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Oral pathology in patients with Highly Active AntiRetroviral Therapy (HAART)

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ABSTRACT

Background: From its origin in the 80´s of XX century, HIV positive and AIDS patients could develop many different oral pathologies (predominantly infectious and neoplastic) depending on its level of immunosuppression. Highly Active AntiRetroviral Therapy (HAART) is the goal standard therapy in the XXI century in HIV infected patients to modify patient´s level of immunity and consequently prevalence of oral manifestation.

Objectives: Review of oral manifestations of patients infected with HIV and treated with HAART. Furthermore, comparing oral pathologies present in patients on long-term HAART against those without HAART.

Methodology: Bibliographic search of published articles from scientific journals and academic literature from PubMed, Google scholar, Nature and JSTOR. Articles selected were evaluated based on their relevance and year published, articles prior 2010 were excluded. MeSH keywords were used in the bibliographic search: Human Immunodeficiency Virus (HIV), Acquired Immunodeficiency Syndrome (AIDS), Opportunistic infection, Antiretroviral Therapy Highly Active mouth; oral cavity, oral Kaposi's sarcoma, oral cancer, oral candidiasis, oral infections. 25 references were included.

Discussion: Patients' prior HAART treatment typically present more frequently with oral candidiasis (OC), Kaposi´s sarcoma (KS), oral hairy leukoplakia and periodontal disease. Whereas the prevalence of these pathologies tends to be reduced in patients with chronic HAART. Other or new oral pathologies can appear as side effect of HAART treatment, such as oral hyperpigmentation or bruxism.

Conclusions: Comparing before and after HAART appearance, there has been an important decrease of many of the typical oral manifestation diagnosis for AIDS as an increase of CD4 lymphocytes and a decrease of level of immunodeficiency.

RESUMEN

Introducción: Desde su origen en los años 80 del siglo XX, los pacientes VIH positivos y sida pueden desarrollar muchas patologías bucales diferentes (predominantemente infecciosas y neoplásicas) en función de su nivel de inmunosupresión. La Terapia Antirretroviral Altamente Activa (TARGA) es el objetivo de la terapia estándar en el siglo XXI en pacientes infectados por VIH para modificar el nivel de inmunidad del paciente y consecuentemente la prevalencia de la manifestación oral.

Objetivos: Revisión de la literatura de las manifestaciones orales de pacientes infectados por el VIH y tratados con TARGA. Además, comparar patologías bucales presentes en pacientes en TARGA crónica con aquellos sin TARGA.

Material y métodos: Búsqueda bibliográfica de artículos publicados en revistas científicas y literatura académica de PubMed, Google Scholar, Nature y JSTOR. Los artículos seleccionados fueron evaluados en función de su relevancia y año de publicación, se excluyeron los artículos anteriores a 2010. En la búsqueda bibliográfica se utilizaron palabras clave MeSH: Virus de Inmunodeficiencia Humana (VIH), Síndrome de Inmunodeficiencia Adquirida (SIDA), Infección Oportunista, Terapia Antirretroviral Boca Altamente Activa; cavidad bucal, sarcoma de Kaposi bucal, cáncer bucal, candidiasis bucal, infecciones bucales. Se incluyeron 25 referencias.

Discusión: El tratamiento previo con TARGA de los pacientes suele presentarse con mayor frecuencia con candidiasis oral (OC), sarcoma de Kaposi (SK), leucoplasia vellosa oral y enfermedad periodontal. Considerando que la prevalencia de estas patologías tiende a reducirse en pacientes con TARGA crónica. Pueden aparecer otras patologías orales nuevas como efecto secundario del tratamiento TARGA, como la hiperpigmentación oral o el bruxismo.

Conclusiones: Al comparar antes y después de la aparición de TARGA, ha habido una disminución importante de muchos de los diagnósticos de manifestaciones orales típicas del SIDA como un aumento de linfocitos CD4 y una disminución del nivel de inmunodeficiencia.

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1.1 HIV infection and AIDS

The human immunodeficiency virus (HIV) negatively affects the immune system, by identifying and destroying CD4+ T cells, which if left untreated can result in acquired immunodeficiency syndrome (AIDS). Immunodeficiency refers to the systemic immune response of an individual; primary immunodeficiencies are hereditary and secondary immunodeficiencies related to other systemic disorders, such as HIV infection, or immunosuppressive treatment. AIDS is defined when an individual has a CD4 cell count below 200 cells/mm^3, indicating that the immune system is compromised and leaving the patient susceptible to opportunistic infections. Two types of HIV can cause AIDS, HIV-1 and HIV-2, with HIV-1 causing more infections. Clinically, infections caused by HIV-1 leads to a faster progression to AIDS, when compared with HIV-2. Epidemiologically, HIV-1 is detected worldwide, whereas HIV-2 is mostly found in Western regions of Africa and areas in Europe with socioeconomic links to these regions. The difference between the two types of virus is related to difference in infectiousness. HIV infection is a process where HIV binds to CD4+ T cells and coreceptors CCR5 or CXCR4 on the host cell, thus permitting entry of the virus and infecting the host cell. AIDS is a symptomatic stage of HIV infection in the late phase, where the infected individual may suffer from opportunistic infections and have a CD4+ T count less than 200 cells/mm^3.[(1)]

HIV is currently a significant public health issue, resulting in deaths of over 33 million to date. The current data available indicates that 38 million people globally have HIV/AIDS, in 2019. Over two thirds of the population in this estimate live in the African region. Currently

there is no cure, though 25.4 million people with HIV were able to access antiretroviral therapy (ART) globally, this number has tripled since 2010. Those who adhere to the prescribed medication can maintain an undetectable viral load and consequently able to live longer and healthier lives. Thanks to advances in treatment options there has been a 23% decline in new HIV infections since 2010, there were approximately 1.7 million HIV infections in 2019.

In 2016, the United Nations General Assembly's Political Declaration on Ending AIDS gave countries the 90-90-90 target, to be achieved by 2020. The target was to have 90% HIV infected individuals being aware of their HIV positive status, 90% of these people who are aware of their HIV status to be undergoing treatment and 90% of people with lowered viral loads, keeping these individuals healthy and preventing the spread of the virus. Although these targets have not been met in 2020, significant improvements in HIV diagnosis and therapy have been made. By the end of 2019, over 80% of individuals living with AIDS knew their HIV status and 67% were taking ART. Consequently, the viral load suppression levels of people infected with HIV increased by 18% from 2015 to 2019.[2]

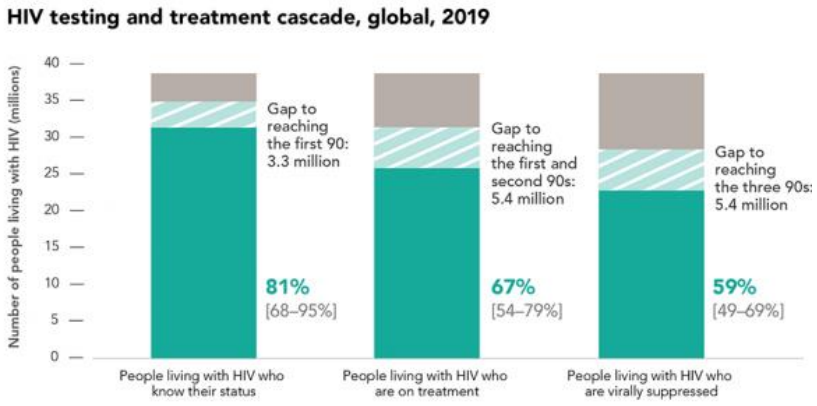


Fig. 1. HIV testing and treatment cascade, global, 2019.[2]

The unprecedented COVID-19 pandemic proved to be an obstacle in meeting the 2020 targets. There was a disruption of access to highly active antiretroviral therapy (HAART), especially in regions with limited access to healthcare, such as sub-Saharan Africa. A few areas reported a reduction in medication collection by almost one fifth. This reduction in collecting essential treatment, lowers patient's adherence to treatment. Some people abandoned treatment due to a lack of food or not having enough medication during lockdown periods. Nonetheless, data reported by some countries to the United Nations between January and June 2020 does not suggest a decline in the number of individuals continuing treatment during this period.

The classification of staging of HIV/AIDS proposed by the WHO in 1999 had an emphasis on clinical factors. This staging was useful in countries with limited access to laboratory assistance, especially in Africa. This classification was revised in 2005, defining four stages of the progression of the disease. Oral pathologies, such as angular cheilitis (AC), can be identified as early as Stage II (the asymptomatic phase). The pathogenesis of HIV infection begins with the primary HIV infection, or acute HIV, occurring 2-4 weeks after exposure to HIV. The process of seroconversion begins at this point, where the immune system responds to the infection by producing antibodies against HIV. Simultaneously, cytotoxic T lymphocytes count increases. Over 65% of cases present mild influenza like symptoms such as fever, sore throat, and headache. In the asymptomatic stage, viral replication slows down, and peripheral blood HIV levels fall. The CD4 cell count is usually above 500 cells/mm^3, though some patients can have a cell count lower than 500 cells/mm^3. This stage lasts approximately 10 years, up to 20 years,

in seropositive HIV patients taking HAART with the objective to maintain viral replication at a low level, so the immune system does not deteriorate. In the next phase, there may be a persistent generalised adenopathy which can last for at least 3 months, causing swollen nodes of >1cm in diameter. Then in the symptomatic stage, there is a sudden decline in the immune status and so, the incidence of opportunistic infections increases.[3]

Stage	Signs and symptoms
Stage I (Primary HIV infection) (Seroconversion)	Asymptomatic acute retroviral syndrome CD4>500 mm3
Stage II Asymptomatic phase	Moderate weight loss Recurrent respiratory tract infections Herpes zoster Angular cheilitis Recurrent oral ulcerations Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections of fingers CD4 >350-499 cells/mm^3
Stage III Generalised Lymphadenopathy	Severe weight loss Unexplained chronic diarrhoea Unexplained persistent fever Oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis (TB) Acute stomatitis, gingivitis, or periodontitis CD4 >200-349 cells/mm^3
Stage IV Symptomatic Phase	HIV wasting syndrome. Pneumocystis pneumonia Chronic herpes simplex infection Oesophageal candidiasis Extrapulmonary TB Kaposi sarcoma Central nervous system toxoplasmosis HIV encephalopathy, etc. CD4 <200 cells/mm^3

Table 1. Classification of staging of HIV/AIDS proposed by WHO in 1999 [3]

1.2 Classification of the oral manifestations of HIV disease

The presentation of oral lesions can be an early sign of HIV infection, suggesting a possible HIV diagnosis if the individual is not aware of their status.

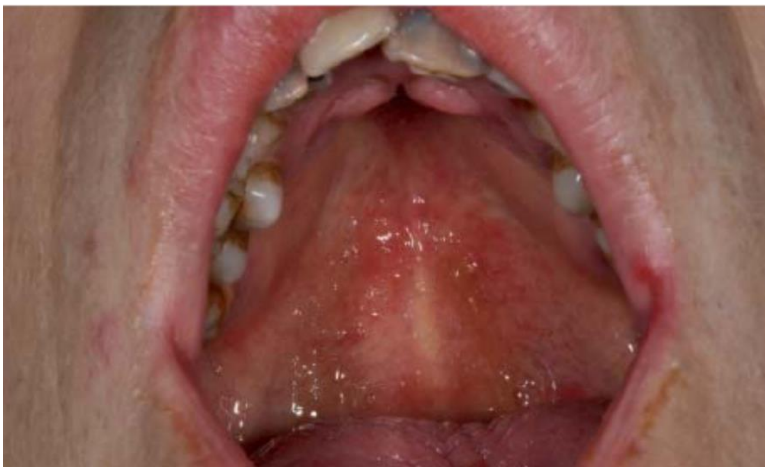
Originally, oral manifestations associated with HIV infection were classified based on aetiology, including fungal, viral, bacterial, neoplastic, or other. In 1991, this classification was modified by the collaboration of the EC-Clearinghouse and WHO. Two years later, this classification was reviewed, and the oral pathologies associated with HIV/AIDS were categorised into three groups; lesions strongly associated with HIV infection, lesions less commonly associated with HIV infection and lesions seen in HIV infection.[4] This review was to highlight the common oral manifestations of HIV infection which includes oral candidiasis (OC), oral hairy leucoplakia (OHL), and Kaposi's sarcoma (KS). Moreover, this classification was updated by the Oral Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome Research Alliance (OHARA) whose principal aim was to present definitions of HIV related oral pathologies based on clinical cases. The symptoms and duration of the signs and symptoms of the patient were included alongside the pre-existing clinical description of oral lesions.[5] Table 2 displays a summary of oral pathologies that may be seen in HIV/AIDS patients.

Lesions strongly associated with HIV infection
1) Candidiasis a) Erythematous b) Pseudomembranous 2) Hairy leukoplakia 3) Kaposi's sarcoma 4) Non–Hodgkin's lymphoma 5) Periodontal disease a) Linear gingival erythema b) Necrotizing (ulcerative) gingivitis c) Necrotizing (ulcerative) periodontitis
Lesions less commonly associated with HIV infection
1) Bacterial infections a) *Mycobacterium avium–intracellulare* b) *Mycobacterium tuberculosis* 2) Viral infections a) Herpes simplex virus b) Human papillomavirus (wart–like lesions) 3) Condyloma acuminatum 4) Focal epithelial hyperplasia 5) Verruca vulgaris a) Varicella zoster virus 6) Herpes zoster 7) Varicella 8) Melanotic hyperpigmentation 9) Necrotizing (ulcerative) stomatitis 10) Salivary gland disease a) Dry mouth due to decreased salivary flow rate. b) Unilateral or bilateral swelling of the major salivary glands 11) Thrombocytopenic purpura 12) Ulceration not otherwise specified
Lesions seen in HIV infection
1) Catscratch disease 2) Neurological disturbances – facial palsy, trigeminal neuralgia 3) Fungal infection (besides candidiasis) and other viral infection (cytomegalovirus) 4) Recurrent aphthous ulcer

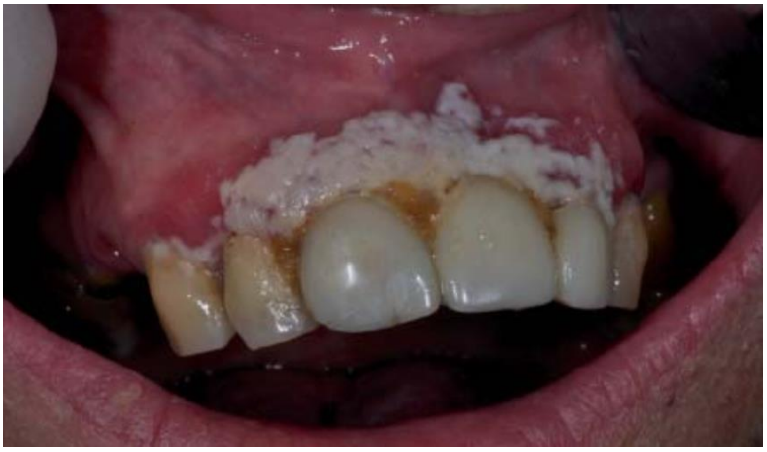
Table 2. Adapted from classification by the EC-Clearinghouse on oral problems related to HIV infection and WHO collaborating centre on oral manifestations of the immunodeficiency virus. [5]

