Clinical manifestations of HIV: An update for dental practitioners

Fatema H Lukmani, Junaid Ahmed and Ravikiran Ongole

Abstract

HIV/AIDS epidemic contributes to the global burden of disease significantly. In India, with initiation of the ART programme in 2004, greater number of people living with HIV have access to treatment. HIV transmission via the oral cavity has been a debatable concept. Multiple studies have failed to isolate the virus in the oral epithelial cells, and therefore, absence of virus in the oral cavity makes its transmission questionable. Global efforts to limit transmission of the disease must be augmented with early recognition, diagnosis and institution of HAART. Oral manifestations of HIV are highly characteristic. Within the purview of dental practice, the most salient clinical features of HIV can be divided based on general clinical features and extra-oral and intra-oral manifestations. Gingival changes such as necrotising ulcerative gingivitis and periodontitis, linear gingival erythema, oral candidiasis and oral hairy leukoplakia are common oral manifestations in almost 60% of HIV infected individuals. It is also believed that approx. 80% of individuals with AIDS exhibit these oral changes. When coupled with knowledge of other cardinal features, an early diagnosis of HIV can be made. As a result, better patient outcomes are seen, with a resultant decline in AIDS-related mortality. This results in more patients requiring oral and dental care who will seek treatment for complaints which may or may not be related to their immune status. This requires clinicians to be abreast of the latest literature in academic forums. Thus, this review aims to update the dental practitioner on the latest clinical attributes and oral manifestations in people living with HIV.

Keywords: HIV, AIDS, oral manifestations, candidiasis, hairy leukoplakia, NUG, gingival erythema, kaposi sarcoma, NHL

Introduction

HIV-1 and HIV-2 belong to the lentivirus subfamily of Retroviridae. The designation retrovirus denotes that genetic code in the form of RNA is incorporated into the host DNA thereby facilitating multiplication of the viral genome. In 1983, human immunodeficiency virus (HIV) was first isolated from a patient with generalised lymphadenopathy, and by 1984 it was demonstrated to be the causative agent of AIDS. Soon after a sensitive enzyme-linked immunosorbent assay (ELISA) was developed (1985) for the diagnosis of HIV/AIDS, which led to an appreciation of the scope and evolution of the HIV epidemic globally.

In India, the national adult prevalence of HIV was found to be 0.38 percent in 2001-2004, which declined to 0.26 percent in 2015. A significant decrease in HIV prevalence was found especially during 2011-15, due to efforts in increasing awareness about safe sexual practices and making anti-retroviral therapy (ART) more accessible. In 2015, HIV prevalence among adult males was estimated at 0.30 percent, and among females at 0.22 percent. However, children aged under 15 years accounted for 6.6 percent of the total HIV infections[1].

Initiation of the Antiretroviral therapy (ART) programme in 2004 in India started to provide treatment to people living with HIV with a CD4 count of ≤200 cells/μl up to 2008, which was gradually increased to a CD4 count of up to <500 cells/μl as of April 2016. In 2015, an estimated 68,000 AIDS-related deaths were recorded; nearly 8,000 of those were among children. The decline in AIDS-related deaths was consistent with the scale-up of the national ART programme from around 65,000 people living with HIV receiving ART in 2004 to around 90,000 in 2014. In total, annual AIDS-related deaths declined by 54 percent from 2007 to 2015[2].

As a result of expanding numbers of people gaining access to treatment, and hence surviving longer, AIDS-related mortality has declined. This results in more patients requiring oral and
dental care who will frequently seek treatment for complaints which may or may not be related to their immune status. Thus, this review aims to update the dental practitioner on the latest clinical attributes and oral manifestations in people living with HIV.

**HIV transmission via the oral route**
Transmission of the HIV virion via the oral route is still questionable. A recent review that studied the inherent immune mechanisms within the oral cavity have not shown the possibility of isolating the virus from epithelial cells. Human beta-defensins and secretory leucocyte proteinase inhibitor (SLPI) which are anti-microbial peptides, are known to be the cause for the reduced rates of HIV transmission via the oral cavity; the reason for lower risk of contracting HIV during oral sex. Additionally, oral exposure due to sexual contact rarely occurs independently of other mucosal exposures.

