Silent saboteurs: Unveiling the role of viruses in periodontal disease (Review)

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Abstract. Periodontal diseases have long been considered primarily bacterial infections driven by the complex interplay of microbial plaque and host immune responses. However, emerging research has highlighted the significant role of viruses, particularly those from the *Herpesviridae* and *Retroviridae* families, in the pathogenesis of periodontal conditions. These viruses are not merely passive inhabitants of the oral environment; rather, they actively modulate host immunity, disrupt periodontal homeostasis and increase the pathogenic potential of coexisting bacteria. Through various mechanisms, such as immune evasion, the induction of pro-inflammatory cytokines and the impairment of local immune surveillance, viruses can facilitate tissue destruction and exacerbate periodontal breakdown. The present narrative review aimed to comprehensively summarize the involvement of viruses in periodontal disease by delving into their structural characteristics, classification, replication strategies and intricate interactions with host immune mechanisms. Special focus is placed on herpesviruses, including Epstein-Barr virus and human cytomegalovirus, and human immunodeficiency virus, which have been implicated in both the aggressive and chronic forms of periodontitis. Diagnostic challenges and molecular approaches for detecting these viral agents in periodontal tissues are also discussed, along with the clinical implications of their presence. Understanding the viral dimension of periodontal disease not only broadens the current knowledge of its multifactorial etiology, but also opens new avenues for the development of diagnostic, preventive and therapeutic strategies. The present review underscores the need for a paradigm shift in both the research and clinical management of periodontal diseases. The emerging role of viral diagnostics, salivary biomarkers and immunologically targeted therapies highlights the potential for more precise risk assessment and personalized periodontal care.

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Contents

1. Introduction

Viruses, as obligate intracellular parasites, represent a significant yet often overlooked component of the oral microbiome, particularly within the context of periodontal health and disease. Viruses are submicroscopic infectious agents composed of genetic material enclosed within a protein shell, often enveloped by a lipid membrane. These entities are incapable of self-replication and rely entirely on the host cellular machinery for propagation (1). Despite their minimalistic structure, viruses are greatly efficient in hijacking host mechanisms, often resulting in chronic, latent, or even oncogenic infections. Within the oral cavity, viruses have been identified in gingival crevicular fluid (GCF), periodontal pockets and oral mucosal tissues, indicating their active involvement in the periodontal microenvironment (2).

Traditionally, periodontal diseases have been viewed as bacteria-driven inflammatory conditions. However, the emerging understanding of the oral microbiome has revealed a complex interplay between host immunity and polymicrobial communities, including viruses. Unlike bacteria, viruses exert

their influence primarily by modulating immune responses and enhancing the pathogenicity of resident bacteria (3). Persistent infections, immune suppression and viral reactivation are all mechanisms through which viruses can exacerbate periodontal inflammation and accelerate the breakdown of periodontal tissues (4). A schematic illustration summarizing viral-host-bacterial interactions in periodontal pathogenesis is provided in Fig. 1. Epidemiological studies have (5-7) reported herpesvirus detection in 30-60% of chronic periodontitis sites, with Epstein-Barr virus (EBV) and human cytomegalovirus (HCMV) frequently isolated from deep pockets (8,9). Previous meta-analyses have suggested a several-fold higher prevalence of these viruses in diseased sites compared to healthy controls (10,11).

2. Literature search methods

A structured literature search was conducted across the PubMed, Scopus, Web of Science and Google Scholar databases. The search strategy used combinations of the following key words and Boolean operators: 'viruses AND periodontitis', 'herpesviruses AND periodontal disease', 'HIV oral manifestations', 'viral-bacterial synergism', 'periodontal virome', 'SARS-CoV-2 and oral health' and 'salivary viral biomarkers'. The search included articles published between 1990 and 2025, and was restricted to English-language publications. Both clinical trials, observational studies, molecular studies and review articles were included, whereas editorials, non-peer reviewed sources, and articles lacking relevance to viral periodontal involvement were excluded. Of note, two authors (AS and VRA) independently screened titles and abstracts, followed by full-text assessment. Data extraction focused on viral mechanisms, immune modulation, diagnostic approaches, clinical manifestations and therapeutic strategies. Any disagreement was resolved by consensus.