1.2.1. Oral candidiasis (OC)

As OC is associated with a CD4 count less than 300 cells/mm^3, it is frequently seen in HIV infected patients before treatment with HAART as these patients tend to be immunocompromised. Those that present OC are patients with limited access to healthcare, thus unable to access HAART, or patients that commence antiviral therapy late. OC is clinically presented as pseudomembranous candidiasis (PC), erythematous candidiasis (EC) and angular cheilitis (AC) and *Candida albicans* is the pathogen most associated with OC in HIV patients. These three clinical presentations of OC are common oral manifestations of HIV patients treated without HAART. PC is presented as an asymptomatic, white, or yellow creamy plaque lesion that can be wiped off and leaving an erythematous surface. It can be located on the dorsum of the tongue, palate, buccal mucosa, or oropharynx. EC clinically is a symptomatic red, flat, atrophic lesion situated on the dorsal surface of the tongue or palate. AC is typically a symptomatic erythema with either fissuring or erosion on the labial commissures unilaterally or bilaterally and may be seen independent of the presence or absence of either EC or PC. There is a relationship between OC and tuberculosis disease, so presentation of OC could suggest an increased risk of tuberculosis, potentially leading to an earlier HIV diagnosis.[5,6]



(A)



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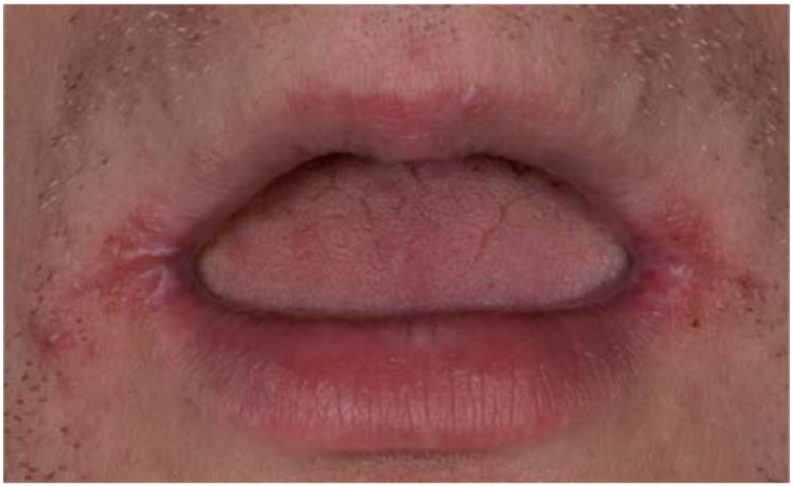

(C)

Fig. 2. Oral candidiasis and its 3 clinical presentations (A) Erythematous candidiasis (B) Pseudomembranous candidiasis (C) Angular cheilitis.[5]

1.2.2 Oral Hairy Leukoplakia (OHL)

OHL is caused by the Epstein-Barr virus. It is not commonly seen in immunocompetent patients and so tends to affect immunocompromised patients with a CD4 count lower than 200 cells/mm^3. Clinically, it is asymptomatic, white, benign, hyperkeratotic lesion located on the lateral surface of the tongue, with possible extension to the dorsal and ventral surfaces, either bilateral or unilateral and seen more often in males. The lesion may vary in size and either appear as white striations, corrugated or plaques. The lesion cannot be wiped off. Incisional biopsy can be performed to identify the typical histopathological characteristics, such as epithelial hyperplasia, acanthosis, and hyperkeratosis. OHL indicates HIV infection, and the presence of this lesion is used as a criterion for the start of therapy, clinical staging, and classification.[6,7]

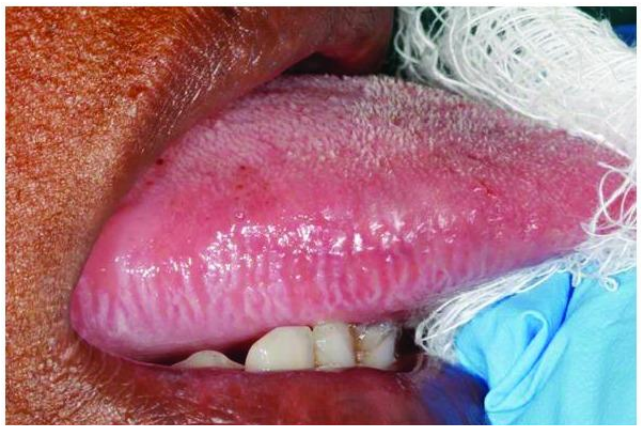

Fig. 3. Oral hairy leukoplakia on the lateral surface of the tongue.[6]

1.2.3 Kaposi´s sarcoma

The clinical manifestation of KS varies, lesions may have a slow or aggressive progression. KS may involve the skin, oral mucosa, lymph nodes or other internal organs. KS is associated with HIV and is caused by the human herpes virus 8 (HHV8). The HHV8 infection may trigger the neoplastic hyperproliferation in the palate or gingiva. The lesion presents as a red-purple macule, nodule or mass and can vary in size depending on the advancement of the malignancy. Initially, a flat red lesion may appear due to an infiltration of B and T lymphocytes, monocytes and increased neovascularity. As the lesion progresses, the lesion would appear as a plaque with increased intensity of red colour. Lastly, the proliferation of spindle cells leads to the nodular phase of KS. There are four variants of KS, based on an epidemiology: Classic KS, endemic KS, iatrogenic KS, and AIDS associated KS. Classic KS typically affecting Mediterranean and Eastern European adult males and the clinical progression is usually indolent, progressing over decades. Endemic KS affects children and adults in Sub Saharan Africa and the KS develops somewhat aggressively. Iatrogenic KS is caused by immunosuppressive therapy and progression is comparable to endemic KS. AIDS associated KS is related to those with HIV and the clinical course of KS is aggressive, survival of these patients is improved with HAART. KS cannot be cured, treatment is symptomatic. Although KS is not a typical malignancy seen worldwide, immunosuppression because of HIV infection is associated with the progression of KS. [8]

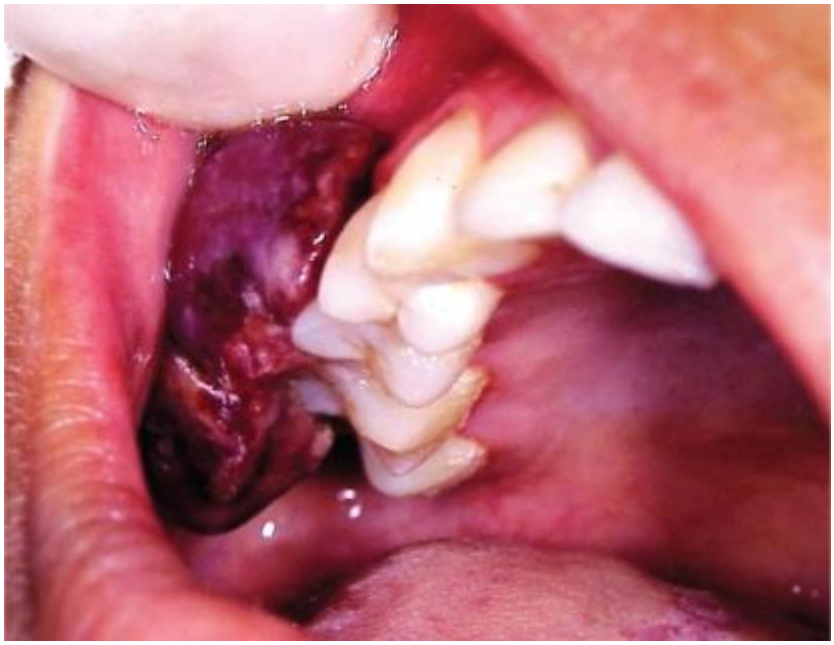

Fig. 4. Kaposi´s sarcoma of the right buccal vestibule [8]

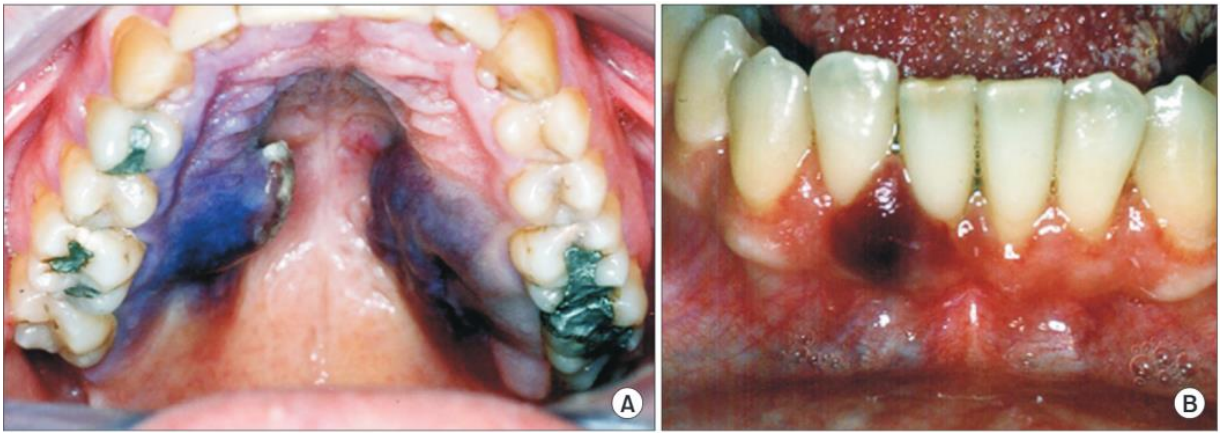

Fig. 5. A) Bilateral, purple tumour located in the palate. B) Local tumefaction in the interproximal papilla between lower right incisors.[4]

1.2.4 Other oral pathologies

Other lesions strongly associated with HIV infection include Non-Hodgkin's lymphoma and periodontal disease. Non-Hodgkin's lymphoma is commonly associated with HIV infection and more often seen in patients in advanced stages and with a low CD4 count. It is a rapidly enlarging mass, on the palate or gingiva. The prognosis is poor with a survival rate of less than 1 year. Oral ulcers (OU) of idiopathic, viral, and neoplastic origin have been documented in HIV patients. Types of OU commonly seen are recurrent aphthous ulcers, necrotising ulcerative stomatitis or ulcers due to herpes simplex.[9]

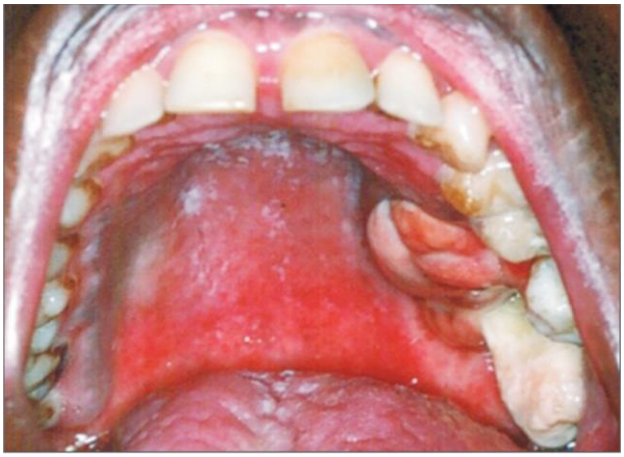

Fig. 6. Tumefaction in palate on left side with displacement of maxillary left molar, biopsy confirms non-Hodgkin's lymphoma.[4]

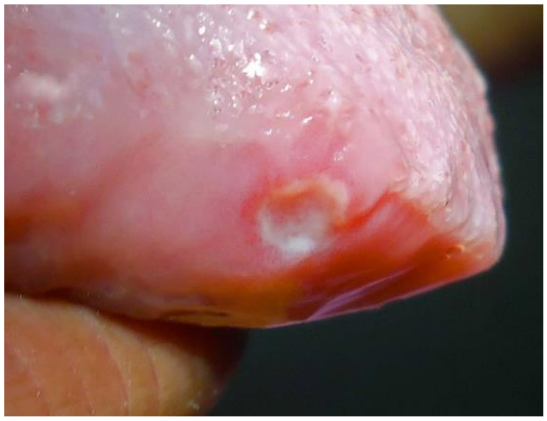

Fig. 7. Aphthous ulcer on the lateral border of the tongue [9]

Periodontal diseases (PD) can be seen in HIV infected patients, including linear gingival erythema and necrotising periodontal disease. Linear gingival erythema is a nonplaque induced gingivitis which is seen clinically as an erythematous band across the marginal gingiva and erythema of the attached gingiva. Necrotising PD can be subclassified to necrotising ulcerative gingivitis (NUG) or necrotising ulcerative periodontitis (NUP), depending on the progression of the disease. NUG is an acute and painful inflammation of the gingiva with destruction of the soft tissue, fast onset. NUP is a periodontal lesion with deep and generalised osseous pain, erythema with possible spontaneous bleeding, with progressive destruction of the periodontium, necrosis of soft tissue, possibly leading to the loss of the entire alveolar process and halitosis is present in these patients. The periodontal microflora is the same as seen in healthy patients, therefore the lesion is a result of the weakened immune response in HIV infected individuals. A low CD4 count is observed in these patients. With the introduction of HAART, the incidence of PD such as necrotising periodontal disease has reduced.[9,10]

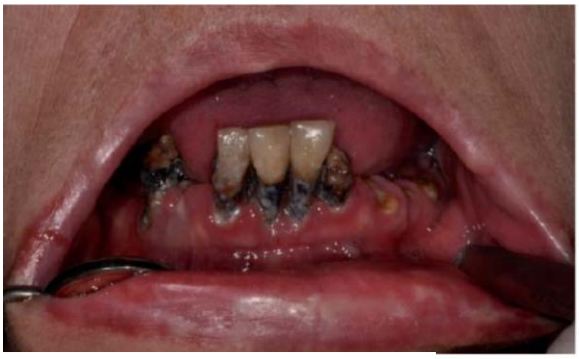

Fig. 7. Linear gingival erythema [5]

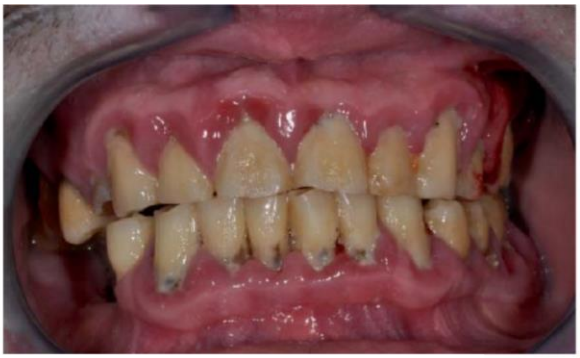

Fig. 8. Necrotising ulcerative disease [5]

1.3 History of HIV antiretroviral treatment

In 1981, the Centre for Disease Control (CDC) in the United States of America (USA) published an article describing five cases of seemingly healthy young homosexual males in Los Angeles, USA suffering from an uncommon lung infection *Pneumocystis carinii* pneumonia (PCP), currently referred to as *Pneumocystis Jirovecii* Pneumonia. PCP typically affects immunocompromised individuals, such as HIV infected patients. It is a respiratory infection where the patient presents with symptoms corresponding to pneumonia such as cough, fever, and dyspnea. Nonetheless, with the introduction of HAART, the incidence of PCP has reduced significantly. In the same year, cases of KS were being diagnosed in the USA, along with increasing number of PCP cases. In this year, 337 cases of immunodeficiency were diagnosed with 4.75% of these cases were children below 13 years of age. By the end of the year 38.58% of these individuals died. In 1983, the retrovirus HIV was identified as the aetiology.

