

Periodontists' perspective of HIV manifestations

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Abstract

Human immunodeficiency virus (HIV) is a retrovirus having special affinity for the CD4 receptor molecule, which is present on the surface of T-helper lymphocytes. There are two genetically different but related forms of HIV, HIV-1 and HIV-2, that have been isolated from patients with acquired immunodeficiency syndrome (AIDS).

The development of periodontal disease in HIV patients is due to its host-microbial interaction. This results in a compromised host immune system leading to the destruction of periodontal supporting structures. The first clinical signs of HIV infection are often associated with various oral and periodontal manifestations. HIV-associated periodontal lesions may be categorized as unusual forms of gingivitis, necrotizing periodontal diseases, and exacerbated periodontitis. These observations have led to the universal inclusion of almost all oral lesions in staging and classification schemes for HIV infection. In the last few decades, the dentists have played a paramount role in identifying and treating both common and uncommon oral and periodontal lesions in HIV-infected patients. This review aims to provide an update on the pathogenesis, re-activation of HIV, various periodontal manifestations of HIV, and recent updates on HIV management. An in depth understanding of AIDS and its oral manifestations is important for appropriate management of oral lesions in patients infected with HIV.

HIV AIDS Rev 2018; 17, 4: 229-235
DOI: <https://doi.org/10.5114/hivar.2018.80253>

Key words: HIV, gingivitis, periodontitis.

Introduction

Acquired immunodeficiency syndrome (AIDS), a retroviral disease caused by the human immunodeficiency virus (HIV), represents the fifth most common cause of death in adults between the age of 25 and 44 years [1]. The condition was first reported in the year 1981 by Centre for Disease Control and Prevention, where 5 homosexual men presented with *Pneumocystis carinii* pneumonia [2]. The condition was originally thought to be restricted to male homosexuals. Subsequently, it was also identified in male and female heterosexuals and bisexuals who participated in unprotected sexual activities or who abused injected drugs [3]. Currently,

sexual activity and drug abuse remain the primary means of transmission [4].

Even though AIDS was reported first in the United States, it has now been detected globally, with almost 70 million people being affected since the initial report of occurrence. Almost 35 million people have died due to HIV infection, and an estimated 36.7 million (30.8-42.9 million) have been living with HIV, with a 0.8% of patients worldwide of age 15-49 years, as reported in 2016. Sub-Saharan Africa remains the epicenter of the epidemic. In the past decade, the most rapid increase in HIV infection have been seen in Southeast Asian countries, including Thailand, India, and Indonesia [5].

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Article history:
Received: 07.04.2018
Received in revised form: 19.04.2018
Accepted: 19.04.2018
Available online: 22.11.2018



In terms of viral diversity, subtype C viruses continue to dominate and account for 55-60% of all HIV-1 infections worldwide. Virus subtype C is most commonly detected in India, South Africa, and China. Subtype B is more common in America and other European countries [6, 7]. Various reports had identified an association between HIV infection and various oral lesions such as oral hairy leucoplakia, Kaposi's sarcoma, non-Hodgkin's lymphoma, and various periodontal diseases such as linear gingival erythema, necrotizing ulcerative gingivitis, and necrotizing ulcerative periodontitis [8, 9].

This present article gives a brief outline of the pathogenesis, re-activation of HIV, various periodontal manifestations of HIV, and recent updates on the management of HIV.

Pathogenesis

The immune system and the central nervous system are mainly targeted by HIV. It results in extreme immune suppression mainly affecting the cell mediated immunity, which is the hallmark feature of AIDS [10]. Profound immune suppression occurs due to infection, severe loss of CD4+ T cells, and impairment in the function of surviving helper T cells (Fig. 1).

HIV strains can be subdivided based on their cellular tropism such 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 mainly infect the peripheral blood mononuclear cells (PBMC), monocytes, macrophages, and T lymphocytes but not T-cell lines, and are present during all stages of infection/disease. T-tropic SI variants 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. Dual-tropic HIV-1 variant infects both monocytes/macrophage and T-cell lines, and hence have a mixed viral population of both NSI/SI phenotypes [11].