**Clinical features of HIV**
The clinical manifestations of HIV disease is related to the CD4+ T-cell count. As the CD4+ T cell count falls, symptoms of the infection worsen and a wide variety of disease processes are exhibited. There may be persistent generalised lymphadenopathy, oropharyngeal and vulvo-vaginal candidiasis in addition to constitutional symptoms like fever and diarrhoea lasting for more than a month. When the CD4+ count falls less than <200/µL or an individual with a diagnosed HIV infection is considered to be suffering from AIDS. Also, any individual with a diagnosed HIV infection who, over time, presents with HIV-associated diseases is considered to be suffering from acquired immunodeficiency syndrome (AIDS). These include secondary infections like *P. jiroveci*, atypical mycobacteria, cytomegalovirus, and other organisms that normally would not cause disease in an immunocompetent individual. In addition to the classic AIDS-defining illnesses, patients with HIV infection also have an increase in cardiovascular, renal, and hepatic disease.

**Classification of oral lesions in HIV infection**
In September 1992 members of the EC-Clearinghouse on Oral Problems Related to HIV Infection and WHO Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus met to review the previously published classifications of oral manifestations of HIV infection and their diagnostic criteria. These ranged from oral lesions which were strongly associated with an HIV infection to conditions which were observed concurrently in HIV positive individuals. However, within the purview of dental practice, the most salient clinical features of HIV can be divided based on general clinical features and extra-oral and intra-oral manifestations. (Table 1)

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<th>Table 1: Clinical manifestations of HIV</th>
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<td><strong>General clinical features</strong></td>
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<td>Vulvovaginal candidiasis; persistent, frequent, or poorly responsive to therapy</td>
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<td>Constitutional symptoms, such as fever or diarrhea lasting &gt;1 month</td>
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<td>Idiopathic thrombocytopenic purpura</td>
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**Extra Oral Features**

**HIV Salivary Gland Disease**
Salivary gland disease in HIV manifests primarily as unilateral or bilateral enlargement of the parotid gland, with or without xerostomia. The swelling may be due to a wide spectrum of pathological conditions that include reactive or inflammatory disorders, acute and chronic infections, and neoplasms. Most commonly, the swelling is due to the development of benign lymphoepithelial cysts (BLEC) within the parotid gland. These are single or multiple cysts within the lymph nodes present along the tail of the parotid gland. Parotid enlargement can also result from proliferation of glandular epithelium that is trapped within these intra-parotid lymph nodes. Elevated titres of the HIV virus have been demonstrated in these intra-parotid lymph nodes. Management in the initial stages usually includes a conservative approach involving serial follow-up, observation and aspiration of lesions for HIV titres and malignancy. Sclerosing therapy, institution of highly active antiretroviral therapy (HAART), radiation therapy and surgery have also been used successfully in the management of HIV salivary gland disease.

**Non-Hodgkin’s Lymphoma (NHL)**
The clinical setting of patients with AIDS-related lymphoma is very different from that of the non-HIV patients with lymphoma, as is their response to treatment. The HIV-infected individual with aggressive lymphoma usually presents with advanced-stage disease that is frequently extranodal. The most commonly involved extra nodal sites include bone marrow, liver, meninges and the gastrointestinal tract. Signs and symptoms may include lymphadenopathy, fever, weight loss and recurring night sweats, accompanied by fatigue and chest pain. NHL is seen more commonly in men over 40 years of age. More than half of the cases of NHL are diagnosed during routine clinical care, signifying its importance. The mean CD4 count at the time of diagnosis of NHL, however, has increased since the beginning of widespread use of ART. Hazard ratio for NHL was higher among those with HIV viremia of 51–500 copies/mL suggesting that individuals with a moderate CD4+ count must also be subjected to a frequent rigorous clinical examination. However, there has been an 8% decrease in NHL incidence rates since 1996. NHL is often treated as a single entity with CHOP regimen being universally applied. CHOP is an acronym for...
cyclophosphamide, hydroxydianorubicin, oncovin (vincristine) and prednisone/prednisolone. Rituximab may be added to this drug regime if the lymphoma is of B-cell origin histologically [14].