In 1987, the first HIV medicine, zidovudine, was approved for use. Utilising antiretroviral therapy (ARV) as treatment for patients with HIV infection was a major advancement in the medical field. In the first 10 years of ARV use, they were able to decrease viral load and increase CD4+ T cell numbers and prolong survival in the short term. Yet, flaws of these drugs included drug toxicity, resistance, and high cost. Combination-based ARV (ART) was introduced in 1996, which led to effective HIV suppression, improved immune function, and extended life span. In figure 9, between 1998 and 2003 there is a correlation between the increased use of HAART with a decline in the mortality rate. Before 1996, there were not many options for ARV treatment for HIV infection and the clinical management was primarily based

on the prophylactic treatment of common opportunistic pathogens and management of AIDS related diseases.[11]

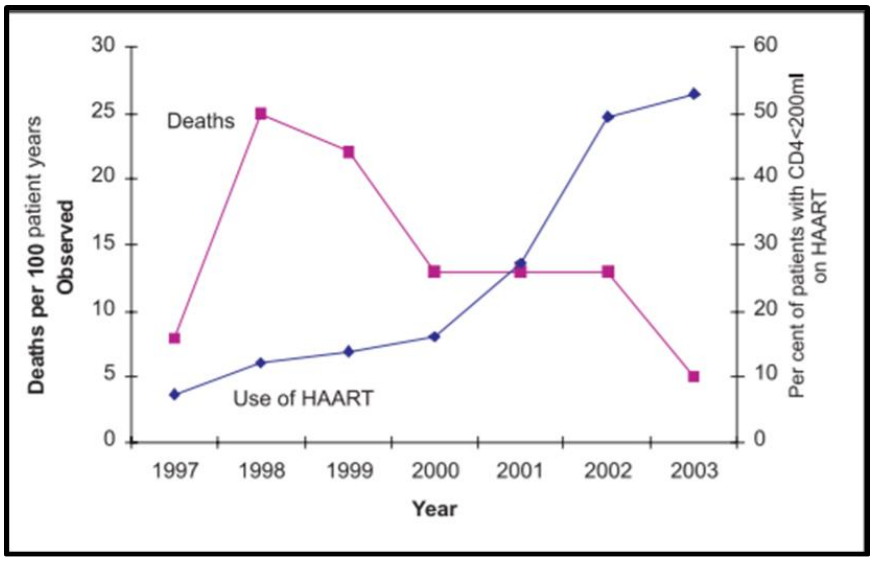

Fig. 9. Graph showing the relationship between the percentage of patients with CD4 less that 200mm^3 on HAART with the mortality rate, data from YRG care, Chennai, India.[11]

HAART therapy consists of a combination of three or more antiretroviral drugs. This co-administration of various drugs enables the inhibition of several mechanisms of viral replication. The principal objectives of HAART treatment are to reduce morbidity and mortality, improve quality of life of the patient, reduce plasma viral RNA load, prevent transmission to others, prevent drug resistance and improve immune function. With patient adherence to treatment, HAART suppresses viral replication for many years which dramatically increases life expectancy of the HIV infected individual. Furthermore, this positive impact of HAART has contributed to the decline in prevalence of oral lesions in HIV positive patients.

Currently, it is recommended that HAART should begin within seven days of a definitive HIV diagnosis. Recent guidelines indicated by the World Health Organisation (WHO), indicate that all restrictions for eligibility for HAART are removed, thus allowing individuals of all ages being eligible for treatment. Early intervention with HAART has been shown to reduce severe AIDS and AIDS-associated illnesses. HAART is usually administered orally, one tablet daily. There are no absolute contraindications to HAART, but there may be contraindications to specific antiretroviral medications. Nevertheless, the healthcare professional should find another HAART combination for that patient. HAART monitoring is essential to ensure the adherence to treatment and to evaluate the effectiveness of the therapeutic response.

In 2006 a review was published highlighting the shift in epidemiology of oral manifestations after the introduction of HAART. This review concluded that there was a reduction in oral manifestations in HIV positive patients after the introduction of HAART, noting the role of HAART in the reduction in opportunistic infections. On the other hand, a limitation of this finding is the difficulty to differentiate between oral lesions caused by HIV infection or an adverse effect of HAART.[12]

1.4 HAART definition and types

Antiretroviral therapy is classified based on the stage of inhibition of the life cycle of the virus. There are six main classes of HAART drugs, as follows:

1) Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs) which require intracellular phosphorylation via the host enzyme before inhibiting viral replication. The competitively binding to reverse transcriptase results DNA chain termination prematurely. Abacavir, didanosine and stavudine are examples of drugs within this category.
2) Non-nucleoside reverse transcriptase inhibitor (NNRTIs) binds to HIV reverse transcriptase at an allosteric, hydrophobic site. This inhibits nucleoside binding and inhibition of DNA polymerase. Delaviridine, efavirenez and nevirapine are examples of this type of medication.
3) Protease inhibitors (PIs) competitively inhibit the proteolytic change in HIV infected cells. PIs are indicated in patients with little success in the initial HAART therapy and should be administered with ritanovir or cobicistat. Examples PIs include atazanavir and darunavir.
4) Integrase strand transfer inhibitors (INSTIs) bind viral integrase and prevent viral DNA from being a part of the chromosome of the host cell.
5) Fusion inhibitors (FIs) bind to glycoprotein gp41 and prevents the viral fusion to the CD4 T cells.

6) Chemokine receptor antagonists (CCR5 antagonists) selectively and reversibly block entry into the CD4 T cells by preventing interaction between CD4 cells and the gp120 subunit of the viral envelope glycoprotein.[13]

From the introduction of the first ARV, Zidovudine, until 1995, the main class of ARV used were NRTIs, NNRTIs and PIs. Then after the introduction of combination therapy, FIs, INSTIs and CCR5 antagonists were primarily used. Figure 10 shows the timeline of the development and changes of drugs approved for use for HIV treatment.

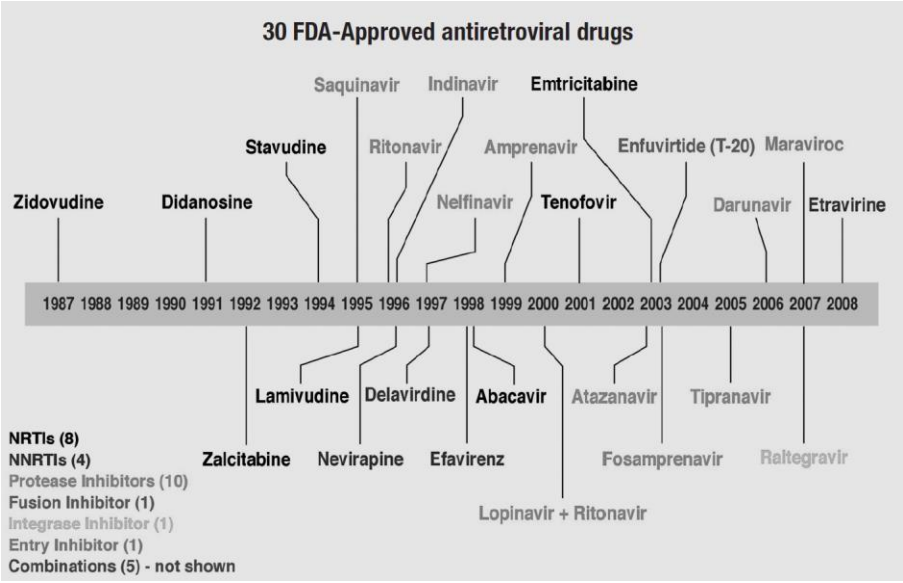

Fig. 10. Antiretroviral drugs approved for HIV infection. [13]

Primary objectives:

- To perform a literature review of the oral pathology presented in patients with HIV and treated with Highly Active Antiretroviral Therapy.
- To compare oral manifestations in patient on long-term HAART versus those without HAART.

Secondary objectives:

- Review most common oral side effects produces by HAART.
- Compare oral diseases in children versus adults treated with HAART.

3. Methodology

The search for articles from scientific journals and books was conducted using PubMed, Google scholar, Nature, JSTOR, ScienceDirect and the CRAI Dulce Chacón library of the European University of Madrid.

- **Inclusion criteria**:
    - MeSH keywords were used in the bibliographic search: Human Immunodeficiency Virus (HIV), Acquired Immunodeficiency Syndrome (AIDS), Opportunistic infection, Antiretroviral Therapy Highly Active mouth; oral cavity, oral Kaposi's sarcoma, oral cancer, oral candidiasis, oral infections.
    - Titles and abstracts of articles included in the bibliography were evaluated for relevance to the subject of interest.
    - Cross sectional studies, longitudinal studies and systematic reviews were included.

- Exclusion criteria:
    - Papers without free access to complete article
    - Time: Articles dated prior 2010 were excluded.

Resulting in 25 articles which were included in this bibliographic review; 13 were used for introduction chapter and 12 for discussion of results.

4.1 HAART vs non-HAART

There have been several studies in which two different group of patients have been reviewed HAART versus non-HAART or a cohort followed before and after HAART. A summary of these findings can be seen in table 3 and 4. From this summary, it can be inferred that OC (including clinical presentations as PC, EC, and AC) are more commonly seen in the cohort prior HAART and non-HAART and the prevalence decreases with long-term HAART use. Few cases of KS are reported in recent literature, given the advent of HAART. Prevalence of oral hyperpigmentation and xerostomia are higher in patients on HAART, than those not taking HAART.

Author, year and country	Number of participants	HAART %	Any OL %	OC (%)	PC (%)	EC (%)	AC (%)	OHL (%)	HSV (%)	OU (%)	Hyperpigmentation (%)	Apthous stomatitis (%)	PD (%)	Xerostomia (%)	Other
Alan G Lourenço et al, 2011 Brazil	148	12.20	60.10	n/a	18.20	25.70	10.10	12.80	2.70	2.70	n/a	n/a	n/a	n/a	Swelling of salivary glands 0.7%
Neelkant Patil et al, 2015 India	50 (total 100)	50.00	56.00	n/a	8.00	4.00	4.00	n/a	n/a	7.00	10.00	n/a	14.00	0.00	PD = periodontitis
K.V.S Eswara Rao et al, 2015 India	320	100.00	100.00	24.38	3.75	11.25	6.88	n/a	0.31	1.25	5.31	n/a	68.75	n/a	Chronic hyperplastic candidiasis 2.50%
Wipawee Nittayananta et al, 2010 Thailand	207	48.53	14.50	n/a	0.48	1.93	n/a	1.45	n/a	n/a	7.73	n/a	0.97	n/a	PD = linear gingival erythema
Wen Shu et al, 2020 China	1812	46.78	52.27	n/a	21.13	15.27	n/a	11.92	5.86	6.69	n/a	n/a	n/a	n/a	Oral Kaposi´s sarcoma 0.21%

Table 3. Results of oral pathologies in non-HAART cohorts. Oral lesion (OL) [14,15,17,19,25]

The introduction of HAART in 1996 had a positive impact on the prognosis of HIV infected individuals and currently is an important aspect of treatment management of the HIV patient. With this treatment, patients were given a chance to reduce prevalence of some oral pathologies, prolong their life and avoid developing AIDS. Oral pathologies typically seen in patients with HIV can vary depending on if they are taking HAART, or not.

In a cross-sectional study of 100 HIV seropositive individuals conducted in India[14], those not taking HAART presented with more oral manifestations when compared with individuals who were taking HAART. Furthermore, there were more individuals taking HAART, that did not present any oral manifestations when compared with those that were non-HAART. This data suggests that HAART reduces the prevalence of oral manifestations and fewer individuals taking HAART may present with oral pathologies. The most common oral pathologies seen in this study by non-HAART patients were candidiasis; PC and EC, and angular cheilitis respectively 8%, 2% and 4%. On the other hand, the most common oral manifestation in this study identified in patients taking HAART was oral hyper pigmentation, recurrent aphthous stomatitis, non-specific ulcerations, PC, respectively 14%, 8%, 4% and 2%. The difference of 6% in the prevalence of PC between those taking HAART and non-HAART may be a result of the increased CD4 count documented in HIV/AIDS individuals with HAART. 14% of individuals presented with oral hyper pigmentation, whereas in patients not on HAART this finding was 4% less. Perhaps, the increase in prevalence of this pathology may be related to the HAART medication itself. This study confirmed that HAART was a safe and effective treatment for adult patients, showing an inverse relationship with an increase in CD4 count

with a decrease in oral pathologies. Despite this, the limitations of this study include the sample size was small and did not include those below 18 years old. Due to these limitations, conclusions cannot be made for children, nor for the population where these individuals are from.

A study of 320 HIV seropositive patients in conducted in South India[15] had the aim to evaluate the difference in prevalence of various oral pathologies present prior HAART and post HAART. All patients in this study presented with CD4 cell counts between 130 and 200 cells/mm^3. After confirmation of diagnosis, these individuals began HAART with a combination of two NRTI´s (lamivudine and stavudine or lamivudine and zidovudine) along with one NNRTI (nevirapine orefavirenz). After three months, CD4 counts were assessed and the presence of any oral pathologies. Table 3 and 4 displays the results of this study of the oral pathologies identified before HAART and after HAART. In both scenarios, before and after starting HAART the most common oral lesion presented was Periodontal disease (PD), 220 and 149 patients, respectively. Although there is a decline of 71 patients presenting with PD after three months of HAART, 46.56% of patients in this cohort still presented with PD. It should be noted, even in patients not infected with HIV, PD is still frequently diagnosed. This decline in number may be a consequence of reduction of the colonization of microbes causing PD due to the elevated CD4 levels post-HAART. In this study, the number of patients presenting with hyper pigmentations, the second most common oral pathology post-HAART, increased significantly from 17 cases pre-HAART to 76 post-HAART. It is possible the cause of this is the deregulation of cytokines in HIV/AIDS leading to an increase of the alpha-melanocyte stimulating hormone.

On the other hand, the second most common oral pathology in pre-HAART patients was OC. The number of patients with OC fell significantly after the three-month period from 78 to 33. Less commonly identified oral manifestations include aphthous ulcers and herpes simplex (HSV), both showing a decrease in number of cases three months post-HAART. In addition, CD4 count improved three months post-HAART. Resulting in, 17.8% of individuals with CD4 cell counts between 150 and 200 cells/mm^3, 58.1% of individuals CD4 cell counts between 200 and 250 cells/mm^3 and 24.1% of individuals with CD4 cell counts between 250 and 300 cells/mm^3.