Reactivation of HIV and periodontal disease

Studies have shown that the immune response and the oral epithelial cells of the gingiva, which have been latently infected with HIV, may have an association with HIV reactivation [12]. The oral pathogens play a role in triggering inflammatory responses, which would release various cytokines (interleukin-1 – IL-1, tumor necrosis factor- α – TNF- α , nuclear factor-kappa B – NF- κ B). The NF- κ B is responsible for induction of viral gene expression by interacting with the long terminal repeat (LTR) of the HIV pro-virus [13]. Other cytokines such as IL-6, IFN- γ , and TNF- α further play a role in upregulating the IFN regulatory factor to result in HIV-1 replication [14]. Similarly, inflammatory mediators such as prostaglandin E2, IL-2, and IL-7 have also shown to upregulate the HIV activation in T-cells [15].

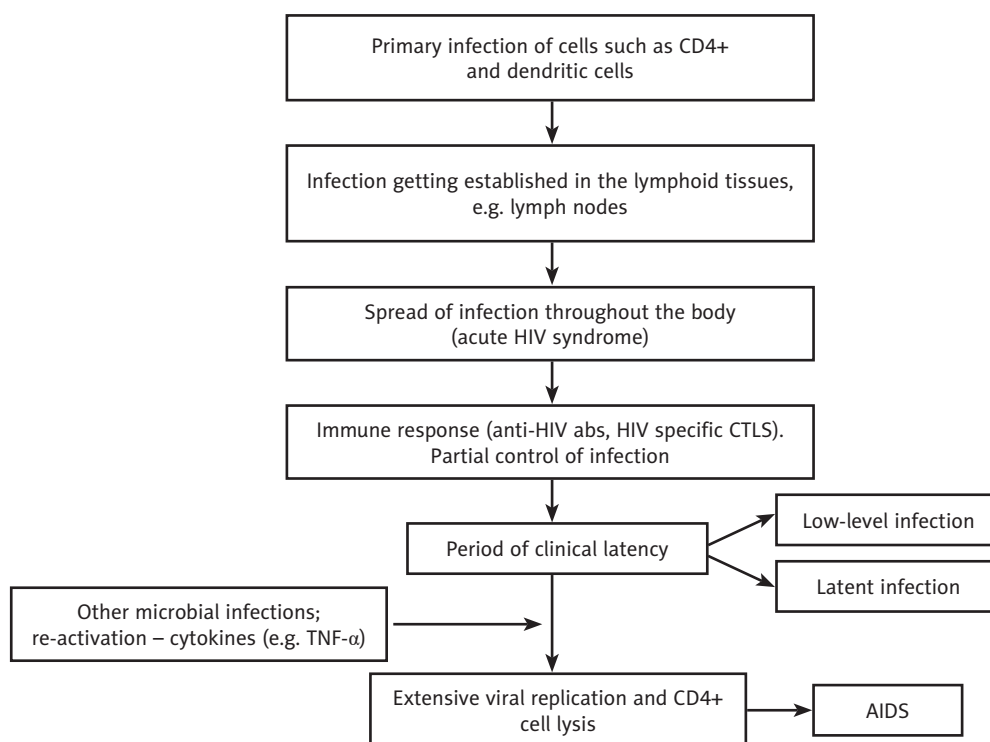


Figure 1. Pathogenesis of HIV infection

Periodontal manifestations of HIV

In 1985, the first evidence of an association between periodontal disease and HIV was documented [16]. Since then, various reports have also been published addressing different forms of the disease. HIV-associated periodontal diseases include various common as well as less common forms [17].

EEC Clearinghouse, in the year 1991, classified HIV-related periodontal disease based on clinical characteristics: 1. HIV-associated gingivitis (presently known as linear gingival erythema); 2. Necrotizing ulcerative gingivitis (NUG); 3. Necrotizing ulcerative periodontitis (NUP). Drawbacks of this characteristics are all the three features are clinical diagnosis without any definitive criteria [18].

In the year 1992, Winkler reported unique microbiological features, along with management of HIV-associated periodontal diseases [19].

In in the year 1994, Holmstrup, to overcome the drawbacks in the EEC Clearinghouse classification for HIV-associated periodontal conditions, came up with a detailed classification, which included [20] gingivitis and periodontitis.

Gingivitis

Gingivitis associated with bacteria and yeast

Studies have demonstrated both conventional form of gingivitis and gingivitis featuring band shaped and/or punctate erythema [20].

Conventional chronic gingivitis: Genco in 1990 had characterized the disease clinically by observing a change in gingival color from pink to red or bluish red, and a change in form to from knife-edge to edematous, often with swollen interdental papillae. It can be sometimes accompanied by change in the inter-proximal position of the gingiva, with an increased tendency to bleeding [21].

