HIV-Related Oral Manifestations and Their Correlation with Haart & Cd4+T-Cells and Oral Considerations-An Insight into Literature

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Abstract
Human immunodeficiency virus (HIV) infection is one of the major health problems of the last decades. This disease causes a chronic infection that can lead to acquired immunodeficiency syndrome (AIDS).The aim of the review is to enlighten the HIV-related oral manifestations and their correlation with HAART & CD4+T-cells.This review also gives an insight into oral consideration in HIV-positive patients.Oral manifestations of human immunodeficiency virus include candidiasis, oral hairy leukoplakia, oral ulcers, oral warts, oral lymphoma and Kaposi's sarcoma and some other presentations.Oral candidiasis, oral hairy leukoplakia, Kaposi's sarcoma and HSV infection are the lesions that have seen the major drop in their incidence after the HAART introduction.The increase in CD4+ T-cell count is not significantly correlated to the decrease of every type of oral lesions, but it is statistically significant only in relation to oral candidiasis.The prevalence of this disease is still high because of many risk factors, like the difficulty to access treatment, poor oral hygiene, low socioeconomic status and late diagnosis.

1. Introduction

Human immunodeficiency virus are a group of retrovius.(1)This disease causes a chronic infection that can lead to acquired immunodeficiency syndrome (AIDS).HIV is a sexually transmitted and it occurs by contact with or transfer through blood,semen and vaginal fluids.(2,3)Non sexual transmission can occur from an infected mother to her infant during pregnancy,child birth when exposure to her blood,vaginal fluid, breast milk takes place.(4)HIV infects vital cells in the human immune system, such as helper T cells specially CD4+ T cells,macrophages and dendritic cells.HIV infection leads to low levels of CD4+ T cells.(5)When CD4+ T cell numbers decline below critical level,cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections, leading to the development of AIDS.According to the global statistics by UNAIDS, 37.7 million people globally were living with HIV in 2020, 6,80,000 people died from AIDS-related illnesses, the same year.According to UNICEF of the estimated 37.7 million people living with HIV worldwide in 2020, 2.78 million were children aged 0-19. It further adds that each day in 2020, approximately 850 children became infected with HIV and approximately 330 children died from AIDS related causes, mostly because of inadequate access to HIV prevention, care and treatment services.Our team has extensive knowledge and research experience that has translated into high quality publications (6–20).Oral health is an important component of the overall health status in HIV infection. Awareness of the variety of oral disorders which can develop throughout the course of HIV infection and coordination of health care services between a physician and a dentist may improve the overall health of the patient. The spectrum of oral manifestations is very vast in HIV-AIDS.(21,22)\

Hiv Related Oral Manifestations

In 1993 members of EC-Clearinghouse on oral problems related to HIV infection and WHO collaborating center on oral manifestations of the immunodeficiency virus produced a classification of HIV-related oral manifestations.(23)
GROUP 1-Lesions strongly associated with HIV infection.This includes Candidiasis(Erythematous,pseudomembranous),Hairy leukoplakia,Kaposi's sarcoma,Non-Hodgkin's Lymphoma,Periodontal disease.
GROUP 2-Lesions less commonly associated with HIV infection.This includes bacterial infection like Mycobacterium avium-intracellulare,Mycobacterium tuberculosis,Melanotic hyperpigmentation,Necrotising stomatitis,salivary gland disease,Thrombocytopenic purpura,Ulceration,Viral infections-HSV,HPV,Varicella zoster virus infection.
GROUP 3-Lesions seen in HIV infection.This includes

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Bacterial infections-Actinomyces israelii,Escherichia coli,Klebsiella pneumoniae;Cat-scratch disease,Drug reactions,Epithelioid angiomatosis,Fungal infections other than candidiasis,Neurologic disturbances,Recurrent aphthous stomatitis, Viral infections like Cytomegalovirus and Molluscum Contagiosum.Oral manifestations of HIV infection occur in 30–80% of the affected patient population.(24)