Another study of 152 seropositive HIV including children as young as seven to adults up to the age of 71 in India.[16]. At the time of the study, all patients were treated with long-term HAART with an average duration of treatment of over 3.5 years. In 51.32% of these patients, oral pathologies were diagnosed. With those presenting with oral pathologies, the most frequent presentation was periodontitis (30.77%). Oral hyperpigmentation (17.44%) was the second most identified oral pathology. OHL and KS can be found in heavily immunocompromised patients, however in this cohort of patients, zero cases were identified. A possible explanation for this is that these pathologies have higher prevalence in more economically developed countries through homosexual way of transmission. This study was conducted in India where the mode of transmission more frequently identified is via heterosexual mode of transmission. 14 participants also presented with xerostomia, potentially caused by long term use of HAART. Although this study accounted for patients taking HAART, these subjects should have had their CD4 cell count monitored prior and post commencement of HAART. With this information the presence, or absence, of oral pathologies

with those taking HAART and with those not taking HAART can be correlated with CD4 levels. Nevertheless, as diseases such as OC, which is typically seen in HIV infected patient's prior HAART, was not as commonly seen amongst this cohort of patients this data suggests that the immunity status of these individuals may be more than those not taking HAART.

An epidemiological study conducted in Ribeirão Preto, Brazil[17] analysed the prevalence of oral pathologies that were associated with HIV prior and post HAART era in this region. The study was divided in two parts; the first part in 1997 where patients were treated with two antiretroviral drugs and the second part between 2004 and 2008 where patients were treated with HAART. A total of 526 seropositive patients were included in both parts of this study, 148 in 1997 and 388 between 2004 and 2008. It´s important to note that not all seropositive individuals were undergoing therapy for HIV infection. In 1997, although 83 out of 148 were not taking ARV or HAART, this population presented with a lower prevalence of oral lesions than those undergoing HIV treatment with ARV or HAART. A possible explanation for the increased prevalence of oral pathologies in those with ARV may be explained by the selection criteria for those receiving ARV. In Brazil, ARV was prescribed to those already presenting with complications of HIV, including oral pathologies. In 1997, ARV was prescribed to serious cases of HIV infection and HAART was only given to those not responding well to ARV. The approach was more therapeutic, as opposed to preventative in this period. However, of those not taking ARV or HAART there was very little change between the percentage of people presenting with oral pathologies between the two time periods. In 1997, 47% of patients not receiving ARV or HAART presented with oral pathologies and between 2004 and

2008, 51.3% of patients not taking HIV therapy presented with oral pathologies. Thus, this study concluded the reduction of oral pathologies of those taking some form of therapy was a due to HAART use. Additionally, the status of smoking of participants was recorded and a lower percentage of smokers were recorded between 2004 and 2008 than 1997. The study discussed that smoking was related to an increase in the prevalence of OC in HIV infected patients, and so this could explain the lower percentage of OC in 2004 to 2008. The results demonstrated an increase in the CD4 count from 193 cells/mm^3 in 1997 to 323 cells/mm^3 between 2004 and 2008. The prevalence of oral lesions associated with HIV fell from 60.1% to 29.9% between 1997 and 2004-2008, respectively. The most diagnosed oral pathologies were PC, EC, AC, OHL and oral ulcers (OU). Notably, OC fell dramatically between the two periods of study. In 1997, 65.4% with AIDS developed oral manifestations and between 2004-2008, this decreased to 33.8%. Supporting the conclusion that HAART is effective in reducing the prevalence and incidence of oral pathologies, even in patients with AIDS.

A study of 80 seropositive HIV adult and paediatric patients[18] were screened to determine the variation of oral lesions present, simultaneously their CD4 count was noted. Patients with HAART were included in this study, the minimum duration of treatment of HAART was 4 years. The results of this study demonstrated that oral hyperpigmentation was the most prevalent oral manifestation amongst adult and paediatric patients, 32.8% and 30.7% respectively. In adult patients, gingivitis, xerostomia, and OC were the other oral manifestations identified, 7.4%, 4.4%, 2.9% respectively. Whereas, in paediatric patients AC, gingivitis and OU were the most prevalent manifestations 23.0%, 7.6% and 7.6% respectively.

Of those with CD4 count with over 800 cells/mm^3, 66.6% of those presented with oral hyperpigmentation and other pathologies were hardly seen. Suggesting that with increase CD4 count, or improved immunity, the prevalence of oral manifestations is reduced. While considering that oral hyperpigmentation is the most common presentation amongst all CD4 levels over 400 cells/mm^3. Protein inhibitor-based HAART is documented to be a risk factor for contributing to a lower salivary flow rate and is involved with salivary gland enlargement in HIV patients. So, xerostomia may be a side effect of HAART. Dental professionals should be aware of the increased risk of caries due to xerostomia by HAART, especially with long term use. Although HAART has shown to reduce oral manifestations due to opportunistic infections, there has been documented an increase in physiological changes in the oral cavity such as oral hyperpigmentation. The patients in this study were from an urban population, with readily available access to treatment and HIV information.

A cross sectional study of 1812 HIV positive patients was conducted in 10 areas of the Yunnan Province, China[19]: 51.27% presented with HIV related oral pathologies. The prevalence of oral pathologies with HAART and without HAART were recorded. Of the seven oral pathologies recorded in this study, the incidence was lower in those with HAART than those non-HAART. Incidence of PC was 21.13% in non-HAART participants and 11.27% in those with HAART. This supports the current literature that HAART improves the immune status of HIV infected individual, reducing incidence of opportunistic infections and oral pathologies related to HIV. EC in these patients also displayed a similar variation, 15.27% in those without HAART and 8.87% in those with HAART. Further supporting the conclusion that HAART is well

documented to reduce the incidence of certain pathologies. OC presented as PC and EC were the most identified oral lesions in this study. OHL and OU also showed a decline of incidence with those on HAART. 11.92% of cases of OHL were recorded in those without HAART and fewer with HAART, 7.91%. Although other studies have demonstrated KS as an oral pathology that is present in HIV infected individuals, there were cases of Kaposi´s sarcoma diagnosed in both groups, with and without HAART were 0.21% and 0.48% respectively. This increase in incidence of KS in those with HAART, when compared to those without HAART, which does not agree with the current literature could suggest that the ethnic variations may influence the incidence of KS. As there are few current studies related to oral pathology in patients on HAART in China, more studies in various provinces in China should be conducted to strengthen conclusions.

A retrospective study of 495 HIV positive individuals between 2001 and 2008 with the objective to evaluate the prevalence of oral pathologies in HIV patients on HAART against those not on HAART.[20] Patients on HAART presented with more linear gingival erythema, human papilloma virus (HPV) and traumatic ulcers. Conversely, those not on HAART demonstrated a higher prevalence of oral candidiasis, acute NUG/NUP, OHL, HSV and KS. Traumatic ulcers (27%) were the most common oral pathologies present in this cohort, greater incidence in HAART patients. The second most seen oral pathology was OC, presenting with a higher incidence in the non-HAART population (28%) than HAART (23%). PC was the most frequent clinical presentation of OC seen, with affectation in either the tongue, palate, buccal mucosa, or soft palate. KS was more frequently observed pre-HAART, with the advent of

HAART the incidence of KS has reduced. KS is not a frequent oral pathology present nowadays, in this cohort of 495 HIV positive patients, eight cases were reported mainly in the non-HAART cohort. KS was diagnosed in the floor of the mouth, palate, and gingiva. In this study, HPV was seen more commonly in the HAART cohort, this finding may be related to the age of the cohort and the general increase in HPV lesions in the population. However, to determine the relation between HPV and long-term HAART, more investigations should be conducted. Although the current literature agrees that the prevalence of certain oral pathologies decline with HAART use, some HIV patients taking HAART still presented with oral manifestations typically seen in those not taking HAART, such as OC. However, these finding may be from those individuals who have recently commenced HAART as oral manifestations of HIV are still present in the first six months of HAART.

5.2 Oral pathologies in patients with HAART

As previously discussed, patients with HIV may present with oral pathologies directly related to the immunosuppression or as a side effect of HAART. On the other hand, patients may present with tooth wear or bruxism due to increased stress or other psychological changes. Table 4 displays results from various studies of oral pathologies in patients with HAART.

Author, year and country	Number of participants	HAART %	Any OL %	OC	PC (%)	EC (%)	AC (%)	OHL (%)	HSV (%)	OU (%)	Hyper - pigmentation (%)	Apthous stomatitis (%)	PD (%)	Xerostomia (%)	Other
Alan G Lourenço et al, 2011 Brazil	388	79.90	29.90	n/a	9.30	6.40	11.90	10.30	0.80	1.80	n/a	n/a	n/a	n/a	KS 0.5%, multifocal epithelial hyperplasia 0.3%, oral lymphoma 0.3%, oral condyloma 0.3%
Neelkant Patil et al, 2015 India	50 (total 100)	50.00	32.00	n/a	2.00	0.00	0.00	n/a	n/a	4.00	14.00	8.00	2.00	2.00	PD = periodontitis
K.V.S Eswara Rao et al, 2015 India	320	100.00	81.60	10.31	1.25	5.94	2.81	n/a	0.00	0.94	23.75	n/a	46.56	n/a	Chronic hyperplastic candidiasis 0.31% , OC 10.31%
Wipawee Nittayananta et al, 2010 Thailand	207	48.53	27.00	n/a	0.97	0.00	n/a	0.48	n/a	1.45	21.26	n/a	0.48	n/a	PD = Linear gingival erythema
Wen Shu et al, 2020 China	1812	46.78	52.27	n/a	11.27	8.87	n/a	7.91	6.24	4.80	n/a	n/a	n/a	n/a	Oral Kaposi´s sarcoma 0.48%

Table 4. Comparison of results of oral pathologies in patients with HAART [14,15,17,19,25]

Table 5 presents a summary of finding in the current literature regarding the prevalence of oral pathologies and long-term HAART use. The consulted literature agrees since the advent of HAART, there has been a positive outcome on reducing the prevalence of oral pathologies typically seen in the HIV seropositive patient prior HAART, including OC and KS. Moreover, studies where the cohort included paediatric patients the conclusions were in an accordance with those drawn for adults.

Author, year and country	Objective	Results	Conclusions
Rao KV et al, 2020	Record and compare oral pathologies in HIV seropositive patients before and after HAART	After chronic use of HAART the prevalence of oral pathologies due to opportunisitic infections decreased, such as oral candidiasis. Additionally, there was a decrease of incidence of PD with chronic HAART use. On the other hand, an increase in introral pigmentations was observed in patients with chronic HAART use	Since the advent of HAART, prevalence of many opportunistic infections and neoplasms has reduced as a result of improved immunity. Prevalence of OC and PD were less commonly seen in patients who had access to HAART. Although, there was noted a risk of hyperpigmentation with chronic HAART use.
Alan G Lourenço et al, 2011	An epidemiological study to determine the prevalence of HIV oral lesions in HIV seropositive participants in two time periods 1997 and 2004-2008	A significant reduction in the prevalence of oral pathologies was observed in those on HAART, pathologies include PC, EC, AC, OHL, OU. The pathology with the most significant reduction in prevalence was OC, of which EC.	There was a significant reduction in oral pathologies in patients taking HAART, when compared with non-HAART
de Araújo JF et al, 2018	A literature review by conducting a bibliographic search of descriptive, cross-sectional and comparison studies regarding oral manifestations in HIV infected children.	19 scientific articles were included in this review of oral pathologies in paediatric patients. Cross sectional and prospective studies show that in HIV infected patients, they will present with some type of oral lesion. The most commonly seen oral pathologies were OC in various clinical presentations, gingivitis, acute herpatic gingivostomatitis, linear gingival erythema, OHL, KS, and parotid enlargement. However, use of HAART has been documented to significantly reduce the prevalance of oral lesions associated with HIV.	The main findings of this literature review were that the most frequent oral manifestation of HIV infected children was OC and gingivitis. Oral manifestiations are common in HIV infected children, HAART has been shown to reduce the prevalece of these oral lesions.
Juvino AC et al, 2017	Pilot study to investigate the relationship between the prevalence of Bruxism in HIV/AIDS patients and psychological factors	64.28% of HIV patients in this study presented with bruxism. The prevalence of bruxism in HIV patients is 3 times higher than the general population.	The psychologial impact of living with HIV, even whilst being treated with HAART, can have a negative psychological impact on an individual. So the dental professional should be aware of these factors which may contribute to the increased prevalence of bruxism in these individuals
Sehgal HS et al, 2019	A cross sectional study to investigate the relationship of tooth wear in HIV patients with HAART	92% of HIV positive patients presented with toothwear and 67% of patients HIV negative presented with toothwear	Findings from this study suggest that HIV positive patients who are on HAART present with significant tooth wear. The number of years on HAART was positively correlated with tooth wear.

Table 5. Findings of 5 studies regarding the variation of oral pathologies with chronic HAART use [15,17,22–24]

In 2019, a systemic review of the most relevant cross sectional and epidemiological studies about oral pathologies in seropositive HIV children.[21,22] The findings of this review indicated many similarities between oral pathologies of adults and children alike. Still, it is important to note the differences between the two population groups. Unlike in adults, the main form of transmission of HIV in paediatric patients is via vertical transmission from mother

to child in three ways. Across the placenta during pregnancy, during delivery or during breastfeeding. In 2017, 80% of pregnant women with HIV were able to access HAART to prevent transmission of HIV to their unborn child, in 2010 this number was 47%. As in adults, the first signs of HIV infection may be oral manifestations because of immunodeficiency. However, the immune system of children is not mature, and so, children infected with HIV are more susceptible to aggressive development of systemic diseases resulting in a higher mortality rate when compared with adults. Nevertheless, as with adults, from the introduction of HAART medication, morbidity and mortality reduced as well as the manifestations of oral pathologies. Also, HAART has been documented to reduce the salivary flow rate in the oral cavity and affect melanocyte stimulating hormone. In turn, leading to side effects such as increased prevalence of hyperpigmentation, xerostomia, and salivary gland hypertrophy. In this systematic review, oral candidiasis was the most identified pathology discovered, along with PD such as gingivitis. However, the prevalence of gingivitis is more related to poor oral hygiene in developing countries as opposed to the HIV infection itself. Oral pathologies in children may be a factor as to why some children have poor oral hygiene, due to difficulty in brushing their teeth. As with adults, but especially with children, it is critical to diagnose and treat HIV infection as early detection would allow for HAART to begin, reducing the likelihood of development of oral pathologies and lowering the mortality and morbidity caused by AIDS. Dentists, especially in developing countries, play a pivotal role in the prevention and treatment of HIV and AIDS in children, allowing for regular screening for oral pathologies, children would be able to commence HAART early and improving the prognostic outcome. HAART has shown

to reduce prevalence of oral pathologies and improve quality of life in children, including the most prevalently seen manifestations such as OC in seropositive HIV children.