3. Evolution and classification of viruses

The evolutionary origin of viruses is a subject of ongoing debate. Three prominent theories provide potential explanations. The virus-early hypothesis suggests that viruses predate cellular life, having evolved from primordial self-replicating molecules. This theory implies that viruses may represent remnants of precellular life, providing insight into early molecular evolution (12). The regression hypothesis posits that viruses are degenerate forms of parasitic cells that gradually lose essential genes over time, reducing themselves to genetic elements capable of hijacking only host cells. Finally, the escaped gene hypothesis theorizes that viruses originate from fragments of host genetic material, such as plasmids or transposons, that gain the ability to exit and enter other cells, becoming infectious in the process (1).

Despite their origin, viruses have co-evolved with host species for millions of years, developing sophisticated mechanisms to persist, evade immune detection and manipulate cellular functions. These evolutionary traits are particularly relevant in chronic infections such as periodontitis, where viruses can remain undetected, yet actively modulate host-pathogen interactions and inflammation (13).

As regards the classification of viruses, according to the Baltimore Classification of Viruses, introduced by Nobel Laureate David Baltimore in 1971, categorizes viruses into seven classes on the basis of their genome type and replication strategy (Table I). This system is particularly relevant in periodontology, where viral infections can modulate host immunity and contribute to the pathogenesis and progression of periodontal diseases (14).

4. Viral components and structure, and replication and spread in the body

Components and structure of a virus. A virus particle, or virion, consists of several key components: The genome (either DNA or RNA) that encodes viral proteins, a protective protein shell called the capsid, and, in enveloped viruses, an outer lipid bilayer derived from the host cell membrane (6,15). This envelope typically adorns glycoproteins or peplomers that facilitate viral attachment to specific host cell receptors, allowing the virus to enter the host cell (16).

Some viruses, such as retroviruses, also carry enzymes, such as reverse transcriptase or integrase, which are essential for replication within host cells. The capsid structure can range from simple icosahedral or helical forms to more complex arrangements, which influence the ability of a virus to interact with host cells, evade immune responses and withstand environmental challenges. In the context of periodontal health, these viral components play crucial roles in the pathogenesis of periodontal diseases (17).

For example, viruses, such as herpesviruses can persist in periodontal tissues by evading immune detection through latency, contributing to chronic inflammation. The presence of viral particles in periodontal pockets may not only increase the severity of gingival inflammation, but can also alter the balance between host immunity and pathogenic bacteria, promoting the progression of conditions, such as periodontitis, particularly in immunocompromised individuals (18).

Viral replication and spread. The Modes of viral replication and spread in the human body are summarized in Table II. There are various steps of viral replication and systemic dissemination with relevance to periodontal tissues (12). In systemic infections, the virus can spread through the bloodstream, nerves, or lymphatic system, where it can reach distant sites in the body, including the oral cavity. Oral tissues, such as the gingival mucosa and periodontal tissues, can function as reservoirs for certain viruses. For example, herpesviruses can remain latent in host cells, such as the sensory ganglia, and re-emerge under certain conditions, such as immunosuppression or stress. This periodic reactivation results in the development of recurrent oral lesions, such as cold sores or ulcers (19). In the context of periodontal health, viral replication and spread can exacerbate existing periodontal conditions by altering the immune response and interacting with periodontal bacteria. Viral infections can lead to persistent inflammation in the periodontium, contributing to tissue breakdown, the destruction of periodontal ligaments and even alveolar bone loss. Over time, viral reactivation and chronic inflammation can aggravate periodontal disease, particularly in immunocompromised individuals (12).