Chronic gingivitis with band shaped/or punctate erythema: In 1988, Winkler *et al.* had described HIV-associated gingivitis as soft tissue lesions presenting with distinct erythema of the free gingiva, attached gingiva, and alveolar mucosa. It was diagnosed as an intense linear band, extending 2–3 mm apically from the free gingival margin, and was recorded in more than 50% of cases with HIV-associated gingivitis and periodontitis. Irrespective of whether the erythema was band-like or diffuse, it was often associated with spontaneous bleeding on probing. Secondly, punctate or diffuse erythema of the attached gingiva was also considered as the other prominent feature in a group of patients [22].

The various differential diagnosis of the lesions made were conventional chronic gingivitis, oral lichen planus (Holmstrup *et al.*, 1989), mucous membrane pemphigoid (Pindborg, 1992), and gingivitis like changes due to thrombocytopenia (Pindborg, 1989) [17].

According to EEC Clearinghouse (1991), HIV-associated gingivitis (presently LGE) was described as any gingiva,

which presented an unusual fiery red band along the margin of the gingiva in an otherwise healthy oral cavity. Ulcerations may not be present, nor pockets or loss of attachment [18].

HIV gingivitis generally showed a bacterial profile similar to that of the HIV periodontitis lesions, except that *Wolinella recta* was significantly more prevalent in HIV periodontitis. This suggested that the HIV gingivitis lesion is a precursor to HIV periodontitis. Thus, the early identification and detection would be useful in the management of high-risk individuals [23].

The term ‘HIV-associated gingivitis’ was renamed as ‘linear gingival erythema (LGE)’ in 1993 [24]. This form of gingivitis was originally believed to be associated with HIV. But later research confirmed that LGE also occurred in HIV-negative immunocompromised patients as well, and it was thus renamed [25]. LGE was classified under the category gingival disease of fungal origin by the American Academy of Periodontology in 1994 [26] because *Candida* had been detected to be the primary etiological factor. An important feature is that LGE is different from plaque-induced gingivitis as it does not correlate with the amount of plaque present in the disease sites [27].

Necrotizing ulcerative gingivitis

According to the glossary of periodontal terms of the American Academy of Periodontology (AAP) from 2018, necrotizing ulcerative gingivitis (NUG) is described as an inflammatory disease of the gingiva, which reflects an impaired host response with signs and symptoms including pain, interdental papillary necrosis, and a tendency toward spontaneous bleeding. Also, occasionally presents with a pseudo-membrane formed over the necrotic, ulcerated gingiva. Predisposing factors may include stress, poor oral hygiene, malnutrition, smoking, and immune-deficiencies [28].

In 1987, Pindborg and Holmstrup described NUG in HIV-infected patients, who presented with a fiery red and swollen gingiva with yellowish-grayish marginal areas of necrosis and loss of interdental papillae [29].

EEC Clearinghouse in 1991, described this condition as a localized or generalized ulceration with necrosis and/or destruction of interdental papillae covered with fibrinous slough [18].

Riley *et al.* in 1992 stated that NUG should be designated to lesions, which involves the gingival tissues only, without any loss of periodontal attachment [30].

Rapid progression and conversion to necrotizing periodontitis is the unique feature of HIV-associated NUG, which occurs when left untreated due to a compromised immune system. It is characterized by the destruction of periodontal structures and alveolar bone associated with severe pain, which is a hallmark feature of NUG. If the 3 factors (interproximal necrosis, bleeding, and pain) are absent, a diagnosis of NUG cannot be made [31].

Based on literature, a wide range in variance had been detected in predicting the prevalence of NUG ranging

from < 0.03 to 9.4% [32, 33]. Highest rates being during the world wars. But since then, there has been a decline in the prevalence. Various studies by Reichart *et al.*, Schulten *et al.*, and Barr *et al.* showed an increased prevalence of NUG in HIV sero-positive individuals [34-36]. Whereas, few studies by Melnick *et al.* and Riley *et al.* showed contradictory results [30, 37]. Even though true prevalence of NUG cannot be accurately predicted as most studies were based on military personnel and did not reflect the general population. Recent reviews have expected the prevalence to be < 1% [38].

Gingivitis caused by virus

Immunocompromised patients such as HIV patients, may show susceptibility to other viral infections affecting the oral and periodontal environment.

