The Importance of the Pathogenesis, Recognition and Management of the Oral Manifestations of HIV-1 Infection to the Dentist

Dr Charles Joffe

Student Number: 14001047
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Introduction

Over the past 20 years, since it was first identified, the HIV-1/AIDS epidemic has continued to exceed all expectations in the severity and scale of its impact.

HIV-1/AIDS is a modern day plague which is evident from its regular mention in both the scientific and popular media.[1] In 1991, the then global programme on AIDS at the World Health Organization forecast that by the year 2000 the cumulative global total of HIV infections in men, women and children would be 40 million.[2] In reality, this prediction has proved a serious underestimate.

Sub-Saharan Africa is the region in the world where the epidemic has been the worst and where the devastation of its impact is increasing.

It has been estimated that 90% of people with HIV-1 disease will present with at least one oral manifestation at some time during the course of their infection.[3]

In South Africa, oral HIV-1 has been reported in 60 % of affected patients[1] and thus indicates the importance of the oral manifestations of HIV-1 infection to the dentist. Oral lesions are common in the individuals with HIV-1 infection and thus the ability to differentiate one manifestation from another, as well as manage some of the more common conditions is fundamental to the overall health care of this Patient Population. As key players in the primary health care of our patients, dentists and dental hygienists have the ability to positively affect the well being of our patients.

It is imperative for a dentist to understand the history and pathogenesis of HIV-1 infection in order to provide this patient population with optimal care, management and treatment.

Clinico-Pathogenesis and History of HIV-1 Infection

Although hundreds of millions of research dollars have been spent seeking successful treatment and the eradication of HIV-1 from infected individuals, that goal has still to be achieved. However, advancements in the knowledge about the pathogenesis and natural history of HIV-1 disease have resulted in significant advancements in the medical and dental management of the disease.[4]

The natural history of HIV-1 disease is now well documented. Primary viral transmission occurs through contact with infected body fluids. Most cases result from sexual intercourse, exposure to contaminated blood, or prenatal transmission. Risk behaviours include injection drug abuse, sexual promiscuity, contact with infected blood and blood products and breast-feeding. Saliva contains at least 2 proteins that are inhibitory to HIV-1 and saliva is not considered to be a body fluid that transmits HIV-1 infection. However, this inhibitory function can be overwhelmed when excessive amount of infected body fluids are introduced into the oral cavity during breast-feeding or oral sexual activity, and oral primary HIV-1 infection can occur.[5]

It must be noted that the dental office is a safe place to provide and receive dental care. Current, generally accepted epidemiological information supports the conclusion that there is no significant risk of contracting blood-borne diseases through the provision of dental treatment when appropriate infection control procedures are followed.[6]

When HIV-1 is transmitted, for example in sexual transmission, the initial target cells are Langerhans cells, dendritic cells of the macrophage line, that reside in the submucosal tissues and are also abundant in tonsillar tissue in the oropharynx.[7,8] These cells express the CD4 molecule on their surfaces, which can serve as receptors for the viral envelope glycoprotein gp120. They also express a coreceptor required for the viral entry into the cell.[9]

The traditional theory is that binding of the extracellular gp120 portion of the envelope protein to CD4 is accompanied by binding to the chemokine coreceptor, resulting in fusion of the viral envelope and the cell membrane and release of the virion core into the cytoplasm. However, there is now evidence that the initial events of HIV-1 infection may not require productive infection of the Langerhans cells.

Studies by Geijtenbeck et al[10] have elucidated the role of a C-type lectin,dendritic cell specific intercellular adhesion molecule 3-grabbing nonintergrin (DC-SIGN), which is abundantly expressed on the immature dendritic cells that first contact HIV-1 at the mucosal surface. This molecule appears to bind HIV-1 from the periphery and allow it to be transported to CD4 T-helper cells. DC-SIGN may also play a role in enhancing infection of the T-helper cell.

It is now clear that different strains of virus have a preferential affinity for different chemokine coreceptors. The major core receptors are the chemokine receptors CCR5 and CXCR4.[9, 12-14] Discovery of coreceptor use has opened new potential treatment options through the selective blockade of these required inter-actions.

In the traditional model of early HIV-1 infection, infected Langerhans cells fuse with CD4 lymphocytes and within 2 days, the virus migrates to the regional lymph nodes. The virus subsequently disseminates haematogenously and vigorous replication occurs in the brain, spleen and gut lymphoid tissue. The time from initial exposure until the virus is detectable in the blood is estimated to be 4-11 days[15], an important point for diagnostic purposes. During the initial viremic phase, virus is present in the plasma at markedly high levels, usually exceeding 1 million RNA/ml.[16] Within 6-12 weeks, antibodies to HIV-1 are detectable in the blood and enzyme-linked immunosorbent assay and western blot testing can document sero-conversion.