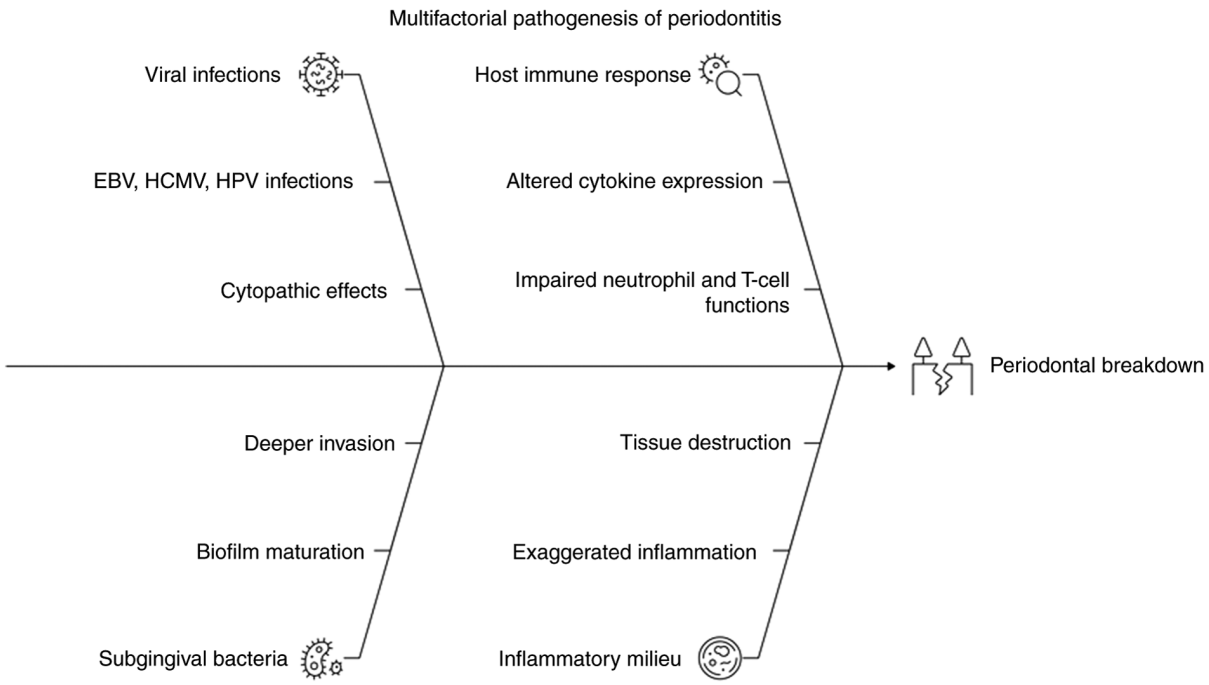

Figure 1. Schematic diagram illustrating the viral-host-bacterial synergy in periodontitis. EBV, Epstein-Barr virus; HCMV, human cytomegalovirus; HPV, human papillomavirus.

5. Host immune response to viruses

The immune system responds to viral infections through a coordinated network of innate and adaptive mechanisms. Innate responses include those involving interferons, natural killer cells and macrophages, which serve as the first line of defense. Interferons function as antiviral cytokines, promoting an antiviral state in neighboring cells and enhancing antigen presentation (20).

Adaptive immunity involves both humoral and cell-mediated responses (21). B-lymphocytes produce neutralizing antibodies (IgG and IgA) that bind viral particles, preventing entry into host cells. In the oral cavity, secretory IgA plays a critical role in mucosal defense. Cytotoxic t-lymphocytes ($CD8^+$) recognize and destroy virus-infected cells by detecting viral peptides presented on MHC class I molecules (22).

Viruses counteract host defenses by downregulating MHC molecules, secreting immunomodulatory proteins, inhibiting apoptosis, and mutating antigenic epitopes to escape recognition. These immune evasion strategies allow chronic persistence and immune dysregulation, a hallmark of virus-related periodontal pathogenesis (23).

6. Diagnostic methods in virology

The accurate identification of viral infections in periodontal tissues requires both direct and indirect diagnostic techniques. Direct methods include the detection of viral antigens via enzyme-linked immunosorbent assays or immunofluorescence, visualization via electron microscopy and polymerase chain reaction (PCR) for viral nucleic acid amplification. PCR has become the gold standard for detecting herpesviruses and human immunodeficiency virus (HIV) in oral tissues due to its high sensitivity and specificity (17).

Indirect methods involve serological tests that detect host antibodies against viral proteins and virus isolation in tissue cultures to observe cytopathic effects (24). Light microscopy can also identify viral inclusion bodies within infected tissues. These methods, particularly when used in combination, allow clinicians to detect latent or active viral infections in periodontal lesions, contributing to targeted therapy and prognosis assessment (25).

7. Different viruses and their periodontal implications

A summary of viral pathogenesis in periodontitis based on the mechanisms of action of viruses is presented in Table III. There are various viruses involved in periodontal diseases:

The Herpesviridae family. *Herpesviridae* family includes several viruses implicated in periodontal diseases: Herpes simplex virus (HSV-1 and HSV-2), EBV and HCMV. These are double-stranded DNA viruses capable of establishing lifelong latency with periodic reactivation.