Undoubtedly, after being diagnosed with HIV a patient's life will change. Although there is no cure to HIV, HAART has been well studied and approved to maintaining a low viral load and increasing CD4 count. Nevertheless, patients may feel apprehension with the new changes in their life, increased stress about the possibility of death, changes to their life after HIV diagnosis. These psychological concerns, such as anxiety and depression, can be a contributing factor to bruxism. In a study of 14 HIV patients in Brazil, subjective data was collected regarding general psychological status in relation to life with HIV and a clinical examination was performed. 64.28% of patients presented with bruxism, compared with 8-21% of those in the general population.[23] Bruxism can provoke temporomandibular joint disorders, headaches and alterations in the periodontal tissues and dentition. Some HIV patients suffering depression may be prescribed with anti-depressants, selective serotonin reuptake inhibitors, which may increase susceptibility to bruxism and thus increasing the likelihood of attrition. Not only does HAART present with side effects affecting the oral cavity, such as oral hyperpigmentation, HAART may have psychological effects such as cause sleep or mood disturbances. Xerostomia, another side effect of HAART, along with increased clenching and grinding of the dentition contributes to the increased risk of tooth wear in a mechanical and chemical manner. The literature regarding the topic of oral pathologies and HAART use, or lack of, are more related to oral manifestations due to immunosuppression. Whereas it is not well reported the oral pathologies due to parafunctional habits, such as bruxism,

associated with HAART use. A cross sectional study, conducted in Portland, Oregon assessed the state of tooth wear among HIV patients with HAART, this study was the first study conducted to investigate this relationship. In the study, 93 patients were assessed, of which 60 were seropositive with HIV. 90% of those HIV positive under treatment with HAART had tooth wear. The results of this study indicated that the longer the patient was taking HAART, the more tooth wear they presented. Even so, with age it is normal for teeth to present some tooth wear. Furthermore, the participants in this study were predominantly male (95% of participants) and males tend to present with bruxism more often than females. It can be concluded that HIV diagnosis, and use of HAART, may lead to psychological alterations and so the dental professional should be aware of this to be able to provide preventative treatment or provide early intervention. Limitations of this study include the small sample size and the lack of current literature regarding this topic. Although the current scientific literature has not explored this subject in depth, further investigations with larger sample sizes and more varied patients would contribute to the future success of improving the quality of life in patients with HAART.[24]

5. Conclusions

1. HAART has been able to successfully decrease morbidity of individuals living with HIV/AIDS.
2. Whilst access to HAART is widely available globally, there is still a significant number of HIV infected individuals in developing countries that have difficulties in access to healthcare, such as those in the African region.
3. Patient adherence to treatment has been shown to increase CD4 count and consequently reduce the prevalence of many oral pathologies, including the most common pathologies such as OC and KS.
4. HAART medication may present with certain side effects that present as oral manifestations, such as oral pigmentation and bruxism.
5. The benefits of this therapy for HIV/AIDS patients outweighs the risks of these side effects.
6. Paediatric patients present with similar oral pathologies that are seen in adults.
7. The dental professional should be aware of the increased prevalence of dental caries due to xerostomia by HAART.
8. Further studies should be conducted to elucidate conclusions drawn regarding the relationship between HIV infected patients and bruxism.

6.1 Governmental responsibility

Governmental bodies have a responsibility on a public level. Public policies should be implemented educating the population about the prevention of transmission of HIV and increasing awareness of the importance of early diagnosis, thus allowing for early commencement of HAART. This education can be conducted though seminars in educational institutes, printed media such as informational brochures in primary care facilities or on the internet. The importance of regular dental visits should be highlighted to the public and the government is responsible for access to healthcare and for HIV individuals to receive HAART.

6.2 Responsibility of the dental professional

Oral pathologies may present in an HIV infected patient prior HAART due to immunosuppression or conversely after HAART, due to the medication itself. In turn, Dental care professionals have a key role to play in the time between HIV diagnosis and the start of HAART, as patients tend to visit the dentist routinely more so than primary medical care. Prevention is crucial to prevent the spread of infection. Prevention strategies may include improving access to HIV screening, allowing for earlier diagnosis which in turn leads to earlier access to HAART, consequently improving prognosis. The dentist can identify oral pathology present in these individuals to ascertain the aetiology. There are characteristic oral pathologies dentists should be aware of in patients with HIV infection, usually due to the lower immune

status of HIV infected individuals. Conversely, some patients may present oral pathologies of HAART because of an identified side effect or psychological factors.

6.3 Patient responsibility

Patients have the responsibility to avoid behaviours that have a risk of HIV transmission. Patients should understand the importance of routine dental appointments and make regular visits to the dentist, not only visit when they are in pain. Lastly, it is crucial that patients inform healthcare workers of their HIV status and that they have perfect adherence to HAART.

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Pathogenesis of HIV infection

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Abstract

Over the past three decades of intense research on the contribution of viral and host factors determining the variability in HIV-1 infection outcome, HIV pathogenesis is still a fascinating topic that requires further study. An understanding of the exact mechanism of how these factors influencing HIV pathogenesis is critical to the development of effective strategies to prevent infection. Significant progress has been made in identifying the role of CCR5 (R5) and CXCR4 (X4) HIV strains in disease progression, particularly with the persistence of R5 HIV-1 strains at the AIDS stage. This indicates that R5 strains are as *fit* as X4 in causing CD4+ T cell depletion and in contribution to disease outcome, and so questions the prerequisite of the shift from R5 to X4 for disease progression. In contrast, the ability of certain HIV strains to readily use CXCR4 for infection or entry into macrophages, as the case with viruses are homozygous for tropism by CCR5delta32. This raises another major paradox in HIV pathogenesis about the source of X4 variants and how do they emerge from a relatively homogeneous R5 viral population after transmission. The interactions between viral phenotypes, tropism and co-receptor usage and how they influence HIV pathogenesis are the main themes addressed in this review. A better understanding of the viral and host genetic factors involved in the fitness of X4 and R5 strains of HIV-1 may facilitate development of specific inhibitors against these viral populations to at least reduce the risk of disease progression.

HIV primary infection and disease progression

There are several viral and host factors determining the variability in HIV-1 infection outcome and in rates of disease progression in HIV-1 infected individuals. Cellular tropism which defines viral phenotype and receptor-coreceptors which determine viral entry into various cell types are the major factors influencing HIV pathogenesis. Despite the intense research for the last 25 years, the exact mechanism of how these factors contribute to the dramatic loss of CD4+ T cells and the persistence of R5 and X4 strains during the AIDS status is still not well identified.[1]

Infection with HIV starts without symptoms or ill-feeling and is accompanied by slight changes in the immune system. This stage spans up to three months after infection until seroconversion where HIV-specific antibodies can be detected in individuals following recent exposure. The outcome of infection and duration for disease progression with clinical symptoms may vary greatly between individuals, but often it progresses fairly slowly.[2] It takes several years from primary infection to the development of symptoms of advanced HIV diseases and immunosuppression.

During primary infection, although individuals may look healthy, the virus is actively replicating in the lymph nodes and blood stream of infected individuals. As a result, the immune system may get slowly damaged by the burst of viral load in their bodies.[3]

Symptomatic stage of disease indicates the late phase of HIV disease (AIDS) where individuals may be susceptible to other opportunistic infections (OIs),[4] such as infections with *Mycobacterium avium*, *Mycobacterium tuberculosis*, *Pneumocystis carinii*, CMV, toxoplasmosis and candidiasis. It is agreed that infected individuals develop an AIDS status when their plasma HIV load is high and the CD4+ T count is less than 200 mm^3 (Figure 1). The availability of the highly active antiretroviral therapy (HAART) may question the dilemma as to whether everyone who seroconverts to HIV will develop AIDS.

One mechanism HIV weakens the immune system is by infecting and destroying CD4+ T cells, which in turn leads to immunodeficiency at later stage of disease.[5] HIV attaches to the CD4+ protein on the surface of these and other cells to gain entry. However, the presence of CD4+ molecules alone proves to be not enough to allow viral entry into other cell types such as monocytes and dendritic cells. Therefore, a second doorway is needed for the virus to gain access to infect cells. This led to the discovery of the chemokine receptor as essential coreceptors for HIV-1. There are different types of these coreceptors for different cell types that HIV variants can use for infection of cells. Two main chemokine receptors have been identified to play a major role in HIV entry, CCR5 and CXCR4 (or fusin).

HIV tropism

HIV-1 is one of the most polymorphic viruses known and exists as a swarm of genetically related variants or *quasispecies*. The polymorphic nature of HIV-1 can be directly attributed to its error prone reverse transcriptase and complexity of its cDNA formation. Together with other host factors, the evolution of the viral genome underlies all of the changes in the biological characteristics of HIV-1 including cytopathic ability, immune evasion, coreceptor usage and tropism.

HIV-1 strains can be subdivided into three main groups based on their cellular tropism. They are referred to as macrophage-tropic (M-tropic) with a non-syncytium-inducing (NSI) phenotype or T-cell line tropic (T-tropic) with a syncytium-inducing (SI) phenotype or dual-tropic HIV-1 strains. M-tropic NSI variants infect peripheral blood mononuclear cells (PBMC), monocytes, macrophages and T lymphocytes but not T-cell lines and are present throughout all stages of infection/disease.[6-8] T-tropic SI isolates preferentially infect T lymphocytes and T-cell lines but not monocytes or macrophages and emerge in late stages of infection and is associated with progression to AIDS.[9] On the other hand dual-tropic HIV-1 variants infect both monocytes/macrophage and T-cell lines, and therefore have mixed viral population of NSI/SI phenotypes.

The prevalence of SI strains usually correlates with rapid decline in CD4+ T cell count and the disease progression rate will be 3-5 fold faster than NSI strains. It is unclear whether the virus converts from an NSI to an SI strain, or an SI viral population emerges. It is worth noting that about 50% of people who die of AIDS still have a predominant NSI strain of HIV.

Defining the viral phenotype can be done by

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Key words: HIV/AIDS, tropism, coreceptor, SI/NSI.

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WHO CASE DEFINITIONS OF HIV FOR SURVEILLANCE AND REVISED CLINICAL STAGING AND IMMUNOLOGICAL CLASSIFICATION OF HIV-RELATED DISEASE IN ADULTS AND CHILDREN

Oral Lesions Associated with Human Immunodeficiency Virus Disease

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KEYWORDS

• HIV • Oral candidiasis • Kaposi sarcoma • Oral hairy leukoplakia
• HIV salivary gland disease

KEY POINTS

- Human immunodeficiency virus (HIV)-associated oral lesions are numerous and diverse and may relate to opportunistic infections that occur in the setting of immune suppression.
- Presumptive HIV oral lesion diagnosis based on clinical appearance and lesion behavior may be sufficient for some benign-appearing lesions; whereas worrisome ulcerative lesions/masses require definitive diagnosis, usually based on histopathology.
- Patterns of oral disease prevalence and incidence have changed with improved HIV disease management and use of highly active antiretroviral therapy (HAART).
- HAART-related immune reconstitution inflammatory syndrome has reactivated some oral diseases and has resulted in other medication oral side effects in some patients.
- Pharmaceutical and nonpharmaceutical management are important considerations for HIV-associated oral lesions.

INTRODUCTION AND EPIDEMIOLOGY

Introduction

Human immunodeficiency virus (HIV) infection affects the host by targeting the CD4 positive T-lymphocyte population.[1] HIV viral particles bind with lymphocytes and use the lymphocyte as a host factory, where additional HIV viral particles are produced. During this repeated process of viral replication, the lymphocyte is exhausted and destroyed, resulting in fewer T-helper lymphocytes available to protect the host from a variety of viral, fungal, bacterial, and protozoal opportunistic infections and other neoplastic diseases (**Fig. 1**).

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Oral manifestations of HIV disease: A review

Daiva Aškinytė, Raimonda Matulionytė, Arūnas Rimkevičius

SUMMARY

The HIV/AIDS pandemic continues to plague the world. Evaluation of oral health status is important at every stage in the management of HIV disease. Oral health services and professionals can contribute effectively to the control of HIV/AIDS through health education, patient care, infection control and surveillance. Dental professionals have an important task of determining accurate diagnosis of oral manifestations and choosing proper treatment for each case. This review provides information on HIV associated orofacial lesions, their clinical presentation and up to date treatment strategies.

Key words: oral lesions, HIV, AIDS, oral health care.

INTRODUCTION

The HIV/AIDS pandemic has become a human and social disaster, particularly in resource limited settings. Oral health is an important component of the overall health status in HIV infection and essential component of quality of life (1,2). HIV-related oral abnormalities occur in 30 to 80 percent of the affected patient population (3). Policies for strengthening oral health promotion and the care of HIV-infected patients have been issued by WHO (2). Oral health services and professionals can contribute effectively to the control of HIV/AIDS through health education, patient care, infection control and surveillance.

Oral lesions are among the early signs of HIV infection and for individuals with unknown HIV status may suggest possible HIV diagnosis. For persons diagnosed with HIV who are not yeat on therapy, the presence of certain oral manifestations may predict progression to AIDS (4). Furthermore, for patients on highly active antiretroviral therapy (HAART) the presence of certain oral manifestations may serve as surrogate markers for the efficacy of antiretroviral therapy (5,6). Even thought the prevalence of specific oral lesions like candidiasis, hairy leukoplakia and Kaposi's sarcoma has been proven to be lower among patients on HAART (7,8,9,10) other conditions such as oral warts (11,12) and salivary gland disease (11,13) have been found to be more prevalent in this population as part of immune reconstitution resulting from antiretroviral therapy initiation.

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CLASSIFICATION

There are two main classifications of oral lesions associated with HIV (HIV-OL). The first is based on the HIV-OLs etiology and according to it, they are classified as bacterial, viral, or fungal infections or as neoplastic lesions or other conditions. In 1993 EC-Clearinghouse on Oral Problems Related to HIV Infection and WHO Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus has reached a consensus on new classification of the oral manifestations of HIV infection. It classifies HIV-OLs into three: lesions strongly associated with HIV infection, those less commonly associated with HIV infection and lesions seen in HIV infection (14). (Table1). The 1993 EC-Clearinghouse classification is still globally used despite controversy on the relevance of periodontal diseases today (15). HIV-OL case definitions were updated in 2009 to facilitate the accuracy of HIV-OL diagnoses by non-dental healthcare workers in large-scale epidemiologic studies and clinical trials (16).

Besides diagnosing, it is essential to choose proper treatment for each case. This review provides

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Oral manifestations of HIV

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Abstract

The infection of the root canal system is considered to be a polymicrobial infection, consisting of both aerobic and anaerobic bacteria. Because of the complexity of the root canal infection, it is unlikely that any single antibiotic could result in effective sterilization of the canal. A combination of antibiotic drugs (metronidazole, ciprofloxacin, and minocycline) is used to eliminate target bacteria, which are possible sources of endodontic lesions. Three case reports describe the nonsurgical endodontic treatment of teeth with large periradicular lesions. A triple antibiotic paste was used for 3 months. After 3 months, teeth were asymptomatic and were obturated. The follow-up radiograph of all the three cases showed progressive healing of periradicular lesions. The results of these cases show that when most commonly used medicaments fail in eliminating the symptoms then a triple antibiotic paste can be used clinically in the treatment of teeth with large periradicular lesions.

