's general health status and, consequently, a poor prognosis. Many of these HIV-positive patients present manifestations involving the maxillofacial region in all

stages of the disease, and, in some cases, the oral lesions are the first signs of infection.^[9,10] With disease progression, the deleterious effect of HIV on the immune system results in an escalating incidence of widely recognized and extensively described OIs and diseases, among which are the oral manifestations of HIV and, since the onset of the HIV pandemic, oral lesions have been well documented as early markers of HIV infection and as predictors of HIV disease progression.^[11,12] Oral manifestations can suggest decreased cluster-differentiated 4 (CD4+) T cell count and increased viral load, which might also aid in the diagnosis, progression, and prognosis of the disease.^[13-15] The risk of oral complication increases with immunologic deterioration. Oral examination is therefore useful for the early diagnosis, which can prolong the asymptomatic period, delay disease progression, and prevent OIs with proper education and

Table 3: Oral lesions associated with HIV

Oral manifestation	Clinical presentation
Pseudomembranous candidosis	Initial manifestation of symptomatic infection with HIV Prevalence has been reported to be as high as 95% Soft white/yellow, curd-like plaques on the oral mucosa Deposits easily removable by gentle scraping
Erythematous candidosis	Flat red patches on the dorsal surface of the tongue and hard palate White spots and plaques may be seen, but these are not usually conspicuous
Angular cheilitis	Red, ulcerated, and fissured lesion at the angle of the mouth
Hairy leukoplakia	Asymptomatic bilateral, vertically corrugated, or hairy white lesions on the lateral borders of the tongue Not removable Lesions may rarely occur on the buccal mucosa
Linear gingival erythema	Well-demarcated, linear band of intense redness along the gingival margins Amount of erythema is disproportionately intense for the amount of plaque seen No ulceration is present
Necrotising ulcerative gingivitis	Painful ulceration of the interdental papillae associated with halitosis and spontaneous gingival bleeding Sloughing may be seen
Necrotising ulcerative periodontitis (NUP)	Rapidly progressive periodontal disease resulting in bone loss Destruction or sequestration of bone may be seen, and the teeth may become loosened Associated with severe pain (tooth sensitivity)
Necrotising ulcerative stomatitis	Extension of NUP into soft tissues Bone sequestra
Kaposi's sarcoma	Painless purple/violaceous lesions on the palatal/anterior gingival mucosa; later becomes raised and ulcerated
Non-Hodgkin's sarcoma	Rapidly enlarging rubbery mass in the tonsillar fossa, palate, or gingival
Herpes simplex (HSV)	Clusters of painful, small vesicles/ulcers on the palate or gingivae Most cases of HSV infections are recurrent. Herpes labialis lesions are on the vermilion or mucocutaneous junction on the lips; form crusts on rupture Herpes labialis is also known as cold sores
Herpes zoster	Prodrome of pain, multiple vesicles on facial skin, lips, and intraoral structures. Follows the nerve distribution May be complicated by post-herpetic neuralgia
Condyloma acuminata	Warts are nodular or cauliflower-like in appearance, often multiple
Xerostomia	Dry mouth, often with fissured tongue. Promotes dental caries
Salivary gland swelling	Unilateral/bilateral salivary gland swellings
Thrombocytopaenic purpura	Bleeding tendencies; petechiae on oral mucosa
Melanotic hyperpigmentation	Melanotic linear lesions on the gingivae
Histoplasmosis	Necrotic growth/ulcers
Cryptococcosis	Necrotic ulcerative lesions
Tuberculous ulcers	Ulcerative lesions usually on the tongue or gingivae Usually patient has pulmonary TB
Lichenoid reactions	White lace-like lesions on the oral mucosa
Erythema multiforme	Ulcerative lip and intraoral lesions
Dental caries	Dental decay
Trigeminal neuralgia	Shock-like pain along the distribution of the trigeminal nerve
Facial palsy	Unilateral paresthesia of the face

counseling of the patient. 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. Oral manifestations frequently observed in HIV patients may be classified according to etiologic factors: fungal, viral,

bacterial, and neoplastic infections. These lesions are often the first clinical symptoms of HIV infection and their diagnosis is an auxiliary method to raise early suspicion of AIDS.^[16] The various commonly associated oral lesions with HIV are illustrated in Table 3. Clinical stages of oral lesions associated with HIV with respect to its occurrence are illustrated in Table 4.

