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Viruses: A Paradox in Etiopathogenesis of Periodontal Diseases.

Dr. Ankita Satija[1], Dr. Jasuma J. Rai[2]
[1](*PG student, Department of Periodontology, K. M. Shah Dental College and Hospital, Sumandeep Vidyapeeth, India)*
[2](*Professor, Department of Periodontology, K. M. Shah Dental College and Hospital, Sumandeep Vidyapeeth, India)*

Abstract: *The purpose of this review is to fill the gap in knowledge of etiopathogenesis of human virus in periodontal diseases. Viruses may play an important role in pathogenesis of periodontal diseases. The role of viruses is significant, as they may induce abnormalities in the adhesion, chemotaxis, phagocytosis, and bactericidal activities of polymorphonuclear leukocytes. Associated with one another, viruses and bacteria have stronger periodontopathogenic potential than individually. It has also been suggested that gingival infection with certain herpes viruses, decreases the resistance of the periodontal tissue, thereby permitting subgingival overgrowth of periodontal pathogenic bacteria and thus, indirectly leading to periodontitis. For full understanding of viruses in periodontal disease, it is significant to know all etiologic factors and such an insight would lead to the better treatment of the disease.*

Keywords: *Etiopathogenesis, Herpes virus, Human Papilloma Virus, Human Immunodeficiency Virus, Periodontitis.*

I. Introduction

Understanding the enormous heterogeneity sheltered within the human microbiome and its role in human health is at its early stages. Viruses and bacteria inhabiting human body are majorly responsible in shaping the human microbial ecology. The potential role of bacteria in relation to periodontal diseases have been well established and documented, on the contrary the role of viruses have been largely unexplored and remains unknown. Although there have been multiple reviews which describe the role of viruses in both systematic diseases and also in oral diseases to a certain extent but not completely.

Paul Keyes wrote [1]:

"I am convinced that although many clinicians and investigators do not exclude the role of bacteria in periodontal lesions, at this point interest in microorganisms often dissipates and attention shifts to other area."

Healthy periodontal sites harbour predominantly gram-positive facultative bacteria; on the contrary periodontitis lesions contain a large variety of gram-negative anaerobic species. This alteration of the periodontal microflora happens with disease development. It is the result of a variable yet versatile interaction of microbiological-specific traits, host humoral and cellular immune responses and oral cavity ecosystem-based factors.

In the 1990s a possible role of viruses in the aetiology of periodontal diseases was suggested. In 1996, **Parra B and Slots J**, demonstrated that human viruses may occur in periodontitis lesions with relatively high prevalence.[2] The hypothesis was based primarily on association studies that demonstrated an increase in the load of Epstein–Barr virus type-1, human cytomegalovirus and other herpes viruses in sites and in subjects with periodontal diseases compared to that of subjects with gingivitis and periodontally healthy controls. This hypothesis posits that subgingival bacteria and viruses infecting the adjacent periodontal tissues would form a pathogenic consortium. [3] Several mechanisms have been proposed to explain the potential role of viruses in the etiopathogenesis of periodontal diseases, such as an impaired local host response or modulation of local cytokine expression induced by viruses, thus increasing the levels and virulence potential of periodontal pathogens. To begin to fill the gap in knowledge of human virus in periodontal diseases, this review article on pathogenesis has been undertaken.

II. Etiopathogenesis of Virus in general:

Pathology is the microscopic level deviation from normal that characterise a particular disease. Viruses as causative organisms have distinct mechanisms by which they produce disease in an organism, this primarily include cell lysis, breaking open and subsequent death of the cell. The steps in viral infection are entry, replication, dissemination and infection of target cells/organs. Fig 1 illustrates the steps for replication of virus once inside the target site. Virions enter the host organism and spread to target tissues ⁄ organs where they can replicate and ⁄ or cause a persistent infection (latency). Latent viruses can become reactivated by several immune compromising events, such as smoking, inflammation, stress, trauma and immunosuppressive diseases.