Keywords: Ciprofloxacin, metronidazole, minocycline, nonsurgical root canal treatment, periradicular lesion, triple antibiotic paste

Around 33.8 million people worldwide are living with HIV-AIDS (WHO 2008 report) of which around 3.8 million are in the Indian subcontinent. The first case of AIDS was reported in the year 1981. Since then the disease has gone through various stages of changes with respect to its epidemiology as well as its manifestations.

HIV disease has an effect over the entire body. It is not practical in the present scenario for any health personnel dealing with diagnosis and treatment in humans to not encounter this dreaded disease and its manifestations. Thus it becomes imperative to be aware of the various forms of HIV manifestations.

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.

Oral manifestations of HIV infection occur in 30–80% of the affected patient population.[1,2] The overall prevalence of oral manifestations in HIV disease has changed since the advent of HAART.

The various oral manifestations can be categorized into

1. Infections: bacterial, fungal, viral

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Review Article

Epstein-Barr Virus and Its Association with Oral Hairy Leukoplakia: A Short Review

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In immunocompromised subjects, Epstein-Barr virus (EBV) infection of terminally differentiated oral keratinocytes may result in subclinical productive infection of the virus in the stratum spinosum and in the stratum granulosum with shedding of infectious virions into the oral fluid in the desquamating cells. In a minority of cases this productive infection with dysregulation of the cell cycle of terminally differentiated epithelial cells may manifest as oral hairy leukoplakia. This is a white, hyperkeratotic, benign lesion of low morbidity, affecting primarily the lateral border of the tongue. Factors that determine whether productive EBV replication within the oral epithelium will cause oral hairy leukoplakia include the fitness of local immune responses, the profile of EBV gene expression, and local environmental factors.

1. Introduction

Oral hairy leukoplakia is a benign, asymptomatic, white, hyperkeratotic lesion affecting primarily the lateral border of the tongue, unilaterally or bilaterally (Figures 1 and 2); but rarely it may occur elsewhere in the mouth. Its surface may be flat, vertically corrugated, or frankly hairy, and it affects severely immunocompromised subjects, most notably those infected with HIV [1–3].

The characteristic microscopical features of oral hairy leukoplakia are epithelial hyperplasia, acanthosis, hyperkeratosis, and presence of koilocyte-like cells, but with little or no inflammatory cell infiltrate in the underlying lamina propria [1]. Candidal hyphae are not uncommonly present, but these represent a secondary fungal infection (Figure 3) [1].

There seems to be a causal link between Epstein-Barr virus (EBV) and oral hairy leukoplakia as EBV DNA, and EBV gene-encoded proteins are present in lesional cells. Oral hairy leukoplakia appears to be caused by productive replication of EBV in the oral mucosal epithelium, particularly of the lateral borders of the tongue [4–6]. In fact, in immunocompromised subjects, the oral epithelium supports both latent and productive EBV infections [2], with EBV replication and spread of virions occurring exclusively in terminally differentiated cells of the stratum spinosum and stratum granulosum [7]. Under these circumstances EBV is almost always present in the oral fluid [2, 8]. Another source of EBV in the oral fluid may be inflamed periodontal sites, as it has been shown that active periodontal pockets may harbour EBV DNA particles that contribute to the EBV load in the oral fluid [6].

EBV-induced oral hairy leukoplakia may be the first clinical manifestation of HIV infection, and in HIV-seropositive subjects it may be an indicator of progression to acquired immunodeficiency syndrome (AIDS). In HIV-seropositive subjects, a high HIV viral load and a low CD4+ T-cell count increase the risk of EBV-induced oral hairy leukoplakia [2–4].

In HIV-seropositive subjects, oral hairy leukoplakia is relatively asymptomatic and does not have any malignant potential, and as a rule it does not need treatment. About 10% of cases may improve spontaneously or may even resolve by improvement of the immune status after institution of highly active antiretroviral treatment (HAART). If for any

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ORIGINAL RESEARCH

The world-wide incidence of Kaposi's sarcoma in the HIV/AIDS era

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Objectives

Kaposi's sarcoma (KS) is a multicentric angioproliferative cancer of endothelial origin typically occurring in the context of immunosuppression or immunodeficiency. Consequently, KS is one of the most common cancers in HIV-infected individuals and frequently occurs among transplant recipients. Nevertheless, its incidence in different populations is not well understood.

Methods

We searched online databases for publications on KS incidence. A random-effect meta-analysis was performed to combine the KS incidences and incidence rate ratios (IRRs) for associated risk factors.

Results

Seventy-six eligible studies representing 71 time periods were included. For HIV-infected people, the overall KS incidence was 481.54 per 100 000 person-years with a 95% confidential interval (CI) of 342.36–677.32 per 100 000 person-years. HIV-infected men who have sex with men (MSM) had the highest incidence of KS (1397.11 per 100 000 person-years; 95% CI 870.55–2242.18 per 100 000 person-years). The incidence of KS was significantly lower in female than in male individuals (IRR 3.09; 95% CI 1.70–5.62). People receiving highly active antiretroviral therapy (HAART) had a lower incidence compared with people who had never received HAART (IRR 6.57; 95% CI 1.91–24.69). The incidence of KS was 68.59 (95% CI 31.39–149.86) per 100 000 person-years in transplant recipients, 52.94 (95% CI 39.90–70.20) per 100 000 person-years in children with HIV infection, and 1.53 (95% CI 0.33–7.08) per 100 000 person-years in the general population.

Conclusions

Globally, a relatively high incidence of KS was found among HIV-seropositive people and, in particular, in HIV-infected MSM. The introduction of HAART has largely prevented the development of KS, but it has not entirely removed the challenge of KS. In Africa, in particular, KS imposes a very heavy disease burden, which can mainly be attributed to the high prevalence of KS-associated herpesvirus and poor access to HAART.

Keywords: HIV/AIDS, incidence, Kaposi's sarcoma, meta-analysis

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Introduction

Kaposi's sarcoma (KS), which can be grouped into four epidemiological forms, is a multifocal mesenchymal neoplasm characterized by neoangiogenesis, inflammatory infiltration and endothelial-derived, spindle-shaped tumour cells [1]. Prior to the 1980s, KS had been a relatively rare cancer world-wide [2]. Classic KS mainly occurred among elderly men of Mediterranean or Eastern European Jewish ancestry [3]. Endemic KS principally existed in parts of central and eastern Africa [4]. Iatrogenic KS mostly occurred among immunosuppressed persons of any age and was caused by autoimmune disease, drugs, or transplantation [5]. From the 1980s onwards, AIDS-associated KS, a major AIDS-defining malignancy, predominantly

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REVIEW ARTICLE

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Common oral opportunistic infections in Human Immunodeficiency Virus infection/Acquired Immunodeficiency Syndrome: Changing epidemiology; diagnostic criteria and methods; management protocols

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1 | BACKGROUND

Globally, 36.9 million people are living with human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS), with 1.8 million new infections in 2017. Antiretroviral therapy (ART) has reached 59% of all HIV infected, and as of 2017 there were 21.7 million people accessing ART globally.[1] In spite of the remarkable and significant effort by the global health community and governing bodies, there are a substantial percentage of people living with, and at risk of HIV infection with no access to prevention, care, and treatment. In the management of HIV infection, surrogate markers of HIV infection play an important role in early diagnosis and in monitoring prognosis, particularly in resource-poor settings. It is well recognized that oral lesions occur in HIV infection/AIDS patients and are important facilitators for recognizing, monitoring, and predicting the course of the disease.[2,3] In this chapter, the status of HIV-related oral lesions is discussed with respect to their pattern of occurrence, their diagnosis, classification, and management protocols. The discussion is based on the etiology, such as fungal infections, viral infections, bacterial infections, AIDS-defining cancers, and idiopathic conditions.[4]

2 | CHANGING EPIDEMIOLOGY AND DIAGNOSTIC CRITERIA OF HIV-RELATED ORAL LESIONS

A formal classification of oral lesions associated with HIV disease was first adopted in 1992, when the Oral Acquired Immunodeficiency Syndrome Collaborative group from the United States published the HIV-related oral lesions definitions and diagnostic criteria.[5] This was followed by the criteria set by the EC-Clearinghouse on Oral Problems Related to HIV Infection and World Health Organization Collaborating Center on Oral Manifestations of the Immunodeficiency Virus,[6] in which the lesions are classified into three groups (Table 1). The 1992 and 1993 diagnostic criteria were further updated by Oral Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome Research Alliance (OHARA), a part of the Acquired Immunodeficiency Syndrome Clinical Trials Group,[4] which is the largest HIV clinical trials organization in the world. The primary objective of OHARA was to present updated case definitions of HIV-related oral diseases that are standardized with respect to precise diagnosis. An important modification incorporated was the inclusion of patient-reported symptoms and the duration of signs and symptoms to the existing clinical description for each lesion. The case definitions proposed were structured and meant for use in large-scale epidemiological studies across the world in both developed and developing countries, by dental and nondental health care providers. The important contribution of OHARA is the development of standardized training modules for measuring oral disease end points.[7]

A comprehensive review of HIV infection in developing countries confirmed that there were considerable regional variations in the oral manifestations.[8] The reported prevalence of any oral lesion was around 96% in Africa,[9] 90% in Thailand,[10] 87% in India,[11] and 71% in Latin America[12] in the era prior to highly active ART (HAART).

The introduction of HAART witnessed a significant difference in the quality of life of HIV-positive patients and resulted in a drop in the morbidity and mortality rates.[13,14] Around five million (4.1-6.7) people of the global total of 36.9 million with HIV infection are from Asia and the Pacific, and ART is currently utilized by around 2.7 million people and has led to a significant decline in the mortality rate. Current recommendations for the initiation of ART in HIV-positive

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REVIEW ARTICLE

Periodontal and other oral manifestations of immunodeficiency diseases

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The list of immunodeficiency diseases grows each year as novel disorders are discovered, classified, and sometimes reclassified due to our ever-increasing knowledge of immune system function. Although the number of patients with secondary immunodeficiencies (SIDs) greatly exceeds those with primary immunodeficiencies (PIDs), the prevalence of both appears to be on the rise probably because of scientific breakthroughs that facilitate earlier and more accurate diagnosis. Primary immunodeficiencies in adults are not as rare as once thought. Globally, the main causes of secondary immunodeficiency are HIV infection and nutritional insufficiencies. Persons with acquired immune disorders such as AIDS caused by the human immunodeficiency virus (HIV) are now living long and fulfilling lives as a result of highly active antiretroviral therapy (HAART). Irrespective of whether the patient's immune-deficient state is a consequence of a genetic defect or is secondary in nature, dental and medical practitioners must be aware of the constant potential for infections and/or expressions of autoimmunity in these individuals. The purpose of this review was to study the most common conditions resulting from primary and secondary immunodeficiency states, how they are classified, and the detrimental manifestations of these disorders on the periodontal and oral tissues.

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Keywords: autoimmune disease; immune defects; periodontium; pathology; immunodeficiency; oral infection

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Introduction

Patients with compromised immune function are predisposed to a variety of systemic and oral manifestations, including inflammation of the periodontium and surrounding tissues (Szczawinska-Poplonyk *et al*, 2009). As the life expectancy grows for many of these patients thanks to advanced therapeutic modalities, oral healthcare providers will no doubt have to take on more responsibility in the treatment of this expanding population (Atkinson *et al*, 2000). Immunocompromised patients often have complex multifactorial histories requiring dental personnel to understand the primary disease processes and to coordinate care with medical specialists. The patients survival followed by the improvement of quality of life is the essential goal. The number of primary immunodeficiencies (PIDs) and conditions that can lead to secondary immunodeficiencies (Verma *et al*, 2013) is extensive, and all cannot be expounded upon in this format. We start with a brief overview of the immune system.

Immunodeficiency relates to the body's immune system being unable to perform its normal functions in protecting the host. Primary immunodeficiencies are hereditary (genetically conferred by progeny), whereas secondary immunodeficiencies are acquired. Secondary immunodeficiencies are much more common, as they relate to other systemic disorders (e.g., diabetes, undernutrition, HIV infection) or immunosuppressive treatments (e.g., cytotoxic chemotherapy, bone marrow ablation before transplantation, radiation therapy). Understanding the basic concepts of how the immune system works helps to appreciate a specific disorder and the components that it affects. A general outline of the immune system is shown in Figure 1. This is not meant to be an all-inclusive guide to the cellular immune system. Innate immunity includes phagocytic cells (neutrophils, dendritic cells, and macrophages), with both dendritic cells and macrophages being antigen-presenting cells, APCs). Also part of the innate immune system are natural killer (NK) cells and complement. The adaptive immune system incorporates T cells and B cells. Crucial to bridging innate and adaptive immunity are APCs, especially dendritic cells, the sole

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Clinical profile of HIV in India

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The clinical course of human immunodeficiency virus (HIV) disease and pattern of opportunistic infections varies from patient to patient and from country to country. The clinical profile of HIV disease in India includes a wide range of conditions like tuberculosis, cryptococcal meningitis, popular pruritic eruptions, and cytomegalovirus retinitis, among others. Tuberculosis is the most common opportunistic infection in Indian patients with HIV. Occurrence of various AIDS-associated illnesses determines disease progression. Mean survival time of Indian patients after diagnosis of HIV is 92 months. In this review, we discuss the clinical profile of HIV disease through an organ system-based approach. With the availability of antiretroviral therapy at lower cost, the clinical profile of HIV disease in India is now changing to include drug-related toxicities and immune reconstitution syndrome.

Key words AIDS - antiretroviral therapy - developing countries - generic - HAART - HIV - India - natural history - OIs - opportunistic infections - tuberculosis

The prolonged course of human immunodeficiency virus (HIV) infection is marked by a decrease in the number of circulating CD4+ T helper cells and persistent viral replication, resulting in immunologic decline and death from opportunistic infections and neoplasms[1,2]. Acute HIV infection is characterized by a rapid rise in plasma viraemia with a concomitant drop in CD4 count within 3-6 wk of exposure (Fig.1). Associated symptoms with this initial stage of infection occur to varying degrees of severity and may include fever, sore throat, skin rash, lymphadenopathy, splenomegaly, myalgia, arthritis, and, less often, meningitis[3]. The acute phase is followed by a clinically latent period with low level viral replication and a gradual fall in CD4 count where the patient can remain asymptomatic for several months to years. Mean duration of survival after diagnosis with HIV in India is 92 months[4].