EBV infects B lymphocytes and epithelial cells and is frequently detected in patients with aggressive periodontitis. It can promote the production of pro-inflammatory cytokines, reduce neutrophil function and synergize with periodontopathogenic bacteria. EBV has also been shown to be associated with oral hairy leukoplakia (OHL), particularly in HIV-positive individuals (26). In EBV, latent membrane protein-1 activates the NF-κB and JNK pathways, promoting the release of pro-inflammatory cytokines and impairing neutrophil oxidative burst (27).

HCMV exhibits broader cell tropism, infecting macrophages, endothelial cells and fibroblasts. It is commonly found in deep periodontal pockets and is associated with severe inflammation and immune suppression. Co-infection with

Table I. Baltimore classification of viruses.

Class	Genome type and replication strategy	Examples	Relevance to periodontology
Class I	Double-stranded DNA (dsDNA)	Herpesviridae (HSV), Varicella-zoster virus (VZV), *Papillomaviridae* (HPV)	• Latent infections in the periodontium • Can reactivate under stress or immunosuppression • HPV associated with oral cancers affecting periodontal tissues
Class II	Single-stranded DNA (ssDNA)	*Parvoviridae*	• Less studied in periodontology • May integrate into host genome • Potential role in chronic oral lesions and gingivitis
Class III	Double-stranded RNA (dsRNA)	Reoviridae (e.g., Rotavirus)	• Rarely cause chronic oral infections • Systemic infections may impair immune responses, indirectly impacting periodontal health
Class IV	Positive-sense single-stranded RNA (+ssRNA)	Picornaviruses (Enteroviruses, Rhinoviruses)	• Can alter immune response • May exacerbate existing gingivitis or oral infections indirectly
Class V	Negative-sense single-stranded RNA (-ssRNA)	Paramyxoviruses (measles, mumps), rhabdoviruses (rabies)	• Not directly involved in periodontal disease • May lead to immunosuppression, increasing susceptibility to periodontal pathogens
Class VI	Single-stranded RNA with reverse transcription	Retroviruses (e.g., HIV)	• Profound effect on immune system ($CD4^+$ T-cell depletion) • Strongly associated with severe periodontal diseases (e.g., necrotizing periodontitis) • Disrupts microbial-immune balance in the periodontium
Class VII	Double-stranded DNA with reverse transcription	Hepadnaviruses (e.g., hepatitis B virus)	• Not directly pathogenic to periodontal tissues • Can cause immune dysfunction • Liver disease affects host response to periodontal pathogens

The information presented in the table was obtained from a previous study (14).

EBV and HCMV in lesions in periodontitis is associated with greater tissue destruction and greater probing depths (23). HCMV expresses immunomodulatory proteins, such as US28, a viral chemokine receptor that dysregulates leukocyte trafficking and enhances inflammatory mediator production. These molecular strategies collectively weaken host defense and facilitate bacterial overgrowth, amplifying periodontal tissue destruction (28).

HSV-1 and HSV-2 are known for their ulcerative manifestations in the oral cavity. HSV-1 primarily causes oral-facial infections and has been linked to necrotizing periodontal diseases, particularly in immunocompromised hosts. These viruses possess the ability to modulate host immunity and trigger apoptosis, contributing to rapid tissue breakdown (29).

Human papillomavirus (HPV). HPV is a non-enveloped DNA virus with a predilection for epithelial tissues. Of note, >200 types have been identified, with HPV-16 and HPV-18 classified as high-risk due to their association with oral and oropharyngeal squamous cell carcinoma. In periodontal tissues, HPV DNA has been isolated from gingival sulci, periodontal pockets and inflamed gingiva, suggesting a possible etiological or contributory role (30).

The E6 and E7 proteins of HPV interfere with tumor suppressor proteins, such as p53 and Rb, promoting cell cycle dysregulation and potential epithelial dysplasia. Although the direct link between HPV and periodontitis remains under investigation, its detection in diseased periodontal tissues, particularly in HIV-infected patients, highlights its potential role in modulating epithelial barrier integrity and immune surveillance (31). Recent research has shown that HPV-associated epithelial dysregulation may enhance microbial adhesion and alter gingival epithelial immune signaling (32).

Picornaviruses and paramyxoviruses. Although less frequently implicated in periodontal diseases, picornaviruses and paramyxoviruses may affect the oral cavity. Picornaviruses, such as coxsackievirus A, are single-stranded RNA viruses responsible for hand-foot-and-mouth disease and herpangina, both of which feature vesicular and ulcerative oral lesions. These typically affect children and may cause discomfort, poor oral hygiene and transient gingival inflammation (33).