Herpetic gingivostomatitis: The greatest number of herpes simplex infections occurring in HIV patients are mainly due to HSV-1 virus and occasionally HSV-2 [39].

A prevalence of 5-13% had been detected in various studies conducted on HIV patients [20]. The lesions seen in HIV-infected patients are characterized by affecting the gingiva, palate, and dorsal tongue, and occasional presence of mucosal vesicles, which when ruptures leaves painful irregular ulcers. Recurrent lesions may coalesce and may often be found in clusters [17].

Herpes zoster: Is caused by varicella zoster virus and is clinically characterized by the occurrence of unilateral vesicles or ulcers in mucosa and/or skin corresponding to the area of innervation by a branch of trigeminal nerve. This can result in extreme pain and if it spreads to the underlying bone, it may result in osteonecrosis [40].

Periodontitis

HIV-associated periodontitis was previously classified based on various descriptions of clinical presentations such as the conventional adult periodontitis [41], rapidly progressive periodontitis [42], periodontitis associated with soft tissue loss and irregular bone destruction in otherwise clean mouth [24], and gingival features of HIV-associated gingivitis related to necrosis of gingival/ periodontal attachment apparatus and rare spontaneous resolution [43].

Periodontitis associated with bacteria and yeast

Conventional adult periodontitis/rapidly progressive periodontitis: In addition to the clinical features of HIV gingivitis, this condition also showed rapid destruction of the periodontal attachment. A substantial variation of 5-69% prevalence was reported with periodontitis among HIV-seropositive patients [20]. Various studies had established a co-relation between progressive periodontitis and reduced number of peripheral T cells. A study by Lucht *et al.* showed that patients who had periodontitis along with a more advanced stage of HIV infection were associated

with a more severe form of systemic disease and was due to decreasing number of CD4 lymphocytes rather than the role of visible plaque or occurrence of periodontal pathogenic micro-organisms [44]. In other studies, a reduction of the CD4 counts < 200/mm³ showed a six-fold increase in the risk of attachment loss of 3 mm or more when compared to CD4 counts exceeding 200/mm³ [3, 36]. In contradiction, Persson *et al.* showed a negative co-relation between the alveolar bone loss and HIV-seropositive patients [45].

Studies have shown that HIV-seropositive patients affected by gingivitis and periodontitis show an increased tendency to harbor periodontal pathogens in the diseased sites compared to HIV-seronegative patients. Nonetheless, the microbial flora did not differ qualitatively in comparison to conventional adult periodontitis [46, 47].

Necrotizing periodontitis (NP): It is an infection characterized by necrosis of gingival tissues and the periodontium. These lesions are most commonly observed in individuals with systemic conditions including, but not limited to, HIV infection, malnutrition, and immunosuppression (AAP glossary) [28]. The prevalence for necrotizing periodontitis in HIV-positive patients varied from 0% to 18% as a result of the diversity of the evaluated populations, methods, and diagnostic criteria considered [30, 48]. In 2010, a more recent study showed patients from South Africa, presented with an estimate of 29.5% of women attending antenatal clinics being infected [49].

The clinical manifestations of NP is an extension of NUG, with the initial stage showing various features such as changes in gingival contour (interproximal necrosis, ulceration, and cratering). Fetid odor has been detected in most cases. A severe and deeply associated pain localized in the jaw bone has been considered as an important feature of HIV-associated NP along with spontaneous bleeding. One of the primary distinguishing features appreciated in NP is the occurrence of soft tissue necrosis along with the rapid destruction of periodontal attachment and bone [22].

As the tissue necrosis is rapid, it results in exposure of alveolar bone, which may lead to sequestration and result in interdental craters [20].

In 1994, Glick *et al.* reported an increased likelihood of about 20.8 times resulting in a decrease of CD4 cell count to 200/mm³ in patients who presented with NP compared to those who did not, therefore suggesting that rapidly progressive nature of periodontitis is mainly due to the impairment of local immune defense [50].

Along with the depletion of the helper T-cells, reports on an increase in the levels of inflammatory mediators such as IL-1b [51] and accumulation of hypersensitive polymorphonuclear leukocytes have been made, which may be responsible for the altered host response [52].