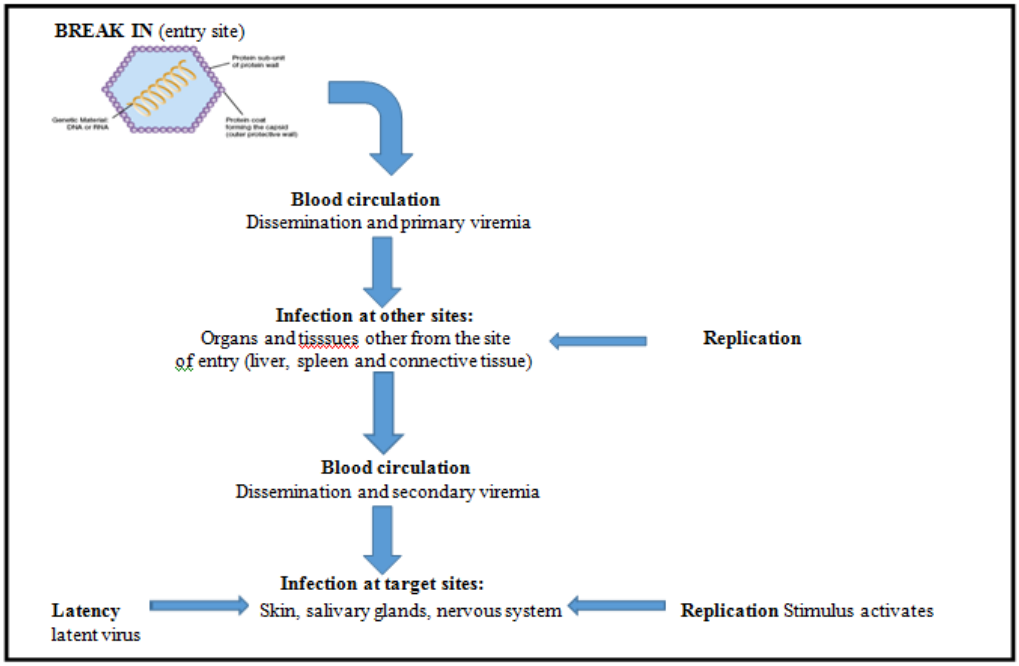

Fig. 1 Viral infection steps: entry, replication, dissemination and infection of target cells/organs. [4]

Table 1 Types of viruses associated with oral lesions

DNA VIRUS	**GENUS**
Herpes virus	Herpes Simplex virus (HSV)
	Epstein Barr virus (EBV)
	Cytomegalovirus (CMV)
	Human Herpes virus 8
Papovaviridae	Papilloma virus
RNA VIRUS	**GENUS**
Retroviridae	HIV

III. Etiopathogenesis of Herpes Virus in Periodontal Diseases:

Since the mid-1990's, herpes viruses have emerged as a putative pathogens in various types of periodontal diseases. Herpes virus may cause periodontal disease as a direct result of infection and replication, or as a consequence of virally induced impairment of periodontal host defences with heightened aggressiveness of resident bacterial pathogens. The eight human members of the herpes virus family affect parenchymal cells, connective tissue cells, epithelial cells, hematopoietic cells and can cause a variety of illnesses by mechanisms that are direct, indirect or immune-regulatory. The hallmark of herpes infection is immune impairment.