**Intraoral Features**

Oral candidiasis (erythematous and pseudomembranous), oral hairy leukoplaikia (OHL), Kaposi's sarcoma, linear gingival erythema, necrotizing ulcerative gingivitis, and necrotizing ulcerative periodontitis are common oral manifestations in AIDS. Literature review reveals that over 60% of HIV infected individuals and about 80% of patients suffering from AIDS exhibit these oral findings [15].

### Table 2: Significance of oral lesions in HIV

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<tr>
<td>Can indicate HIV infection</td>
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<td>Early manifestations of HIV infection</td>
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<td>Predict progression of HIV disease to AIDS</td>
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<td>Used in staging and classification of disease</td>
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<td>Determinants of opportunistic infection and anti-HIV therapy</td>
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**Oral Candidiasis (OC)**

*Candida albicans* is a commensal organism that is normally found in the gastrointestinal and reproductive tracts. Under immune compromised conditions, *C. albicans* can turn pathogenic and cause symptomatic disease. Infections with *Candida albicans* may be the first indication of immunodeficiency [16].

Oral candidiasis is the commonest lesion observed in HIV positive patients. As per the WHO clinical staging system, it is believed that individuals in Stage 3 (clinical signs of severe weight loss, unexplained chronic diarrhea, unexplained fever, primary tuberculosis) are four times more likely to develop oral candidiasis than those in Stage 1. This finding is presently employed to categorise patients as Stage 3 under the WHO clinical staging system, which helps in tracking disease progression in HIV positive individuals. It has been proposed that HIV patients complaining of chewing inability are more likely to exhibit oral candidiasis [17].

A significant association has also been reported with CD4+ count and oral candidiasis. It is believed that individuals with CD4+ count of less than 350 cells/mm³ have increased candidial infection [18]. Weakened cell-mediated immunity (CMI) and depletion of CD4+ T cells are the main factors contributing to OC in HIV-positive individuals. Statistically significant difference in the plasma concentration of IFN-γ, IL-6 and IL-17 in HIV-positive individuals with OC was found, suggestive of a heightened inflammatory state [19].

Strong association between oral candidiasis and tuberculosis (TB), independent of CD4+ count was found. This can be of significant aid in resource-limited settings, where oral candidiasis may provide clinical evidence for increased risk of TB [20].

According to the publication by Infectious Diseases Society of America (2016), for HIV-infected patients, antiretroviral therapy is strongly recommended to reduce the incidence of recurrent candidal infections. For moderate to severe disease, oral fluconazole, 100–200 mg daily, for 7–14 days is recommended. For fluconazole-refractory disease, itraconazole solution, 200 mg once daily for 3 days followed by 400 mg daily, for up to 28 days is recommended [21].

Recently, studies have shown that antimicrobial photodynamic therapy is as effective as nystatin to inactivate *C. albicans* in the oral lesions of immune-suppressed mice with oral candidiasis [22].

**Oral Hairy leukoplaikia (OHL)**

The clinical description of OHL was first published in 1984 (Greenspan *et al.*, 1984), following which its relationship with EBV was established in 1985. The relationship with AIDS was confirmed soon thereafter [22-25].

Clinically, OHL is a painless white plaque with a corrugated surface, which cannot be removed by scraping, seen predominantly on lateral borders of the tongue. The histopathological characteristics are not exclusive to this lesion, which may include hyperkeratosis, epithelial hyperplasia, ballooning degeneration, and discrete or even absent inflammatory mononuclear cells infiltrate [26].

A retrospective review of records of 1600 HIV-infected patients found OHL in 13.4% of patients, majority of them were males in the age group of 30 to 50 years. Oral hairy leukoplaikia was common (55.5%) in individuals with CD4+ cell counts ranging between 200–500 cells/mm³. The use of a minimum of one non-nucleoside reverse transcriptase inhibitor in the ART regime significantly reduced the incidence of oral hairy leukoplaikia [27].