Table II. Mode of viral spread and replication.

Step	Process	Description
1	Attachment	Virus binds to specific receptors on the host cell surface, ensuring target specificity.
2	Entry	Virus enters the host cell via endocytosis or direct fusion with the cell membrane.
3	Uncoating	Viral genetic material (DNA or RNA) is released into the cytoplasm or nucleus of the host.
4	Transcription and translation	Virus hijacks the host machinery to transcribe its genome and translate viral proteins using host ribosomes and enzymes.
5	Assembly	Newly synthesized viral genomes and proteins are assembled into new virions.
6	Release	New virions exit the host cell by budding (for enveloped viruses) or by cell lysis (for non-enveloped viruses), often leading to host cell destruction.

The information presented in the table was obtained from a previous study (29).

Paramyxoviruses, such as the measles virus and mumps virus can also be present in the oral cavity. Measles present with Koplik's spots, whereas mumps cause parotitis. Although these viruses are not directly involved in periodontal tissue destruction, they can alter host immunity and mucosal barriers, indirectly influencing periodontal health, particularly in susceptible populations (33). RNA viruses may modify interferon pathways and innate antiviral signaling, indirectly heightening periodontal tissue vulnerability.

HIV. The most clinically significant retrovirus in periodontology is HIV. HIV is a single-stranded RNA virus that integrates into host DNA via reverse transcriptase and targets $CD4^+$ T-lymphocytes, leading to progressive immunosuppression. The oral cavity is a sentinel site for HIV-related manifestations and often reveals early signs of systemic disease (20).

In the context of periodontal disease, HIV is associated with linear gingival erythema (LGE), necrotizing ulcerative gingivitis (NUG), necrotizing ulcerative periodontitis (NUP), and necrotizing ulcerative stomatitis (NUS). These conditions are characterized by the rapid and severe destruction of soft and hard tissues, spontaneous bleeding and halitosis. They are frequently accompanied by systemic symptoms and often occur at low $CD4^+$ counts (<200 cells/μl) (34).

HIV also facilitates co-infections with herpesviruses, HPV and fungal pathogens, such as *Candida albicans*. Saliva and gingival crevicular fluid in HIV-positive individuals often harbor detectable levels of HIV RNA, indicating the role of the oral cavity as a potential reservoir and site of viral transmission (35).

While previous studies have established associations between herpesviruses, HIV, HPV and periodontal destruction, the strength of evidence varies considerably (5,34). Mechanistic insights are strongest for EBV and HCMV, whereas HPV and RNA viruses rely largely on correlative or preliminary reports. Conflicting findings, particularly regarding virus detection across populations and methodologies, suggest the need for standardized sampling and molecular protocols. Future studies are warranted to integrate longitudinal designs and metagenomic approaches to clarify whether viruses initiate, accelerate, or merely amplify periodontal breakdown.

8. Clinical oral manifestations of viral infections

The oral manifestations of viral infections represent a critical aspect of oral diagnostics (20), particularly in immunocompromised individuals, such as those with HIV/AIDS. These manifestations can range from lesions and gingival inflammation to severe forms of periodontal disease, underscoring the need for a careful assessment of the viral etiology of oral pathologies (25).

OHL. OHL is a distinctive condition caused by EBV. It typically presents as white, non-removable plaques on the lateral borders of the tongue and is often associated with HIV-positive patients, particularly those with advanced immunosuppression. These plaques are asymptomatic, but can be diagnostic markers for HIV progression, indicating a decline in immune function. Lesions are considered a marker of immunocompromised status rather than a direct indicator of malignancy, although their presence may increase the risk of further oral lesions and opportunistic infections (19).

Candidiasis. Although candidiasis is a fungal infection, it often co-exists with viral infections, particularly in individuals with HIV or other forms of immunosuppression. It is considered a diagnostic marker of immune decline, particularly when it presents as oropharyngeal candidiasis (thrush). Fungal infection caused by *Candida albicans* can be exacerbated by viral infections, particularly HIV, as the capacity of the immune system to fight opportunistic infections is significantly diminished. Candidiasis manifests as white patches on mucosal surfaces and is often accompanied by redness or ulceration in severe cases. Its recurrent presence in patients with HIV is often associated with advanced immunosuppression and serves as an indicator for assessing immune system function and the progression of the underlying viral infection (20).