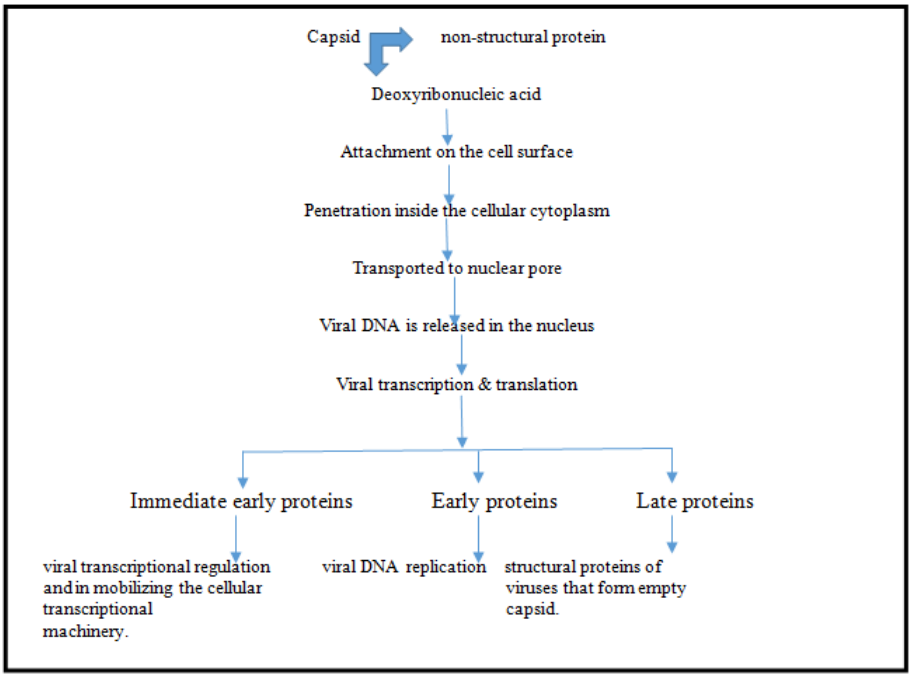

Fig. 2 Replication cycle of herpes virus [5]

The herpes virus replication-cycle comprises binding of viral envelope glycoproteins to cell-membrane receptors, internalization and dismantling of the virus particle, migration of the viral DNA to the cell nucleus, transcription of viral genes, assembly of the virion and viral egress from the infected cell. Herpes viruses ruin infected cells by active lytic replication. Following replication in epithelial cells, some viral nucleocapsids ascend the local sensory neurons by retrograde axonal transport and establish lifelong latency in corresponding spinal or cerebral ganglion (e.g. trigeminal ganglion following oral infection). After primary infection, herpes viruses remain dormant with limited expression of viral genes, albeit retaining the transcriptional and replicational capacity.

Dormancy is maintained for Herpes virus in the DNA of macrophages, T lymphocytes and B lymphocytes, for Epstein–Barr virus in resting memory B lymphocytes, and for human cytomegalovirus in dendritic cells and in monocytes and their progenitors. Reactivation of latent herpes virus can occur spontaneously or during the period of decreased host defence seen because of drug induced immunosuppression, emotional stress, concurrent infection, hormonal changes, or physical trauma. [6]

Herpes virus reactivation causes a major spike in cytotoxic T cells and pro-inflammatory cytokines, but also produces virus-derived homologues of human IL-10 and other inhibitors of the antiviral Th1 cell-mediated defence. Herpes virus DNA reacts with toll-like receptor 9, which is remarkably up-regulated in periodontitis lesions compared with gingivitis lesions. Toll like receptors (TLR) are a class of proteins that play a key role in the innate immunity system. The TLRs expressed on T lymphocytes and their respective ligands can directly modulate T cell function. These TLRs act as co-stimulatory receptors to enhance proliferation and/ or cytokine production of T-cell receptor-stimulated T lymphocytes. Over-production of pro-inflammatory cytokines due to chronic stimulation of TLRs may lead to tissue destruction. TLR-9 is present in gingival epithelial, fibroblasts, osteoblasts and they are associated with IL-8, which is a pro-inflammatory cytokine. Herpes viral infection shows altered inflammatory mediators and cytokines response.

3.1 Etiopathogenesis of Epstein Barr Virus (EBV) in Periodontal Disease:

Epstein-Barr virus-cytomegalovirus co-infection is often seen to be associated with different types of oral diseases. A concomitant infection with two herpes viruses may activate latent viral genomes by the mechanism of reciprocal transactivation, which connotes that gene products of one virus trigger the transcription of another virus. Two active viruses, each providing their own unique set of virulence factors, can result in a particularly severe disruption of the immune system and accelerate a disease process.

In periodontitis, the presence of EBV DNA is related to an elevated occurrence of Porphyromonas gingivalis, Tannerella forsythia, Campylobacter species and other periodontopathic bacteria. Bacterially induced gingivitis permits EBV-infected B lymphocytes to enter the periodontium. An activation of latent EBV in the periodontium may then occur spontaneously or as a result of a concurrent infection, fever, drugs, tissue trauma, emotional stress or other factors impairing the host immune defence. EBV activation takes place during periods

of inadequate EBV- restricted cellular cytotoxicity, causing an outgrowth of EBV-infected B lymphocytes and a release of tissue-damaging mediators. There is a shift in lymphocytes counts towards predominance of B lymphocytes/plasma cells in EBV infection. These cells are prominent in progressive periodontal lesions.