Effect of antiretroviral therapy on oral lesions

In the recent years, the management of HIV-positive

individuals has been based on highly active antiretroviral therapy (HAART), comprising a combination of nucleoside analogue RT inhibitors and at least one protease inhibitor and/or one non-nucleoside analogue RT inhibitor. HAART induces a marked reduction of viral replication and increases the CD4+ cell count. Since the introduction of HAART in the mid-1990s, it has been accompanied by a reduction in the frequency of many of the secondary events caused by HIV infection, including some oral lesions.^[17] Since the advent of HAART, studies had shown a decline in the prevalence of oral lesions associated with HIV/AIDS. These lesions include: oral candidiasis, hairy leukoplakia, Kaposi's sarcoma, herpes simplex labialis, and periodontal disease.^[18]

CONCLUSION

The World Health Organization (WHO) Global Oral Health Program recently formulated policies for the prevention of oral manifestations in HIV/AIDS.^[19] Prevention of HIV/AIDS-related oral disease is based on the involvement of primary healthcare workers as well as oral health professionals in the early detection and screening, on the integration of oral disease prevention and oral health promotion into community and national HIV/AIDS programmes, and on the WHO technical support to build capacity in countries. By using a systematic approach and giving the patient a complete oral examination, the dentist will be able to diagnose oral lesions in patients with HIV disease. Rather than trying to guess the correct diagnosis, a good diagnostician should obtain the history of the lesion, should evaluate signs and symptoms, and should determine the possible etiology. Important factors to be considered in the differential diagnosis are the history of the lesions, the clinical appearance, location, and symptoms like pain, burning sensation, and discomfort upon deglutition. It is also important to consider the nature of the lesion. An oral mucosal lesion can be reactive, inflammatory, infectious, or malignant. It

can be a localized process or part of a systemic disease. From the analysis of the data collected during clinical examination, the dentist can construct a list of differential diagnoses, listing the most probable disease that could cause that particular lesion. This procedure should lead to the final diagnosis of the disease and indicate the most appropriate treatment. Not uncommonly, oral lesions in HIV patients can cause severe impairment of oral functions as well as pain and discomfort and, in addition, they are a manifestation of opportunistic diseases secondary to systemic immunosuppression. Therefore, from the oral cavity, they may disseminate systemically and cause a much more dangerous threat to the patient's health. Some of the lesions may be transmissible and patients must be counseled on the prevention of transmission (e.g., Herpes, syphilis, tuberculosis). HIV-related oral abnormalities are present in 30–80% of the HIV-infected individuals, and these abnormalities are often inaccurately described in medical care. Dental expertise is necessary for the 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. At the tertiary level of oral care, a dentist should be available to make definitive diagnoses of oral lesions and provide professional oral services such as prophylaxis, restorations, biopsies, and the prescription of appropriate medication. There is a need for dentists to be involved throughout the management of HIV patients and not only at the tertiary level of care. There is also a need for training and retraining of medical personnel in the diagnosis and management of HIV-associated oral lesions and appropriate patient referral.

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Table 4: Clinical stages associated with HIV

Association with HIV	Oral lesions
Strong association	Candidiasis Hairy leukoplakia Kaposi's sarcoma Non-Hodgkin lymphoma Periodontal disease
Moderate association	Bacterial infection Hyperpigmentation Necrotizing stomatitis Salivary gland disease Viral infections
Mild association	Drug reactions Fungal infections Neurological disturbances

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