LGE. LGE is closely associated with HIV and presents as a distinct red band along the gingival margin, characterized by minimal plaque accumulation and a poor response to conventional treatment. It is a manifestation of immune dysregulation and the inflammatory response within the gingiva and is often observed in individuals with HIV/AIDS. Gingival inflammation is not typically caused by bacterial plaque

Table III. Classification of viral pathogenesis in periodontitis based on the mechanisms of action.

Category of pathogenesis	Definition/focus	Key viruses	Mechanism in periodontitis
1. Direct viral cytopathic effects	Viral destruction of host cells, leading to localized lesions or tissue necrosis.	Herpes simplex virus (HSV)-1/2, human papillomavirus (HPV), picornaviruses (e.g., coxsackievirus)	The virus directly infects and destroys epithelial and fibroblast cells, causing ulceration, vesiculation and tissue breakdown, particularly in primary or acute infections. HPV infection can lead to epithelial dysplasia in the sulcus.
2. Indirect immune-mediated effects	Viruses manipulate and dysregulate the host immune response, creating chronic inflammation and systemic immune deficiency.	Human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), human cytomegalovirus (HCMV)	Viruses establish latency and periodic reactivation, actively suppressing local immune surveillance (e.g., inhibiting MHC molecules or reducing neutrophil function) and driving chronic, non-resolving inflammation via the induction of pro-inflammatory cytokines (e.g., IL-6, TNF-α).
3. Viral-bacterial synergism in periodontal pockets	Viruses create a pathological microenvironment that enhances the survival and virulence of periodontopathic bacteria.	EBV and HCMV (co-infection), viruses that cause immunosuppression (e.g., HIV)	Viral immune dysregulation and inflammation favor dysbiosis by impairing the host's ability to clear bacteria. This allows the proliferation and increased virulence of key periodontopathogens (e.g., *P. gingivalis*), leading to accelerated and more severe tissue destruction than either pathogen could achieve alone.

The information presented in the table was obtained from previous studies (3,9,11,12).

accumulation, but rather by the immune response of the host to the presence of oral pathogens, including viral and fungal elements. LGE may be one of the first clinical signs of immune decline in patients with HIV, and is a key oral manifestation requiring careful management alongside antiviral therapy and periodontal care (36).

Necrotizing gingival and periodontal diseases (NUG/NUP/NUS). NUG, NUP and NUS are severe oral conditions often observed in individuals with HIV/AIDS, and they are frequently complicated by viral co-infections [e.g., HSV and cytomegalovirus (CMV)]. These conditions are characterized by rapid and severe tissue necrosis in the gingiva and periodontium, leading to painful ulcers, bleeding and a foul odor (37). Viral co-infections aggravate the clinical presentation, as they suppress the immune response and hinder the ability of the body to effectively manage both viral and bacterial pathogens. The rapid progression of these diseases can result in significant tooth loss and oral disfigurement if not promptly treated with a combination of antiviral and antibacterial therapies (34).

Ulcers and erosions. Oral ulcers and erosions are common manifestations of viral infections triggered by viruses, such as HSV, Coxsackievirus and paramyxoviruses. These painful, shallow ulcers typically appear on non-keratinized mucosal surfaces, such as the buccal mucosa, tongue and soft palate. Characteristic painful lesions are often recurrent, particularly in individuals with HSV infections, which can be reactivated by stress, immune suppression, or other triggers. Viral ulcers can greatly impair oral function, causing difficulty in eating and speaking, and are often accompanied by swelling and redness. The presence of herpetic ulcers in the oral cavity is often an indication of active viral replication, requiring appropriate antiviral treatment to control symptoms and reduce the risk of transmission (38).

9. Clinical implications and management

The recognition of viral involvement in periodontal disease requires a multifaceted management approach that not only targets the viral pathogen, but also addresses the immune status of the patient and the complexity of coinfections. Given the increasing interplay between viral infections and periodontal diseases, it is essential for clinicians to implement comprehensive strategies to control viral replication, maintain oral health and reduce the risk of disease progression, particularly in immunocompromised patients, such as those living with HIV/AIDS (34).