Patients who often neglect treatment or present a reduced defense mechanism may develop clinical appearance of a more severe disease, Noma. The necrotic tissue creates a favorable environment for unusual opportunistic agents to further multiply, thus resulting in a progressive mycotic infection, such as mucormycosis. Once these organisms enter

Table 1. Anti-retroviral therapy guideline WHO, 2016 [59]

Patients	Preferred first-line regimens	Alternative first-line regimens
Adults	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG TDF + 3TC (or FTC) + EFV400 TDF + 3TC (or FTC) + NVP
Pregnant or breastfeeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF (or ABC) + 3TC (or FTC) + DTG TDF (or ABC) + 3TC (or FTC) + EFV400 TDF (or ABC) + 3TC (or FTC) + NVP
Children 3 years to less than 10 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + EFV (or NVP)
Children less than 3 years	ABC (or AZT) + 3TC + LPV/r	ABC (or AZT) + 3TC + NVP

TDF – tenofovir, 3TC – lamivudine, FTC – emtricitabine, EFV – efavirenz, AZT – zidovudine/azidothymidine, NVP – nevirapine, DTG – dolutegravir, ABC – abacavir

the blood vessels, it results in thrombosis further leading to a more rapid destruction of the surrounding oral hard and soft tissues within weeks. Fulminant disease is associated with a high mortality [17]. Despite similarities in the microflora of both NP and chronic periodontitis, few atypical microorganisms were also identified such as enteric rods, pseudomonas, isolated yeasts, and non-oral bacteria from NP lesions [8].

Management of periodontal diseases

In the recent years, the introduction of HAART therapy has helped to manage the HIV infection in a much more effective way on a systemic level but the periodontal therapeutic principles, which were introduced in the mid 1980's have mostly remained the same standard of care [53].

The treatment principles include gross scaling for the removal of plaque, soft debris, and necrotic tissue if present. Povidone iodine irrigation is the most commonly used irrigation during the debridement procedure due to its an aesthetic and antiseptic effects [54].

In another study, favorable results were achieved with 0.2% chlorhexidine rinse along with a 3-day course of systemic metronidazole. In necrotizing forms of periodontal disease, the therapeutic approach should be given as soon as possible because bone and soft tissue necrosis may extend into the palate and adjacent tissues, leading to a life-threatening condition such necrotizing stomatitis [55]. Patients who have been affected by the severe form of the disease would usually present with permanent areas of gingival recessions, large irregular embrasure spaces, and reverse gingival architecture. In such patients, plaque control becomes essential and require special brushes, toothpicks, or specially shaped cleaners to access these larger residual defects [56].

Adjunctive antibiotic therapy has played a useful role in the management of the HIV-associated periodontal disease.

Large cohort studies involving HIV-infected patients have recommended the use of certain antibiotics, such as metronidazole, as a valuable adjunct to treatment. However, antibiotics are to be used with extreme caution due to the risk of candida overgrowth. Narrow-spectrum antibiotics, such as metronidazole helps prevent candida overgrowth by leaving a greater proportion of gram-positive flora intact [57]. In contradiction, reports on the development of superinfections by resistant bacteria and candida species have also been noted when broad-spectrum antibiotic such as tetracycline or metronidazole have been used as an adjunct to periodontal therapy [58].

In order to combat gingival diseases affected by candida species, the generally accepted approach is to use a variety of combinations i.e., topical antifungal agent such as clotrimazole troches or nystatin vaginal tablets, and systemic fluconazole or itraconazole in severe cases of immune suppression [53].

The latest anti-retroviral therapy guideline WHO, 2016 recommend the following first line medications for systemic management of HIV in adults, pregnant or breastfeeding women and children [59] (Table 1).

Conclusions

HIV/AIDS is a global phenomenon and requires a multifaceted global effort in curbing this pandemic. Medicine has come a long way and achieved great success in striving for a cure for HIV prevention by expanding testing, treatment, and performing comprehensive prevention programs. The advent of antiretroviral therapy has significantly improved the health and longevity of individuals infected by HIV by suppressing the viral loads in blood. But these antiviral approaches may act as a double-edged sword by showing both beneficial and detrimental effects on oral/periodontal health and disease [59]. In addition, reports have indicated

that the chronic local and systemic dissemination of the microbiota and inflammatory products of common periodontal diseases may have an adverse effect by triggering HIV infection [2] leading to its progression and in the effectiveness of the antiretroviral therapies. Therefore, there is a need for more extensive collaborative multi-center longitudinal studies to monitor the progression of periodontal disease and HIV infection on a regular basis with appropriate multidisciplinary therapies.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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