2. Oral Candidiasis

Oral candidiasis(OC) is the most common opportunistic fungal infection in individuals infected with the human immunodeficiency virus (HIV) and is considered an independent predictor of immunodeficiency in patients with acquired immunodeficiency syndrome (AIDS).(25)Oral candidiasis can extend to involve the pharynx, larynx, and oesophagus as well.Majority of the studies conducted around the world mentions that candidiasis is the most common HIV-related oral lesion,both in patients undergoing HAART and in untreated cases.. In a study by Kumar et al.Oral candidiasis is the main HIV-related oral manifestation, with a prevalence of 36.5%.(26)Studies by Bodhade et al. and Sontakke et al.,had prevalence of 39.3% and 32.3% prevalence respectively.(21)(27)

Two forms of Oral Candidiasis are mainly observed. Pseudomembranous candidiasis(PC) and erythematous candidiasis(EC).Several studies showed that pseudomembranous candidiasis is the most common variant.(27)(28,29)However,there are several studies reporting the prevalence of erythematous candidiasis higher than pseudomembranous candidiasis.(21,30)This difference may be due to smoking habit if the patients,varying geographical distribution and use of different antibiotic therapies.

Oral Hairy Leukoplakia

Oral Hairy Leukoplakia (OHL) is a hyperplastic mucocutaneous epithelial cell disease, induced by Epstein Barr virus (EBV). The clinical appearance of OHL is as white, corrugated, painless, and asymptomatic lesion, as a patch that cannot be removed by scraping, located often bilaterally on lateral borders of the tongue.(31) It is frequently observed in many studies(27)(32,33).Hairy leukoplakia is one of the most common virally induced, oral diseases of HIV-infected individuals, with a point prevalence as high as 25-53%.

Periodontal Disease

The role of HIV in periodontal disease is unclear.This disease caused by the alteration of the oral microbiota in seropositive patients,includes linear gingival erythema (LGE),necrotizing gingivitis (NUG) and necrotizing periodontitis (NUP).The periodontal manifestation with higher prevalence is LGE.Some LGE could evolve in NUG and NUG could predispose to the development of NUP.The average prevalence is between 3% and 8%.(34)

Kaposi's Sarcoma

Kaposi's sarcoma is the HIV-related neoplasia with the highest prevalence.It affects the palate,oropharynx and gums and average prevalence varies between 0.5% and 3.5%.(35)

Non-Hodgkin's lymphoma is also an important HIV-related neoplasia with an average prevalence of 0.5-1.5%.

Xerostomia,Ulcers and HSV infection are also reported in HIV-positive patients.The prevalence of ulcerative lesions is between 1.5% to 12%.(21)HSV related lesions found in 1-3% of seropositive patients.Xerostomia has a prevalence rate of 32%.(30)

HAART, CD4+ T-cell count and viral load are the main factors affecting the number and the type of lesions.Other factors include poor oral hygiene and low socioeconomic status and alcohol abuse.

Correlation With Highly Activated Antiretroviral Therapy (Haart)

The introduction of HAART has led to a significant decrease in the prevalence of HIV-related oral lesions.(36)(37)(34).

Goals of HAART in Patients with HIV Infections(38–41)

Reduce morbidity and mortality (AIDS and non-AIDS associated causes)

1. Improve the quality of life
2. Reduce plasma viral RNA load
3. Prevent transmission to others (sex partners, needle-sharing partners, mother to infant)
4. Prevent drug resistance
5. Improve immune function

Satyakiran et al. report a direct correlation between the reduction of oral lesions prevalence and the duration of HAART.(42)HAART with reduced viral load and increased CD4 count help a significant reduction in the prevalence of OHL patients.(31)There are some HIV-related oral manifestations, which have seen an increase in their incidence after the introduction of HAART, like hyperpigmentation, xerostomia and salivary gland hypertrophy. This is due to the effects of antiretroviral drugs on melanocyte-stimulating hormone (MSH) and on salivary flow rate.(30)

Correlation With Cd4+T-Cell Count

The effect of HAART in reducing the incidence of HIV-related oral lesions is to be found not only in increasing the CD4 count, but also in the direct effect that therapy has on every kind of lesion. The increase in CD4+ T-cell count is not significantly correlated to the incidence decrease of every kind of oral lesions, but it is statistically significant only in relation to oral candidiasis(p-value <0.001).(29)OHL has been associated with more rapid progression to AIDS among HIV viral-infected individuals, and with HIV viral loads exceeding 20.000 copies/ml, and with CD4+ counts below 200/mm.(43).Non-Hodgkin's lymphoma 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.Oral hairy leukoplakia occurred mostly in patients with CD4 counts of 200-500/µL.