Median time for progression from HIV infection to acquired immunodeficiency syndrome (AIDS) was 7.9 yr in one study of patients from Mumbai[5]. This number is subject to a reporting bias given that fewer than 10 per cent of AIDS cases in India have been reported. With CD4 counts less than 200 cells/µl, patients are at high risk for developing opportunistic infections (OIs) like tuberculosis (TB), *Pneumocystis carinii* pneumonia (PCP), toxoplasmosis, and cryptococcal meningitis (Fig.2). Before the availability of antiretroviral therapy, median survival after diagnosis of AIDS was 12 to 18 months[6]. This has changed dramatically since the advent of highly active

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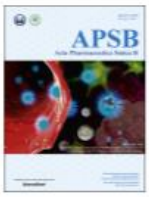

REVIEW

Anti-retroviral drugs: current state and development in the next decade

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KEY WORDS

Antiretroviral drugs;
Long-acting formulations;
Attachment inhibitors;
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Abstract The pace of discovery of new antiretroviral (ARV) drugs has slowed, although the efficacy and safety of once-daily fixed dose combinations have been extensively investigated. Several traditional ARV drugs remain in phase III clinical trials. This review summarizes current information on ARV drugs in phase III clinical trials and focuses on the development of ARV drugs in the next decade.

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Original Article

The effect of highly active antiretroviral therapy on the prevalence of oral manifestation in human immunodeficiency virus-infected patients in Karnataka, India

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ABSTRACT

Objectives: Acquired Immunodeficiency Syndrome (AIDS) is a highly lethal, progressively epidemic viral infection characterized by profound impairment of the immune system. Oral manifestations are common in Human Immunodeficiency Virus (HIV) infected AIDS patients, and are usually the first indicator of symptom and disease progression. The main objective of the current study was to compare the prevalence of oral manifestations in HIV patients on Highly Active Antiretroviral Therapy (HAART) with those, not on HAART therapies. **Materials and Methods:** A cross sectional study was conducted among 100 patients diagnosed as human immune virus sero-positive. These patients were divided equally into two groups (50 each); Group I patients on HAART and Group II patients who were not on HAART. Information regarding age, sex and cluster of differentiation 4 cell count was obtained from the medical records. Oral examination was done, and findings were recorded by using internationally accepted presumptive clinical criteria. Statistical analysis was performed using Chi-square statistical test. **Results:** The presence of oral manifestations was significantly decreased in subjects on HAART (32%) compared to those who are not on HAART (56%). The most common oral lesions detected in patients on HAART were increased oral hyper-pigmentation (14%), recurrent aphthous stomatitis (8%), non-specific ulcerations (4%), pseudo-membranous candidiasis (2%), periodontitis (2%) and xerostomia (2%), whereas in non HAART oral hyperpigmentation (10%), pseudo-membranous candidiasis (8%), angular cheilitis (4%), and erythematous candidiasis (4%) and Periodontitis (14%) were more prevalent. **Conclusion:** The number and severity of oral manifestation decreased, and even there was a change in the type of oral manifestations on HAART, which may be because of the improvement in immunity gained by the therapy.

Key words: Cluster of differentiation 4 cell, highly active antiretroviral therapy, immunodeficiency virus/acquired immunodeficiency syndrome, oral manifestations

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Impact of highly active antiretroviral therapy on oral manifestations of patients with human immunodeficiency virus/acquired immuno deficiency syndrome in South India

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Abstract

Background:

Human immunodeficiency virus (HIV) infection remains a global health problem, although the development of highly active antiretroviral therapy (HAART) has significantly modified the course of HIV disease into a manageable disease with improved quality-of-life mainly in the developed countries. Very few studies are available regarding effect of HAART on oral lesions in developing countries like India.

Aims and Objectives:

The aim was to document and compare oral lesions in HIV-seropositive patients before and after HAART.

Materials and Methods:

Oral manifestations were recorded in 320 HIV seropositive patients attending to the Voluntary Counseling and Confidential Testing Centre at the Government General Hospital, Guntur, before and after treating with HAART and the results were statistically analyzed using Student's *t*-test and Chi-square test.

Results:

Oral Candidiasis was significantly reduced in patients under HAART after 3 months. Furthermore, there was decreased incidence of periodontal diseases, but increased hyperpigmentation in patients undergoing HAART.

Conclusion:

The oral manifestations of HIV infection have changed due to the advent of HAART. Many opportunistic infections have resolved as a result of an improved immune system. Though the risk of hyperpigmentation in those with HAART has increased the prevalence of oral candidiasis and periodontal diseases were less in patients who had access to HAART.

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Prevalence of oromucosal lesions in HIV positive patients receiving haart-A prospective clinical study

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Abstract

Aim:

To determine the preponderance of oral mucosal lesions and conditions in patients receiving highly active antiretroviral therapy (HAART) for Human Immunodeficiency virus (HIV).

Material and Methods:

Patient tested Seropositive for HIV and on HAART therapy were clinically examined to evaluate prevalence of oral lesions.

Results:

In the pool of 152 HIV positive patients in the study, age ranged from 7 to 71 years, 67 were males and 85 females. The duration of the HAART medication was 43 months. Oral lesion was present in 51.32% of patients related to infection. Oral lesions seen in descending order of frequency were periodontitis, mucosal hyperpigmentation, acute gingivitis, oral candidiasis, linear gingival erythema, stomatitis, and nonspecific ulcers. Totally, 48.68% of patients had no oral lesions.

Conclusion:

Majority of the HIV patients on HAART exhibited periodontitis (30.77%), mucosal hyperpigmentation (17.44%), gingivitis (10.77%), anemic stomatitis (11.28%), and other oral lesions accounted to 29.74% which may be attributed to Anti Retro Viral Therapy.

Keywords: HIV patients, hyper-pigmentation, oral lesions

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Original

Oral lesions associated with HIV infection before and during the antiretroviral therapy era in Ribeirão Preto, Brazil

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(Received 24 March and accepted 21 July 2011)

Abstract: We estimated the prevalence of oral lesions associated with human immunodeficiency virus (HIV-OLs) before and during the antiretroviral therapy (ART) era. The first period was 1997, when many patients received two types of antiretroviral (ARV) drugs. The second study period was 2004 through 2008, when all patients were treated with ART (a combination of two or three classes of drugs, including protease inhibitors). A total of 148 and 388 seropositive participants were examined in 1997 and 2004-2008, respectively. The evaluation consisted of anamnesis and physical examination. The prevalence of HIV-OLs decreased between 1997 (60.1%) and 2004-2008 (29.9%). The HIV-OL responsible for the greatest reduction in prevalence between the two periods was oral candidiasis, of which erythematous candidiasis was the clinical form that decreased most, followed by pseudomembranous candidiasis. In conclusion, we observed a significant reduction in HIV-OLs, which was closely associated with the use of ART. In addition, among patients with a clinical diagnosis of AIDS, we confirmed a significant reduction in HIV-OL prevalence between 1997 and 2004-2008. (J Oral Sci 53, 379-385, 2011)

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Keywords: AIDS; ART era; HIV; oral lesions; pre-ART era.

Introduction

Acquired immunodeficiency syndrome (AIDS) is a severe disease and is the late manifestation of human immunodeficiency virus (HIV) infection (1-3). It has been estimated that 33.4 million people are infected by HIV worldwide (4). In Brazil, 544,846 cases were reported from 1980 through 2009 and 217,091 deaths occurred between 1980 and 2008 (5).

In 1986, the capacity of zidovudine (AZT) to inhibit HIV replication was discovered, and the Brazilian government authorized the free distribution of this drug in 1992 (6). In 1996, the efficacy of antiretroviral therapy (ART) in treating HIV was proved. ART, which has been defined as the combination of two or three classes of drugs (7), reduced the number of deaths and significantly increased quality of life among people with AIDS (8, 9). In 1996, the Brazilian government signed a law establishing the free distribution of AZT, which gave HIV-seropositive patients access to antiretroviral (ARV) drugs. Later, and particularly after 2001, the Brazilian government was able to markedly reduce the prices of ARV drugs by means of patent infringement. Such efforts further increased the distribution of these medicines by the public health network. The number of patients receiving free ARV drugs through the public health system was 55,600 in 1997, 73,000 in 1999, and approximately 105,000 in 2001 (7).

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A relationship between CD4 count and oral manifestations of human immunodeficiency virus-infected patients on highly active antiretroviral therapy in urban population

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Abstract

Introduction: Human immunodeficiency virus (HIV) infection gradually destroys the body«SQ»s immune system, which makes it harder for the body to fight infections. HIV infection causes a quantitative and qualitative depletion of CD4 lymphocyte count, which increases the risk of opportunistic infections. Thus, CD4 count is one of the key factors in determining both the urgency of highly active antiretroviral therapy (HAART) initiation and the need of prophylaxis for opportunistic infections. **Aim:** This study aims to evaluate the prevalence and variations in the oral manifestations of HIV/acquired immune deficiency syndrome patients on HAART therapy in urban population and their association with CD4 count. **Materials and Methods:** A study was conducted by screening eighty patients who were HIV positive in an urban location. Both adult and pediatric patients were screened for oral manifestations and simultaneously CD4 count was also evaluated. Patients with HIV infection for variable time period who are under HAART were considered. **Statistical Analysis:** Measures of central tendency were used to analyse the data. **Results:** HIV infection destroys the immune system of an individual, making the patient susceptible to various infections and malignancies. With the advent of antiretroviral therapy, the scenario has changed drastically. We have observed that patients with CD4 counts between 164 and 1286 show relatively few oral manifestations. Long-term HAART therapy causes pigmentation, xerostomia and angular cheilitis but is taken up quite well by the patients. **Conclusion:** In this study, eighty patients with HAART from urban population showed very minimal oral findings because of good accessibility for treatment and awareness about HIV infections. The patients who were on long-standing HAART treatment also showed minimal oral manifestation such as pigmentation and xerostomia. Hence, we conclude that recognition, significance and treatment of these lesions in patients with HIV infection do not require elaborate setup and can be treated with basic primary health care.

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Full Text

INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV) and is highly lethal. [1] India is the third largest country in the number of HIV-infected patients and according to the WHO, in 2012, an estimated 2.3 million individuals worldwide were newly infected with HIV. [2] It is a critical disorder of the immune system which severely damages the body's normal defense to infections, thereby making the host vulnerable to various infections and conditions including malignancies, which then become life-threatening. [1] With the advent of highly active antiretroviral therapy (HAART), people are living longer and are suffering fewer opportunistic infections. The primarily targeted cells in HIV are CD4 helper T lymphocytes. [1],[2],[3]

In people with HIV infection, antibodies are developed but are not protective. The virus may remain silent and causes CD4 cell death. This results in a subsequent decrease in T-helper cell number, with a resultant loss in immune function which hampers the body's ability to fight infections. [3]

The most common signs and symptoms seen with HIV/AIDS patients are generalized lymphadenopathy, sore throat, fever, dysphagia, night sweat, maculopapular rash, headache, myalgia, diarrhea and peripheral neuropathies. Oral changes include mucosal erythema, focal ulcerations, [4] candidiasis and hairy leukoplakia.

The most frequently associated oral lesions in HIV-infected children are candidiasis, herpes simplex infection, linear gingival erythema, parotid enlargement and recurrent aphthous stomatitis. Other viral and bacterial infections, including periodontal infections are less commonly associated, while hairy leukoplakia and Kaposi's sarcoma are rarely seen in HIV-infected children. [4],[5],[6]

HIV infection causes a quantitative and qualitative depletion of CD4 lymphocyte count, which increases the risk of opportunistic infections. It is one of the key factors in determining both the urgency of HAART initiation and the need for prophylaxis for opportunistic infections. [1],[3]

Dental expertise is necessary for the proper management of oral complications in HIV infection or AIDS, but many patients do not receive adequate dental care. [7]

Medical clinicians should be able to recognize HIV-associated oral disease and provide appropriate care and referral. Factors that predispose to HIV-related oral conditions include CD4+ cell count of <200/μL. [1],[7]

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. [1],[2],[7]

HIV-related oral abnormalities are present in 30%-80% of HIV-infected individuals and these abnormalities are often inaccurately described in medical literature. Treatment for oral conditions are also very low. Factors predictive of receiving oral care include education beyond a high school level, participation in clinical trials and utilization of support services such as medical social workers. The overall prevalence of oral manifestations of HIV disease has changed since the advent of potent antiretroviral therapy (ART). [5],[6],[7],[8]

One study by Patton et al. noted a reduction of oral lesions from 47.6% prepotent ART to 37.5% during the potent ART era. [5] 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

Observational Study

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A real-world, cross sectional study of oral lesions and their association with CD4 cell counts and HIV viral load in Yunnan, China

Wen Shu, DDS[a], Chengwen Li, MD[b], Fei Du, DDS[a], Jinsong Bai, MD[c], Kaiwen Duan, DDS, PhD[a,*]

Abstract

Human immunodeficiency virus (HIV) supresses immune system, primarily cell-mediated immunity. Cluster of differentiation 4 (CD4) cell count, viral load, and oral lesions are the most important laboratory parameters to evaluate the evolution of acquired immunodeficiency syndrome. The present study aims to determine the incidence of HIV-related oral lesions with CD4 cell count and viral load in Yunnan, China.

A cross-sectional study was conducted from December 2007 to December 2009, in 1812 HIV positive patients from Department of Infectious Diseases in Kunming Third People's Hospital. CD4, CD8, and viral load data were collected and analyzed statistically using SPSS 11.3.

Out of 1812 HIV positive patients, 929 (51.27%) were associated with 1 or more oral lesions. The most common oral lesions observed were Candida Pseudomembranous (13.75%), Candida erythematous (10.93%), Oral hairy leukoplakia (7.95%), Aphthous ulcer (6.18%), Herpes simplex infection (5.58%). In most patients with oral lesions, the CD4 cell count was $<200/\mu L$. The incidence of oral lesions was lower when CD4 count was $>200/\mu L$ and with undetectable ($P<.01$) HIV viral load. Almost no oral lesions was observed when CD4 count $>500/\mu L$ ($P<.01$). With highly active antiretroviral therapy, reduction in HIV-related oral lesions was observed especially in Candida erythematous, Candida Pseudomembranous, Oral hairy leukoplakia, and Aphthous ulcer.

The higher incidence of oral lesions with lower CD4 count ($<200/\mu L$) in HIV-infected patients indicated importance of CD4 cell count in identifying disease progression.

Abbreviations: AIDS = acquired immunodeficiency syndrome, bDNA = branched DNA, CD4 = cluster of differentiation 4, CD8 = cluster of differentiation 8, CDC = centres for disease control and prevention, HAART = highly active antiretroviral therapy, HIV = human immunodeficiency virus, KS = Kaposi Sarcoma, NNRTIs = non-nucleoside reverse transcriptase inhibitors, NRTIs = nucleoside reverse transcriptase inhibitors, OC = oral candidiasis, OR = odds ratio, OHL = oral hairy leukoplakia, PI = protease inhibitor.

Keywords: CD4, highly active antiretroviral therapy (HAART), HIV-viral load, human immunodeficiency virus (HIV), oral lesions

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All authors contributed to data analysis, drafting, or revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The authors have no conflicts of interest to disclose.