At this time, patients are confirmed as HIV-1 positive. Most persons are sero-positive within 3-6 weeks and more than 95% of patients sero-convert within 5-8 months, as determined by standard serologic tests after HIV-1 transmission. However, a small

percentage may have a protracted sero-conversion of 10 months or greater. The time between viral infection and sero-conversion is referred to as the window period. During this period, HIV is present in body fluids and can be transmitted, but the HIV serology may be non-reactive. Because of this potential for inadvertent infection and to minimise transmission, blood screening, using sensitive and expensive testing, can detect HIV DNA very soon after primary viral transmission. This can significantly reduce the risk of HIV-1 infection in those requiring blood and blood products.[5]

Acute HIV-1 infection is symptomatic in the majority of infected persons, perhaps as many as 90%.[19] The clinical manifestations of acute HIV-1 infection appear within days to weeks, most often 2-6 weeks after the initial exposure.

Symptoms commonly include fever, night sweats, fatigue, headache and a maculopapular, non-pruritic rash that predominantly involves the trunk

During the first 6 months of infection, referred to as "Early HIV Disease", the immune system attempts to contain the infection. The initial burst of viraemia is inhibited by the onset of the immune response and thus a viral set point is determined. This equilibrium between virus and host can persist in a steady state for years. However, great variation exists in the viral set point from person to person and that set point is a major predictor of long term clinical outcome. The higher the viral set point, the higher the plasma viral load. This is the level of HIV in the plasma, and the higher the viral load, the poorer the prognosis and the faster the disease will progress to AIDS and death. Thus, one goal of early intervention is to institute antiviral therapy and to attempt to reset the viral set point to a lower value and delay the development of AIDS.[5]

The disease progresses to an "asymptomatic chronic infection with or without persistent generalised lymphadenopathy". In the absence of other systemic disease, most individuals are healthy and immune function is essentially normal during this phase of HIV.

However, viral replication is occurring at a rapid rate and at this time, the lymphatic tissue serves as the major reservoir for HIV, the follicular dendritic cells filter and trap free virus and infected CD4 cells and the viral burden in peripheral blood mononuclear cells is relatively low. With progressive disease, the lymph node architechture is disrupted, and more HIV is released. As more virus is generated and released, more CD4 cells are destroyed, leading to decreased immune function and disease progression.[5]

Patients generally remain asymptomatic until the CD4 count falls below 500cells/mm^3, at which time the patient enters "symptomatic HIV infection" (previously known as ARC – AIDS Related Complex and more recently referred to as 'stage B', according to the 1993 Centre for Disease Control and Prevention [CDC] Classification), which is characterised by the development of opportunistic infections. As HIV continues to replicate, the CD4 count dramatically decreases.

AIDS is diagnosed when the CD4 count falls below 200cells/mm^3, or when one of the AIDS defining illnesses is documented. Eventually, immune function ceases, resulting in advanced HIV infection; characterised by a CD4 cell count <50mm^3, overwhelming opportunistic infections and death.

Without antiretroviral therapy, the progression of HIV from transmission to death is approximately 10-12 years.[5,11]

The clinical symptoms of acute HIV-1 infection most frequently resemble those of acute infectious mono-nucleosis due to Epstein-Barr virus infection. In fact, entertainment of a diagnosis of infectious mono-nucleosis should always prompt consideration of acute HIV-1 infection, or appropriate questions regarding exposure must be asked.[17] Other considerations in the differential diagnosis, in addition to mono-nucleosis, include secondary syphilis, acute viral hepatitis, viral respiratory tract infections, streptococcal pharyngitis, acute toxoplasmosis and other viral exanthemata. Since non of the clinical or laboratory findings are pathognomonic of acute retroviral syndrome, the key to the

diagnosis is a history of exposure and all patients who present with a compatible syndrome should be questioned about their risk for HIV-1 infection.

If suspicion is high on the basis of clinical findings and a recent high- risk exposure, a presumptive diagnosis can be made by testing for the presence of viral RNA in plasma. Since this test is not yet licensed for the diagnosis of acute HIV infection, confirmation requires subsequent documentation by use of antibody tests e.g. ELISA and the Western blot.