The clinical characteristics of OHL have evolved compared to the historical pattern: from an ample, flower-shaped lesion occupying a large area of the lateral border of the tongue to a much more discrete lesion with clinical characteristics less exacerbated than those found at the beginning of the epidemic is seen although no correlation between presence of EBV and AIDS progression was evident. Biopsy followed by EBV in-situ hybridization using polymerase chain reaction (PCR) remains the gold-standard for differentiating OHL from other white lesions seen on the lateral border of tongue [28].

Gentian violet, retinoids, podophyllin, acyclovir and podophyllin in combination with topical antiviral drugs have been used to treat OHL successfully. Of these, a combined topical therapy of 25% podophyllin and 5% acyclovir cream is most effective, demonstrating fast healing (in six weeks) without recurrence over a 5-year follow-up [29].

**Kaposi sarcoma**

Kaposi sarcoma (KS), a cancer of endothelial cells, is etiologically linked to the human herpesvirus 8 (HHV-8), or more popularly known as Kaposi sarcoma-associated herpesvirus (KSHV), and highly associated with immune suppression. Kaposi sarcoma is the most common cancer in individuals living with HIV/AIDS today [30,31].

KSHV DNA is found in all KS lesions. KSHV infection is thought to enter cells predominantly through the endocytic pathway and can be transmitted via asymptomatic oral shedding as well as through bodily fluids [32,33]. CD4+ cell count and HIV RNA levels are strongly associated with an increased risk of Kaposi sarcoma. KS develops in response to severe T-cell depletion or inactivation [34]. The clinical presentation is of one or more erythematous, slightly bluish or violaceous macule or swelling(s), with or without ulceration, seen commonly on the gingiva or palate.

Treatments are targeted at the interruption of KS angiogenesis; vascular endothelial growth factor (VEGF), stem cell factor (SCF, also known as KIT ligand), and platelet-derived growth factor (PDGF) are the best-characterized paracrine drivers of KS angiogenesis. VEGF-neutralising antibodies (bevacizumab) and receptor tyrosine kinase (RTK) inhibitors, such as imatinib, have shown efficacy in treatment of KS. These are used in combination
due to redundancies in the paracrine network from which KS is derived. Clinical studies investigating the role of thalidomide, lenalidomide, and pomalidomide in KS have found promise in the anti-angiogenic properties of these agents although the exact mechanism of action still remains unclear [35].

Necrotising ulcerative gingivitis/periodontitis
Necrotising ulcerative gingivitis (NUG) has been recognized for centuries by various names such as Vincent’s disease, fusospirochetal gingivitis, trench mouth, acute ulcerative gingivitis, necrotizing gingivitis, and acute NUG. NUG was classically seen among military personnel during World War I. However, the incidence increased in patients with an immunocompromised condition, especially in HIV-infected individuals [36].

Patients may complain of black discoloration on the gingiva with bleeding on slight provocation accompanied by fevers, malaise, chills and pain on mastication. Oral examination usually reveals significant halitosis and necrotic, sloughing gingival tissue with pseudomembrane formation, erythema and multiple ulcerations prominent especially in the interdental papilla, along with tenderness. Submandibular lymphadenopathy may be present [37]. Differential diagnosis may include neutropenic mucositis, HSV gingivostomatitis, HIV-associated periodontitis and invasive fungal disease.

Conclusion
Diagnosis and management of HIV/AIDS has improved significantly in the last decade. However, global efforts to limit transmission of the disease must be augmented with early recognition, diagnosis and institution of HAART. This will lead to better patient outcomes and subsequent increase in quality of life of individuals with HIV. With more individuals having access to treatment, more patients continue to require oral and dental care and will constitute a significant portion of the population and may seek treatment for complaints which may or may not be related to their immune status. Oral manifestations of HIV are highly characteristic and when coupled with knowledge of other cardinal features, an early diagnosis can be made. Hence, it is imperative for dental practitioners to be aware of the oral manifestations of the HIV/AIDS complex and be abreast of the latest developments in recognition and diagnosis of HIV infection.

References
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