3.2 Etiopathogenesis of Cytomegalovirus Virus (CMV) in Periodontal Disease:

Cytomegalovirus has been identified immune-histologically in biopsies from marginal and apical periodontitis lesions, in gingival monocytes, in T-cells from periodontitis patients, and in periapical cysts. An active cytomegalovirus periodontal infection has been associated to disease-active periodontitis, and the virus may play a role in other types of periodontal disease such as aggressive and refractory periodontitis. [7]

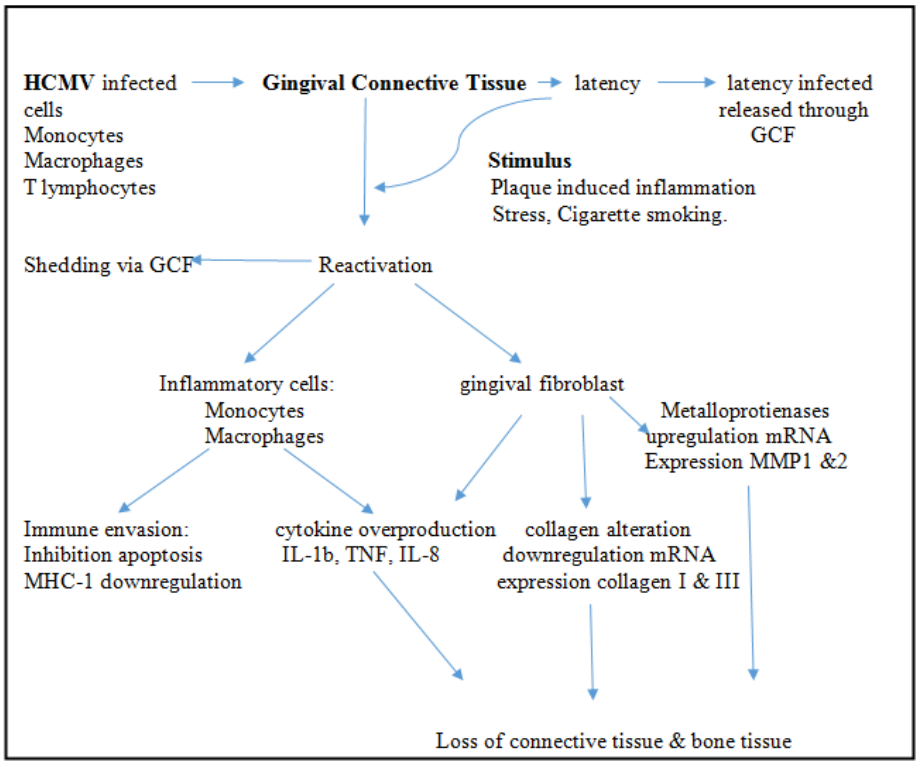

Fig. 3 Proposed model linking cytomegalovirus to periodontal breakdown [7]

Abb: GCF: gingival crevicular fluid; IL: interleukin; MHC-I: major histocompatibility complex class I; MMP: matrix metalloproteinase; TNF: tumor necrosis factor-alpha.

The exact mechanism of periodontal breakdown due to cytomegalovirus is not been hypothesised. A number of theories have been put forth. (Fig.3) HCMV infects many different epithelial cells, endothelial cells, smooth muscle cells, mesenchymal cells, hepatocytes, granulocytes and monocytes derived macrophages. The first cells to respond to the bacterial challenge are sulcular and junctional epithelial cells, which release defensins and cytokines, particularly interleukin- 8 and interleukin-1b. The gingival connective tissue reacts by recruiting monocytes, macrophages and neutrophils, followed by CD4 cells in a T helper-1 and T helper-2 combined response. The cytomegalovirus latent genome is carried into the periodontium by infected macrophages and T-cells, and cytomegalovirus activation may eventually give rise to infection of additional cell types. An active cytomegalovirus infection in macrophages and T-cells triggers release of interleukin-1β and tumor necrosis factor-α. These pro-inflammatory mediators recruit antiviral inflammatory cells to the site of infection but also induce osteoclast differentiation and the release of matrix metalloproteinases.