Antiviral therapy. In the management of viral periodontal diseases, antiviral medications play a critical role in reducing the viral load and preventing the progression of lesions:

i) Acyclovir, ganciclovir and valganciclovir are commonly used in the treatment of HSV and CMV infections. These drugs inhibit viral replication by targeting viral DNA synthesis, and they are particularly effective in preventing recurrent outbreaks of HSV and controlling CMV-related oral manifestations, including oral ulcers and gingivitis (39).

ii) Highly active antiretroviral therapy (HAART) is the cornerstone for the management of HIV and preventing the immunosuppressive effects that exacerbate periodontal disease. HAART functions by inhibiting various stages of the HIV replication cycle, thereby controlling the viral load and improving the immune response, which can help reduce the severity of oral manifestations such as oral candidiasis, OHL and gingival inflammation associated with HIV. By restoring immune function, HAART can reduce the frequency of periodontal infections and complications related to immunosuppression (40).

Combined antiviral and antibacterial therapies. In a number of cases, particularly those involving coinfections (viral and bacterial), a combination of antiviral and antibacterial therapies may be necessary. This is particularly true for conditions, such as NUG or NUP, where viral infections such as HSV or CMV cause bacterial infection (41). The use of antibiotics such as metronidazole (effective against anaerobic bacteria) and doxycycline (which also has anti-inflammatory properties) helps control bacterial overgrowth, preventing further tissue destruction. In such cases, the dual approach ensures that both the viral and bacterial components are managed effectively, reducing the risk of systemic spread and improving oral outcomes (39).

Standard periodontal therapy. Standard periodontal therapy remains an essential part of managing viral periodontal diseases, particularly when combined with antiviral medications, such as the following: i) Scaling and root planing helps to remove bacterial biofilms and calculus deposits, reducing inflammation and increasing the effectiveness of antiviral treatments (42). ii) Chlorhexidine irrigation can be used to irrigate periodontal pockets, reducing plaque accumulation and controlling bacterial growth, while allowing antiviral treatments to target the viral load more effectively. iii) Antibiotic coverage (e.g., metronidazole or doxycycline) is often administered to manage the bacterial component of coinfections, which can exacerbate the clinical presentation of viral periodontal diseases.

However, beyond mechanical and antimicrobial management, it is crucial to consider the systemic health and immune status of the patient. In patients with HIV, the regular monitoring of $CD4_+$ T-cell counts and the viral load is necessary. These markers help assess the degree of immune suppression, predict periodontal risk and guide treatment modifications. Lower $CD4^+$ counts are associated with more severe periodontal disease progression, and higher viral loads suggest poorer immune control, necessitating more aggressive periodontal and antiviral management (43).

Recent periodontal consensus reports emphasize adjunctive host-modulation therapies, such as sub-antimicrobial doxycycline, NSAID-modulating regimens, and complement-targeting agents, which may be particularly valuable when viral-driven immune dysregulation underlies periodontal destruction (44,45).

Preventive strategies. Prevention plays a critical role in reducing viral transmission and disease recurrence in individuals who are at a high risk of developing viral infections:

i) Vaccination against human papillomavirus (HPV) and varicella (chickenpox) can significantly reduce the risk of developing virus-related oral diseases, such as oral cancers or varicella-zoster-related oral lesions. The HPV vaccine, in particular, has been shown to reduce the incidence of oral cancers, whereas varicella vaccination helps prevent reactivation of the virus, which can result in shingles with oral involvement (39).

ii) Immune support through the use of nutritional supplements, such as vitamins D and C, zinc and prebiotics/probiotics (46), appropriate antiretroviral therapy (ART), typically a combination of drugs, such as non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors and protease inhibitors (47), and other immune-boosting treatments, including certain immunomodulatory cytokines (e.g., IL-2 or IFN-γ in select contexts) or therapeutic vaccines (48), can help strengthen the defence system of the body against opportunistic viral infections.

iii) Strict oral hygiene practices are essential for reducing the risk of developing oral viral infections and preventing the recurrence of candidiasis and other opportunistic infections. Brushing with fluoride toothpaste, regular flossing and antiseptic mouthwashes (such as those containing chlorhexidine) can help reduce the bacterial and viral loads in the mouth (43).

10. Emerging viral pathogens and periodontal health

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been implicated in various systemic effects that in turn affect periodontal health. SARS-CoV-2, an RNA virus, is capable of inducing widespread immune system dysregulation and inflammatory responses, both of which can exacerbate pre-existing periodontal diseases. Patients with COVID-19 have been reported to experience oral manifestations, such as dry mouth, oral lesions and an altered taste, which contribute to periodontal inflammation and tissue breakdown (49,50).