Due to the stigma associated with HIV-1/AIDS, disclosure of HIV-1 status by patients themselves and to other health care workers may give rise to unwillingness/falsification of information by patients and a duty on the part of the provider to store data. There is an inherent conflict between the patient's interests in confidentiality and the public's interest in protection from infectious diseases. The presumption is that only patients themselves can know which disclosures to third parties will have consequences on their private, public and professional lives (Bok, 1984). A person with HIV/AIDS has a right to privacy, especially with regards to the doctor/patient privelage.[18]

Some oral health care workers feel strongly that they should know the HIV status of high-risk patients. Testing for HIV should only be suggested if the degree of security it affords the oral health care worker is substantially more than the potential harm it may cause the patient. It is the duty of the practitioner to prescribe the tests to be carried out and a patient refusing to undergo a test recommended by the oral health care worker should be advised to seek a second opinion, if such a test is deemed essential to the management of the patient.[18]

Recognition and Management of Oral Manifestations in HIV-1 Infected Persons

In general, patients are very sensitive to oral stimulation, so one should use a gentle touch. Placing a hand on their shoulder for example, works wonders. A gentle touch says "I have to do this to help you, but I care about you".

After one has donned his gloves, he can no longer place a kind hand on the patient's non-sterile shoulder. Face masks, eye protection, gowns and gloves tend to depersonalise the dentist/patient relationship, so one should take a moment to establish the "I care" feeling before donning one's infection barriers.

In no way should an HIV infected patient be treated any differently from any other patient.

Oral lesions are common in individuals with HIV-1 infection and thus a detailed oral examination is imperative. All signs, symptoms and special test information must be considered in the light of basic science knowledge and then analysed logically at the level where the disease is located. Early recognition and treatment of these oral lesions may reduce morbidity and enhance the well being of this patient population. Oral lesions cause significant discomfort and other problems, yet most are readily treated. They may be the first clinical features of HIV-1 infection and lead to its diagnosis. There presence is an indication of immunodeficiency and predicts the progression of HIV-1 disease.

A study by R. Hastreiter and P. Jiang, Delta Dental Plan of Minnesota, USA, on "Does visiting a dentist regularly affect the oral health care provided to persons living with HIV?" highlighted the need for dentists to educate and encourage persons living with HIV-1 infection to integrate oral health care into the ongoing maintenance of their overall health and well being.

Gary D. Slade from the University of North Carolina at Chapel Hill conducted a study to develop and validate a modular instrument measuring quality of life outcomes from oral health care. The need for such an instrument has emerged from oral health surveys that have demonstrated poorer quality of life among people with untreated oral disease and inadequate dental care. One can see the importance for the dentist to be as thorough as possible in an intra-oral examination and to keep up to date with the treatment modalities for the varying oral manifestations of HIV-1.

At least 40 oral manifestations of HIV-1 infection have been recorded.[21] In this report I am going to focus on the more common manifestations and their treatment and management.

The following is a list of the more common lesions associated with HIV-1 infection:

- Candidiasis
- Hairy Leukoplakia
- Periodontal Problems
- Kaposi's Sarcoma
- Oral Ulcerations
- Xerostomia

Candidiasis

There are three predominant types of Candidiasis seen in the HIV infected population namely Erythematous candidiasis, Pseudo membranous candidiasis and angular cheilitis.

Erythematous candidiasis is a red flat lesion that may appear anywhere in the oral cavity but the majority of the time presents on the dorsal surface of the tongue and/or the roof of the mouth. This lesion, probably the most undiagnosed oral disease seen in people living with HIV-1 infection, tends to be symptomatic with the chief complaint being burning, usually associated with eating salty or spicy foods. Erythematous candidiasis is usually an early manifestation of immune dysfunction.[22] This form of candidiasis is managed with topical antifungal therapies.

Pseudomembranous candidiasis is the lesion most often called "Thrush". It appears as white patches that can present anywhere in the mouth. These patches or plaques can be wiped away, leaving a red and sometimes bleeding surface. Thrush is often the first indicator of HIV infection. In patients known to be HIV positive, thrush may be an indicator of disease progression.[23] In late stage patients, thrush may be complicated by xerostomia.[24]

Angular cheilitis of itself is not diagnostic of HIV infection however, even though it occurs in both the HIV positive and the HIV negative populations, the lesion is more prevalent I the HIV positive population. It appears as cracks or fissures radiating from the corners of the mouth, which may or may not be accompanied by intra-oral "thrush".[25]

Initial bouts or mild infections of candidiasis should be treated with topical antifungal preparations for a period of at least 2 weeks. Acceptable medications include Clotrimazole troches and fungizone oral suspension. Nystatin Swish and Swallow, which needs to be held in the mouth for 5 minutes each use, contains a high sugar content, which can lead to dental caries and should be accompanied by a prescription fluoride.[26]

It is very important for people who wear partials and/or full dentures to treat these appliances when they have candidiasis. The protocol utilized at the Oral Health Care Centre of the Infectious Disease Programme in the United States of America involves thoroughly cleaning the partial or full denture once a day and soaking it overnight in a 1:1 dilution of Chlorhexidine solution. Patients are also instructed to place 1ml of Fungizone oral suspension on the acrylic of their appliance, two to four times per day before inserting the prosthesis.