Cytomegalovirus activation takes place with decreased cellular immunity and the activation process itself can further reduce the host immunity. Macrophages infected with cytomegalovirus or Epstein– Barr virus exhibit a decreased host response, with inhibition of phagocytic activity, tumor necrosis factor-a production and toll-like receptor-9 expression. If the duration of reduced immunity is long enough, an upgrowth of specific periodontopathic bacteria and destructive periodontal disease may fortify. Cytomegalovirus can replicate in cultured gingival tissue and enhance the adherence of Aggregatibacter actinomycetemcomitans to such cells, thereby providing an additional mechanism for increasing the pathogen load. [7] CMV infects periodontal monocytes/macrophages and T-lymphocytes in periodontitis lesions. The down regulation of these cells involved in the periodontal defense may lead to bacterial superinfection resulting in increased virulence of

resident bacteria including Porphyromonas gingivalis, Prevotella intermedia, Prevotella nigrescens, Campylobacter rectus, Treponema denticola and Aggregatibacter actinomycetemcomitans. [8]

IV. Etiopathogenesis of Human Immunodeficiency Virus (HIV) in Periodontal Diseases:

Oral lesions associated to HIV are often the first clinical signs of this infection and can play a specific role in the diagnosis of patients with unknown HIV serostatus. **Patton et al** [9] in 2002 reported oral candidiasis and hairy leukoplakia as the most prevalent HIV associated oral disease. This has also been reported previously by other authors like **Lamster IB** and **Reylonds HS.** [10] Other oral lesions which are strongly associated with HIV infected patients are non-Hodgkin's lymphoma and Kaposi's sarcoma. They together with oral candidiasis are pathogenic against the periodontium. In addition to all this, HIV is associated with a number of periodontal diseases such as linear gingival erythema, necrotizing gingivitis, necrotizing periodontitis and chronic periodontitis. In the recent years, the interesting insights into the microbial etiology and contribution to the incidence and progression of periodontal disease in HIV infected patients is the role of opportunistic infections such as that of candida. [11]

HIV virus plays a local role in the destruction of periodontal tissues by suppressing T-helper cells and by acting as a 'super antigen' which may provoke an unregulated and destructive host response.

- HIV has a strong affinity for cells of the immune system, most specifically those that carry the CD4 cell surface receptor molecule
- Helper T lymphocytes (T4 cells) are most profoundly affected.
- Overall effect is gradual impairment of the immune system by interference with T4 lymphocytes
- B lymphocytes are not infected, but the altered function of infected T4 lymphocytes secondarily results in B-cell dysregulation and altered neutrophil function.
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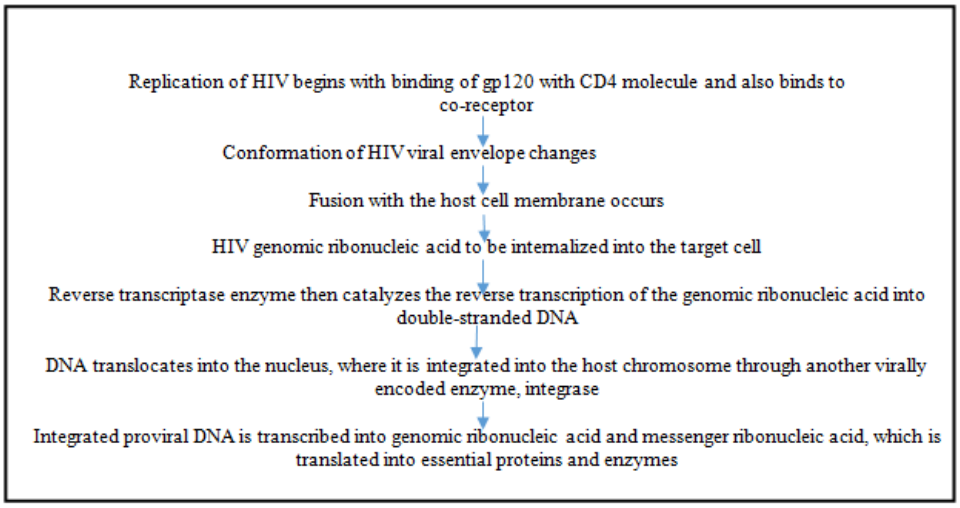

Fig 4 Replication of HIV virus [12]

Abb.: gp: envelope glycoprotein exposed on the surface of HIV virus

Ryder et al. [13] examined peripheral blood PMN activity in HIV+ individuals with HIV associated Periodontitis and intraoral candidiasis. As compared to controls, PMN from HIV patients demonstrated an increase in the percentage of cells that phagocytized microspheres, an increase in the number of microspheres phagocytized per cell, and an increase in both the oxidative burst and actin polymerization. The enhanced response may have been the result of the absence of an intact cellular immune response. It was proposed that priming of PMN was the result of infection, possibly in the oral cavity. The resultant hyper responsive PMN may ultimately be involved in tissue damage in the periodontium.