COVID-19 is also associated with increased levels of cytokines and pro-inflammatory mediators, which may exacerbate gingival inflammation and accelerate the progression of periodontitis. Furthermore, the ability of the virus to suppress immune function and cause immunosuppression in severe cases enhances susceptibility to secondary infections, including bacterial periodontal pathogens. This immunosuppression, along with increased viral load, can lead to worsening periodontal conditions, particularly in patients with underlying chronic diseases such as diabetes or HIV (51).

Additionally, patients with COVID-19 may have a greater incidence of co-infection with periodontal pathogens, which can increase the severity of periodontal destruction. The stress associated with the pandemic and reduced access to dental care may also contribute to the neglect of oral hygiene, further exacerbating the progression of periodontal disease. These

factors collectively underscore the need for comprehensive oral health care and preventive measures during and after COVID-19 infection (52).

Recent studies have demonstrated that SARS-CoV-2-induced lymphopenia, elevated levels of IL-6, and ACE2 overexpression in the gingival epithelium may heighten periodontal inflammatory responses (49,50).

11. Future directions: Unlocking new avenues in viral periodontology

The recognition that viruses are not bystanders, but silent saboteurs in periodontal disease necessitates a paradigm shift in both research and clinical management. To translate this knowledge into tangible clinical benefits and to strengthen the multifactorial etiology model of periodontitis, future investigations must prioritize the following innovative areas:

i) Non-invasive viral biomarkers (salivary diagnostics): Future research is required to focus on developing highly sensitive, rapid and chair-side assays to detect and quantify the viral load (e.g., EBV, HCMV and HIV) directly in non-invasive samples, such as salivary fluid and GCF. Salivary diagnostics provide a potential tool for early risk assessment, monitoring disease activity and predicting the need for aggressive antiviral/antibacterial therapies, particularly in immunocompromised individuals (34).

ii) Omics technologies for the periodontal microbiome: Employing advanced technologies, such as shotgun metagenomics and RNA sequencing will allow for the simultaneous analysis of the complete viral, bacterial, and fungal communities (the 'virome', 'bacteriome' and 'mycobiome') within periodontal lesions. This approach will move beyond simply detecting presence to understanding the precise transcriptomic and proteomic interactions that facilitate tissue destruction (6), providing a high-resolution map of the viral-host-bacterial synergy described in the present review.

iii) Novel antivirals and targeted therapies: Research is required to investigate next-generation therapeutic agents beyond conventional antivirals (e.g., acyclovir and ganciclovir) and HAART. This includes exploring the potential of host-modulation therapies and advanced gene-editing techniques such as CRISPR-based technologies to target and inactivate the specific latent viral DNA of persistent viruses like herpesviruses (EBV and HCMV) within periodontal host cells. Such targeted approaches may provide a cure for virus-driven chronic inflammation (39).

iv) Vaccine development for viral periodontal risk: Given the strong association between viruses, such as EBV, HCMV and HPV with severe and aggressive forms of periodontitis, public health strategies should consider the impact of viral vaccination. Widespread vaccination against these specific periodontitis-associated viruses, similar to existing HPV and varicella vaccines, may offer a potent long-term preventive measure against disease initiation and recurrence.

Emerging approaches, such as salivary virome assays, metagenomic sequencing and CRISPR-based antiviral platforms may enable personalized risk prediction and targeted suppression of latent viral reservoirs in periodontal tissues. Integrating these tools into diagnostic workflows could transform early detection and individualized periodontal care.

12. Conclusion

Viruses are no longer considered passive bystanders in periodontal diseases. The ability of viruses to establish latency, evade host immunity, modulate inflammatory pathways and synergize with bacterial pathogens positions them as significant contributors to periodontal pathogenesis. Their presence in periodontal pockets and gingival tissues underscores the need to expand current diagnostic frameworks beyond bacteria-focused models. Integrating viral detection, through molecular diagnostics, salivary biomarkers and chairside assays into routine periodontal evaluation represents a critical future direction that may transform risk assessment and early diagnosis.

Furthermore, the complex interplay among viruses, host immunity and the oral microbiome highlights the necessity for interdisciplinary collaboration among periodontists, virologists, immunologists and infectious disease specialists. Such collaborations are essential for developing targeted antivirals, vaccines, host-modulation strategies and personalized treatment protocols.

As the understanding of viral contributions deepens, periodontology should embrace a more holistic, multi-pathogen approach to prevention, diagnosis and management, paving the way for more accurate prognostication and improved clinical outcomes.

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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