Moderate to severe candidiasis may require systemic therapies such as Ketoconazole or Fluconazole. As with topical antifungals, treatment should last 2 weeks.[27]

Oral Hairy Leukoplakia

Oral hairy leukoplakia was first described by Greenspan et al[28] in 1984 as an oral manifestation in male homosexual patients. The most common site of involvement is the ventrolateral surfaces of the tongue[29], but it may infrequently be found on the cheek mucosa, lip mucosa, floor of the mouth, soft palate and oropharyngeal mucosa, according Syrjänen's study.[30]

Althogh usually asymptomatic, oral hairy leukoplakia may occasionally cause discomfort when superficially infected by candida.[31] The presence of Epstein Barr virus is sometimes necessary to diagnose oral hairy leukoplakia.[32]

This lesion does not wipe away, which helps to differentiate oral hairy leukoplakia from "thrush". Treatment is usually not necessary, unless taste or appearance is compromised.

Kaposi's Sarcoma

Kaposi's sarcoma is the most common tumour associated with AIDS and has been reported in 15% of the AIDS population. Intra-oral Kaposi's saroma may be the initial presentation in as many as 60%of these reported cases.[33] Biopsy is necessary for a definitive diagnosis. Appearance of these lesions can range from flat to raised and red to purple. Location is possible anywhere in the oral cavity. There is a correlation between a Kaposi's herpes virus (HHV8) and Kaposi's sarcoma.

HHV8 has been found in semen leading to the theory that Kaposi's sarcoma may be sexually transmitted.[35]

Treatment decisions are based on the extent of the disease. Small lesions confined to the mouth may be treated with intralesional injections of 0,2mg/cc of Vinblastine Sulfate,

cryotherapy, surgical excision or radiation therapy. Systemic therapy is reserved for patients with widespread disease or visceral involvement.[33]

Communication between the primary care physician, dermatologist, oncologist and dentist is very important in the proper management of Kaposi's sarcoma.

Kaposi's lesions around the gum line should be kept very clean as suprainfection is possible as plaque accumulates. It is very important to stress home care.

Oral Ulcerations

Oral Ulcerations may occur in up to one half of HIV infected people at some time during the course of infection. Differential diagnosis of ulcers presenting in the oral cavity include recurrent apthous ulcers and those caused by herpes viruses.

Recurrent Apthous Ulceration

These ulcerations are of unknown aetiology and tend to occur on non keratinised tissues such as buccal mucosa, posterior oropharynx and the nodes of the tongue. Whereas Recurrent Apthous Ulceration may not be more frequent in people with HIV disease, they are more severe and prolonged.[36] Treatment involves the use of topical steroids suchas Celestone syrup for most cases or systemic corticosteroid therapy for major lesions.[33] In cases that are refractory to steroid therapy, thalidomide (100mg-200mg per day) has proven to be effective.[37]

Herpes Simplex Virus Ulcerations

Recurrent herpes simplex affects the lips and intra-oral mucosa and affects approximately 10% to 25% of people with HIV infection when considering outbreaks of cutaneous lesions.[38] Inside the oral cavity the herpes simplex virus is usually confined to keratinised tissues such as the hard palate and gingival tissue. Treatment involves

acyclovir 200mg five times per day for 10 days to 2 weeks. As with any other oral ulceration, care should be taken to ensure the cleanliness of the lesion. Rinsing with hydrogen peroxide basedmouth rinses can be helpful.

Xerostomia

Dry mouth is a common complaint among HIV positive people and should be aggressively managed to prevent dental decay and periodontal problems.[26] This condition may be due to salivary gland involvement or medications used therapeutically in people with HIV. Several types of medication are known to cause dry mouth, including anti-depressives, anti-hypertensives, anti-anxiety and anti-histamines. Candidiasis becomes more difficult to treat without adequate salivary flow.[39] Patients comfort and protection are important issues that need to be addressed by the health care team. Patients can chew sugarless gum to increase salivary flow. There are some oral moisturisers and even substitute saliva that patients can try. Fluoride should be prescribed to patients to prevent cavities that occur as a result of decreased salivary flow.

Periodontal Disease

Linear gingival erythema and necrotising ulcerative periodontitis are unique to HIV infection.