Salo et al. [14] have compared matrix metalloproteinases in gingival crevicular fluid (GCF) and saliva from HIV+ patients HIV- patients with adult Periodontitis, and controls. They determined that PMN-derived metalloproteinases in GCF and saliva from H1V+ patients were present in the activated form, and proposed that these activated enzymes may contribute to periodontal destruction in HIV+ patients.

V. Etiopathogenesis of Human Pappiloma Virus (HPV) In Periodontal Diseases:

HPV belongs to papilloma viridae family and is a double stranded, non-enveloped DNA virus. HPV has tropism for epithelial tissue thus; it can affect both skin and mucosa. A mechanism has been proposed by **Hormia et al** [15] in 2005 of HPV virus leading to periodontal destruction which has been illustrated in fig.5. **Hormia et al** [15] (2005) in a study confirmed that HPV types 6, 11, and 16 DNA are detected in gingival samples from patients with periodontal disease. While not necessarily indicating a direct relationship between viral DNA detection and periodontal disease, it suggested that marginal periodontal epithelium can serve as a reservoir of HPV in the oral mucosa which could also explain the development of gingival papillomas and condylomas in the oral cavity.

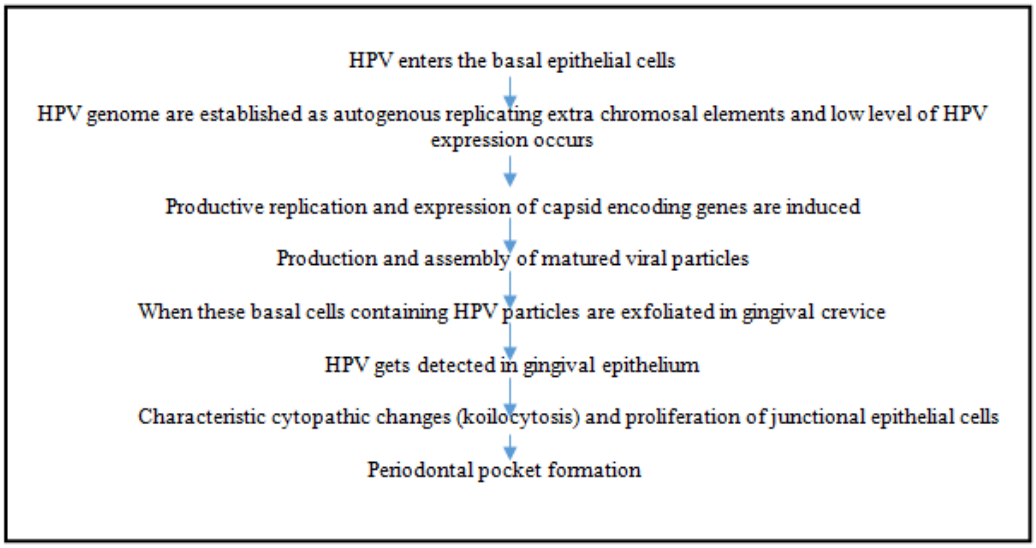

Fig. 5 Proposed model linking human papilloma virus to periodontal breakdown [15]

VI. Conclusion:

Human viruses are involved in the development of various types of oral ulcers, oral tumours, classical oral infectious diseases and periodontitis. Herpes simplex virus-1 and Cytomegalovirus are linked to oral ulcers; Ebstein-Bar virus, Herpes virus-8 and Papillomaviruses to oral tumors; and Ebstein-Bar viruses and Cytomegalovirus to aggressive periodontitis. Rapid advances in medical virology may also help to uncover the pathogenesis and treatments of viral diseases of mouth. Prevention and therapy based upon antiviral approaches may avert the debut of periodontitis or result in long lasting arrest and ultimate cure of existing periodontitis, as well as of other virally related diseases of the human mouth.

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