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1. Introduction

Acquired immunodeficiency syndrome (AIDS) is caused by a retrovirus known as human immunodeficiency virus (HIV) which breaks down the body's immune system leaving a complex of symptoms, neurological disorders, unusual malignancies, and infections.[1]

HIV is a global pandemic disease affecting around 37.9 million people around the world.[2] Two major targets of HIV infection are the central nervous system and the immune system. Profound immunosuppression, primarily affecting the cell-mediated immunity, is the hallmark of HIV. It has a specific affinity for cluster of differentiation 4 (CD4) T cells[3] with at least 1 manifestation in the head and neck area,[4] such as oral lesions.[5] CD4 cell count, viral load, and oral lesions are significant predictive markers of severe immunosuppression and disease progression because they may represent the early signs of the disease.[6]

Oral manifestations such as Kaposi's sarcoma (KS), oral candidiasis, and oral hairy leukoplakia (OHL) were reported to have high incidence in HIV-positive patients.[7] For oral diseases described in HIV-positive patients, 3 main groups were established: Group 1: lesions seen (occasionally) in HIV infection and exhibiting a potential association; Group 2: lesions less commonly associated with HIV infection; and Group 3: lesions strongly associated with HIV infection. These oral lesions may lead to compromised facial appearance, difficulty in eating,

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Oral health in Australian HIV patients since the advent of combination antiretroviral therapy

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ABSTRACT

Background: The introduction of combination antiretroviral therapy (cART) for the treatment of human immunodeficiency virus (HIV) has resulted in changes to the oral health of infected individuals. Little data are available describing prevalence and severity of oral manifestations in a post cART cohort of HIV positive patients.
Methods: A retrospective case note analysis was performed at the Special Needs Unit (SNU), Adelaide Dental Hospital with emphasis on identifying the prevalence of HIV related oral manifestations (OM). A total of 498 (474 males: 24 females) HIV positive individuals were identified who had attended SNU for dental care between 2001 and 2008.
Results: There were significant differences observed in the prevalence of oral manifestations between cART and non-cART groups, and also in comparison to a previous pilot study. Individuals taking cART therapy tended to present with more evidence of linear gingival erythema, angular cheilitis, human papilloma virus associated squamous papillomas and xerostomia.
Conclusions: The widespread adoption of cART in the treatment of HIV has altered the oral health profile of these individuals. These findings provide information on the incidence of oral conditions and demonstrate the need to identify and address oral health needs for people living with HIV.

Keywords: HIV, cART, oral manifestations, pathology.

Abbreviations and acronyms: ANUG = acute necrotizing ulcerative gingivitis; ANUP = acute necrotizing ulcerative periodontitis; ASHM = Australian Society of HIV Medicine; cART = combination antiretroviral therapy; HIV = human immunodeficiency virus; HPV = human papilloma virus; HSV = herpes simplex virus; IRIS = immune reconstitution inflammatory syndrome; NUG = necrotizing ulcerative gingivitis; OHIP = Oral Health Impact Profile; OHL = oral hairy leukoplakia; OM = oral manifestations; SNU = Special Needs Unit; ZDV = zidovudine.

(Accepted for publication 21 May 2012.)

INTRODUCTION

Recent studies have shown that despite initial successes, there has been a resurgence of HIV incidence and prevalence within the Australian community.[1] Dentists are likely to encounter individuals infected with HIV and therefore require knowledge of the oral manifestations of this infection.

The oral manifestations of HIV infection are well documented and numerous.[2] These manifestations are associated with losses in cell-mediated and humoral immunity as a result of $CD4^+$ T-lymphocyte deficiencies, and may serve as early markers of HIV infection and progression.[3,4] The continuous assessment of oral health has therefore been suggested as an alternative or adjunctive method of assessing HIV disease status and progression.

While the use of cART has led to a reduction in the majority of oral manifestations related to HIV infection, there has been an increase in the prevalence of a selected number of non-HIV related oral presentations.[4–12] There is currently little data available with regard to the oral manifestations of HIV in the post cART era and a lack of evidence with regard to appropriate dental management of this group.[13]

This study aims to describe the prevalence of various oral manifestations in individuals with HIV infection amongst an Australian population. Analysis of this group will demonstrate the relative oral health needs for people with HIV and should qualitatively describe the burden of oral manifestations in these individuals. Particular emphasis is placed on changes in the prevalence of HIV-related oral manifestations of

pathogens

MDPI

Review

Oral Manifestations in HIV-Positive Children: A Systematic Review

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Abstract: Background: The number of pediatric patients affected by HIV still remains high, mainly in developing countries, where the main cause of infection is vertical transmission from the mother. Even today, a large number of these children do not have access to treatment, and, without proper care, they die in the first few years of life. **Objective:** The aim of our review was to assess the prevalence of oral hard and soft tissue lesions in HIV-positive pediatric patients by identifying the most common manifestations and the overall impact that they may have on the children's quality of life. **Study design:** A systematic review of the articles in the English language in PubMed and Scopus was conducted in March 2019 in order to identify the main epidemiological and cross-sectional studies on the topic. **Results:** Oral diseases are still one of the most common manifestations in HIV-positive pediatric patients, and they often represent the first form in which immunosuppression shows itself. An analysis of the literature shows that candidiasis is the most common oral lesion found in HIV-positive children. A significant incidence of gingivitis and gingival disease is also evident, though not strictly correlated to HIV infection. However, thanks to the introduction of new antiretroviral therapies, the incidence of HIV-related oral lesions is decreasing. **Conclusions:** An HIV-positive children care program should also include dental protocols, as oral disease negatively influences the quality of life, affecting both functional and social aspects.

Keywords: HIV; AIDS; oral diseases; children; highly active antiretroviral therapy

1. Introduction

HIV infection could be defined as the major epidemic of our century, with dramatic human, social and economic implications. It is a chronic infection that is first characterized by an asymptomatic phase that can stay unchanged for years and, subsequently, by the appearance of the first symptoms due to immunosuppression. In the end, it can lead to acquired immunodeficiency syndrome (AIDS).

The cause of the symptoms is to be found in the destructive effect of the HIV virus on T-helper lymphocytes, in which the virus completes its replication cycle.

The Joint United Nations Programme on HIV/AIDS (UNAIDS) of 2018 recorded, at the end of 2017, 36.9 million HIV-positive people, 1.8 million of whom were pediatric subjects up to 14 years of age [1].

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Most common oral manifestations in pediatric patients HIV positive and the effect of highly active antiretroviral therapy

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Abstract *This integrative literature review aims to identify the main oral lesions affecting pediatric patients with HIV, and describe the effect of highly active antiretroviral therapy (HAART) on these injuries, comparing it to antiretroviral therapy (ART). A search was conducted in PubMed and Scielo databases, following predetermined inclusion and exclusion criteria. 19 papers were selected and the main information on the prevalence and frequency of oral manifestations in HIV-positive pediatric patients and effect of therapy applied were extracted. The most frequent injuries were oral candidiasis, gingivitis, parotid gland enlargement and linear gingival erythema. The use of HAART shown to reduce the prevalence of oral manifestations in pediatric patients with HIV and be more effective than ART. The findings of this study suggest that the most frequent oral manifestation in HIV-infected children is oral candidiasis, followed by changes such as gingivitis and enlargement parotid glands. The use of HAART appears to reduce the prevalence of these oral lesions, showing more effective results than ART.*

Key words *Child, Acquired Immunodeficiency Syndrome, Oral manifestations, Antiretroviral therapy*

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Research Article

Diagnosis of the Prevalence of Bruxism in HIV/AIDS Patients, Associated with Psychological Factors: Pilot Study

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Keywords

- HIV
- Bruxism
- Psycological aspects

Abstract

The Human immunodeficiency virus (HIV) is a pathology that caused a global pandemic, developing a series of social and psycological problems on the population like conflicts, preconceptation, self discrimination, anguish, depression, rejection, abandonment, social isolation, fear to die, etc. Being those cofactors of stress it can influence directly making some conditions worse like bruxism. This study contains a sample of 14 patients with positive HIV, a clinic exam followed by 15 questions about stress factors, habits and the influence of HIV on the patients life's. According to the research, 64,28% of the interviewed patients presented bruxism, a highest percentage comparing with the general population (8 to 21%), 9 patients (64,28%) with joint changes, joint blockage or dislocation was reported on 4 patients (28,57%) and only 2 were following the treatment. The bruxism patients, only 2 never had symptoms of HIV or medication, 2 reported thinking on the actual health condition and 7 think a lot, none of the patients that had never thought about their health condition had bruxism, 7 of 10 bruxist patients reported that think sometimes and 1 reported that think with frequency. It was conclude that the prevalence was higher on HIV patients when compared to the not HIV population. The psycological profile showed an influential factor, being worse on bruxist patients.

INTRODUCTION

Syndrome of Human immunodeficiency (AIDS) is caused by the Human Immunodeficiency Virus (HIV) that can be transmitted by sexual contact, blood and vertical contamination; affects mostly the immune system and nervous system making the clinic symptoms look like opportunistic infections; taking to the higher stage of AIDS desease [1,2].

The cure and vaccines to prevent AIDS hasn´t being developed, although antiretroviral were discovered acting on inhibition of HIV replication, so the viral load stays lower and improves the immune system, with great benefit in reducing mortality and morbidity [3-6]. It's important to recognize the importance of multi professional treatment for those patients, with emphasis on dental and psychological treatment, since we know that there are sequela and psychological consequences.

It's possible to see psychological changes on the HIV/AIDS patients during all the phases since the suspected contamination to the disease evaluation. Studies have shown that emotion changes happens because of the death possibility, fear, anxiety, uncertain prognosis, effects of medication, isolation and rejection; depression caused by lack of cure, self blame, and limits imposed by illness; anger and frustration, the inability to overcome the virus and the uncertainty of the future, guilt for the possibility and to have infected others involuntarily and obsessive problems due to concern about illness and death, and a tendency to avoid new infections [7].

Social unpreparedness often leads the HIV/AIDS sufferer to fell doomed to death, along with fear and distress, may contribute to increase stress. Stress can cause a change on the organism with the intention of adapting, causing degeneration of immune system, reaching even more the defense of those individuals [8-10]. As symptoms of stress we have depression, discouragement, apathy, emotional hypersensitivity, irritability, anger, anxiety and, in addition, we have contributing stress of various diseases [11-13].

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RESEARCH ARTICLE Open Access

Tooth wear in patients treated with HIV anti-retroviral therapy

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Abstract

Background: The objective of this study was to elucidate the relationship between HIV anti-retroviral therapy and tooth wear.

Methods: Assessment of tooth wear was conducted both with a survey questionnaire and clinical assessment at Russell Street Dental Clinic in Portland, Oregon. The survey questionnaire comprised of questions on study participant's gender, age, HIV status, current medications, awareness of tooth grinding or clenching, jaw soreness, tooth or gum soreness, and frequency of headaches. For the clinical evaluation, a dental provider recorded the degree of wear on each tooth using a scale of 0–3. An individual tooth-wear index was used to rank patients with regard to incisal and occlusal wear. Data analysis included descriptive analysis, tests of association and regression analysis using SPSS V.24.

Results: The study sample involved 93 patients (HIV + ve = 60, HIV–ve = 33) with age range of 20-90 yrs. (mean = 49 yrs., s.d = 13.3). 92 and 67% participants of the HIV + ve and HIV-ve groups, respectively, presented with tooth wear. The mean tooth wear index was higher in HIV + ve patients than HIV–ve patients (8.2 vs. 7.8), however, this difference was not statistically significant ($p > 0.05$). A significant, positive correlation was found between HIV presence and tooth wear index, after accounting for age (B = 0.71, $p < 0.05$). The number of years on anti-retroviral therapy alone was positively correlated with tooth wear index ($R^2 = 0.116$, $p < 0.05$). After controlling for age, years of anti-retroviral therapy use was positively correlated with tooth wear index (B = 0.047, $p > 0.05$).

Conclusions: The findings from this study suggest that HIV + ve patients, who are on anti-retroviral therapy have significant tooth wear, although more studies with larger sample size are needed to confirm this. There is a critical need to initiate a dialogue with medical providers about tooth wear as a possible side effect of antiretroviral therapy and to introduce appropriate preventive measures.

Keywords: Tooth wear, Bruxism, Community dentistry, Dental, Anti-retroviral therapy

Background

People living with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) (PLWHA) face tremendous problems regarding their oral health. PLWHA have an increased incidence of poor oral health, which further exacerbates their other medical conditions. PLWHA have reported high unmet oral health needs and low utilization of oral health services [8, 19]. Furthermore, PLWHA face many barriers to acquiring oral health care, including lack of dental insurance, limited financial resources [8], shrinking adult dental Medicaid services [19], and perceived stigma within health care systems [28, 29].

Clinical observation has suggested that many PLWHA are diagnosed with bruxism. Bruxism is characterized by the involuntary clenching or grinding of the teeth especially during sleep and can cause severe oral health problems, including the destruction of tooth structure, temporomandibular joint dysfunction, myofascial pain, and severe sleep disturbances [13, 14, 17, 30]. Bruxism has been reported to occur about two times more frequently in PLWHA than in the general population. In a systematic review of 26 papers, researchers found two articles stating bruxism has a prevalence of up to 31% of

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Effects of long-term use of HAART on oral health status of HIV-infected subjects

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Abstract

BACKGROUND—The aim of this study was to determine the effects of long-term use of highly active antiretroviral therapy (HAART) on oral health status of HIV-infected subjects.

METHODS—Oral examination and measurement of saliva flow rate of both unstimulated and wax-stimulated whole saliva were performed in HIV-infected subjects with and without HAART, and in non-HIV individuals. The following data were recorded; duration and risk of HIV infection, type and duration of HAART, CD4 cell count, viral load, presence of orofacial pain, oral dryness, oral burning sensation, oral lesions, cervical caries, and periodontal pocket. Multiple logistic regression analysis was performed to determine the effects of long-term use of HAART on oral health status of HIV-infected subjects. RESULTS: One hundred and fifty-seven HIV-infected subjects – 99 on HAART (age range 23–57 years, mean 39 years) and 58 not on HAART (age range 20–59 years, mean 34 years) – and 50 non-HIV controls (age range 19–59 years, mean 36 years) were enrolled. The most common HAART regimen was 2 NRTI + 2 NNRTI. HIV-infected subjects without HAART showed greater risks of having orofacial pain, oral dryness, oral lesions, and periodontal pockets than those with short-term HAART ($P < 0.01$). The subjects with long-term HAART were found to have a greater risk of having oral lesions than those with short-term HAART ($P < 0.05$). The unstimulated and stimulated salivary flow rates of the subjects with HAART were significantly lower than in those without HAART ($P < 0.05$).

CONCLUSION—We conclude that long-term HAART has adverse effects on oral health status of HIV-infected subjects.

Keywords

HAART; HIV; oral health; oral lesion; risk factor; salivary flow rate

Introduction

Highly active antiretroviral therapy (HAART) has become a standard treatment for HIV infection. It induces a marked reduction in viral load and increase in the $CD4^+$ cell count (1) leading to a declination in morbidity and mortality of HIV-infected subjects (2). At present,

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