Linear gingival erythema is marked by profound red bonding along the necks of the teeth where the gingival tissue and teeth meet. Linear gingival erythema is a probable precursor for the more destructive necrotising ulcerative periodontitis.

Similar principles of treatment should be applied to both the linear gingival erythema and necrotising ulcerative periodontitis. These principles involve gross scaling to remove visible plaque, soft debris and necrotic tissue when present. Povidone iodine irrigation is recommended during this debridement procedure due to its anaesthetic and antiseptic effects. Following this initial debridement, frequent follow up visits are recommended to remove any remaining plaque, debris or calculus and to provide oral 'instruction' to the

patient for home care. One has to be careful to institute these treatment principles as soon as possible due to the possibility that the bone and soft tissue necrosis can extend further into the palate and adjacent tissues leading to a life threatening Noma condition.[42]

Antibiotics should be used with caution due to the risk of overgrowth of *Candida albicans*. A 0,12% solution of Cholrhexidine Gluconate should be given for 2 weeks. Pain management is very important. Pain management is very important and nutritional supplements should be considered, as with any other painful oral manifestation that interrupts eating.[43]

However, if there is no resolution of these lesions with the above-mentioned therapeutic approach, the practitioner should consider other oral lesions associated with HIV infection that may give a similar clinical picture. These include lymphomas, neoplastic growths and severe herpetic or apthous ulcerations of the gingival.[42-43]

With the development of new strategies for controlling the HIV virus, there may be a significant delay in the development of overt AIDS in a larger portion of the infected population. This may, in turn, lead to a downward trend in the occurrence of acute ulcerative periodontitis and linear gingival erythema in HIV infected patients.

However, the dental practitioner will still be faced with the problem of treatment and maintenance of HIV patients with more common periodontal conditions such as chronic adult periodontitis and acute gingivitis.

The question facing dental practitioners is how the HIV infection in general and specifically the immune status may affect conventional therapeutic approaches to these diseases.

When performing oral surgery for example periodontal surgery, a dentist must take into account a potential bacteraemia and as in all patients who are immunocompromised. One must also be aware that healing may be retarded.

One must bear in mind that the criteria for diagnosis of HIV related oral lesions in adults are well established, but corresponding criteria in the paediatric population are not as well defined. Some oral lesions are common in children and their occurrence is not necessarily associated with immunosuppression. Sometimes poor oral hygiene habits and poor diet may be involved.

Results of a study[44] led to the following conclusions that psuedomembranous candidiasis was the most common oral manifestation in HIV positive children with AIDS.

It must be noted that very few people in South Africa, perhaps even fewer in the rest of Africa, have access to or are able to afford antiretroviral drug therapy. Nationally, an even greater percentage of individuals living with the HIV infection have neither access to nor are they able to afford the costs of the required dental treatment. Management of the associated oral lesions therefore represents an enormous challenge because it has a marked effect on the overall quality of life of these patients. To this end, the role of determinant factors such as malnourished states (protein-energy malnutrition, kwashiorkor and micronutrient deficiencies) and poverty needs to be addressed to provide holistic treatment for these patients. Also, the role of oral sexual practices in oral HIV lesion presentation as well as a prospective mode of transmission in South Africa and the rest of Africa needs to be investigated. These include cultural beliefs with regard to multiple sexual partners and condom usage.[20]

The extent of reported HIV infection and the fact that a large proportion of the South African population reside in remote areas emphasises the need to enhance the capacity of all health care workers, traditional or other, in both rural and urban facilities to provide the most appropriate treatment. With Sub-Saharan Africa still bearing the brunt of the HIV epidemic, every effort should be made to improve the quality of life of these infected individuals.

Conclusion

In recent years, the most encouraging news with regards to the management of the oral manifestations of patients with HIV infection comes from the new treatment approaches to the disease on a systemic level.

These new approaches prolong lives of the HIV infected patient by reducing the levels of virus to undetectable levels through the use of a combination of nucleoside antagonists such as Zivovuodine and Didanosine combined with the newly developed protease inhibitors.[40]

For the dental practitioner, these new developments in therapeutic approaches may alter the incidence, severity and management of oral manifestations of HIV infection. In addition, while a single simple vaccine approach to preventing HIV infection may not be feasible due to the genetic variation of different HIV viral strains, the use of multiple vaccines to build up both humoral and cellular immunity may have future promise.[41]

HIV/AIDS affects the broad medical industry in South Africa and it is therefore imperativefor all health care workers to keep up and maintain the knowledge that is being developed, as this is constantly changing. We ,as dentists, can have an impact on the HIV population in a very posotive way and thus improve the oral health status of these persons infected with HIV and thus enhance a state of well being.

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