Table 1-Staging Of Hiv Infection Based On Cd4 Cells Count And Percentage(44)		
CD4 Cells/µL.,Absolute Count	CD4%	STAGING FOR ADULTS
>600	32-50	Normal
<500	<29	Initial Immune Suppression
<400	<29	Oral lesions may appear
200-400	14-18	Increased severity and number of opportunistic infections and oral lesions
<200	<14	AIDS,severe immune suppression

Sontakke et al. reported that pseudomembranous candidiasis was found in 27.4% of patients with a CD4 count <200 cell/mm3 , in 8.1% of those with a CD4 count between 200 and 500 cell/mm3 , and in 1.6% of those with CD4 count >500 cell/mm3 : this correlation is statistically significant (p-value <0.05).(27)It is possible to affirm that oral candidiasis could be a valuable index of a low CD4 T-cell count and therefore also of immunosuppression (PPV: 68%).(28)Many studies correlated between the incidence of HIV-related oral lesions and viral load (HIV-RNA). In this case, there was also a statistically significant correlation: a high viral load (>20.000 copies/ml) increases the risk of developing HIV-related oral manifestations.(30)

Oral Health Considerations

LESION ASSOCIATED WITH HIV	DRUG
Oral Candidiasis	A single-dose regimen of 750mg Fluconazole and in situ Fluconazole gel-14-day Regimen
Esophageal Candidiasis	Posaconazole
Oral hairy leukoplakia	Topical 25% podophyllin resin,followed by the application of 5% acyclovir cream

Immunologically stable (undetectable viral load and T-cell(CD4) count over 200/mL)HIV-positive patients on ART may be considered the best dental treatment risk.However,patients with profound immunodeficiency(those with neutropenia and/or CD4 T-lymphocyte count below 200/mL) may require antibiotic cover with metronidazole,amoxicillin plus clavulanic acid, or clindamycin before surgery or after maxillofacial injuries.HIV disease is a major risk factor for adverse drug reactions;the incidence of reactions to penicillin is inversely proportional to CD4+ cell counts.Dental treatment should be carried out with standard precautions and additional attention given to the postoperative infection and prolonged haemorrhage.Medical consultation is mandatory for symptomatic HIV-infected patients before any dental surgical procedure,although no serious postoperative complications have been found at many instances.

Factors increasing the potential for postoperative complications include Low CD4 count,High viral load,Low lymphocyte count,Neutropenia,Bleeding tendency(i.e,thrombocytopenia,liver damage etc),Another concomitant infection.

3. Conclusion

With the widespread availability and usage of antiretroviral therapy for the management of HIV, the clinical picture now has shown a paradigm shift.Thus,the overall prevalence of oral manifestations in HIV disease has changed since the advent of HAART.Nevertheless, developing countries still have a high prevalence of these manifestations because of the persistence of many risk factors, such as difficulty in accessing treatment, poor oral hygiene, low socioeconomic status and late diagnosis.Dental surgeons may have a potential role, not only in the treatment of HIV-related oral manifestations, but also in monitoring the evolution of HIV infection, because of the strong correlation between the presence of oral lesions and a low CD4+ T-cell count persists.Further, an oral examination might help in the early diagnosis and prognosis of HIV infection.

For OHL,Systemic anti-herpesviral therapy produces rapid resolution, although sometimes the recurrence can be expected when therapy is discontinued. Systemic anti herpesviral therapies known to be used are acyclovir and valacyclovir, with several reports of the use of desiclovir and famciclovir. Acyclovir is a nucleoside analog available in the form of oral, intravenous, and topical. The triphosphate form of the drug is the active form, which has a potent inhibitory effect on herpesvirus-induced DNA polymerases but relatively little effect on host cell DNA polymerase. In OHL, acyclovir effectively resolves the permissive infection, although cessation of treatment often results in a recurrence of lesions within 1-4 months.(45)

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